ICRP ref: 4902-4124-8907

Annals of the ICRP

ICRP PUBLICATION 1XX

Factors Governing the Individual Response of Humans to Ionising Radiation

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PUBLISHED FOR

The International Commission on Radiological Protection

by

SAGE

Please cite this issue as 'ICRP, 20xx. Factors Governing the Individual Response of Humans to Ionising Radiation. ICRP Publication 1XX, Ann. ICRP xx(x).'

CONTENTS

ICRP Publication XXX

FACTORS GOVERNING THE INDIVIDUAL RESPONSE OF HUMANS TO IONISING RADIATION

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Approved by the Commission in 20YY

Abstract–The current system for radiological protection of humans is largely based on populations rather than individuals – ICRP risk estimates for cancers are provided as age-, sex- and population averages, for example. In this publication an extensive review of the literature has been undertaken to consider which factors influence individual response to radiation in terms of normal tissue reactions following radiotherapy, circulatory diseases, cataract, cognitive impairment, and cancers. These include individual intrinsic such as sex, age, and genetic attributes, or extrinsic factors such as co-exposures to other agents or co-morbidities.

While the literature related to individual factors is extensive, robust evidence exists for only a few factors. Age influences risk of cancer, cognitive impairment, and other normal tissue reactions; biological sex influences cancer risk; some genetic factors influence normal tissue reaction risk (inherited monogenic disorders) and possibly cancer risk; concurrent chemotherapy influences risk of normal tissue reactions and possibly circulatory disease risk; some underlying conditions/comorbidities influence normal tissue reaction risk and possibly cataract risk; and smoking influences cancer risk (with most evidence available from studies of radon exposure related lung cancer risk). While investigations have considered other factors such as alcohol consumption, body mass index, and the immune system, only limited and often conflicting evidence is available.

While some studies suggest that individual risk of normal tissue reactions may be predicted by use of simple cellular or genetic tests, the overall evidence base is mixed, and no clear consensus exists that risk can be predicted. The situation is similar in terms of prediction of cancer risk.

ICRP Task Group 128 will be considering the implications of the evidence presented here on the system of radiological protection.

Keywords: Radiation; Cancers; Tissue reactions; Influencing factors

MAIN POINTS

- **There is robust evidence for the severity of normal tissue reactions to radiotherapy being influenced by genetic factors (inherited monogenic disorders), concurrent chemotherapy, comorbidies (cardiovascular disease, diabetes, inflammatory bowel disease and hypertension), and age; additionally, some evidence supports a role of smaller genetic changes (single nucleotide polymorphisms) in some genes. Prediction of normal tissue reactions using cellular and other assays has been reported, but it remains unclear if prediction is possible.**

- **For circulatory diseases, concurrent chemotherapy with anthracyclins may influence risk, convincing evidence in relation to other factors is lacking, although age and sex may influence the liklihood of certain circulatory disease outcomes; investigation of the prediction of individual response has not been conducted.**

- **Only limited evidence is available in relation to cataract risk, some evidence suggests that concurrent diabetes increases risk; investigation of the prediction of individual response has not been conducted.**

- **For cognitive effects, there is robust evidence for age at exposure influencing risk, with those exposed at younger age being at greater risk; investigation of the prediction of individual response has not been conducted.**

- **In terms of radiogenic cancers, robust evidence indicates that risk is influenced by age-at-exposure (younger ages at elevated risk, but with variation between cancer sites), biological sex (in terms of excess relative risk females are at greater risk, but with variation between cancer sites), and smoking (notably radon lung cancer risk higher in smokers); some evidence exists for genetic factors and female sex hormones influencing risk; prediction of radiation cancer risk by means of simple tests has not been convincingly demonstrated.**

- **Overall, only limited robust evidence is available on the influence of specific factors on responses to radiation exposure. The most secure evidence is in relation to age and biological sex, particularly with respect to radiation-related cancer. The ability to predict responses at the individual level remains a challenge.**

EXECUTIVE SUMMARY

(a) Tissue reactions and stochastic effects after exposure to ionising radiation are variable in presentation between individuals. Factors and mechanisms governing individual responses to ionising radiation are complex and not well understood. These responses can be measured at different levels of biological organisation following varying doses of radiation by analysing different endpoints such as cancers, non-cancer diseases, and mortality in the whole organism; normal tissue reactions after exposures clinically scored by radiation therapists using standardised Common Terminology Criteria for Adverse Events (CTCAE)/Radiation Therapy Oncology Group (RTOG) scales; and cellular endpoints such as chromosomal damage and molecular alterations. There are many factors that, to different degrees, influence the responses of individual people to radiation. There are the treatment/exposure-related factors, such as radiation quality, dose, dose rate, and the tissue (sub)volume irradiated; these are not the subject of this publication. The individual-related factors that are considered here include, among others, age and sex, genetic and epigenetic factors, systemic comorbidities such as diabetes or viral infections, life-style factors (e.g., smoking, diet, and possibly body mass index), and environmental factors. Genetic factors are commonly thought to be a substantial contributor to individual response to radiation. While there are recognised high penetrance radiosensitive syndromes, the inheritance of an abnormally responsive phenotype among a population of healthy individuals does not follow a classical Mendelian, monogenic heredity pattern. Rather it is considered to be a multi-factorial, complex trait.

(b) The Task Group aimed to review the currently available scientific information on individual radiation responses and the variation observed in the population.

(c) The literature describing relevant epidemiological and clinical studies, experimental animal studies, and cellular/molecular studies were within scope for this publication. However, the focus is largely on the epidemiological/clinical and experimental animal studies.

(d) Only limited robust evidence is available on the influence of specific factors on responses to radiation exposure. The most secure evidence is in relation to age and biological sex, particularly with respect to radiation-related cancer. The ability to predict responses at the individual or population sub-group level remains a challenge.

1. INTRODUCTION AND REVIEW METHODOLOGY

(1) The overarching aim of radiological protection is '*to manage and control exposures to ionising radiation so that deterministic effects are prevented, and the risks of stochastic effects are reduced to the extent reasonably achievable*' (ICRP, 2007). This is achieved for occupational groups and the public though justification of any decision that alters the radiation exposure situation, the optimisation of protection, and limitation of individual doses to those exposed from regulated sources in planned exposure situations. In the medical context where there is direct benefit to the individual patient, each procedure involving radiation exposure should be considered in terms of the benefits accrued and the risks from the exposure, and then tailored such that the benefits outweigh the risks. There are no dose limits for patients because justification and optimisation are applied on a case-by-case basis – exposures are patient specific, diagnostic images must be of sufficient quality to reach the required diagnostic level of disease detection and radiotherapeutic doses must be appropriately high for effective therapy. The evaluation of cancer and hereditary risk to health in occupational and public settings is based on the calculation of radiation detriment, which is an age- and sex-averaged quantity. Where there is risk of tissue injury due to public and occupational exposures, ICRP determines threshold doses, at the level where one percent of exposed persons are expected to show the specific tissue injury. In some cases, tissue-specific dose limits are derived from the threshold values as is the case for the lens of the eye (ICRP, 2012). Thresholds for tissue injury apply to all ages and both biological sexes. In medical settings the threshold values do not apply, rather a clinical judgement is made balancing the benefits of the exposure to the patient and the risks posed by the exposure as noted above; dose constraints may apply also.

(2) The system of radiological protection, outside of medical settings, has developed primarily to protect populations, rather than individuals within populations. Risk evaluation on the basis of effective dose is not applicable to patients in the same way as it is for public and occupational exposures because the risk is reasonably targeted to the exposed organ and not to non-exposed organs, and thus a risk evaluation on the basis of absorbed dose or equivalent dose is desirable and should be included as part of clinical decision making (ICRP, 2022). There is a role for the use of effective dose in CT imaging where many organs can be within the scan field. However, there is good evidence for age- and sex-dependent variation in cancer risks (ICRP, 2021, 2022), and some evidence that other non-modifiable (genetic) and modifiable (non-genetic, lifestyle/environmental) factors can affect risks of radiation-related cancers. Furthermore, in clinical practice, cancer radiotherapy is limited by the risk of normal tissue damage in those undergoing treatment, and dose constraints are used to limit the damage to the organs at risk, which are specific for each type of irradiated organ. While treatment-related factors affecting the prevalence of normal tissue damage are well characterised – for example, radiation dose, irradiated volume, these are not the subject of this publication. The individual factors underlying the severity of normal tissue reaction after standardised radiotherapy as scored by CTCAE/RTOG (Common Terminology Criteria for Adverse Events/ Radiation Therapy Oncology Group) scales, indicating the existence of additional individual factors affecting response, are clearly within scope.

(3) It is the issue of individual variation in response, and the factors that govern individual responses, that are the focus of this publication. In the past, ICRP has considered genetic susceptibility to cancer (ICRP, 1998), but has not previously considered variation in response in relation to tissue and cellular injury (El Nachef et al., 2024). As will become clear in section 1.1, the publication will focus on the evidence for variation in response and the underlying factors. This publication does not consider the implications of the evidence for variation in

response for the system of radiological protection which will be considered within ICRP Task Group 128.

(4) Medical exposures are, on average, the most substantial non-background radiation exposures of humans in terms of dose and frequency [e.g., computerised tomography (CT), interventional radiology, positron emission tomography-computerised tomography (PET-CT) and radiotherapy] and in the number of persons exposed: about 4 billion diagnostic exposures per year and 8 million patients benefiting from radiotherapy each year (UNSCEAR, 2020/2021). These exposures are steadily increasing worldwide. Thus, medical patients represent the majority of cases of individuals in whom severe individual responses to ionising radiation may be observed.

(5) Should there be sufficient information available on the range of variation in response amongst the population for specific health endpoints, and a suitable means by which to evaluate the sensitivity of an individual or population sub-group, there could be a rationale for moving to more individualised radiological protection. As an example of a situation where a population-stratified approach to protection may be applicable, Stricklin et al. (2020) have developed age-LD50 (lethal dose for 50% of a given group) dose modification factors to adjust for the relative sensitivity of broad age groups (infant, juvenile, late adult, elderly adult) on the basis of data available from large experimental animal studies. This approach was subsequently applied in accident consequence modelling to estimate the numbers of radiation casualties in nuclear detonation scenarios (Bellman et al., 2020). Depending on the age structure of the exposed population modelled, up to a 10% difference in the estimated casualty number was observed. This publication considers only the underlying evidence for variation in response between individuals or population sub-groups, consideration of the implications of such evidence for the system of protection is being examined by ICRP Task Group 128.

(6) The example above demonstrates that consideration of age may be applicable in serious radiation accident response. Similarly, variation in response to low doses in terms of cancer risk, if quantifiable, could impact approaches to protection of populations in occupational and public settings.

(7) Individual normal tissue reactions to ionising radiation in humans appear as a continuum between normal response and clearly significant pathologic response, and the evidence is clearest in clinical radiotherapy studies. Radiotherapy regimens have been developed to maximise tumour control while keeping severe normal tissue reactions to an acceptable level. This acceptable level has generally been taken to be an occurrence of severe normal tissue reactions in around 5% of treated patients, although there is large variation in the frequency of presentation of severe reaction by cancer site and between different studies (Le Reun et al., 2022) and differences in opinion as to what is acceptable (see Section 2.2.1). There is continuing debate on what is in fact an ‘acceptable’ level of severe normal tissue reactions; clearly radiotherapy regimens need to provide effective tumour control in a good majority of treated patients, but this needs to be balanced with the understandable concerns expressed by those that suffer severe normal tissue damage as a consequence of therapy; the patients’ perception of their treatment and side effects, i.e., their quality of life, is usually worse than their physicians’ perception, and that can lead to a loss of trust (Dilhuydy and Hoarau, 2002; Préau et al., 2009; Miravitlles et al., 2013; Nuijens et al., 2022).

(8) A range of response can be observed ex vivo in cellular assays with the surviving fraction of human cells at 2 Gy (e.g., Burnet et al, 1996; Foray et al., 2016) and some studies using human fibroblasts of over-reactive patients during radiotherapy reporting good correlation with the patients’ CTCAE grade (Granzotto et al., 2016; Le Reun et al., 2022). Furthermore, it appears that the DNA damage response is an important determinant of cellular radiosensitivity and many other genotoxic compounds. It has been proposed that tissues which have been exposed to radiation during radiotherapy sustain a long-term “dose memory” that

render them more sensitive to re-irradiation (Maciejewski et al., 2024). These observations have two implications: (i) exposures even to low doses of genotoxic agents, including ionising radiation should not be neglected since their impact can be assumed to be additive, and (ii) persons exhibiting an abnormal response may be at higher risk of clinical severe reactions, as observed in ataxia telangiectasia patients. Consequently, the abnormal response to ionising radiation needs to be more thoroughly investigated. French authorities have included this issue of individual response to ionising radiation in a ministerial decree dealing with the optimisation process of medical exposures (www.legifrance.gouv.fr/jorf/id/JORFTEXT000038121063).

(9) This publication will consider and review the evidence available relating to the factors that govern individual response to radiation. It does not consider the implications of the available evidence on individual responses to ionising radiation for the evolution of the ICRP system of protection, which is considered by ICRP Task Group 128.

1.1. Remit of the Task Group & publication

(10) This publication provides a review of the currently available scientific information on individual radiation responses and the variation observed in the population, irrespective of source of exposure (i.e. medical, occupational, accidental, public). Cancers as well as early- and late-developing tissue injuries are considered, in addition to the underlying contributory mechanisms and evidence drawn from animal studies and cellular radiobiology.

(11) The publication has been developed by ICRP Task Group 111. The terms of reference for the Task Group identify the following key issues for consideration:

- What is the impact of age, sex, and other determinants on normal tissue reactions and incidence of cancers and other diseases following radiation exposure?
- What is the contribution of genetics to individual normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy? Is it possible to predict a patient´s reaction to radiation exposure with the help of a predictive test or biomarker? How specific and sensitive are the tests which are currently proposed? Would such tests contribute to a better radiation protection of radiotherapy patients without compromising cancer cure rates?
- What is the contribution of genetics and epigenetic factors to tissue radiation response with respect to cancer induction at relevant doses and dose rates? How far does the inherent spontaneous cancer susceptibility contribute to this? Does individual radiation response differ among cancer types? How does understanding of individual risk to radiation influence the transfer of risks between populations with different background cancer incidence?
- What is the evidence that modifiable factors can affect individual risk of radiation-related cancer, tissue reactions, and other non-cancer diseases?
- What are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases, and normal tissue reactions?

1.2. Approaches taken/methodology

(12) As stated above observations related to medical exposures constitute a large pool of data regarding the individual response to ionising radiation and its variation. Two different abnormal individual responses to ionising radiation can be observed in different clinical situations: (i) the appearance of abnormal early- or late-developing tissue effects, including

circulatory diseases, cataract and cognitive dysfunction, (ii) the onset of cancers in patients, either second primary cancers after radiotherapy outside of the planning target volume (PTV), i.e., in the, non-targeted, low dose region (observed in around 8% of patients) (Cosset et al., 2018) or in patients after repeated medical exposures. In these patients and in many patients with mutations or familial risk of cancer, the onset of cancers raises the issue of inherent cancer proneness, either spontaneous or radiation-related.

(13) At the cellular level, two basic situations can be identified that contribute to the response to IR: cell death and cells that survive IR exposure with altered phenotype. Cell death is clearly involved in the onset of some tissue reactions, particularly those developing early after exposure, while cancer results from the proliferation of genetically or epigenetically altered cells. Thus, it is possible, based on in vitro assay of cellular radiosensitivity, to differentiate between susceptibility to cancer, e.g., Cockayne syndrome sufferers present with severe clinical and cellular radiosensitivity without showing predisposition to cancer; to the contrary, Li Fraumeni syndrome is associated with high cancer susceptibility but not high tissue radiosensitivity (for example see AGIR, 2013). For the sake of clarity, it has been proposed that three different words/concepts are used to identify the three different groups of health endpoints that are taken as expressions of individual responses to IR – early- or late-developing tissue reactions and cancers (Foray et al., 2016; Gomolka et al., 2019): radiosensitivity for the early-developing tissue effects after high dose exposures, delivered today mainly in the course of radiotherapy (the original meaning of radiosensitivity), radiosusceptibility for cancer-proneness (the terminology used by ICRP in 1998) and radiodegeneration for late-developing diseases. This strict application of these terms has been questioned (Wojcik et al., 2018). In order to avoid extensive discussion on the terminology used, this publication prefers the use of the term *individual response to radiation* with appropriate definition of the endpoint/outcome under consideration in each case.

(14) In this publication we consider separately radiation-related tissue injury outcomes and cancer outcomes and the factors that contribute to variation in individual response in relation to these endpoints. Tissue injury outcomes are either early- or late-developing. Here we consider those occurring from radiotherapy and targeted tissue exposure (early – those that occur within 90 days of termination of therapy and late – those manifesting at greater than 90 days after termination of therapy) separately from the late developing non-cancer diseases such as circulatory diseases, cataracts and neurological outcomes, generally arising substantially later (usually many years) due to either partial or total body irradiation. Section 2 considers tissue reactions, starting with an overview of acute effects in animal models and then considering in Section 2.2 early tissue reactions after radiotherapy, before in Section 2.3 reviewing available data on circulatory diseases, cataract and cognitiave effects. Section 3 is devoted to consideration of the evidence in relation to cancer, covering relevant human and animal model studies. Specific consideration of the role of biological sex is provided in Section 4 and Annex A. Sections 5, 6, and 7 cover, respectively research needs in the area, an assessment of the uncertainty associated with the findings in this publication, and conclusions.

(15) The aim of the work underpinning this publication has been to identify where there is evidence that factors of any type – genetic, physiological and environmental or lifestyle – affect individual response, and this has been achieved through systematic review of the available peer reviewed scientific literature. We also consider approaches for predicting individual responses to radiation through the use of specific tests or assays for the various endpoints. The availability of such predictive tests could provide guidance on individual risk of tissue injury or cancer. Such information from predictive tests could be of use in medicine, notably cancer radiotherapy where it might be possible to optimise doses to maximise tumour cure rates while minimising the incidence of severe late tissue reactions. There are of course ethical considerations

associated with the usage of any predictive tests, these are not considered in detail in this publication.

1.3. Approaches to assessment of individual response

(16) There are many ways to assess individual response to radiation exposure, including at the level of the whole organism, within specific tissues and in cells. Clinical observation and assessment are commonly used to monitor for radiation-related tissue injury and identify cases of cancer following therapeutic radiation exposure. Such clinical data are of particular relevance for individual response to IR in humans, but they can be supplemented by experimental studies using animal models and/or cellular systems (preferably with human cells). When discussing individual response to radiation it is critically important to be clear which endpoint is under consideration, for example, a cellular assay such as the induction of chromosomal damage, a whole animal $LD_{50/30}$ assay, or a clinically defined tissue injury, because the different endpoints indicate different things about how the cells/tissues respond to IR. The most promising way to develop predictive assays is in cohorts of patients selected for their increased response to IR from a clinical point of view – e.g., using the CTCAE scales) or in persons with an *a priori* risk of abnormal response (e.g., persons with a familial increased risk of cancer even in the case of unidentified genes).

(17) An on-going challenge for utilising individual responses to radiation for treatment guidance is the time delay required for a variety of responses to manifest. The relationships between the differing outcomes used to assess individual responses are not clear, but the search for simple predictive tests to assess individual response is predicated on the assumption that clinical outcomes relate to cellular or molecular alterations occurring relatively soon after exposure, although long term reactions at the tissue level will very likely also play a role since the response is organ dependent (Dörr and Hendry, 2001).

1.4. Metrics: relative risk/absolute risk

(18) Epidemiological investigations commonly use the measures of Absolute Risk (AR) and/or Relative Risk (RR) to describe the effect of the factor under investigation. Excess AR (EAR) is the additional risk conferred by the factor, simply added to the underlying background risk. Excess RR (ERR) is the proportionate increase over background risk conferred by the factor, radiation exposure in this case. These measures generally describe the effect of an exposure (for example to radiation) but can be used to describe the impact of a genetic or other environmental factor. ARs are absolute values while RRs are ratios of the risk in the presence of the factor against the underlying risk in the absence of the factor.

(19) Similar absolute and relative measures can be applied to studies of other types, for example ratios of response in clinical radiosensitivity studies are frequently used and these are similar to RR values in epidemiological investigations. Cellular studies also frequently use measures based on ratios of response, and thus can be interpreted similarly to RR values.

(20) Relative risk measures the strength of an association between the dose and the effect by comparison with a control, unexposed, population whereas absolute risk is used to assess the probability of the association. If the risk analysis is carried out to analyse the impact of an effect on the population from which the data arises, it makes little difference whether the excess risk is expressed in relative or absolute terms. However, the situation is different when the calculated excess risk is transferred to another population (Wakeford, 2012). Here, transfer of ERR assumes a multiplicative joint effect between radiation and factors responsible for the baseline incidence. Transfer of EAR assumes that radiation induces the effect independently of the background (see Section 3.1.3). For radiation-related cancer, *Publication 103* (ICRP,

2007) assumes that the choice of the model for transfer depends on the cancer type: for example, ERR:EAR weights of 0:1 are assigned for breast and bone marrow, 1:0 for thyroid and skin, 0.3:0.7 for lung, and 0.5:0.5 for all others. ICRP does not give any recommendations for the transfer of risk for tissue effects, but in radiation oncology, uniform exposures that should not be exceeded are recognised for critical organs assuming that the risk of toxic tissue effects is independent of factors such as intrinsic sensitivity. Given the fact that, apart from at the very highest of exposure levels where death is inevitable, individual response to radiation is a multifactorial trait, that always results from an interaction of the genome with the environment, this strategy will likey change in the future based on better understanding of the underlying mechanisms.

(21) The terms relative risk and absolute risk are defined in the ICRP Glossary as follows:

- Absolute risk (AR): The probability or rate of the occurrence of a particular health event (e.g., disease incidence) over a specific period.
- Relative risk (RR): The ratio of the incidence rate or the mortality rate from the disease of interest such as cancer in an exposed population to that in an unexposed population.

(22) This topic is discussed in greater detail in Section 3.2.

1.5. Systematic review criteria

(23) It is widely recognised that the review and synthesis of scientific literature is best conducted in a systematic and rigorous fashion. This is reflected in the ever-growing number of schemes to guide review/synthesis work, e.g., GRADE (Guyatt et al., 2011), PRISMA (Moher et al., 2009), etc. The approach requires much the same approach as adopted in any scientific investigation:

- Define and document the study question.
- Define and document the method – in this case literature search criteria and databases searched.
- Document the results of searches – how many papers identified from which source.
- Refine/clean – remove duplicate publications.
- Evaluate each publication against a standard set of quality criteria.
- Synthesise the results and draw conclusions on the basis of those papers that meet the quality criteria.

(24) To identify relevant literature for this publication, searches were undertaken with search terms as indicated in each section with results recorded allowing evaluation of each paper against quality criteria:

- Consideration of the quality of the study population or experimental model.
- Consideration of the exposure assessment used in populations studies or exposures delivered in experiments.
- Consideration of confounders or biases in each study.
- Consideration of the statistical methods and their robustness.
- Consideration of any conflicts of interest that the authors of each paper declare.

2. TISSUE REACTIONS

(25) Tissue reactions were considered in detail in *Publication 118* (ICRP, 2012). There is a diverse range of tissues that may be damaged by radiation exposure and the threshold doses above which tissue injury is observed vary. The ICRP system of protection aims to avoid tissue injury, and indeed in most situations exposures are low and below threshold levels. A notable exception is where radiation is used for cancer therapy. In the sections that follow, tissue injury is considered from two different perspectives. Firstly, tissue injury as studied in experimental animal models is reviewed, secondly the medical radiotherapy situation is considered. From both areas data are available relevant to understanding, and to an extent quantifying, the factors that govern individual variation in response to radiation although dose extrapolation from mice to humans is very complex.

2.1. Radiobiology of acute reactions in whole animals and tissues

2.1.1. Dose-Time Relationships

2.1.1.1. The Discovery of Radiation Dose-Time Relationships and Onset of Damage

(26) Radiation-related acute damage was first recognised when early radiation workers, who were trying to reproduce Röntgen's findings on x-rays, developed dermatitis. A few years later, Becquerel found natural sources of radioactivity caused similar skin lesions. Unlike fire burns, radiation burns appeared only after a latent period, with the length this period dependent on the dose received. In fact, inflammatory erythema at around 10 days after human skin exposure was predictable enough that it was used to calibrate tubes for clinical radiodosimetry; the minimal erythematous dose became the first radiation dose unit. Dose-time relationships for radiation effects became a subject of keen interest for many radiobiologists, and animal models were developed to better understand them (Kaplan, 1970). Using several species, Heineke noted that the time required for a radiation effect to develop differed between cells and tissues (Heineke, 1903; Heineke, 1905). Lymphopenia developed within hours, severe dermatitis took about two weeks, while liver and kidney showed little change over the study period; a chronology that was found to be relatively constant across species, encouraging the view that animal models could guide human investigations (Heineke, 1914; Bond et al., 1965b). The extreme radiosensitivity of circulating lymphocytes in interphase, and the lymphopenia that it caused, were early radiobiological observations (Heineke 1903), which can be of clinical relevance (Yovino et al., 2013). At relevant doses, most lymphocytes are killed as they circulate through the radiation treatment field (Yovino et al., 2013) and, as a result, long-course, fractionated RT reduces lymphocyte levels more than short hypofractionated courses (Crocenzi et al., 2016; Sanguineti et al., 2019). Variation in the extent of radiation-induced apoptosis of T-lymphocytes between patients receiving radiation therapy has been observed, and correlated with late radiation toxicity (Ozsahin et al., 2005; Azria et al., 2015).

(27) Variation of cellular radiation responses within one tissue was first noted by Regaud and Blanc. By careful examination of testicular responses in several species, he recognised that immature, rapidly proliferating cells were more radiosensitive than mature subpopulations (Regaud and Blanc, 1906). They also noted that if fractionated rather than single doses were given, the skin on the scrotum was spared while spermatogenesis was still inhibited. Taking this as an analogy for cancer, he speculated that dose fractionation would differentially disadvantage rapidly proliferating cancerous over normal tissues. This paved the way for Coutard to establish fractionation as the standard means of delivering radiation therapy

(Regaud and Nogier, 1911). Bergonie and Tribondeau (Bergonie and Tribondeau, 1905) built on Regaud's work with rat testes to demonstrate differences in response between proliferating and differentiated cells in different tissue sites (Bergonié, 1906), but there are exceptions. For example, non-cycling lymphocytes tend to die rapidly in interphase by what is now called apoptosis (Kerr et al., 1972). However, responses depend on many factors and can be changed, for example by cytokines and growth factors (McBride and Dougherty, 1995; Beerman et al., 2014).

(28) Early observations, therefore, identified both inflammation and loss of a proliferating stem/progenitor subpopulation as aspects of acute radiation tissue damage. If the dose is sufficiently high and tissue regeneration is unable to maintain a functional tissue compartment, morbidity and mortality may result. However, it took the Manhattan Project and recognition of the risks associated with the development of the nuclear industry in the 1950s to concentrate interest on dose-time concepts in radiobiology (Paigen, 2003; De Chadarevian, 2006), through studies on the acute effects of whole-body irradiation (WBI), largely using inbred mouse strains. Information on the genetics of normal tissue radiation responses and radiocarcinogenesis was also generated.

2.1.1.2. Dose-Time Relationships for Acute Radiation Syndromes

(29) Arguably, the most important finding to emerge from murine studies on acute lethality after WBI in the post-World War II period was the stepwise nature of the curve obtained when lethality from increasing single radiation doses is plotted against mean/median survival time (MST) (on a log-log scale). Several acute radiation syndromes (ARS) were identified, each with a fairly characteristic dose-time framework and distinct pathogenesis (Quastler, 1945a,b,c; Bond et al., 1954; Austin et al., 1956; Sacher and Grahn, 1964; Bond et al., 1965b). Lethality in the lowest dose range occurs within weeks and is usually ascribed to hematopoietic failure (H-ARS). As dose is increased, another mortality phase was observed at around 3.5–9 days that is ascribed to intestinal failure (GI-ARS). After even higher doses (e.g., >20 Gy), a cerebrovascular/central nervous system syndrome (CVS/CNS-ARS) was found 1–2 days after exposure (Bond et al., 1965b; Schaue and McBride, 2019). Lethality for each ARS increases rapidly from 0% to 100% over a narrow dose range, which is accompanied by a slight decrease in MST, but between syndromes the MST is fairly constant.

(30) The mechanisms responsible for H-ARS and GI-ARS are primarily depletion of proliferative stem/progenitor hematopoietic or intestinal crypt cells, respectively (Bond et al., 1965b). However, CVS/CNS-ARS lethality is associated with edema, hemorrhage, and neutrophil infiltrates as a result of direct radiation cell killing and radiation-induced inflammation (Daigle et al., 2001). The order in which these ARS syndromes occur in time and their relative dose-dependencies are roughly similar across mammalian species, including humans, with occasional exceptions (Bond et al., 1965b). These H-ARS and GI-ARS studies were important because they indicate that the time to an acute radiation effect (latency) reflects the tissue turnover time and is not directly related to radiosensitivity. It is often difficult to be exact about causes of death and there are usually many possible confounding factors but the hierarchical and compartmentalised structure of many acute responding tissues provide a generalizable conceptual framework within which the effects of radiation therapy (RT) on acute responding normal tissues can be understood.

2.1.1.3. Modelling Dose-Time Relationships for Acute Effects

(31) After single radiation doses, the incidence of a specific acute radiation effect follows a steep sigmoid curve rising from 5 to 95% incidence within a narrow dose window of around 2 Gy (Bond et al., 1965a; Mason et al., 1989; Schaue and McBride, 2019). This relationship is

most often modelled using a probit transformation, although Poisson and logistic models are also applicable (Bentzen and Tucker, 1997). The slope of any probit curve (which is difficult to quantify unambiguously (Bentzen and Tucker, 1997)) is also a measure of its variance, and this is important because flatter curves signify heterogeneity within the system, whatever the cause (Grahn and Hamilton, 1957; Plett et al., 2012). The position of the dose-response curve is fixed by the dose required for a specific level of effect; the dose causing 50% lethality (LD50) being the quantity most commonly reported (Bond et al., 1954). For H-ARS in mice, lethality within 30 days (LD50/30) is most often chosen as an endpoint, though in humans 60 days is more appropriate (Bond et al., 1965b). The endpoint chosen for GI-ARS is more variable, but it is usually around 10 days.

(32) The time to occurrence of an acute effect is quite reproducible and can help dissect different syndromes. The time window is generally narrow and unimodal. “Within 30 days” and “less than 10 days” conventionally ascribed to H-ARS and GI-ARS, respectively, are an obvious oversimplification, meant to reflect the high degree of uncertainty overall. Biphasic time responses have, however, been reported (Austin et al., 1956; Kohn and Kallman, 1956; Yuhas et al., 1966). Yuhas et al. (1966) found that the LD50/30 for inbred DBA/2J and outbred WR-BS Swiss mice were very similar, but they had very different MSTs. The MST for the WR-BS strain was ~ 13 days, but ~ 25 days for DBA/2J mice, decreasing to 13 days only at doses that caused 95% lethality. Using a wide range of doses, Austin et al. (Austin et al., 1956) found several peaks for time to lethality in C57Bl/6 and LAf1/J mice. Most mice died ~ 3.5 or ~ 11.5 days after exposure that were interpreted as GI-ARS and H-ARS, respectively. However, there were deaths between 5–8 days that could not be assigned to GI-ARS by histopathology, suggesting “early H-ARS” (Austin et al., 1956). In support, Mason et al. (1989b) gave C3H mice various doses of WBI and showed that those dying within the GI-ARS time frame (<10 days) could be rescued by bone marrow transfer up to 17 Gy, also suggesting “early H-ARS”. Since the mice were gnotobiotic, infection could be ruled out. An alternative explanation would be that marrow-derived cells protect against GI-ARS, but this seems unlikely as survival of intestinal crypt clonogenic cells was unaffected by bone marrow transfer (Mason et al., 1989b). Others also have presented evidence for the independence of H-ARS and GI-ARS (Leibowitz et al., 2014). The easiest explanation is that different cellular subpopulations, or mechanisms, become critical as dose is changed, even within one manifestation of ARS. One factor that is known to differ between mouse strains, and change with age, sex, microbiome, diurnal rhythm, amongst others, is the rate of tissue turnover, which could account for MST differences (Potten, 2004; Wabik and Jones, 2015).

2.1.2. Clonogenic Cells in Acute Responses

2.1.2.1. Clonogenic Assay Development

(33) The development of clonogenic assays directed radiobiology towards a new approach to quantify the radiation tolerance of different normal tissues. Till and McCulloch (1961), who were to become known as the “Fathers of the Stem Cell”, showed that a dose-related number of colonies formed endogenously in the spleen of mice 10 days after WBI, each representing a colony forming unit (CFU-S). CFU-S also formed after injection of syngeneic bone marrow cells that could prevent lethal H-ARS. The colonies were of mixed myeloerythroid origin (granulocytes, macrophages, red cells, megakaryocytes). By irradiating bone marrow inocula with varying radiation doses prior to injection, they could use the CFU-S assay to assess the radiosensitivity of hematopoietic stem/progenitor cells (HSPC). Building on these studies, Withers and colleagues developed in situ clonogenic assays for radiation responses in skin (Withers, 1967a), jejunum (Withers and Elkind, 1968), colon (Withers and Mason, 1974),

stomach (Chen and Withers, 1972), testes (Withers et al., 1974a), and kidney (Withers et al., 1986), while Kember developed one for cartilage (Kember, 1967) and Jirtle for hepatocytes (Jirtle et al., 1981). Non-clonogenic assays have also been developed for tissue functions, including lung (pneumonitis and fibrosis), spinal cord (paralysis), wound healing (breaking strength), mucosa (inflammation), and hair follicles (epilation).

2.1.2.2. Modelling Using Clonogenic and Non-Clonogenic Assays

(34) Withers and coworkers developed a robust and simple iso-effect formula with linear (α) and quadratic (β) components to describe differences in radiosensitivity of cells and tissues. Differences in the dose required to reach a given level of clonogenic survival or functional effect (isoeffective doses) were established (Withers et al., 1983). When they applied this to fractionated radiation responses, the slopes of iso-effect curves for acute and late responding tissues were found to differ and this could be described by the α/β ratio. The total dose for an iso-effect changes less with size of the dose per fraction for acute than for late responding tissues (Thames et al., 1982; Withers et al., 1983), with the former having high and the latter low α/β ratios, respectively. These models have guided clinical radiation oncologists for decades and prompted clinical trials designed to explore the efficacy of fractionated dose protocols that differ from the classical 2 Gy per fraction; with some success (e.g., Withers, 1985).

(35) The biology behind the effects of dose fractionation on normal tissue responses were summarised by Withers as the 4Rs (Withers, 1975). These are: Repair of sublethal damage between fractions, which spares late responding tissues that turn over slowly, Redistribution of cycling cells into the radiosensitive G2/M phase of the cell cycle, which also spares tissues with slow turnover, Repopulation/regeneration, which can spare acute responding normal tissues with rapid turnover because they can regenerate during a fractionated course of radiation, and Reoxygenation between fractions which decreases the hypoxic radioresistant fraction within tumors, and is less relevant for normal tissues. Others have added additional Rs, the most compelling of which is "intrinsic" Radiosensitivity that refers to the very initial slope of the dose-survival curve; more radiocurative tumors having a steeper initial slope (Steel et al., 1989).

2.1.3. Regeneration in Acute Radiation Responses

(36) Under homeostatic conditions, tissues must produce cells at the same rate as they are lost; by definition, the cell loss factor $\phi = 1.0$. Acute responding tissues in steady state conditions turn over rapidly but the size and rate of production of their stem/progenitor cell compartments and kinetics of tissue turnover varies greatly with the tissue and mouse strain, and these are also influenced by age, sex, microbiome, and many other factors (Potten, 2004; Wabik and Jones, 2015). As a general rule, irradiation decreases the rate of cell production by the stem/progenitor cell compartment but does not affect the rate of loss of differentiated cells. As a result, the time to expression of damage (latency) is little different from the steady state tissue turnover time. For example, in C3H mice after 14 Gy x-rays, epithelial depletion takes ~3 days in the jejunum, 5 days in the colon, 10 days in the stomach, 12–24 days in the skin, 30 days in seminiferous tubules of the testis, and 300 days in kidney tubules (Withers et al., 1986).

(37) Regeneration is essential for survival of irradiated tissues and is triggered by cell loss. Under normal homeostasis, tissues retain their "stemness" either by each individual "stem" cell undergoing asymmetric division or by a population of "stem" cells stochastically producing on average 50% "stem" and 50% differentiating cells (Watt and Hogan, 2000; Wabik and Jones, 2015); processes that are executed through the exercise of structural constraints or with support

and control from a "niche" (Schofield, 1978). To regenerate, ϕ must decrease to <1.0. The timing, rate and extent of regeneration can be estimated from the extent of recovery with time using split radiation doses (Withers, 1971; Withers et al., 1974a; Withers and Mason, 1974; Withers et al., 1986), with the general assumption that repair is complete within 24 hours and thereafter regeneration is responsible for recovery. Using this approach, irradiation was found to decrease ϕ for jejunum to almost zero, indicating a complete switch by stem/progenitor cells to regeneration prior to later differentiation (Withers, 1971), for skin, radiation reduced ϕ to about 0.5 (Withers, 1967a; Masuda et al., 1982), while testis and kidney were slow to show any regeneration (Withers et al., 1974a; Meistrich et al., 1978; Stewart et al., 1989), explaining why sperm counts often take a very long time to recover after radiation therapy, if they do at all.

(38) The advent of lineage tracing technology has given new insights into the movement of cells within, and between, tissue compartments. This has illuminated the considerable heterogeneity in numbers, organisation, and turnover rates in steady state stem cell compartments in different tissues. Challenges like irradiation, wounding, and infection increase this heterogeneity and different tissues use different means to meet cellular demands (Wabik and Jones, 2015). Some cellular compartments display "plasticity", most notably by reprogramming more differentiated cells towards stemness, while others recover by calling on "reserve" stem cell populations or on stem cells able to make early lineage declarations (Seita and Weissman, 2010; Mills and Sansom, 2015; Chiche et al., 2017; Elias et al.; 2017; Yu et al., 2017). These discoveries support the use of the term "clonogen" in radiobiology, which represents a functional regenerative unit without prejudice as to origin (Ganuza et al., 2019).

2.1.4. Functional Subunits and Tissue Radiosensitivity

(39) The intrinsic radiosensitivity, number and kinetics of stem/progenitor cells are important factors in determining tissue tolerance to radiation; but so is the tissue organisation. This has been conceptualised in terms of functional subunits (FSU), where an FSU represents the volume that can be regenerated from one surviving clonogenic stem cell (Withers et al., 1988). A tissue with a large number of stem cells per FSU will be more radioresistant than one with a smaller number even if each cell has the same intrinsic radiosensitivity. This may be why depigmentation, epilation, and desquamation require increasing doses for an effect (Vegesna et al., 1988); because hair follicles have less melanocytic than follicular clonogens per FSU, both of which have less melanocytic clonogens than the interfollicular epidermis. An FSU may correspond to a structural element, for example a kidney nephron, or it may be poorly defined; for example, it may simply depend on the tissue volume one "stem" cell can restore. The FSU concept helps explain one of the "true" volume effects in radiation therapy (Withers et al., 1988). If FSUs are arranged in series, like links in a chain, as seems to be the case for spinal cord and nerves, these tissues are likely to demonstrate a strong volume effect; the dose needed for an isoeffect being dramatically larger if small volumes are irradiated. On the other hand, if FSUs are arranged in parallel, as in skin, lung and liver, the tissue will be better able to tolerate high doses to small volumes than low doses to large volumes; tissue function will depend largely on the volume not irradiated. The number and organisation of FSUs in a tissue is therefore an additional consideration for tissue tolerance to irradiation.

2.1.5. Acute Tissue Radiation Responses

2.1.5.1. Skin

(40) Radiodermatitis on the hands of workers using early radiation devices was the first observed acute radiation effect, and the subsequent development of basal cell skin carcinoma was the first evidence that radiation was a carcinogen. Several distinct, dose-time dependent skin radiation reactions have been reported in humans and other species. In the 1920s, Miescher noted several "waves" of radiation-induced erythema in human skin (Miescher, 1924), which Pohle linked to changes in capillary density (Pohle, 1926; Roth et al., 1999). In humans, the first "wave" is dose-dependent acute erythema within hours after doses in the range 2–8 Gy. The main erythematous reaction occurs 10–14 days after doses >5 Gy. This can progress to dry and moist desquamation at 4–6 weeks after higher doses of ~13 and 18 Gy, respectively. Epilation occurs around 3 weeks, and is temporary after 3 Gy and permanent after ~7 Gy. Re-epithelialisation occurs after 6–8 weeks. At doses >10 Gy, this may fail to prevent late erythema, atrophy, and necrosis at 8–16 weeks. Later effects after 6 months include further atrophy, while telangiectasia and necrosis may occur after >1 year (Hopewell, 1990).

(a) Early Radiation-induced Acute Skin Erythema

(41) The early erythematous response is transient and mediated by radiation-induced pro-inflammatory cytokine/chemokine expression, including interleukin (IL)−1 and tumour necrosis factor (TNF)-α. This response is initiated within minutes to hours, and fades within 24–48 hours. The cytokines upregulate expression on endothelium of cell adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and E-selectins; a response that is required for inflammatory cells to exit the bloodstream and enter tissue (Schaue et al., 2015). Early histopathological observations on vascular effects of IR documented swelling and degeneration of endothelium and capillary occlusion (Gassman, 1898), hyperemia and exudation of serum and red cells (Halkin, 1903), capillary leakage (Mottram, 1933), and inhibition of vascular capillary budding (Takahashi, 1930). Intrinsic to this response is increased procoagulant activity and cellular thrombogenicity through tissue factor expression and release by peripheral mononuclear cells (Goldin-Lang et al., 2007). This explains the now superseded use of radiation to staunch blood flow in patients. The vascular response contributes to the formation of neutrophil extracellular traps (NETS) that can trap microorganisms but also to capillary damage, depending on the state of neutrophil activation (Cahilog et al., 2020). Rapid cell death by apoptosis and NETosis (a program for formation of neutrophil extracellular traps (NETs), which consist of modified chromatin decorated with bactericidal proteins from granules and cytoplasm) after irradiation may in part be an inflammation-induced bystander effect (Mukherjee et al., 2014).

(42) An important hallmark of radiation dermatitis is the impairment of the mitotic ability of the stem/progenitor cells in the basal cell layers due to radiation-induced DNA damage, leading to suppressed cell renewal in the epidermis. However, this mechanism alone does not adequately explain the complex pathogenesis of radiation-related skin injury. Current studies show that skin exposure to ionising radiation induces cellular senescence in the epidermal keratinocytes (Tewary et al., 2023). As part of their epithelial stress response, these senescent keratinocytes secrete pro-inflammatory mediators, thereby triggering skin inflammation. Keratinocyte-derived cytokines and chemokines modulate intercellular communication with the immune cells, activating skin-resident and recruiting skin-infiltrating immune cells within the epidermis and dermis, thereby orchestrating the inflammatory response to radiation-induced tissue damage. The increased expression of specific chemoattractant chemokines leads

to increased recruitment of neutrophils into the irradiated skin, where they release cytotoxic granules that are responsible for the exacerbation of an inflammatory state. Moreover, the importance of IL-17-expressing γδ-T cells to the radiation-induced hyperproliferation of keratinocytes was demonstrated, leading to reactive hyperplasia of the epidermis. Radiation-induced, reactive hyperproliferation of the keratinocytes disturbs the fine-tuned keratinisation and cornification processes, leading to structural dysfunction of the epidermal barrier. In summary, in response to ionising radiation, epidermal keratinocytes have important structural and immunoregulatory barrier functions in the skin, coordinating interacting immune responses to eliminate radiation-related damage and to initiate the healing process (Rübe et al., 2024).

(b) The Main Erythematous Radiation Reaction

(43) Squamous epithelia in the skin form an organised architecture that varies with the species, strain, and body location. The inter follicular epidermis (IFE) is thin in rodents, but thick in humans and pigs, where it is punctuated by hair follicles and sweat glands, and undulates, projecting into the dermis in the form of rête ridges separated by dermal papillae (Chacko and Vaidya, 1968; Hopewell, 1990). In spite of these species differences, there are many commonalities. All proliferative cells in the IFE are in the basal cell layer and are the progenitor cells that maintain epidermal homeostasis. Basal progenitor cells undergo random symmetric and asymmetric division with a cell cycle time of between 3.5–6 days, varying with body site (Piedrafita et al., 2020). Both progenitor and differentiating daughters are generated with equal probability and at a rate that ensures homeostasis across the progenitor cell population (Clayton et al., 2007; Doupé et al., 2010; Alcolea and Jones, 2014; Wabik and Jones, 2015). On commitment to differentiation, proliferating basal cells exit the cell cycle, lose integrin expression (Hotchin and Watt, 1992), enter the suprabasal layer, and migrate upwards, going through a series of morphological changes that culminate in the formation of a cornified layer of protein-filled, anucleate keratinocytes that is constantly shed (Alcolea and Jones, 2013; Wabik and Jones, 2015). This process is largely dose independent, while the loss of basal cells in the IFE is dose-dependent.

(44) The presence of an additional rare, slow-cycling “stem” cell population in the IFE has been suggested (Sada et al., 2016), but linage tracing combined with cell cycle analysis in mouse skin has produced little proof that this additional population exists, or at least that they have a significant role in IFE homeostasis (Piedrafita et al., 2020). There is more evidence of a “stem” cell population in the bulge region of hair follicles and other glands in the skin, although they are hard to resolve in these sites. The bulge lies about one third of the way down the hair shaft and contains a subpopulation of cells capable of generating both hair follicles and IFE. However, they normally remain lineage-restricted (Tumbar et al., 2004), although they may be involved in skin response to injury (Watt and Hogan, 2000; Alcolea and Jones, 2014).

(45) After a single dose of 12.5 Gy, the main skin erythematous reaction in humans starts ~day 7 and peaks ~day 30 (Field et al., 1976). The inflammatory response associated with, and preceding, moist desquamation is often thought to be of minor mechanistic relevance to stem/progenitor cell loss (Hopewell, 1990), but mice lacking either IL-1 or the IL-1 receptor developed less inflammation and less severe pathological changes in the skin, especially at later time-points (Janko et al., 2012). This, and the finding that keratinocytes produce IL-1, and that it shapes the skin’s immune environment, suggests that radiation-induced cytokines, and perhaps inflammasomes that release IL-1, modulate skin responses (Lamkanfi, 2011).

(46) After skin irradiation, non-proliferative cells continue to differentiate and be shed, and the epidermis becomes denuded with time due to natural turnover. The rate of loss of basal cells varies with the strain, species, and location on the body (Roberts and Marks, 1980). In

Large White pigs, the rate of loss is ~2.6%/day (Morris and Hopewell, 1986), which is probably similar to humans (Hopewell, 1990). In Yorkshire pigs it is about 4%/day (Archambeau et al., 1979; Potten et al., 2001), and in DBA/2 mice 8.3%/day (Potten and Bullock, 1983). These differences dictate the different latent times to erythema in the different species.

(47) Regeneration after irradiation begins after ~10 days in Large White pig skin, with the labelling index increasing to about 20% and the density of cells in the basal layer increases after ~20 days (Morris and Hopewell, 1986). Withers scored epithelial cell clones arising in small areas of irradiated mouse skin that had been shielded by tiny metal spheres of various diameters within a field that was heavily irradiated to prevent ingress of migrating cells. This in vivo clonogenic assay indicated that approximately ten surviving epithelial cells, or survival of $>10^{-6}$ clonogens, were needed to repopulate 1 cm^2 of denuded skin in ten days, so as to prevent radiation-induced moist desquamation (Withers, 1967a). Using multifraction radiation, he concluded that the epidermis has a high α/β ratio of 9–12 Gy (Withers et al., 1977).

(48) The suggestion, supported by measurements of skin shrinkage (Masuda et al., 1982), was that after irradiation clonogenic progenitor cells increase after a lag phase of about 7 days by ~30% per day. This is equivalent to a sparing effect during standard RT of about 1 Gy/day. The cell loss factor was estimated to drop to ~0.5, suggesting that differentiation is not totally halted during regeneration (Withers, 1967a,b; Withers et al., 1977; Masuda et al., 1982). In any event, regeneration is initiated prior to the peak skin reaction. Regenerating clones similar to those observed in mouse skin can be sometimes seen, or induced, in patients undergoing RT (Arcangeli et al., 1980). Studies on radiation-induced depigmentation of resting hair follicles in mice suggested that each follicle contained about 4 melanocytic stem cells (Vegesna et al., 1987), while radiation-induced epilation in mice occurred at ~8 weeks and had a low α/β ratio for resting murine follicles that increased if they were induced to proliferate by plucking (Vegesna et al., 1988, 1989).

(c) Later Skin Radiation Erythema

(49) A later phase of erythema has been reported with a latency of 70–120 days in the Large White pig after doses of 15–20 Gy (Hopewell and Van den Aardweg, 1988). It is often accompanied by edema and necrosis, indicating dermal damage. It is the predominant reaction after irradiation with single doses of x-rays (Hopewell and Young, 1982), but less so after fractionated irradiation, indicating a low α/β ratio typical for dermal damage (Gorodetsky et al., 1990). Late erythema was a significant complication in Chornobyl nuclear accident victims where the depth-dose distribution of beta-radiation to the skin influenced both acute and late effects (Barabanova and Osanov, 1990). About 20% of Chornobyl patients who developed ARS had skin lesions that could contribute to lethality if the area of the lesions exceeded about 50% of the total body surface or after high doses to a large area. A small number had beta burns as a primary cause of death (Mettler et al., 2007).

(d) Volume Effects in Skin

(50) The FSU concept predicts that acute radiation erythema would not change much with increasing skin field size. Hopewell found this was true in the pig for epidermal and late dermal responses to single radiation doses delivered to skin areas of 4 × 4 cm and 16 × 4 cm (Hopewell and Young, 1982). Clinical experience, however, is that a large area of skin erythema is poorly tolerated and more debilitating than a small area, even if the level of reaction is similar. Obviously, as tissue tolerance is reached, the likelihood of any area within the irradiated region not healing increases with an increase in the size of the area irradiated. However, it is also possible that fractionated irradiation has more of an effect on larger areas by affecting the

dermal vascular network, which would be expected to affect primarily later erythematous reactions (Shymko et al., 1985). Increased bystander effects (e.g., Butterworth et al., 2012) are another possible explanation for this type of "volume" effect.

2.1.5.2. Esophagus and Oral Mucosa

(51) Acute oral mucosal reactions result not only from epithelial cell depletion, but also from inflammation in the basement membrane and submucosa. A mouse model has been developed to assess reactions to single and fractionated radiation doses to the lip using a scoring system that takes account of erythema, focal desquamation, exudation, and edema (Parkins et al., 1983; Xu et al., 1984; Ang et al., 1985a,b). Reactions started at day 7, reaching a maximum ~day 11–12, and regressed over the following week. Regeneration became important after a 3-day lag period and increased exponentially over the next 10 days. It was estimated that this regeneration was equivalent to an increase in tissue tolerance by about 1 Gy/day and represented a doubling in clonogenic cell number every 2 days (Xu et al., 1984).

(52) In humans, scoring criteria often include ulceration, dysphagia, and pain (Wygoda et al., 2009). Mucositis begins usually ~2–3 weeks after the start of a standard course of RT with regeneration at ~10–12 days, prior to evident mucositis. Regeneration can increase radiation tolerance of the mucosa by ~1.8 Gy per day toward the end of a 6-week course, and on average about 1 Gy/day (Fletcher et al., 1962). Interestingly, if mucositis was scored regularly every day, severity-time curves could often best be characterised by a ''wave-like'' pattern of mucositis and "healing", rather than simply onset, peak, and healing phases (Wygoda et al., 2009).

(53) The oral and esophageal epithelia are, in many ways, architecturally similar to skin epidermis, except that they have no appendages like hair follicles and sweat ducts and lack their associated stem cell contents. Lineage tracing experiments show that basal cells in esophageal epithelium and oral mucosa divide about every 2.4 days, which is faster than the ~3.6–6 days of the IFE (Doupé et al., 2012; Piedrafita et al., 2020). Another difference is that after wounding, progenitor cells in the esophageal epithelium switch to produce more proliferating daughters, in other words the cell loss factor approaches zero. This may be because in the IFE, but not the esophagus, other proliferative compartments, such as hair follicles and sweat ducts, assist the healing process (Piedrafita et al., 2020). There is also no evidence of plasticity with more differentiated lineages converting to a "stemness" phenotype, as has been suggested to occur in intestine (van Es et al., 2012), trachea (Tata et al., 2013) and stomach (Stange et al., 2013).

(54) The skin (Murai et al., 2018; Hall et al., 2019), and the esophagus develop a patchwork of mutant clones with age, including many with mutations in the p53 tumour suppressor gene (Fernandez-Antoran et al., 2019; Colom et al., 2020). Only a small number of these clones will accumulate more mutations and become cancerous. There is however ongoing competition between p53 mutant and wild type clones. Interestingly, low radiation doses (50 mGy) were found to cause wild type murine esophageal keratinocytes to differentiate, tipping the balance in favor of the p53 mutated, more radioresistant clones. In contrast, low dose radiation combined with antioxidant treatment reversed the outcome promoting wild-type cell proliferation but p53 mutant clone differentiation. The suggestion is that external interventions, such as redox manipulation, in the context of low dose irradiation can raise the competitive fitness of wild-type clones above mutants and potentially deplete tissues of potentially harmful mutations (Fernandez-Antoran et al., 2019).

858 2.1.5.3. Intestine

859 *(a) Structure of Small Intestine*

860 (55) The small intestine is an excellent acute responding tissue for the study of radiation
861 responses because of its highly structured and polarised epithelial cell content (Gehart and
862 Clevers, 2019). The intestinal mucosa is the innermost of 4 concentric layers found throughout
863 most of the intestinal tract, the others being the submucosa, the muscularis externa, and the
864 serosa. The mucosa itself is further subdivided into 3 layers. The epithelium is a single-cell
865 layer lining the interior lumen of the gastrointestinal tract. Immediately adjacent is the lamina
866 propria with a rich vascular and lymphatic network and abundant leukocytes. The third is the
867 muscularis mucosae, which is composed of smooth muscle fibers. In general, the epithelium
868 of the colon and stomach contain the same cell types as the small intestine, except for the
869 Paneth cells at the bottom of crypts and the M cells that overlay Peyer's patches, both of which
870 are unique to the small intestine. The small intestinal epithelium can be considered as having
871 3 compartments:

872 • A basal columnar epithelial stem cell (BSC) compartment lies wedged between ~20
873 columnar epithelial Paneth cells in the base of the crypt of Lieberkuehn. These fulfil the
874 stem cell criteria of being multipotent and having long-term, self-renewing ability
875 (Barker et al., 2008) and express the leucine-rich repeat-containing G-protein coupled
876 receptor 5 (Lgr5). Lgr5+ cells respond to R-Spondin to signal the Wnt/ß pathway
877 (Haegebarth and Clevers, 2009; Sato et al., 2011; Hua et al., 2012; Clevers et al., 2014).
878 They divide symmetrically every 21.5 hrs (Schepers et al., 2011) under the influence of
879 niche signals, such as EGF, TGF-ß and Notch ligands from Paneth and stromal cells.
880 Contact with Paneth cells limits the number of BSCs per crypt (Sato et al., 2011). Excess
881 Lgr5+ cells differentiate to populate the transit-amplifying compartment. Paneth cells
882 have a turnover time of 3–4 weeks (Pull et al., 2005; Sehgal et al., 2018) and, as well as
883 stimulating continuous BSC cycling, they redirect undifferentiated transit-amplifying
884 cells through Notch inhibition to enter a secretory lineage as precursors of Paneth, goblet,
885 and endocrine cells, rather than continuing as enterocytes (van Es et al., 2012; Basak et
886 al., 2017).

887 • Transit-amplifying progenitor cells fill the rest of crypt. These proliferate rapidly with a
888 cell cycle time of about 12 hours. Proliferation ceases when they reach the crypt-villus
889 junction. A putative stem cell population was described by Potten at position +4 from
890 the base of the crypt, based on ^{3}H-Tdr label-retaining i.e. slowly proliferating (Potten et
891 al., 1978; Potten, 2004). More recently, a population of quiescent, Bmi1+ and Hopx+
892 cells have been described around this position that may act as a "reserve" stem cell
893 population after intestinal injury (Tian et al., 2011; Yan et al., 2012). These, and other
894 crypt cells, are capable of displaying "plasticity" after injury, converting to Lgr5^{+} cells
895 that repopulate empty stem cell niches (Tetteh et al., 2015; Wabik and Jones, 2015;
896 Beumer and Clevers, 2016; Jones and Dempsey, 2016; Gehart and Clevers, 2019). It
897 seems possible, then, that "stemness" in the small intestine is as much associated with
898 the niche as with cells within the niche.

899 • A post-mitotic, differentiated, functional compartment in the villus, each of which sheds
900 1000–1400 cells per day into the gut lumen. The number of cells in the villus is the
901 product of the crypt cell production rate times the number of crypts serving each
902 villus, which is estimated to be 6–9 depending on position within the intestine (Wright
903 and Irwin, 1982; Bach et al., 2000; Potten, 2004; de Lau et al., 2014). In the mouse
904 jejunum, migration from the crypt to the tip of the villus, where cells die by apoptosis

and are shed into the lumen, takes about 3–4 days; although the rate of migration shows a strong circadian dependency (Potten et al., 1977; Potten, 2004). This is also the time when the jejunal epithelium in a C3H mouse takes to be depleted after irradiation (Withers et al., 1986), and the MST plateau time for GI-ARS after supralethal WBI doses (Quastler, 1956), which strongly suggests that epithelial cell loss is the primary cause of GI-ARS. The transit time in the jejunum is shorter than in the bone marrow, which is why GI-ARS occurs earlier than H-ARS.

(b) Irradiation Responses of Small Intestine

(56) There is a low background level of ongoing apoptosis in the murine crypt, which is independent of p53 and Bax (Potten and Grant, 1998; Kirsch et al., 2010; Leibowitz et al., 2011). Ongoing apoptosis is common in sites of rapid proliferation within tissues and is thought to control cell number (Potten, 2001). Its relationship to radiation-induced apoptosis is unclear. Irradiation induces a rapid p53-mediated wave of crypt apoptosis within 3–6 hours followed by p53-independent mitotic cell death after 1–2 days (Potten et al., 1987; Clarke et al., 1994; Potten et al., 1994; Merritt et al., 1997; Potten, 2004; Miyoshi-Imamura et al., 2010; Hua et al., 2012). Loss of *p53* has been reported to prevent radiation-induced crypt apoptosis, and accelerate intestinal damage and death, while increasing the regeneration rate (Kirsch et al., 2010; Leibowitz et al., 2011). However, in other studies, loss of *p53* had little effect on clonogenic cell survival in the small intestine, while making the large intestine more radiosensitive (Hendry et al., 1997; Hoyes et al., 2000). Differences in radiation-induced jejunal crypt cell apoptosis between mouse strains have been found with consistently lower levels in C3H than in C57BL/6J strains (Weil et al., 1996, 2001; Coates et al., 2003). Radiation-induced apoptosis is controlled by multiple genes that are distinct from those controlling thymocyte apoptosis levels in the same strains, and several quantitative trait loci having been identified (Weil et al., 1996, 2001). Overall, radiation-induced apoptosis in intestinal epithelial cells may be of lesser relevance for outcome than cell cycle arrest and mitotic death, and p53/p21 may be more important to the kinetics of the response than to survival. Indeed, a lot of the radiation responses in the gut can be ascribed to survival or loss of Lgr5+ BSCs (Hua et al., 2012). In addition to loss in the epithelial compartment, endothelial cell apoptosis has also been proposed as a mechanism responsible for GI-ARS death (Paris et al., 2001). However, this is not a universal finding (Potten, 2004; Kirsch et al., 2010) and may be due to NETosis and dependent on the extent of microbial activation of myeloid cells (Cahilog et al., 2020). Crypt fission or budding appears to be a later radiation response and unlikely to make a contribution to GI-ARS (Hua et al., 2012).

(57) Radiation responses vary along the length of the intestine. For example, in the rat, injury develops faster in the proximal than in the distal 40 cm of the small intestine (Vriesendorp et al., 1992). After irradiation, mouse jejunal crypts degenerate within hours, a process that continues for 36 hours, while potentially surviving cells undergo cell cycle arrest and repair (Withers and Elkind, 1968, 1969; Gillette et al., 1970; Withers and Elkind, 1970; Withers, 1971; Withers et al., 1974b; Withers et al., 1975; Masuda et al., 1977; Potten, 1977; Hendry et al., 1983; Potten et al., 1987; Taylor et al., 1991; Hendry et al., 1992; Potten and Hendry, 1995). The villi remain long but by 48 hours regeneration has started, the villi become shortened and depleted (Withers ,1971), at a rate that is hard to determine because of their 3D structure and crypt shrinkage (Wright and Irwin, 1982).

(c) Clonogenic Responses in Small Intestine

(58) Clonogen development after irradiation is considered largely due to survival of one or more Lgr5 + BSCs that can regenerate the whole crypt (Hua et al., 2012). The crypt is fully

repopulated by clusters of clonogens at the base of the crypt dividing symmetrically every 8 hours up to 4 days. The number of clonogens overshoots but the rapid growth phase is over at 4 days and cells begin to enter the villus (Withers, 1971). If the radiation dose is sufficiently high, the epithelial surface is denuded, exposing the connective tissue.

(59) Crypt clones can be counted either macroscopically around 13 days after irradiation (Withers and Elkind, 1968, 1969) or, more commonly, and with similar results, microscopically in stained tissue sections as clones containing at least 10 cells at day 3.5 after irradiation (Withers and Elkind, 1970; Withers, 1971). The clones in the crypt are assumed to be derived from 1 surviving "stem" cell, with Poisson correction for >1, and the number per circumference can be converted into a clonogenic survival curve. This assay has been very useful in relating "stem" cell responses to dose and GI-ARS. Lgr5+ BSCs have been reported to be intrinsically relatively radioresistant (Hua et al., 2012). The "shoulder" on the radiation survival curve in the mouse is about 10 Gy (Withers and Elkind, 1970; Withers, 1971) and when survival is decreased to on average one clonogen per crypt, the survival curve falls log-linearly. The number of clonogenic regenerators per crypt appears to depend on the radiation dose (from 6–40 cells) suggesting that the stimulus for regeneration may depend on both cell loss from the villi and the strength of the insult, which may represent reprogramming of transit amplifying cells at higher doses (Potten et al., 1987; Bach et al., 2000). A normal-looking small intestinal epithelium can be regenerated from about 4% surviving crypts (Potten, 2004).

(d) Large Intestine and Stomach

(60) Radiation-induced damage to the colon is similar to that in the jejunum, but the clonogenic cells are more radioresistant (Withers and Mason, 1974; Hamilton, 1977; Tucker et al., 1983; Cai et al., 1997; Hua et al., 2017; Martin et al., 2020), their cell cycle times are longer, and responses are slower (Withers and Mason, 1974; Potten and Hendry, 1995; Potten and Grant, 1998; Bach et al., 2000). Colonic epithelial turnover is driven by crypt-base proliferative stem cells that express Lgr5, with $Lgr5^-$ cells contributing to crypt regeneration upon $Lgr5^+$ cell depletion (Harnack et al., 2019). The Lgr5+ population of stem cells relies on niche signals from stromal cells as there are no Paneth cells in the colon (Harnack et al., 2019). By 36 hours after irradiation, there is some crypt hypocellularity but depopulation takes 60 hours and regeneration does not start until 3.5–4 days after exposure (Withers, 1971). Proliferation is generally about 1.5 times greater in the small than in the large intestine, reflecting a difference in turnover rate. Stem cells in the large intestine are located at the base of the crypt and appear to be prevented from undergoing spontaneous apoptosis by expression of the cell survival gene *BCL2* (Watson and Pritchard, 2000).

(61) Death by apoptosis appears to be randomly distributed throughout the crypt in the small intestine, unlike in the bowel where it is at the base (Potten and Grant, 1998; Potten, 2004). Radiation-induced apoptosis in both the small intestine and colon varies between neonates (1 day postpartum), infants (2 weeks postpartum) and adults (7 weeks postpartum) of C57Bl/6 mice (Potten et al., 2001; Miyoshi-Imamura et al., 2010). Deficiency of p53 has been reported to sensitise clonogenic cells to irradiation in the large but not the small intestine (Hendry et al., 1997), but others have found that selective depletion from the intestinal epithelium sensitised mice to GI-ARS and that epithelial cells die by a p53-dependent, non-apoptotic mechanism (Kirsch et al., 2010).

(62) The radiation response of the gastric mucosa seems to have similar characteristics, though is less well studied. Clonogenic assays have been performed and a high capacity for repair and rapid regeneration with a doubling time of 43 hours has been noted (Chen and Withers, 1972; Masuda et al., 1977).

2.1.5.4. Hematopoietic Tissue Radiation Responses

(63) The hematopoietic stem/progenitor cell (HSPC) compartment in the bone marrow is radiosensitive, as exemplified by the low dose required to cause H-ARS. It is also highly heterogeneous, consisting of epigenetically fixed subpopulations that display differences in size, self-renewal ability, kinetics, and differentiation capacity; regulated by a myriad of intrinsic and extrinsic factors. These subsets and their influences have been dissected using a combination of assays of colony formation, biomarker assessment, and ability to reconstitute WBI recipients.

(a) Colony Forming Units (CFU)

(64) The number of intrinsic CFU-S (day 10) that form in the spleen after WBI generally correlates with H-ARS lethality for an individual mouse strain (Till and McCulloch, 1964; Puro and Clark, 1972), but not across multiple strains (Yuhas and Storer, 1969). In other words, radiation resistance among inbred strains cannot be predicted from CFU-S formation. Other factors that vary between mouse strains, like the number, nature, and diversity of cells within the bone marrow hematopoietic compartment, must play a role (Miousse et al., 2017).

(65) Day 10 splenic CFU-S are clonally distinct. This was first shown by introducing radiation markers into bone marrow cells prior to their transfer into irradiated recipients (Becker et al., 1963). Splenic CFU-S are however transient (Magli et al., 1982), and their phenotype depends upon the day of assay after bone marrow cell transfer e.g., at days 5, 7, 10, or 14 (Wolf and Trentin, 1970; Gaidul et al., 1986). CFU-S colonies that form early (Day 5–10) are mainly of erythropoietic or myelomonocytic lineages and originate from oligopotent progenitors (Wolf and Trentin, 1970), while Day 12–14 colonies are derived from more multipotent cells like short-term HSCs (ST-HSC) and their multipotent progenitor (MPP) progeny. None of these are, however, fully capable of long-term reconstituting a complete hematopoietic system in heavily WBI mice, especially after repeated serial cell transfer, which has become the criterion for long-term stem cell (LT-HSC) functionality. This is in spite of the fact that myeloerythroid progenitors are able to prevent H-ARS when injected into WBI recipients (Na Nakorn et al., 2002), and enhancing this population mitigates against lethality from H-ARS (Micewicz et al., 2017). It is hypothesised that these progenitors allow mice to survive after WBI long enough for more primitive HSC compartments to recover and regenerate the complete hematopoietic system (Na Nakorn et al., 2002).

(66) Further evidence in support of a hierarchical “age” structure for HSCs, with cells differentiating through layers of progressively restricted lineage potential, comes from in vitro CFU assays. Colony stimulating factors (CSFs) or stromal feeder layers, which can be considered as replacing the in vivo bone marrow “niche”, are essential for these assays (Istvanffy et al., 2011; Sasine et al., 2017; Bujko et al., 2019). Several in vivo bone marrow niches have been reported, but the vascular niche probably the most relevant for hematopoiesis (Mendelson and Frenette, 2014; Sasine et al., 2017; Pinho and Frenette, 2019). Short-term clonogenic assays exist for progenitor cell populations, but the nearest approximation to the LT-HSC is the cobblestone area-forming cell (CAFC) assay, where colonies take more than 35 days to develop, reflecting their primitive position within the hierarchy. Using this assay, the number of LT-HSCs per murine femur was found to vary 7-fold between different mouse strains (de Haan and Van Zant,1997; de Haan et al., 2000). CAFC have a low α/β ratio relative to day 8–11 CFU-S, indicating their slow turnover rate and role in hematopoiesis (Down et al., 1995).

(b) Long Term Hematopoietic Stem Cells (LT-HSC)

(67) Single cell transfer into WBI mice has demonstrated the existence of a self-renewing LT-HSC population capable of symmetric or asymmetric division in the bone marrow and of multi-lineage differentiation, producing erythrocytes, megakaryocytes, and all the immune cells involved in innate and adaptive immunity (Yamamoto et al., 2013; Birbrair, 2019). They are rare, at a frequency of about 0.006–0.011% of total nucleated cells in bone marrow yielding ~5,000–17,000 LT-HSC cells from an individual mouse depending on the age, sex, strain, and purification scheme (Challen et al., 2009; Busch et al., 2015). The values change with age, presumably reflect changes in the regulatory mechanisms controlling them, which has implications for tumorigenesis (Feinberg et al., 2006; Oakley and Van Zant, 2007).

(68) Distinguishing murine LT-HSC from other HSPC populations was facilitated by discovery that they express signaling lymphocyte activation molecule (SLAM) family markers. Flow cytometry showed that mouse LT-HSCs lack mature lineage markers $(Lin)^-$, express $Kit^+Sca\text{-}1^+$ (LSK), and are $CD150^+CD48^-$ (Challen et al., 2009). It should be noted that mouse and human markers are different, for example humans do not express CD150 and express CD48 (SLAM 2) on both HSC and HPC (Sintes et al., 2008; Parekh and Crooks, 2013). Murine HSC markers also show strain variation, and some are modulated by irradiation. Sca-1 is minimally expressed in BALB/c, C3H, and CBA mice, and after irradiation Kit is downregulated and Sca-1 levels increase (Vazquez et al., 2015). In steady state, only about 3% LT-HSCs are cycling at any one time, dividing about once a month in mice and every 6–12 months in humans (Kiel et al., 2005; Oguro et al., 2013; Parekh and Crooks, 2013). LT-HSCs are therefore largely quiescent and relatively radioresistant, in keeping with their low α/β ratio. (Geiger, 2014; Shao et al., 2014; Rodrigues-Moreira et al., 2017).

(c) Aging, Radiation, and LT-HSCs

(69) In mice, LT-HSC numbers generally increase into middle age (around 10–14 months, approximating to 38–47 years in humans) before falling (Busch et al., 2015). LD50/30 values for H-ARS and WBI-induced CFU-S numbers in the spleen follow the same pattern (Yuhas and Storer, 1967). A recent study using non-invasive strategies to study clonal dynamics of HSC indicate that the number of clones supporting the major blood and bone marrow hematopoietic compartments decline with age by approximately 30% and 60%, respectively (Ganuza et al., 2019).

(70) Mouse strains differ with respect to LT-HSC aging. An in vitro CAFC assay showed that young DBA/2 have higher LT-HSC numbers than C57Bl/6 mice, but this strain difference is reversed in old age (de Haan et al., 2000; Dykstra and de Haan, 2008). The ability of bone marrow from CBA, Balb/c, and DBA/2 mice to competitively repopulate irradiated recipients also decreased markedly with age; especially after serial transplantation. In contrast, this decrease with age was much less in C57Bl/6 mice, even after serial transfer (Van Zant et al., 1983). C57Bl/6 are a long-lived strain and one hypothesis is that there is a trade-off between the rate of hematopoiesis and longevity, with DBA/2 LT-HSC cycling more in young mice but becoming exhausted with age (Dykstra and de Haan, 2008; Muller-Sieburg and Sieburg, 2008; Seita and Weissman, 2010; Nakamura et al., 2012).

(71) Irradiation appears to accelerate LT-HSC exhaustion by inducing senescence (Meng et al., 2003; Muller-Sieburg and Sieburg, 2008; Geiger, 2014; Shao et al., 2014) and this may be relevant to strain differences in radiation-related carcinogenesis. Compared to acute myelogenous leukaemia (AML)-prone CBA/J mice, C57Bl/6 mice resist radiation-related AML and have higher numbers of bone marrow cells, HSPCs, and endogenous ROS and γ–H2AX foci in their HPSCs (Oakley and Van Zant, 2007). In response to leukemogenic

radiation doses, decreased DNA methylation within the 5′-UTRs (untranslated regions) of retrotransposon Long Interspersed Nuclear Element 1 (LINE-1) of HSPCs was seen in CBA/J, but not in C57BL/6J, mice indicating that epigenetic alterations may be one of the forces driving radiation-related experimental carcinogenesis (Oakley and Van Zant, 2007).

(72) One mechanism of LT-HSCs aging appears to involve sensitivity to oxidative stress, which radiation can generate directly, or indirectly through radiation-induced inflammation (Chua et al., 2012; Lorimore et al., 2013). Even low (0.02 Gy) WBI doses can cause a state of persistent oxidative stress in LT-HSCs of C57Bl/6 mice, decreasing their self-renewal capacity (Shao et al., 2014; Rodrigues-Moreira et al., 2017). The accumulated DNA damage and high levels of intracellular reactive oxygen species in aged LT-HSCs may be associated with their relative quiescence where DNA repair and response pathways are attenuated (Dykstra and de Haan, 2008). However, when these cells are stimulated to cycle, these pathways are activated (Beerman et al., 2014).

(73) LT-HSCs also have an increased expression of genes involved in leukemic transformation (Rossi et al., 2005) and a shift towards genes specifying myeloid fate and function at the expense of the lymphoid compartment (Rossi et al., 2005; Pilzecker et al., 2017). How LT-HSCs perform repair and response functions and the influence of mutations on these processes may be critical for the risk of radiation-related leukaemia.

(d) Short Term HSCs, Multipotent Progenitor (MPP) and Lineage Restricted Stem/Progenitor Cells

(74) The LT-HSC compartment transfers only a small number of polyclonal cells to the $CD150^-$ ST-HSC compartment every day. ST-HSCs have a high rate of self-renewal and form a long-term amplifying cell compartment (Oguro et al., 2013; Busch et al., 2015). These are the primary source for haematopoietic maintenance in mice (Sun et al., 2014; Busch et al., 2015). One result of this structure is that LT-HSC deficiency may go unnoticed for extended periods of time as the peripheral compartment may be little influenced. In contrast, if ST-HSC and MPP compartments are damaged, as after WBI, acute bone marrow failure occurs fairly rapidly. It has been estimated that in mice, on average, only about 1% of LT-HSCs differentiate into ST-HSC per day, and about 5% of ST-HSCs differentiate into CD48+ multipotent progenitor cells (MPP), although there are large strain differences (Busch et al., 2015).

(75) MPPs also are capable of substantial self-renewal (Oguro et al., 2013; Busch et al., 2015). Lymphoid, myeloid, and erythroid cells bifurcate at this stage, first generating common myelo-lymphoid and myelo-erythroid progenitors and then uni-lineage common lymphoid and myeloid progenitors (CLP and CMP) (Miyawaki et al., 2015). More myeloid than lymphoid progenitors are produced during normal hematopoiesis (Sun et al., 2014; Busch et al., 2015).

(76) Unlike LT-HSCs, ST-HSC and MPP transit amplifying cell populations have high α/β ratios, in keeping with loss of these populations being responsible for H-ARS. New technology that interrogates HSPCs at the individual, clonal or near-clonal level have confirmed that self-renewing stem cells express transcripts from multiple differentiated hematopoietic lineages, whereas progenitor cell populations are more limited (Akashi et al., 2003). However, individual LT-HSCs can give rise to myeloid-biased, lymphoid-biased, or more balanced differentiation, with the lineage bias being influenced by extrinsic, as well as intrinsic factors (Rossi et al., 2005; Elias et al., 2017).

(77) Intriguingly, many of the progeny appear to form an ever-changing clonal landscape with some clonal dominance over time, which is impacted by oncogenic mutations (Lee-Six and Kent, 2020). The role of lineage pathways that drive LT-HSC directly into lineage-committed myelo-erythroid progenitors has yet to be fully established (Yamamoto et al., 2013).

(e) The Lymphoid to Myeloid Switch

(78) Gene expression studies have shown that LT-HSC with a lymphoid bias appear to be depleted with age, while myeloid-biased LT-HSC are enriched, and it is tempting to think that the distinct behaviors associated with LT-HSC in aged hosts is due to this increased myeloid bias (Muller-Sieburg and Sieburg, 2008). Age-dependent alterations in LT-HSC gene expression may therefore presage downstream events, including age-dependent myeloid dominance and increased leukemic incidence (Rossi et al., 2005; Elias et al., 2017). Radiation and other stresses accelerate the LT-HSC changes associated with aging (Bertell, 1977; Wang et al., 2006; Richardson, 2009; Hernandez et al., 2015) and parallels between radiation and premature aging have frequently been drawn (Bertell, 1977; Wang et al., 2006; Richardson, 2009).

(79) Myeloid cells have long been known to have important roles in tissue and immune homeostasis (Amodio et al., 2019), but the lymphoid to myeloid shift after irradiation, which has been associated with recurring phases of morbidity and mortality after WBI in mice (Schaue et al., 2015; Micewicz et al., 2019), may impact many radiation effects, such as premature aging, chronic inflammation, late radiation effects, and radiocarcinogenesis. In human atomic-bomb survivors, increases in blood monocyte percentages and counts were associated with a higher risk of all-cause mortality (Yoshida et al., 2019), and monocytosis has been reported in patients receiving radiation therapy, coincident with neutropenia and lymphopenia (Rotman et al., 1977). Increases in peripheral myeloid cells are also increasingly becoming recognised as an aging-associated indicator of low-grade inflammation (Elias et al., 2017) and chronic infections and autoimmune diseases increase myeloid cell representation in blood and may precipitate aging-related hematopoietic disorders, such as myelodysplastic syndrome and cancer (Barreyro et al., 2018; Banerjee et al., 2019).

2.1.6. The Impact of Mouse Models

2.1.6.1. Genetics

(80) Genetically homozygous inbred strains have been developed in several animal species for scientific studies, but only in mice has a sufficient number of strains been available for evaluation of the impact of inter-strain variability, and hence of genetics, on radiation responses (Beck, 2000; Paigen, 2003; Haston, 2012). Large comparative studies of different inbred mouse strains have been performed using WBI (Reinhard et al., 1954; Kohn and Kallman, 1956; Grahn and Hamilton, 1957; Grahn, 1958; Guttman, 1963; Roderick 1963a; Sacher and Grahn, 1964). For 9 strains of 3–4 month old mice from the Jackson Laboratories (excluding Balb/c) LD50/30 values ranged from 6.2 to 7.5 Gy (average 6.7 Gy +/− 0.12 standard error of the mean) (Storer, 1966). A repeat study with 8 of the same strains 3 years later gave a range of 6.8 to 7.8 Gy (average 7.1 Gy +/− 0.1) (Yuhas and Storer, 1969), with a very similar rank order of strain radiosensitivity. However, if fractionated daily doses of 1 Gy WBI were given, the rank order differed significantly, with MST values ranging from about 16 to 30 days (Yuhas and Storer, 1969), presumably because of differences in rates of recovery between fractions.

(81) It should be noted that data from early studies were frequently confounded by primitive husbandry, such as seasonal variations in temperature and humidity. Roderick measured the survival times for 27 inbred mouse strains exposed to daily fractions of 110 R (~1 Gy) to the whole body (WBI) (Roderick, 1963a). The most resistant 129J strain survived for 34 days, twice as long as the most sensitive CBA/J strain; a difference that was almost totally negated if the experiments were performed between May to October (Roderick, 1963a). Intercurrent infections can also contribute to post-irradiation mortality as opportunistic bacteria cross the radiation-damaged intestinal barrier and spread easily in an immunosuppressed host (Gonshery

et al., 1953). Additional possible influences included cage effects, age, weight, sex, animal source, extent of inbreeding, and other factors, (Raventos, 1955; Hann and Howland, 1963). Overall, studies also concluded that heritability has an influence on survival after WBI (Grahn and Hamilton, 1957; Grahn, 1958; Frölén et al., 1961; Roderick ,1963a; Hanson et al., 1987).

(a) Genealogy of Mouse Strains

(82) One concern that has to be taken into account in all murine studies is that many classic inbred mouse strains have common progenitors, and as a result have large regions of their genomes in common. Most of the commonly used strains originated in the 1920–30s from a relatively small number of sources (Staats, 1964; Beck et al., 2000). Little bred the first inbred strain, DBA, in 1909 (Staats, 1964; Beck et al., 2000). Strong mated two albino strains to establish the A strain, from which Balb/c mice were bred by Snell. Mating of A and DBA strains gave rise to numerous hybrid CBA and C3H strains. By way of contrast, C57BL and C57BR (black and brown) lineages were distinct as they were developed by Little using mice from Miss Lathrop, a fancier in Granby, Massachusetts. The 129 strain, and its genetically diverse substrains, came from English coat colour fanciers (Simpson et al., 1997). SWR, SJL, and similar lineages were derived from outbred Swiss albino mice by various laboratories. Genealogy therefore can influence the extent of strain variation observed for any effect, as can genetic drift and contamination from long-term breeding in different laboratories.

(83) The impact of genealogy appears in H-ARS and other radiation responses. When strains are ranked by LD50/30 values, related strains tend to cluster with A, C3H and CBA strains more radiosensitive than C57BL, SWR, and SJL strains (Yuhas and Storer, 1969; Storer, 1975), although divergent reports exist (Kohn and Kallman, 1956). There seems little strain correlation between H-ARS and GI-ARS sensitivity (Yuhas and Storer, 1967; Bhat et al., 2019) suggesting that “radioresistance”, perhaps unlike radiosensitivity due to DNA repair defects, needs to be qualified by an endpoint. In general, crosses between resistant and sensitive inbred mouse strains show that resistance is most often dominant (Grahn, 1958; Frölén et al., 1961) and selection of a radiation resistant phenotype is, to an extent, possible. Roderick selected offspring of randomly mated C57BL/6J, BALB/cJ, C3HeB/FeJ, and DBA/2J mice resistance and sensitivity to 1 or 4 Gy WBI daily. Selection was successful for both doses but was more pronounced for the 1 Gy/day schedule (Roderick, 1963b). Roderick considered radiation resistance to correlate with life span, litter size, and resistance to S. typhimurium (Roderick, 1963a) and postulated that, in addition to specific genetic factors, radioresistant animals displayed a general “resilience” to tissue damage.

(84) After local thoracic irradiation, C57Bl/6 and C3H/HeN mice have very different radiation phenotypes. They classically develop fibrosis and the pneumonitis, respectively (Franko et al., 1991). These endpoints are associated with markedly different cytokine, immune, (Johnston et al., 1995; Williams et al., 1996; Hong et al., 2000; Jackson et al., 2010; Groves et al., 2015) and miRNA (micro-RNA) responses (Rogers et al., 2020), involving multiple genes (Haston et al., 2002; Paun and Haston, 2012). These two strains also diverge in their IgG and IgE antibody responses to low antigen doses, along with other genealogically related strains (Levine and Vaz, 1970).

(b) DNA-dependent Protein Kinase (DNA-PK) and Murine Radiosensitivity Syndromes

(85) Multiple reports on strain sensitivity to H-ARS identify Balb/c mice as being radiosensitive (Grahn and Hamilton, 1957; Kohn and Kallman, 1956; Yuhas and Storer, 1969; Storer, 1975; Hanson et al., 1987; Okayasu et al., 2000a), with an LD50/30 of around 6 Gy, ~12% less than average (Yuhas and Storer, 1969; Storer, 1966). For GI-ARS, Balb/c mice were

twice as sensitive as C57BL/6 mice (8.8 compared with 16.4 Gy) (Hanson et al., 1987). Balb/c x A F1 crosses were more similar to A than Balb/c strain for H-ARS and GI-ARS sensitivity, suggesting that the Balb/c mice carry an autosomal recessive gene (Kohn and Kallman, 1956). More recently, the probable cause of radiosensitivity in Balb/c mice was identified as a truncating mutation in the Prkdc gene that codes for the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) (Hanson et al., 1987; Okayasu et al., 2000a; Anderson et al., 2001). Similar Prkdc genetic alterations in humans have been associated with increased cancer risk (Auckley et al., 2001; Bhatti et al., 2008).

(86) Balb/c DNA-PK mutations cause defective DNA double strand break repair by non-homologous end joining (NHEJ) (Hanson et al., 1987), resulting in high, persistent levels of radiation-induced micronuclei and γ-H2AX foci (Bhogal et al., 2010). Defective repair was demonstrated in skin (Bhogal et al., 2010), blood lymphocytes, intestine, lung, and heart (Rübe et al., 2008). The Balb/c defect is not seen in the A strain, from which it was derived, even though the A strain is frequently ranked towards the radiosensitive end of the radiosensitivity spectrum (Grahn and Hamilton, 1957; Yuhas and Storer, 1969). This defect also confers genomic instability and an increased incidence of radiation-related mammary tumours and thymic lymphomas (Yu et al., 2001). Balb/c mice, unlike the C57BL/6 strain, develop radiation-related mammary cancer and the F1 hybrids follow the C57BL/6 phenotype (Ullrich, 1983). On the other hand, Okumoto found that Balb/c mice were more susceptible to radiation-related lymphomas than the radioresistant MSM strain, but in this case, the F1 hybrid mice were closer in sensitivity to Balb/c (Okumoto et al., 1995), perhaps indicating the importance of background genetics in carcinogenesis.

(87) It has been suggested that individuals differ in radiosensitivity within human populations, and that the variations in DNA repair genes might determine part of this heterogeneity. There are many defects in DNA repair that have been associated with clinical syndromes in humans and for which there are mouse models. The natural DNA-PKcs (catalytic subunit of DNA-PK) repair defect in C.B.−17-SCID (severe combined immunodeficiency) mice has much greater impact than that in the Balb/c strain (Blunt et al., 1995; Danska et al., 1996; Rübe et al., 2008; Bhogal et al., 2010). SCID mice have an LD50/30 of around 3–4 Gy, about half that of Balb/c mice (Fulop and Phillips, 1990; Budach et al., 1992). They are also prone to lymphoma development and lack mature B and T cells but have natural killer (NK) cells. This defective immunophenotype is characteristic of defects in V(D)J recombination, and is also seen in mice with mutations in the recombinase-activating genes RAG1 and RAG2 that initiate V(D)J recombination, which is an essential step in the maturation of pre-B and pre-T cells. After break induction by RAG proteins, the end-joining process is defective in SCID mice. A similar phenotype is seen in mice lacking other NHEJ proteins like Artemis (Rooney et al., 2002) and LIG4 (Nijnik et al., 2009). SCID mice can develop thymic lymphomas whose incidence is enhanced by p53 knock out and significantly reduced if Rag2 is also mutated, demonstrating that DNA breaks generated during V(D)J recombination are required for oncogenic transformation (Vanasse et al., 1999). Irradiation seems to facilitate V(D)J joining through a DNA-PK independent pathway, but promotes the oncogenic misjoining of the RAG-induced breaks (Williams et al., 2001).

(c) Ataxia-telangiectasia and Defective DNA Damage Responses

(88) Ataxia-telangiectasia (A-T) emerged as the classic radiosensitive genetic syndrome when A-T patients were shown to develop potentially lethal adverse reactions to radiotherapy. Lymphocytes and fibroblasts from AT patients were rapidly shown to be highly radiosensitive in vitro compared to controls (Taylor et al., 1975). A-T individuals were also shown to have genomic instability, predisposition to cancer (Chen et al., 1978), and defective humoral

immunity (Stobo and Tomasi, 1975). Other examples of radiosensitive disease are Nijmegen breakage syndrome (NBS gene – NBS1), ataxia-telangiectasia-like disorder (ATLD gene – MRE11A) and Nijmegen breakage syndrome-like disorder (NBSLD gene – RAD50) (Masuda and Kamiya, 2012) that vary from A-T in disease manifestation depending on the nature and type of mutation.

(89) The product of the gene mutated in A-T (ATM) has emerged as a central controller of the DNA double strand break (DSB) damage response, as well as of other types of genotoxic stress, and to modulate many other cell signalling pathways. Irradiation strongly activates ATM kinase activity by virtue of inducing DNA DSBs, which has many downstream effects including but not limited to effects on DNA repair, cell cycle arrest and apoptosis (Khanna et al., 2001). In fact, generally A-T cells are not completely deficient in repairing DNA DSBs, although repair is delayed and incomplete (Khanna et al., 2001). Mice deleted in ATM have a low LD50/30 of around 3–4 Gy (Laiakis et al., 2018). Like A-T patients, ATM null mice have markedly reduced titers of antigen-specific IgG1 and total IgE, as well as significant decreases in antigen-specific IgA, IgG2b, and IgG3 compared with wild type controls, suggesting defects in immunoglobulin class switch recombination (Lumsden et al., 2004). ATM null mice are similarly susceptible to thymic lymphoma, especially after irradiation, although the genetic background has a strong modifying effect (Genik et al., 2014a).

(90) ATM null and heterozygous mice may however not accurately recapitulate the human condition. For example, while human heterozygous carriers of ATM have a higher-than-normal risk of developing cancer, ATM heterozygous mice show no increase in cancer, unless they harbor the human 7636del9 mutation that has as a dominant negative effect in inhibiting radiation-induced ATM kinase activity and cell survival (Spring et al., 2002).

(91) The impact of differing truncating or missense mutations may also be why irradiated human A-T heterozygote cell lines often vary considerably in survival, even if cell cycle progression can often be normal (Chen et al., 1978; Fernet et al., 2004). Similarly, human ATM heterozygous cell clones generated by CRISPR varied in radiosensitivity but, overall, this was not significantly higher than amongst wild type cells (Khanna et al., 2001; Royba et al., 2017).

(92) Radiosensitivity can be modified by activation or loss of other molecules downstream of DNA damage that affect apoptosis or cell cycle arrest. Radiation-induced apoptosis is largely ATM/p53-dependent, but varies between different tissues, cell type, organ, and strain (Potten et al., 1977; Weil et al., 1996; Kerr et al., 1998; Weil et al., 2001; Coates et al., 2003; Lindsay et al., 2007). There is also a later p53-independent wave of radiation-induced apoptosis (Uberti et al., 1999) that may be due to either mitotic death (Hendry and West, 1997) or mediated by tumour necrosis factor (TNF) family members or other pro-inflammatory pathways (Mukherjee et al., 2014). Only some tissues, such as spleen, thymus, epithelia of the digestive tract and tongue, skin, and testis exhibit p53-dependent radiation-induced apoptosis, and not all cells within these tissues (Komarova et al., 2000). Strain differences were shown in the extent of radiation-induced apoptosis in thymic lymphocytes. C57BL/6J and AKR/J mouse strains had high apoptosis levels, A/J intermediate, and C3H/HeJ and DBA/2J low levels, indicating genetic regulation of the process (Nomura et al., 1992). Radiation-induced apoptosis was also higher in C57Bl/6 than C3H jejunal crypt cells (Weil et al., 2001), and higher for C57Bl/6 than for DBA/2 mice in spleen, small intestine, and colon (Coates et al., 2003). Multiple quantitative trait loci (QTLs) seem to differ between tissues (Weil et al., 2001). C57BL/6 and DBA/2 mice also have significant differences in p53 and p21 responses in different cell types and in different cells of the same type (Donehower et al., 1992; Coates et al., 2003; Lindsay et al., 2007). The role of DNA damage response in radiation effects, including in carcinogenesis, has a high level of complexity that is reflected in some reported findings. For example, p53 null C57Bl/6 mice survive H-ARS better than wild type, but mice deficient in p53 or in the cyclin-dependent kinase inhibitor p21 are more sensitive to GI-ARS

(Komarova et al., 2004). Apoptosis in the crypts of the small intestine does not correlate with GI-ARS, but does in the colon (Hendry et al., 1997). The multiple mechanisms underlying these strain differences in radiation-induced responses are emphasised by their variation in dose and time, their dependencies upon p53 and p21, and differences in the extent of involvement of bystander inflammatory action, which could be relevant for tissue-specific radiocarcinogenesis (Coates et al., 2003; Lorimore et al., 2013).

(93) In humans with a normal ATM protein, a delay of nucleo-shuttling has been observed in a large series of patients with degenerative diseases presenting with moderate radiosensitivity as determined by survival fraction at 2Gy (SF2) assays. The maximal number of nuclear phosphor-ATM (pATM) foci after irradiation of skin fibroblasts provided the best discrimination among post-radiation therapy overreactive patients (N = 100) and a significant correlation with each patient's CTCAE severity grade, independently of tumour localisation and of the early or late nature of reactions (Granzotto et al., 2016). The radiation-induced nucleo-shuttling of ATM (RIANS) from the cytoplasm to the nucleus appears to reflect several aspects of radiation sensitivity. Delays in nucleo-shuttling can be observed in many human syndromes, especially those syndromes with an accumulation of damaged proteins in the cytoplasm. Notably, a delay in the ATM nucleo-shuttling is associated with radiosensitivity, cancer proneness and/or degenerative diseases (Berthel et al., 2019). More recently, Le Reun et al., have shown that the maximal number of early pATM foci (pATMmax) (molecular scale), SF2 (surviving fraction at 2 Gy, a cellular scale) and CTCAE grade (clinical scales) are mathematically linked in humans (Le Reun et al., 2022).

2.1.6.2. Age and Acute Radiation Syndromes

(94) Crosfill and colleagues (Crosfill et al., 1959; Lindop and Rotblat, 1962) found that resistance of inbred albino SAS4 mice to WBI with 15-MeV x-rays fell from about 8.5 Gy at 1 day to 7 Gy at 1 month (LD50/30). Values increased in adulthood to peak at 9.5 Gy around 48 weeks of age, before declining at 80 weeks to 6.8 Gy. Young females were slightly more sensitive than the males, but after the age of ten weeks the reverse was true. This age-response relationship for H-ARS is generally similar to the findings of others. Grahn (Grahn and Hamilton, 1957) reported that radioresistance of Balb/c, A, C3Hf/He and C57BL/6 mice increased between 2 to 4 months of age (LD50/30) with considerable inter-strain but no sex differences. Spalding (Spalding and Trujillo, 1962) showed that radioresistance of RF female mice to 4.5 Gy (^{60}Co) WBI every 2 weeks changed little from 2–12 months of age, but thereafter declined towards the end of the normal lifespan at 21 months. Kallman and Kohn (Kallman and Kohn, 1956) using CAF1 mice, found that the LD50 increased as a linear function of the log of age from 37 to 105 days but was nearly constant from 115 to 709 days. Yuhas and Storer (Yuhas and Storer, 1967) irradiated C57BL/6J female mice at 6–22 months of age and found that LD50/30 values increased by 1 Gy between 6–16 months before decreasing to 6-month levels at 22 months. There is less information on the age-dependency of GI-ARS, but Yuhas showed that, in contrast to H-ARS, LD50/7 (seven-day post-exposure LD50) values decreased progressively from 4 to 23 months. Gut and marrow are therefore dissimilar in their age-dependent change in sensitivity to radiation. This suggests that any interaction between intestinal and marrow injury, if it exists, will vary with age and become more important at advanced age. Consistent with this hypothesis is the finding by Yuhas and Storer in mice given 1.5 Gy 5 days a week until death, that the shortest survival times were in mice irradiated at 3 months and 22 months, with the distribution being skewed with time towards what was interpreted as greater intestinal damage (Yuhas and Storer, 1967). However, body weight and dehydration could confound the effects of age and sex on radioresistance, as could changes in the stem/progenitor cell compartments with age.

2.1.6.3. Sex Differences in Acute Radiation Syndromes

(95) Sex differences have been found for the H-ARS LD50/30 endpoint, although they are relatively minor. Females were found to be more resistant than males for 6 (Kohn and Kallman 1956) and 9 out of 10 strains (Storer, 1966), but the average difference was less than 0.5 Gy (Crosfill et al., 1959; Kohn and Kallman, 1956) On the other hand, Roderick (Roderick, 1963a), using 1 Gy/day found males survived significantly longer than females (22.6 vs 24.2 days) in twenty-one out of the twenty-seven strains, and Hamilton et al (Hamilton et al., 1963) using 1.45 Gy/day found young adult males lived 33 days, about 7 days longer than females. Gonadectomy reduced the sex difference to 2 days and the weight difference between males and females from 6g to 1g, suggesting a possible explanation. Roderick's data suggested a sex reversal in resistance from low to high chronic irradiation, with the females being more resistant under 4 Gy/day and the males more resistant under 1 Gy/day.

2.1.6.4. The Influence of the Microbiome

(96) Germ-free (axenic) mice tend to be more ARS radioresistant than conventionally housed mice of the same strain (Wilson, 1963). Wilson reported a higher LD50/30 (7.05 Gy vs 6.6 Gy) for axenic than conventional Swiss Webster (SW/ND) mice, with a dose-related prolongation in MST. In the 6–11 Gy range, the MST was about 4 days longer for axenics than for conventional mice (12.5 vs. 8.5 days). In axenic mice the MST continued to decrease progressively above 11 Gy in a log linear fashion to 8 days, whereas for conventional mice it plummeted rapidly to plateau at 3- and 4-days post-exposure. The suggestion is that the microbiome impacted lethality more above than below 11 Gy WBI, or GI-ARS more than H-ARS. Estimates of the LD50/10 for GI-ARS in gnotobiotic C3H/He mice in one study were almost 20 Gy, with a surviving fraction of 8x 10^{-6} crypt stem cells, compared with those for conventionally housed mice of 12.5–13 Gy LD50/5 and a surviving fraction of 3.5×10^{-3} (Mason et al., 1989b).

(97) McLaughlin (McLaughlin et al., 1964) reached similar conclusions using the same strain given between 5 and 400 Gy WBI. The LD50 dose and the MST for hARS, GI-ARS, and CVS/CNS-ARS were always higher in axenic than conventional mice, with the greatest difference for GI-ARS. Also, bloody diarrhea, and hyperexcitability and convulsions that marked CVS/CNS-ARS in conventional mice were absent in axenics. Matsuzawa (Matsuzawa, 1965), also using SW mice, found that axenics had a higher LD50/30 by about 1 Gy and an increased MST by 1.3 days. However, GI-ARS values were different by 8 Gy with an almost 2-fold difference in MST (3.8 days to 7.6 days). They did not find much difference in time or dose for CVS/CNS-ARS. In general, histopathological changes in axenics were less severe and delayed. Without irradiation, migration of cells from crypt to villus tip was 4.3 days in axenic and 2.1 days in conventional mice, which was thought to be the reason for the delay in MST. Also, axenics had fewer apoptotic cells in the vascular endothelium and mucosa-associated lymphoid tissue, suggesting that other cellular responses to radiation were influenced by the microbiome.

(98) Since radiation-induced p53-mediated apoptosis in epithelial cells is in part influenced by TNF-α, a contribution of inflammation to radiation tissue damage cannot be excluded (Inagaki-Ohara et al., 2001). Inflammation reduces epithelial cell turnover along the crypt-villus axis and decreases villus length (Parker et al., 2019). Antibiotics have been employed to reduce the impact of the microbiome on ARS, and they can increase LD50 and MST values (Hendry et al., 1983, Booth et al.; 2012). However, tetracyclines and fluoroquinolones can act as protectors and mitigators of H-ARS in gnotobiotic mice even at relatively low doses, suggesting other mechanisms in addition to inflammation may be involved (Kim et al., 2009).

The general conclusion is that the microbiome determines the tissue turnover rate in the intestine and probably the resilience of its barrier function to impact the MST and radioresistance. In addition to concerns regarding opportunistic infections, slower turnover could allow more time for repair and regeneration of stem/progenitor cell pools. These considerations have implications for mitigation of ARS. The role of the microbiome in radiation response can be considerably more complex than this as microbial products can activate epithelial and immune cells locally and systemically to alter radiation resilience (Crawford and Gordon 2005).

(99) It is important to note that GI-ARS is often associated with weight loss, loss of appetite and water intake, loss of intestinal barrier function that disturbs the electrolyte and water balance, diarrhea, bleeding, ulceration, bacterial translocation across the gut, susceptibility to opportunistic bacterial infection, bacteremia, and sepsis. Following acute exposures, death occurs within about 3.5 – 9 days. In germ-free mice the MST is later and some of these phenomena are absent or delayed, suggesting that earlier deaths are associated with infection, especially after lower doses than those that denude the epithelial surface (Wilson, 1963; Matsuzawa, 1965). It is important to consider the role of the microbiome and associated inflammation and immunity in GI-ARS.

(100) TNF-α, which can be induced by radiation (McBride et al., 1991), as well as microbial products, and is made mainly by T cells and macrophages, can radioprotect against ARS (Riehl et al., 2004; Wang et al., 2004). It has Janus-like features, being capable of mediating both inflammatory disease and healing in the intestine (Bradford et al., 2017; Schreurs et al., 2019). It can modulate intestinal mucus secretion and tight junctional control, as well as influence cell fate decisions through Wnt/β-catenin signaling to stimulate proliferation and survival of BSCs, or cause them harm, as can effector T-cell-derived interferon-γ (Leppkes et al., 2014; Kretzschmar and Clevers, 2019; Leppkes and Neurath, 2019). Pro-inflammatory cytokines have also been implicated in late complications of intestinal irradiation. These occur after months and are normally consequential to loss of the epithelial lining and include bleeding, fistula formation, adhesions, and gut obstruction (McBride et al., 1989a,b; Coia et al., 1995). The estimates of the LD50/10 for GI-ARS in gnotobiotic C3H/He mice are almost 20 Gy, with a surviving fraction of $8x\ 10^{-6}$ crypt stem cells, compared with those for conventionally housed mice of 12.5–13 Gy LD50/5 and a surviving fraction of 3.5×10^{-3} (Mason et al., 1989b).

2.1.7. Summary of section 2.1

(101) Radiation research in the immediate post-WWII period had a major focus in elucidating the time-dose relationships for failure of different tissues, often with acute lethality after whole body exposure as an endpoint. This identified distinct acute radiation syndromes and laid a strong groundwork for better understanding how different normal tissues respond to radiation. The development of inbred mouse strains was critical for these studies and variation between strains and their genealogy pointed to the role of genetics in determining the time-dose effects and pathophysiology of the response. Better husbandry and strain rederivation were important in providing specific pathogen free conditions, so animals were free of infections, that complicate interpretation of results of extensive irradiation and germ-free mice that are generally better able to resist acute radiation syndromes, especially if the intestine is involved. A potential role of the microbiome in radiation effects is emerging and likely to be complex. There is no doubt that microbial products can activate epithelial and immune cells locally and systemically, alter the turnover of populations in transit and the pathophysiology of radiation damage. Numerous animal studies have shown radiosensitivity to vary with age at exposure, although the pattern of change varies considerably with strain and, most likely, tissue type. Sex differences have been found, but mechanisms are largely obscure.

(102) Studies in normal tissue radiobiology were greatly strengthened by the development of clonogenic assays for "stem" cell populations in different tissues. This informed on the organisational structure of cell populations in different tissues and how they respond to cell loss with regeneration. They provided ways to better quantify in situ cellular responses, evaluate number and kinetics of stem/progenitor cells and tissue organisation. It promoted mathematical modeling of normal tissue responses, how different tissue responses vary with time and dose, and with organisation around functional subunits; a volume that can be regenerated from one clonogenic stem cell. These models have guided decision making in clinical radiotherapy for many decades and will continue to do so.

2.2. Early/late tissue reactions following radiotherapy in humans

2.2.1. Importance for radiation protection and medical uses of radiation

(103) Tissue reactions are a major concern for patients undergoing radiotherapy. In *Publication 118* dedicated to tissue reactions (ICRP, 2011) one can count 250 occurences of the word "radiotherapy" and 52 of the word "radiosensitivity". In the glossary, Radiosensitivity (associated with the adjective cellular) is defined as "The sensitivity of cells to ionising radiation in vitro. Usually indicated by the surviving fraction at 2 Gy (i.e. SF_2) or by the parameters of the linear-quadratic or multitarget equations." These parameters have been defined and used in the context of radiotherapy to good effect.

(104) Interventional radiology constitutes a second domain of medical exposures to high doses of radiations can be very high for any given procedure, and doses can be very high when the sum of exposures is considered. Cardiology patients are a particular concern, where the repetition of interventions can lead to tissue reactions of the skin (due to high entrance doses) and of the myocardium. In 2020/2021, UNSCEAR estimated that about 24 million interventional radiology procedures were performed every year worldwide, a substantial increase on the 2008 estimate of 3.6 million procedures (UNSCEAR, 2021). In Europe, 5131 diagnostic heart procedures per million people (median value) have been reported (Barbato et al., 2020). Severe radiation-induced dermatitis (i.e., with necrosis) is also not rare, and is more frequent in case of cumulative exposure from multiple interventional radiology procedures and may be initially overlooked by confusion with other skin diseases such as morphea (Wagner et al., 2007; Wei et al., 2015; Guesnier-Dopagne et al., 2019).

(105) Medical workers, i.e., medical practitionners who perform the investigations, are also concerned because their intense daily practice may lead to high exposures of their hands and the lens of their eyes. Workers performing or assisting in fluoroscopically guided interventional (FGI) procedures receive the highest doses in medical practice and one study from the United States 15 percent of these occupational doses exceeded the current 20 mSv/year eye dose limits recommended by ICRP (Borrego et al., 2019).

(106) There are about 18.1 million persons living with a cancer worldwide, with 0.5 million new cases every year (IARC, 2018 – Cancer Today) and with projections for 2040 of 29.5 million and 0.75 million respectively (IARC 2018 – Cancer Tomorrow). About 50% of cancer patients are treated by radiation therapy: 8 million treatments in about 250,000 patients (UNSCEAR, 2008) – with a rate of success (cure of cancer) of about 80%. The growing population of radiation-treated cancer survivors has allowed more precise assessment of early and late effects of radiotherapy in human studies. However, each year 9.6 million patients die from cancer (WHO, 2018).

(107) The heterogeneity in tissue radiation response has been addressed in *Publication 118* (paragraphs 51, 573, and 574) (ICRP, 2012). Defects in many genes involved in DNA repair, cell-cycle checkpoints, or tumour suppression genes are known to be associated with the

severity of skin reactions: *about 1% for homozygotes mutations in critical repair genes and are consequently two- to three-fold more sensitive than the average person. The remainder are heterozygotes for these and many other relevant genes, having less contribution to radiosensitivity. The total population has a spread of sensitivities that governs the slope of dose–incidence curves for tissue or organ damage. In addition, there are epigenetic factors that result in comorbidities*…. There are no very precise evaluations available of the number of patients with significant tissue reactions in radiotherapy; a minimum of 5 % of patients has been suggested (Foray et al., 2016) although there is a large variety in the numbers reported, as indicated in the following paragraphs. Overall one can estimate that about 12,500 new patients internationally per year treated with radiotherapy present significant tissue reactions (ICRP, 2012) with a frequency (evaluated by the SF2) decreasing with the severity of the CTCAE grades: grade 0: 62.1 ± 1.4%; grade 1: 51.0%; grade 2: 37.2 ± 3.8%; grade 3: 23.0 ± 1.4%; grade 4: 17.8 ± 0.6%) (Le Reun et al., 2022).

(108) In 71 patients treated for head and neck carcinoma the overall incidence of acute grade≥3 toxicities were mucositis 32%, pain 11%, xerostomia 7%, dysphagia 53%, radiodermatitis 44%, and osteonecrosis 1% and late grade≥3 toxicities were fibrosis 6%, dysphagia 21%, fistula 1%, and skin necrosis 1% (Santa Cruz et al., 2018). Janssens et al. (2016) reported that at 2 years from baseline, the percentage of head and neck cancer patients reporting moderate to severe complaints of dry mouth, sticky saliva, or changes in taste/smell was 30%, 22% and 18%, respectively, while the majority of patients had no or few complaints of swallowing (79%) or speech (64%).

(109) Ghadjar et al. (2008) reported that acute and maximal late grade 2 gastrointestinal (GI) toxicity was 3% and 8%, late grade 2 GI toxicity dropped to 0% at the end of follow-up. No acute or late grade 3 GI toxicity was observed. Grade 2 and 3 pre-treatment genitourinary (GU) morbidity (PGUM) was 20% and 5%. Acute and maximal late grade 2 GU toxicity was 56% and 28% and late grade 2 GU toxicity decreased to 15% of patients at the end of follow-up. Acute and maximal late grade 3 GU toxicity was 8% and 3%, respectively". GI adverse reactions were listed as diarrhea, rectal pain, and rectal bleeding. GU adverse reactions were listed as dysuria, incontinence, retention, and hematuria (Ghadjar et al., 2008). Ohri et al. (2012) reported median rates of moderate late toxicity in prostate cancers:15% (GI) and 17% (GU). For severe effects, these values were 2% (GI) and 3% (GU) (Ohri et al.; 2012). Akimoto et al. (2004) reported that 25% of patients developed Grade 2 or worse rectal bleeding with a median time of 11 months.

(110) Early rectitis in rectal cancer patients undergoing radiotherapy requiring the interruption of the radiotherapy treatment has been reported to occur in only 1% of cases (de Parades et al., 2007). However late-stage rectitis, involving the deeper layers of the digestive track wall, occurs in 20% of patients, in general between 6 and 24 months after radiotherapy, and sometimes more than 10 years later (Bauer et al., 2007). 5 to 10% of patients receiving radiation in the pelvis are reported to develop severe intestinal complications within 10 years after treatment (Chapel et al., 2013). In 2002, Glimelius acknowledged that toxicity of radiotherapy of rectal cancer is a concern (e.g., pre-surgery radiotherapy appears to be more toxic than post-surgery radiotherapy (grade 4/5 toxicity 34% versus 24%, $p = 0.07$)) (Glimelius, 2002).

(111) Radiation-related lung disease (RILD) is a frequent complication of radiotherapy of lung tumours (30–40%): acute and late phases are described, corresponding to radiation pneumonitis and radiation fibrosis respectively. These occur at different times after completion of radiotherapy and RILD almost always occurs when radiation is >40 Gy (Śliwińska-Mossoń et al., 2020). Radiation pneumonitis (RP) and radiation fibrosis (RF) are two dose-limiting toxicities of radiotherapy (RT), especially for lung, and esophageal cancer. They occur in 5–20% of patients and limit the maximum dose that can be delivered, reducing tumour control

probability (TCP), and may also lead to dyspnea, lung fibrosis, and impaired quality of life (Giurano et al., 2019). Kocak et al. (2005) reported 18.7 % of 251 patients irradiated for lung cancer had radiation induced lung injury (pneumonitis) persisting after 6-month follow-up. The liklihood of myocardial infarction after lung radiotherapy treatment: the reported relative risk of death from a fatal myocardial infarction in patients treated with mediastinal radiotherapy, is increased from 1.5 to 3.0 times that of non-irradiated patients (Yusuf et al., 2011). In young patients undergoing mediastinal irradiation, myocardial ischemia and coronary artery disease is very prevalent. A meta-analysis of eight randomised trials found a 62% increase in cardiac deaths among women who were treated with radiation therapy. In a review of stereotactic ablative radiotherapy of lung tumours, different grades of toxicity were reported: there is less than 1% risk of treatment-related mortality, and 9% risk of high toxicity due to treatment (Senthi et al., 2013).

(112) In the REQUITE study as of October 2018, follow-up CTCAE v4.0 toxicity data are available for about 1700 breast (82% of recruited patients) and 1430 prostate (79%) at 24 months and for 330 lung cancer patients (59%) at 12 months. For breast, common toxicity frequencies with grade ≥2 at 2 years were ~5–13%, for prostate below 5% for GI toxicities, ~3–8% for GU toxicities and ~20–31% for sexual problems. Common lung toxicity rates at one year were ~4–7% and dyspnoea rates at 27% (Seibold et al., 2019).

(113) A more precise evaluation of the grade distribution of tissue over reactions after radiotherapy in patients of the COPERNIC cohort has been shown to present a semi-gaussian (normal) shape with subsets of CTCAE grade 0, 1, 2, 3, 4 and 5 representing from about 65, 17, 10, 5, 2.5 and 0.5% RT-treated patients, (with a relative error of about 20% each), respectively (Granzotto et al., 2016, Sonzogni et al., 2024). If one excludes CTCAE grades 0 and 1, the percentage of patients with significant tissue reactions after radiotherapy (grades 2 to 5) would reach 18% of treated patients (Le Reun et al., 2022).

2.2.2. Acceptability of severe tissue effects

(114) The objective of radiation protection is to limit the risks of late effects to an acceptable level (ICRP, 1966) and more specifically to manage and control exposures to IR so that deterministic effects [tissue reactions] are prevented (ICRP, 2007). More recently, optimisation is recommended to aid keeping doses below the nominal threshold that is supposed to keep the incidence of tissue effects below 1% of exposed individuals (ICRP, 2012). The incidence of most late reactions increases and hence the threshold of dose decreases with increasing time after irradiation; currently thresholds are estimated to be 0.5 Gy for cardiovascular, cerebrovascular diseases and cataract, though the evidence base appears incomplete (ICRP, 2012). However, doses to non-target organs are not in general routinely monitored and collated with a view to avoidance of exceeding the 0.5 Gy threshold.

(115) The goal of radiation therapy is to treat the patient, i.e., to cure the cancer by delivering a tumouicidal dose to the tumour. This intent is compromised by the organs at risk (OAR) within the applied radiation field which can be impacted by radiation therapy doses. Current protocols have resulted progressively from empirical evaluation (SF_2 and parameters of the linear-quadratic or multitarget equations) in tissue specific standardised protocols. In most cases, all patients receive standardised treatment protocols, irrespective their individual intrinsic radiosensitivty, which is not assessed. Toxicities can be reduced by improving the precision of dose delivery to spare functional organ substructures (Barazzuol et al., 2020) and by medications and adoption of good behavioural habits (Anderson et al., 2021). Numerous patients have tissue reactions which alter their quality of life to a varying degree. The patients' perception of their treatment and side effects, i.e., their quality of life, is usually worse than their physicians' perception, which may lead to a loss of trust (Dilhuydy and Hoarau, 2002;

Nuijens et al., 2022). Thus, the true frequency of tissue reactions after radiotherapy may be greater than usually estimated and this is intrinsically related to the issue of the individual response to IR.

(116) Furthermore, many of these patients are lost to follow-up in studies for two major reasons: (i) the side effects/complications can occur much more than 10 years after the radiation therapy, and (ii) the better survival of cancer patients. These patients may seek multiple medical consultations in order to find someone who will be able to relieve their symptoms.

(117) In the context of individual response to IR after radiation therapy, it is those patients who present severe tissue effects although there was no error in the dose delivered and in the way it was delivered that are of most concern. It has been proposed that those individuals have some personal characteristics which have influenced the poor outcome. If it were possible to predict patient intrinsic radiosensitivity prior to therapy, clinicians may be able to personnalise protocols to reduce the occurrence of severe tissue effects while maintaining tumour cure rates. Britel et al., (2015) noted the interest of radiotherapists in personalised medicine and the use of predictive tests of tissue reactions, while highlighting certain limitations and concerns in relation to organisational, legal and ethical issues.

2.2.3. Evidence for variation in response of normal tissues to radiation

(118) This section considers the early and late tissue reactions associated with targeted therapeutic exposure to IR. It is important to remember that ‘early’ and ‘late’ are operational terms and an absolute definition is not possible. *Publication 118* defined early effects as occurring ‘within ~90 days after onset of radiotherapy’. Sometimes they are defined as occurring during/within 90 days of the end of treatment or within 6 months of the start of treatment. Early effects (α/β >6 Gy) occur in tissues with a rapid turnover (e.g., oral mucosa, intestinal mucosa, epidermis) due to the loss of post-mitotic functional cells. Examples of early reactions are mucositis, diarrhoea, erythema. ICRP 118 defined late effects as occurring ‘later than ~90 days after the onset of radiotherapy’. The pathogenesis is tissue dependent and involves damage to parenchyma, endothelium and stroma. Examples are xerostomia (dry mouth), telangiectasia and fibrosis (Barnett et al., 2009)). Manifestation of damage is tissue dependent, e.g., fibrosis can lead to rectal and urethra obstructions following pelvic irradiation, shortness of breath (dyspnoea) following thoracic irradiation or inability to open the mouth fully (trismus) following head and neck irradiation.

(119) Late toxicity (α/β ratio <5 Gy) is dose-limiting and radiotherapy schedules developed (larger fractions increase risk) so that ~5% of patients suffer long-term side-effects. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) reviews recommend dose constraints used in radiotherapy planning, e.g., 5% of patients are likely to have systematic pneumonitis after a mean lung dose of 7 Gy rising to 40% at 27 Gy (https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/QUANTEC). Dose constraints have been revised as new cohorts are analysed, e.g., a 2019 systematic review recommended a mean anal canal dose of <40 Gy to reduce risk of rectal incontinence following pelvic irradiation (Jadon et al., 2019).

(120) Tissue reactions are generally continuums graded using CTCAE or RTOG scales, which can be objective (assessed by healthcare professionals) or subjective (patient reported). Items are graded by radiation therapists for each organ on the basis of clinical signs (and laboratory values) on a spectrum from 0 (no effect) to 4 (life threatening) and even 5 (death related to the adverse effects) (NHI-NCI, 2017). The spectrum of tissue reactions can be presented for example as the proportion of patients suffering with grade ≥ 2 (moderate) or grade ≥ 3 (severe) toxicity. In general, it is the late tissue effects that are of interest because they are dose-limiting. To illustrate prevalence, the UK Conventional versus hypofractionated

high-dose intensity-modulated radiotherapy for prostate cancer (CHHiP) trial (n = 3,216) reported estimated cumulative 5-year prevalences of grade ≥ 2 bowel and bladder toxicities of 13.7% and 9.1% (74 Gy group), 11.9% and 11.7% (60 Gy), and 11.3% and 6.6% (57 Gy), respectively Dearnaley et al., 2016). A trial of >4,000 breast cancer patients reported up to a third of women having grade ≥ 2 pain in the arm and shoulder over 5 years (Hopwood et al., 2010).

(121) The spectrum of variation can be illustrated by the distribution of standardised total average toxicity (STAT) scores (Barnett et al., 2012). STAT scores were proposed as a scale- and grade-independent measure of radiotherapy toxicity to enable comparisons and pooling of studies. Histograms of STAT scores show a distribution of tissue reactions with no indication of a defined proportion of 'at risk' individuals. Another approach proposed for summarising adverse tissue effects involves consolidating into three risk domains: short-term (acute) Toxicity (T), Adverse long-term (late) effects (A), and Mortality risk (M) generated by a treatment programme (E = End results) (Trotti et al., 2007). There is no consensus approach.

(122) Abnormal responses are seen in individuals with homozygous mutations in genes involved in response to IR-induced DNA damage. Severe acute reactions to RT have been described in patients with ataxia telangiectasia (AT), even when the disease remained undetected prior to RT (Asadollahi et al., 2020), Nijmegen breakage syndrome (Hasbaoui et al., 2020) and Fanconi anemia (Birkeland et al., 2011). These diseases are very rare, the prevalence of AT, for example, being approximately 1:40,000 to 1:100,000 live births. Besides those severe acute reactions observed in identified cases of genetically determined radiosensitivity, a patient may express a radiosensitivity which can force the radiotherapist to modify, stop or prohibit the correctly delivered treatment. New pathologies linked to radiosensitivity are being observed by irradiating cells from such more sensitive patients *in vitro*. These patients carry mutations both homozygous and heterozygous in genes involved in molecular response to IR-induced DNA damage or in degenerative diseases: 27 syndromes have been already identified in 2016 (Foray et al., 2016). A significant correlation between pATMmax, SF2 and CTCAE grades has been pointed out (Granzotto et al., 2016; Le Reun et al., 2022) but this correlation is clearly independent of the early/late nature of the tissue reactions.

2.2.4. Modification by lifestyle and environmental factors such as smoking status, alcohol consumption, chemotherapy treatment, dietary factors/BMI

(123) Studies on the impact of tobacco smoking on the liklihood of radiotherapy toxicities have been summarised in the AGIR report (AGIR, 2013). These are shown in Table 2.1. A PubMed query focusing on radiotherapy toxicity and smoking, restricted to randomised trials, revealed no satisfactory results. A systematic review on the impact of continued smoking on the outcome of radiotherapy in head and neck cancer patients was published by Smith et al. (2019), and a systematic review on risk factors, that includes smoking, related to dermatitis in breast cancer was published by Xie et al. (2021). A recent, non-systematic review of the impact of smoking on the outcomes of radiotherapy for all cancers was published by Perdyan and Jassem (2022). There is clear evidence that smoking increases clinical radiosensitivity in most cancers. For head and neck cancers smoking potentiates the liklihood of late but not early toxicities. For dermatitis following breast cancer radiotherapy, the impact of smoking is seen in studies from some but not all geographical regions and depends on study design and toxicity scale used. The mechanisms of the potentiating effect of smoking on radiotherapy toxicities are not clear. Smith et al. (2019) pointed out that in most studies the information regarding smoking behavior before, during and after treatment is missing. Hence, it is difficult to ascertain whether the toxicities are attributed to the effects of smoking on radiotherapy, past

burden of smoking or the cumulative effects of smoking after treatment. Smoking is associated with poor locoregional tumour control, an observation that is explained by decreased tumour oxygenation due to respiratory insufficiency and increased carboxyhemoglobin levels (Perdyan and Jassem, 2022). However, these mechanisms could also be expected to result in lower levels of normal tissue toxicities, which is not the case. An alternative explanation may be that the increased clinical radiosensitivity in smokers is related to their often lower socioeconomic status (Hitchman et al., 2014) and lower level of healthiness (Pechey and Monsivais, 2016). However, this hypothesis has not been tested.

(124) An interesting observation is the frequently reduced level of pneumonitis in smokers treated for lung cancer. This is evident from Table 2.1. A problem is that most lung cancer patients smoke, making comparisons with much less numerous groups of non-smokers difficult (Perdyan and Jassem, 2022). Nevertheless, the reduced level of pneumonitis in smokers has also emerged from a meta-analysis carried out by Vogelius and Bentzen (2011). The authors suggest that it may result from a lower inflammatory radiation response in smokers as compared to non-smokers.

(125) Assessing the impact of alcohol consumption on radiotherapy-related toxicities is difficult because alcohol-containing beverages are highly variable with respect to both alcohol concentration and other components. Alcohol is a scavenger of hydroxyl radicals (Miller and Raleigh, 1983) but when consumed, it is metabolised in the liver and this process is associated with increased free radical production and decreased antioxidant defence (Donohue and Thomes, 2014). The consumption of alcohol corelates with cigarette smoking (Friedman et al., 1991) making it difficult to attribute the effect of one factor on radiotherapy-induced toxicities. Moreover, the prevalence of moderate and high levels of drinking is common among cancer survivors, so finding appropriate control groups for comparison studies may be a challenge (Shi et al., 2023).

(126) Alcohol consumption is associated with a significantly enhanced liklihood of osteoradionecrosis in oral and oropharyngeal cancer patients (Owosho et al., 2017) that can be explained by inducing inflammation of a sore mouth or throat. It has also been correlated with the prevalence of oral candidiasis during radiotherapy treatment (Epstein and Freilich, 1993) that can be explained by its weakening effect on the immune system. Interestingly, a study on radiotherapy-induced toxicities in breast cancer patients found a reduced incidence of skin toxicities in patients who reported regular wine consumption prior to starting treatment (Morganti et al., 2009). It is not clear whether the effect is attributed to alcohol or other wine components such as the antioxidant resveratrol (Singh et al., 2015). Indeed, Greenrod et al. (2005) found that intake of de-alcoholised red wine, but not alcohol, is protective against in vitro radiation-induced cytogenetic damage in peripheral blood lymphocytes.

(127) Combined treatment of cancer by radiotherapy (RT) and cytotoxic chemotherapy, termed chemoradiotherapy (CRT), is commonly used to treat malignancies such as cancer of breast, gastrointestinal tract, head and neck, cervix and endometrium, lung, genitourinary cancers as well as glioblastoma and sarcoma (Rallis et al., 2021). Most commonly used chemotherapy drugs are alkylating agents such as platinum compounds, antimetabolites such as 5-fluorouracil, plant alkaloids such as etoposide and antitumor antibiotics such as doxorubicin. Similarly to RT alone, the development of CRT is empirically driven and the mechanisms explaining the combined actions of cytotoxic agents and radiation both on cancer and normal cells are not fully understood (Brunner, 2016). The first model explaining the possible modes of interaction between RT and chemotherapy was proposed by Steel and Peckham (Steel and Peckham, 1979). It assumed four modes of action: spatial cooperation, toxicity independence, protection of normal tissues and enhancement of tumour response. Interesting from the perspective of the present publication is the idea of a protective effect of cytostatic drugs on normal tissue. This concept, based on the promising results of Millar et al.

(1978) was later discarded. A further weakness of Steel´s model was that it was based on results from cell experiments, assuming that the mechanisms of interaction between radiation and chemotherapy drugs can be explained by studying cytotoxic effects of combined exposure in cellular model systems. Indeed, many chemotherapy drugs interact with radiation at the subcellular level, either by potentiating the level of critical DNA lesions and/or by inhibiting DNA repair (UNSCEAR, 2000). Nevertheless, the reaction of tissues to radiation is the outcome of complex mechanisms that cannot be reduced to cytotoxic effects in parenchymal cells. In 2007, Bentzen et al. (2007) updated the Steel and Peckham model to include spatial cooperation (related to the impact of different treatment modalities on distinct disease locations), cytotoxic enhancement (related to potentiated killing effect of radiation thanks to enhanced DNA damage and inhibited DNA damage repair), biological cooperation (related to inactivation of cancer cells by modulating various mechanisms and targeting distinct cell populations), temporary modulation (related to interactions between molecular targeted therapies and radiotherapy) and normal tissue protection (related to the interaction of radiotherapy with radioprotective drugs such as amifostine, and not with regular chemotherapy drugs). Cytotoxic enhancement and biological cooperation represent mechanisms that potentially apply to the combined effect of RT and chemotherapy on normal tissue.

Table 2.1. Effect of smoking (current/long-term) and alcohol consumption on radiotherapy toxicity

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Smoking							
Defraene et al, 2011	Prostate	512	Rectal bleeding	Bleeding requiring laser treatment or transfusion	No association		0.16 (MVA)
Jenkins & Welsh, 2011	Lung	146	CT scan changes	SWOG	↓ toxicity	Not specified	0.02 (UVA) 0.15 (MVA)
Barnett et al, 2011b	Breast	1503	Overall toxicity (STAT)	START LENT-SOMA EORTC BR23	↑ toxicity	Coef 0.21* [0.12–0.30]	<0.0005 (MVA)
Chen et al, 2011	Oropharynx / oral cavity	202	≥ Gr 3 late toxicity	RTOG /EORTC	↑ toxicity	49% in active smokers *vs* 31% in former smokers	0.01
Barnett et al, 2011c	Breast	1014	Pigmentation	LENT-SOMA	↑ toxicity	MVA OR 2.06 [1.22, 3.49]	0.007 (MVA)
Wedlake et al, 2010	Pelvis	193	Acute and at 1 year	Modified Bowel Disease Questionnaire-Bowel subset	↑ toxicity	Current smokers had lowest presenting mean IBDQ-B score (63.7), suffered a fall during treatment (–12.0) and failed to recover at 1 year (4.3-point difference between baseline and 1 year)	Not specified
Roeder et al, 2010	Lung	242	Pneumonitis	Symptoms and radiographic finding	No association		
Dehing-Oberije et al, 2009	Lung	438	Dyspnea	CTCAEv3.0	↓ toxicity	OR 0.64 [0.39–1.04]	0.07 (MVA)
Purkey et al, 2009	H&N	52	Aspiration pneumonia	Clinical diagnosis	↑ toxicity	OR 1.04 per pack-year [1.01 to 1.07]	0.011 (MVA)
Zevallos et al, 2009	H&N	86	ORN	Hospitalisation	↑ toxicity	RR 1.46 [1.05–2.02] hospitalisation RR 1.32 [1.09–1.6] ORN	0.04 (UVA) 0.03 (UVA)
Jin et al, 2009	Lung	576	≥Gr 3 1 yr pneumonitis	CTCAEv3.0	↓ toxicity	37% non-smokers *vs* 23% former smoker *vs* 14% smokers	0.001 (UVA)
Huscher et al, 2009	Gynae	806	Acute toxicity Late toxicity	Need for surgery	No association		
Lilla et al, 2007	Breast	416	Telangiectasia	RTOG/EORTC and LENT/SOMA	↑ toxicity	OR 2.3 [1.2–4.6]	0.004 (MVA)

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Table 2.1. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Smoking							
Iraha et al, 2007	Gynae	1349	Enterocolitis	Enterocolitis requiring surgery	↑ toxicity	RR 4.05 [1.58–6.51]	<0.001 (UVA) 0.002 (MVA)
Merrick et al, 2007	Prostate	161	Late rectal function	R-FAS Rectal function assessment score)	↑ toxicity	Spearman's Rho = 0.18	0.02 (UVA)
Koper et al, 2004	Prostate	199	Rectal bleeding	Questionnaires	No association		
Tsujino et al, 2003	Lung	71	Pneumonitis	CTCAEv2.0	No association		
Hernando et al, 2001	Lung	201	Pneumonitis	CTC	↓ toxicity	OR 0.42	0.05 (UVA) 0.05 (MVA)
Eifel et al, 2002	Cervix	3489	Any late	Major late complications	↑ toxicity	HR 2.30 [1.84–2.87]	<0.0005
van der Voet et al, 1998	Glottis	383	Any late	Own scale	↑ toxicity	28% in smokers *vs* 15% in ex-smokers; 16% in non-smokers;	0.0014(UVA) 0.0038 (MVA)
Johansson *et al*, 1998	Breast / Oesophagus	606	Pneumonitis	X-ray changes combined with clinical symptoms	↓ toxicity	5/6 breast and 8/8 oesophageal patients with RP were non-smokers	0.18 (UVA breast) 0.02 (UVA oesophagus)
Monson *et al*, 1998	Lung	83	Pneumonitis	Acute or sub-acute dyspnoea with no other aetiology	↑ toxicity	23% in smokers *vs* 0% in non-smokers	<0.01 (UVA)
Kucera et al, 1987	Cervix	1304	Severe late	Not specified	↑ toxicity	Serious and irreversible effects 28% in smokers and 15.2% in non-smokers	<0.01 (UVA)
Alcohol							
Lilla et al, 2007	Breast	416	Telangiectasia / fibrosis	RTOG/EORTC and LENT/SOMA	No association	OR 1.41 [0.76–2.64]	ns (MVA)
Morganti et al, 2009	Breast	348	Acute skin	RTOG	↓ in patients with regular wine intake	OR 0.49 [0.28–0.86] (MVA)	0.013 (MVA)
Owosho et al, 2017	Head and neck	1023	Osteoradionecrosis	Glanzmann and Graetz grading system	↑ toxicity	OR: 3.22 [1.47 – 7.07] (MVA)	ns (MVA)
Rades et al., 2023	Head and neck	96	Acute in the oral cavity and fibrosis	RTOG/CTCAE v5.0	No association		$p = 0.025$

MVA, multivariate analysis; UVA, univariate analysis; SWOG, Southwest Oncology Group; LENT-SOMA, Late Effects Normal Tissue/Subjective Objective Management Analytic; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events.

(128) A summary of selected, mainly randomised, studies on the impact of chemotherapy on RT-induced normal tissue toxicities is given in Table 2.2. Information from publication years 1997–2011 was extracted from the AGIR 2003 report (AGIR, 2013). Later studies were identified via a PubMed query that focused on randomised trials. Despite variability with respect to tumour location and the applied chemotherapy drugs, the results clearly show that chemotherapy potentiates the incidence and severity of both early and late side effects. The result is consistent throughout the publication years 1997–2022 demonstrating its general validity, being independent of potential changes in treatment techniques during a period of 25 years.

(129) Chemotherapy can be applied in a neoadjuvant (preceding), concurrent or adjuvant (following) setting to radiotherapy. Very often, concurrent CRT is applied in an adjuvant setting to surgery. An interesting question is whether the sequencing of RT and chemotherapy has an impact on the potentiating effect of chemotherapy on normal tissue toxicities. An exclusively potentiating effect of chemotherapy on RT-induced toxicities in the concurrent setting would suggest cytotoxic enhancement as the main mode of action. A different result would point towards biological cooperation. Several studies looked into this, focusing on the curative outcome, but also reporting side effects that are relevant for this publication.

(130) Back et al. (2004) compared the impact of concurrent or sequential chemotherapy on RT-induced early toxicities in breast cancer patients and found no difference between the settings. Collette et al. (2008) analysed the risk of fibrosis 10 years after RT for breast cancer and observed that it was potentiated by both concurrent and adjuvant chemotherapy although the effect was stronger for concurrent treatment.

(131) Curran et al. (2011) compared concurrent and sequential CRT in non-small cell lung cancer patients and found higher rates of acute grade 3–5 nonhematologic toxic effects with concurrent than sequential therapy, but late toxic effects were similar. Lu et al. (2017) did not observe any difference in early and late toxicities induced by chemotherapy given concurrently or as neoadjuvant treatment to RT of breast cancer. Several studies compared the effect of RT and chemotherapy sequence when given separately. Recht et al. (1996) analysed breast cancer patients and found a higher incidence of fever and neutropenia requiring hospitalisation in the RT prior to chemotherapy group as compared to the chemotherapy prior to RT group. No other toxicities were observed, so further comparison was not possible. Hardenbergh et al. (1999) found that sequencing of chemotherapy and RT had no significant effect on the liklihood of cardiac toxicity, cellulitis, arm oedema or brachial plexopathy. Hickey et al. (2013) carried out a metanalysis of studies on breast cancer patients and found that neutropenic sepsis was worse with RT prior to chemotherapy but late toxicity: pneumonitis, cosmesis and cellulitis in lymphoedema, did not differ between RT prior to chemotherapy versus chemotherapy prior to RT.

(132) The results summarised above suggest that the potentiating effect of chemotherapy on RT-induced normal tissue toxicities is rather the outcome of biological cooperation than of cytotoxic enhancement. This conclusion fits well with the findings that the immune system plays an important role in modulating the liklihood of side effects to RT.

Table 2.2. Summary of studies on the effect of chemotherapy on radiotherapy-related normal tissue toxicity

Source	Cancer	n	Drug	Toxicity	Toxicity system	Finding: trend	Effect size (CL)	*p*
Tseng et al., 1997	Cervix	122	Cisplatin, vincristine, bleomycin	Any late	GOG	Non-significant increase	23% CRT vs 13% RT	0.13 (UVA)
Morris et al., 1999	Cervix	403	5-FU, cisplatin	Gr 3/4 late	RTOG / EORTC	No association	12% vs 11% RT	
Whitney et al., 1999	Cervix	368	5-FU	Gr 3/4 late	GOG	No association	16.2% vs 16.5%	
Green et al., 2001	Cervix	>2000	Mainly cisplatin	Acute leucopaenia	RTOG	↑ toxicity	lOR 2.21 [1.72–2.93]	<0.0001 (UVA)
				Acute thrombocytopaenia		↑ toxicity	OR 3.73 [1.53–9.10]	0.004 (UVA)
				Acute GU		↓ acute	0.43 [0.20–0.92]	0.03 (UVA)
				Acute GI		↑ toxicity	2.22 [1.58–3.11]	<0.0001(UVA)
Hernando et al., 2001	Lung	201	Not specified	Pneumonitis	CTC	No association		
Denis et al., 2003	HNC	226	5-FU, carboplatin	≥Gr3 mucositis	RTOG / CTCAE	↑ toxicity with CRT	71% vs 39%	0.005 (UVA)
				Late toxicity	RTOG, CTCAE and LENT/SOMA	↑ late toxicity with CRT	82% vs 47% ≥grade 3	0.02 (UVA)
Bernier et al., 2004	HNC	234	Cisplatin	≥Gr3 acute	CTCAEv2.0	↑ toxicity	41% vs 21%	0.001 (UVA)
				≥Gr3 late	RTOG/EORTC	No association		
Cooper et al., 2004	HNC	459	Cisplatin	≥Gr3 acute	CTCAEv2.0	↑ toxicity with CRT	77%vs 34%	<0.001 (UVA)
				Late toxicity	RTOG/EORTC	No association	21%vs 17%	0.29 (UVA)
Bosset et al., 2006	Rectum	1011	5-FU, leucovorin	≥Gr 2 acute	WHO	↑ toxicity	38% vs 17%	<0.001 (UVA)
				Late toxicity		No association		
Gerard et al., 2006	Rectum	733	5-FU	≥Gr3acute	WHO	↑ toxicity	14.6% vs 2.7%	<0.0001 (UVA)
				Late toxicity	WHO	No association		

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Table 2.2. (*continued*).

Source	Cancer	n	Drug	Toxicity	Toxicity system	Finding: trend	Effect size (CL)	*p*
Metzger et al., 2006	Lymphoma	461	Polytherapy	Hypothyroidism	Biochemical measurement	No association	HR 1.0 [0.7–1.6]	0.93 (UVA)
Bhandare et al., 2007	HNC	325	Cisplatin	Ototoxicity, Hearing loss	Review of records from otolaryngology and audiology departments	↑ acute otitis externa	41.8% of patients exhibited some ototoxicity: 33.2% had external ear complications, 28.6% had middle	0.045 (MVA)
						↑ chronic otitis externa	ear toxicity, 26.8% had inner ear toxicity	0.039 (MVA)
						↑ tympanic perforation		<0.01 (MVA)
						↑ labyrinthitis		<0.01 (MVA)
						↑ sensorineural hearing loss		0.028 (UVA)
Ryan et al., 2007	Multiple sites	656	Not specified	Patient-reported skin problems	Nationwide Symptom Inventory	No association		0.2 (UVA)
Braendengen et al., 2008	Rectum	207	5-FU, leucovorin	≥Gr 3 acute toxicity	WHO	↑ toxicity with CRT	29% vs 6% for RT alone	0.001 (UVA)
				Late toxicity		No association		
Collette et al., 2008	Breast	5178	Not specified	Fibrosis	None, minimal, moderate, severe	↑ with concurrent chemo	HR 2.40 [99% CI 1.48, 3.91] boost arm, HR 2.52 [99% CI 1.38–4.62] no boost arm	<0.0001 (MVA)
Kuoppala et al., 2008	Endometrium	156	Cisplatin, cyclophosphamide, epirubicine	Late GI	Need for surgery	↑ with concurrent chemotherapy	9.5% for CRT vs 2.7% for RT alone	Not specified
Palazzi et al., 2008	HNC	149	Cisplatin, 5_FU, taxol	Acute dysphagia	CTCAEv3.0	↑ with concurrent chemotherapy	Not specified	0.002 (MVA)
				Acute mucositis				0.004 (MVA)
				Acute weight loss				
				Acute salivary changes				

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Table 2.2 (*continued*).

Source	Cancer	n	Drug	Toxicity	Toxicity system	Finding: trend	Effect size (CL)	*p*
Vale et al., 2008	Cervix	>2000	Cisplatin, 5-FU, MMC	Acute GI	5 point scale in all trials included in the meta-analysis	↑ toxicity for trials using platinum-based CRT	Available data suggest 1% to 3% experienced serious late toxicity	0.00002 (UVA)
Dehing-Oberije et al., 2010	Lung	469	Cisplatin, carboplatin, etoposide	Acute dysphagia	CTCAEv3.0	↑ toxicity	OR 2.54 [1.64–3.91]	<0.001 (MVA)
Barnett et al., 2012	Breast	1503	Not specified	STAT	START trial	↑ toxicity in patients treated with sequential chemo then RT	0.13* [0.046–0.21] MVA	0.0008 (UVA)
					EORTC BR23			0.002 (MVA)
					LENT-SOMA			
Curran et al., 2011	Lung	610	Cisplatin vncristine	Acute oesophagitis	Not specified	↑ toxicity with concurrent vs. sequential chemotherapy	Acute oesophagitis ≥gr3 occurred in 4, 22 and 45% for sequential vin/cis, concurrent vin/cis, and concurrent etop/cis (arms 1, 2 & 3)	
				Late oesophagitis			Acute lung toxicity 14,13 and 17% for arms 1, 2 and 3	
				Acute lung toxicity		↑ ≥gr3 acute lung toxicity with sequential chemotherapy	Late oesophagitis 1–4%	
				Late lung toxicity		No significant difference in late oesophagitis or lung toxicity	Late lung toxicity 13–17%	
Allegra et al., 2015	Rectum	1608	Oxaliplatin	Diarrhea	Not specified	↑ grade 3–4 diarrhea	not calculated	<0.0001
Lee et al., 2017	HNC	352	Cisplatin, 5-FU	Late	RTOG	No difference for late effects (10 years)		
de Boer et al., 2018	Endometrium	686	Cisplatin and taxol	Acute and late	CTCAE V3	↑ acute reaction	incidence 60% vs 12%	<0.0001
						↑ late reaction (neuropathy)	incidence 8% vs 1 %	<0.0001

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Table 2.2. (*continued*).

Source	Cancer	n	Drug	Toxicity	Toxicity system	Finding: trend	Effect size (CL)	*p*
Shrivastava et al., 2018	Cervix	850	Cisplatin	Acute and late	Not specified	↑ grade 3 and 4 leukopenia ↑ grade 3 and 4 gastrointestinal effects ↑ Rectosigmoid adverse effects	6.8& vs 4.5%	
Gillison et al., 2019	HNC	849	Cetuximab vs cisplatin	Acute and late	CTCAE V4	↑ early effects in cisplatin arm No association for late effects	T-score 3.19 cisplatin vs 2.39 cetuximab	<0.0001
Mehanna et al., 2019	HNC	334	Cetuximab vs cisplatin	Acute and late	CTCAE v4 (acute) EORTC QLQ-H&N35 (late)	No association for acute or late		
Ji et al., 2021	HNC	298	S-1	Acute and late	Not specified	No association ↑ leukopenia	9.5% vs 2.7%	<0.01
Guo et al., 2022	Cervix	Meta-analysis	Mainly cisplatin and 5-FU	Variable	Variable	↑ haematological 3–4 toxicity ↑ non-haematological 3–4 toxicity	OR 7.7 OR 2.6	<0.0001 <0.0001
Jin et al., 2022	Rectum	599	5-FU	Acute	NCI-CTCAE	↑ acute 3–5 toxicity in TNT (25 Gy/5f and CT after) vs CRT (50Gy/25f and concurrent CT)	26.5% vs 12.6%	<0.001

HNC, Head and Neck Cancer.

(133) Studies on the impact of body mass index (BMI) and diet on the liklihood of radiotherapy toxicities have been summarised in the AGIR report (AGIR, 2013). They are shown in Table 2.3 together with studies published between 2013 and 2020 that were identified via a PubMed query focusing on radiotherapy toxicity, BMI and diet, restricted to randomised trials.

(134) BMI correlates strongly with breast volume. In breast cancer patients, a large breast volume is often associated with increased skin toxicity. This is explained by increased dose heterogeneity and auto-bolusing effects at the inframammary fold (Das et al., 1997). In line with this, Ho et al. (2018) observed no impact of BMI on skin in postmastectomy women treated by radiotherapy.

(135) In cancers other than breast, a low BMI is sometimes associated with increased toxicities. This may be related to the fact that wound healing is impaired in underweight patients. Nutrient deficiency was shown to be associated with longer inflammatory phase, decreased fibroblast proliferation and altered collagen synthesis (Stechmiller, 2010), likely leading to poor recovery from radiation-related tissue damage. The observation that healthy diet containing such ingredients as fiber and fish oil is associated with lower treatment-related toxicities (Chitapanarux et al., 2020) may be explained by improved nutrition status and less underweight of the patients.

Table 2.3 Effect of body mass index (BMI) and dietary intervention on radiotherapy toxicity.

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
BMI							
Cordoba et al., 2021	Breast	122	Acute skin	RTOG	↑ toxicity with ↑ BMI and ↑ breast size	OR for obesity = 2.9, OR for medium-large breast = 4.1–5.5	<p0.02
Ho et al., 2018	Breast, postmastectomy	124	Acute skin	CTCAE	No association with BMI		
Lee at al., 2018	Cervix	245	Late gastrointestinal	RTOG	↑ toxicity with ↓ BMI	Grade >2 toxicities: <18.% = 13.9; 18.5–24.9 = 4.0%; >24.9 = 4.2%.	0.002
Hoopfer et al., 2015	Breast	248	Acute skin	CSSP	↑ toxicity with ↑ BMI and ↑ breast volume	1.3, 1.8, 2.6 for breast cup size B, C, D, respectively	<0.02
Kiser et al., 2011	Cervix	404	Gr 3/4 enteritis Gr 3/4 fistula GI obstruction Lymphoedema	CTCAEv4.0	↑ toxicity with ↓ BMI: ↓ toxicity for >24.9 *vs* <18.5 *vs* >24.9 kg/m^2	13.6% *vs* 16.7 8.8% *vs* 11.1%, 4.4% *vs* 33.3% 1.2% *vs* 5.6%	0.03 0.05 <0.001 0.02
Barnett et al., 2011c	Breast	1014	Acute and late	RTOG (acute) START trial scale (late) Photo assessment of breast shrinkage	↑ toxicity with ↑ BMI and ↑ breast volume	MVA Shrinkage OR per 1litre ↑ in volume = 1.98, [1.41–2.78;), Telangiectasia OR = 3.94 [2.49, 6.24] Oedema OR = 3.65 [2.54, 5.24] Pigmentation OR = 1.75 [1.21, 2.51]	MVA shrinkage, telangiectasia, oedema $p < 0.0005$ Pigmentation $p = 0.003$
Wedlake et al., 2010	Pelvis	193	Acute & 1 year	Modified Bowel Disease Questionnaire-Bowel subset	↓ acute toxicity with ↑ BMI	BMI < 18.5 (n = 6) had worst toxicity during treatment	
Patil et al., 2009	Prostate	407	Acute toxicity	RTOG	No association		
Lilla et al., 2007	Breast	416	Telangiectasia / fibrosis	RTOG/EORTC and LENT/SOMA	No association	OR 1.41 [0.76–2.64]	ns (MVA)
Werner et al., 1991	Breast	282	Arm oedema prevalence at 5 yr	Difference of ≥ 2.5 cm in arm circumference between ipsilateral and contralateral arms	↑ toxicity with ↑ BMI	12.5% for BMI ≤27.2 27.4% for BMI >27.2	$p = 0.002$ (UVA) $p < 0.0005$ (MVA)

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Table 2.3. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Diet							
Wedlake et al., 2017	Pelvis	166	Acute and late gastrointestinal toxicity	Bowel Disease Questionnaire–Bowel Subset score	↓ toxicity with ↑ fiber in diet	8.5 score difference between baseline and high fiber intake	0.004
Sasidharan et al., 2019	Cervix	100	Acute proctitis and diarrhoea	CTCAEv3.0/RTOG	No association between oral resistant starch and proctitis		
Chitapanarux et al., 2020	H&N, esophagus, and cervix	88	hematologic toxicities	CTCAEv4.03	↓ toxicity in patients with arginine, glutamine, and fish oil supplementation	OR: 6.1 (1.2–30.6)	0.03
Ravasco et al., 2005	Colorectal	111	Acute toxicity QoL	EORTC/RTOG and EORTC QoL questionnaire v3.0	↓ toxicity ↑ QoL with diet counselling or protein supplements	Not stated	<0.05 (UVA) 0.02UVA)

2.2.5. Modifications by the immune system

(136) Clinical investigations on the role of the immune system and its modulation in radiotherapy focus on the therapeutic efficacy of combining radiotherapy with the currently approved checkpoint inhibitors CTLA-4 and PD-1/PD-L1 (Jagodinsky et al., 2020). Both inhibitors counteract the strategy of tumour cells to inhibit the activity of cytotoxic T-lymphocytes. They thus boost the cellular adaptive immune response which could potentially lead to augmented auto-aggression (Rosenblum et al., 2015) and increased normal tissue reactions. Boosting the adaptive immune response may lead to unbalanced immune response and, in consequence, induce inflammation-related toxic side effects in normal tissues (Wirsdörfer et al., 2018). However, the results of limited studies on combining radiotherapy and checkpoint inhibitors to mainly treat melanomas do not demonstrate an increased level of toxicity (Barker et al., 2013; Postow et al., 2020). Yet, it is too early to draw firm conclusions on the impact of immunotherapy on the liklihood of radiotherapy-related normal tissue toxicity in view of the low number of studies and patients involved.

(137) As discussed in section 2.1, an important element of normal tissue complications induced by radiotherapy is inflammation. Inflammation is a response of the innate immune system, triggered by pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs). DAMPs include intra- and intercellular DNA fragments that are released by dying cells. These act as ligands to Toll-like receptors (TLRs) which form a family of transmembrane or intracellular receptors belonging to the superfamily of pattern recognition receptors (PPRs). Activation of TLRs leads to modified expression of genes that orchestrate inflammatory responses (Fitzgerald and Kagan, 2020). Specifically, activation of TLRs can lead to release of cell communication signalling peptides (cytokines) that inhibit apoptosis and promote cell proliferation (Liu et al., 2018). In experimental setups it has been demonstrated that the activation of some, but not all, TLRs by agonists or by microorganisms can increase survival of irradiated cells in culture and laboratory animals as well as reduce tissue pathologies (reviewed in (Wirsdörfer and Jendrossek, 2017; Liu et al., 2018). The list of TLR agonists includes flagellin, lipopolysaccharide (Lacave-Lapalun et al., 2014) and fibroblast–stimulating lipopeptide (FSL–1) (Kurkjian et al., 2017) and they can act both as radioprotectors (given before exposure) and radiomitigators (given after exposure). However, no clinical studies have been carried out to date where the modulating effect of TLR agonists on normal tissue toxicity in patients receiving radiotherapy was tested. Thus, a direct demonstration of the impact of TLR activation on modulation of radiotherapy toxicities is pending.

(138) Genes encoding proteins belonging to the major histocompatibility complex (MHC) are the most polymorphic genes known in humans and some variants are associated with a high susceptibility to complex diseases (Matzaraki et al., 2017). It could be assumed that an association exists between MHC haplotypes (the set of alleles) and the liklihood of radiotherapy-induced toxicity. However, very few studies exist where this was tested. Gallegos et al. (2014) have shown that HLA-G1 confers higher radiosensitivity to HLA-G1 expressing tumoral cell lines. Also, the blood group is known to be associated with an enhanced liklihood of some complex diseases, such as cancer and cardiovascular disorders (Liumbruno and Franchini, 2013). Surprisingly, no reports exist where an association was analysed between the blood group and the liklihood of developing normal tissue side effects to radiotherapy. Two studies report an association between a high level of ex-vivo radiation-induced cytogenetic damage in peripheral blood lymphocytes and blood groups A and O (Elahimanesh et al., 2013) as well as the rhesus factor plus (Rh+) (Khosravifarsani et al., 2016). The analyses were carried out with samples from healthy people, so it is not known if the results correlate with a high risk

of developing radiotherapy-induced normal tissue toxicities. Moreover, both studies come from the same group of researchers and require independent validation.

2.2.5.1. Impact of the microbiome

(139) The microbiome collectively describes the microorganisms that colonise the human body including the gut, skin and other mucosal environments. It is now clear that the gut microbiome configuration influences the performance of the immune system not only located in the mucosa associated lymphatic tissue but also in other organs and tissues of the body. Results from experiments with laboratory animals demonstrate that a bidirectional relationship exists between microbiome perturbation and immune dysregulation (Zheng et al., 2020a). Thus, it is reasonable to assume that the composition of the microbiome, influenced by radiotherapy and the diet may have an impact on the immune system and on the inflammatory response and liklihood of normal tissue complications. The role of the gut microbiome in radiosensitivity is a new concept with potential impact on radiotherapy-associated toxicity. Consequently, few original clinical studies have been published up to date that report convincing results (Liu et al., 2021).

(140) Manichanh et al. (2008) published the first clinical study where the faecal bacteria composition was correlated with the liklihood of diarrhoea in 10 patients undergoing pelvic radiotherapy. They observed that patients who developed diarrhoea had a different bacterial composition at the end of radiotherapy than those who did not. Mitra et al (Mitra et al., 2020) correlated changes in the gut microbiome and gastrointestinal toxicity in 35 patients undergoing chemoradiotherapy for cervical cancer. Gut microbiome diversity continuously decreased over the course of therapy and patients with high toxicity demonstrated different compositional changes from those with low toxicity. A similar result was reported by Wang et al (Wang et al., 2015) for diarrhoea in 20 patients receiving pelvic radiotherapy. Patients who developed diarrhoea showed a significantly lower faecal microbial diversity than non-symptomatic patients. A larger study (Reis Ferreira et al., 2019) compared the microbiome composition in faeces of 134 patients with and without early and late enteropathy after pelvic radiotherapy. They observed that a low bacterial diversity associates with radiation enteropathy. Moreover, enteropathy showed a depletion of rectal mucosa cytokines regulating gut microbiota and homeostasis, correlating with higher counts of specific bacterial species. Five studies with laboratory mice confirm the clinical studies in that radiation to the animal abdomen induces significant changes in the gut microbiome (reviewed in (Liu et al., 2021)). The somewhat preliminary clinical results, mainly carried out on small patient groups, along with the animal studies, suggest that gut microbial dysbiosis prior to, or occurring during radiation therapy, may be causally related to and exploited to predict the lilkihood of radiotherapy side effects.

(141) Oral microbial composition also appears to have an impact on the progression and aggravation of radiotherapy-induced mucositis in patients treated for head and neck carcinomas. (Zhu et al., 2017) studied radiotherapy-related changes in the mucosa of 41 patients with nasopharyngeal carcinoma undergoing radiotherapy. The results showed that the microbial diversity decreased during radiotherapy and changes in the microbial community correlated with the progression and aggravation of radiotherapy-induced mucositis. The authors claim that microbiota-based strategies can be used for the early prediction of the incidence of severe mucositis during radiotherapy. Similar results were achieved by Hou et al. (2018) based on analysis of 19 patients treated by radiotherapy for nasopharyngeal carcinoma.

(142) An interesting question is whether the development of mucositis can be prevented or reduced by administration of probiotics. Here, the results are scarce and not consistent. A randomised study on 99 patients (Jiang et al., 2019) showed that administration of a probiotic

combination of *Bifidobacterium longum*, *Lactobacillus lactis* and *Enterococcus faecium* reduced the severity of mucositis through modification of gut biota. Similar results were reported by Sharma et al. (2012) who tested the efficacy of *Lactobacillus brevis* to reduce mucositis in a randomised study on 200 head and neck cancer patients. In contrast, no impact of *Lactobacillus brevis* on reducing the severity of mucositis was observed by de Sanctis et al. (2019) in a randomised study with 75 head and neck cancer patients undergoing radiotherapy.

(143) An emerging intervention to restore gut microbial composition in order to cure a specific disorder is faecal microbiota transfer, which is the infusion of healthy donor faeces in the recipient's gut. The concept is new and has recently been demonstrated to improve tyrosine-kinase inhibitor-dependent diarrhoea in patients with renal cell carcinoma (Ianiro et al., 2020). Very few studies exist where faecal microbiota transfer was tested as a method to restore microbial composition and mitigate radiation-related injury. Using laboratory mice (Cui et al., 2017) demonstrated that faecal microbiota transfer resulted in better survival of irradiated animals, improved gastrointestinal tract function and intestinal epithelial integrity. Similarly promising results were reported by Guo et al (Guo et al., 2020) who observed restored haematopoiesis and gastrointestinal recovery in mice exposed to a single high radiation dose that were kept in cages contaminated with faeces of old mice that in earlier experiments expressed a radioresistant phenotype. With respect to clinical studies, only two could be identified: one case report on successful treatment of chronic haemorrhagic radiation proctitis (Zheng et al., 2020b) and one pilot study with five patients treated for radiotherapy-related enteritis (Ding et al., 2020). Although highly preliminary, these reports not only suggest a potential safe treatment of radiotherapy-related injuries but further confirm the role of the microbiome in normal tissue toxicity.

2.2.6. Modification by age[1]

(144) The United Nations Convention on the Rights of the Child[2] states in the preamble that "the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth". Implicit in this statement is the assumption that the child, defined as a human being below the age of 18, is particularly vulnerable. With respect to radiological protection, the term "vulnerable" translates into "sensitive to radiation effects", and is considered further in relation to emergencies and post-accident in *Publication 146* (ICRP, 2020). The text below focuses on the question whether children are at a higher risk than adults of developing tissue reactions following radiation exposure.

(145) Tissue reactions are the consequence of inflammatory responses and cell killing induced by radiation exposure. Cell killing results in tissue damage that triggers tissue healing processes. It is known that wound healing and tissue regenerative capacity declines with age (Gosain and DiPietro, 2004). Evidence in relation to changing DNA repair capacity with age has been reviewed (Gorbunova et al., 2007). Hence, it could be assumed that children are more radioresistant than adults with respect to deterministic effects. On the other hand, adults are characterised by a lower level of organisational and maturational processes, and have a shorter life expectancy, so healing processes may be associated with lower probability of complications. It appears that some factors inherent to childhood are responsible for a high radiosensitivity and other for a low radiosensitivity, as compared to adults. A summary of the

[1] The text of Section 2.2.4 is reprinted (with some modifications by the author) with permission from the proceedings of the EU Scientific Seminar 2020 "Radiosensitivity of children" – Health issues after radiation exposure at young age, RP 196.

[2] https://www.unicef.org/child-rights-convention

factors is given in Fig. 2.1 and more details on sensitivities of selected organs and tissues in paediatric cancer patients for developing late effects are given in Table 2.4.

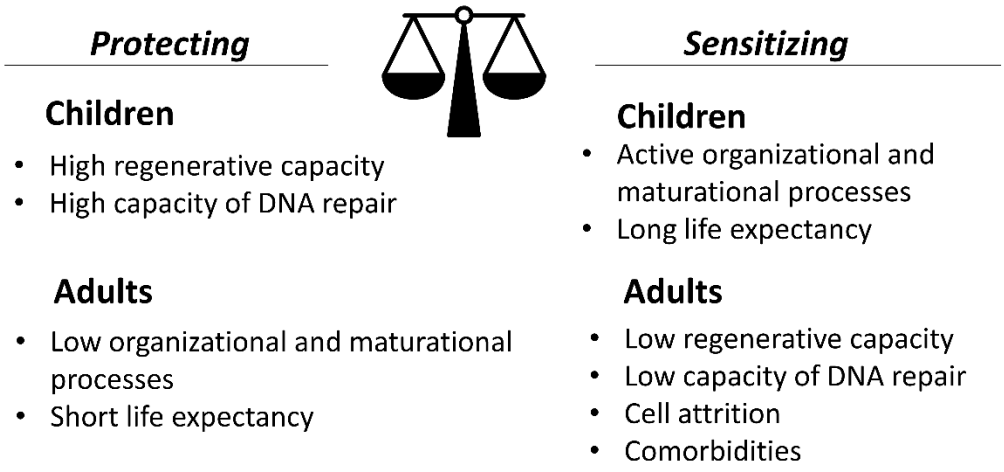

Fig. 2.1. Factors responsible for protecting against and sensitising towards deterministic effects of radiation of children and adults.

(146) Tissue reactions are subdivided into early and late effects. In connection with the acute radiation syndrome, early effects are described as the prodromal phase and late effects as the acute phase (Bertho et al., 2004). Late effects occur after a latency period which is proportional to the dose but also to the type of effect. In radiotherapy, as discussed above, early effects are broadly defined as those occurring within 90 days following starting therapy. All effects occurring thereafter are defined as late (Dörr, 2015).

2.2.6.1. Acute effects – lethality after whole body exposure.

(147) The acute radiation syndromes can have lethal consequences and the dose that leads to 50% lethality is termed LD_{50}. The LD_{50} can be used as a measure of radiation tolerance, with a low value indicating high sensitivity and high value – high resistance. The impact of age on LD_{50} in humans cannot be measured in a controlled, experimental setup, so estimates must be inferred from animal experiments. In the aftermath of atomic bomb explosions in Hiroshima and Nagasaki and the following onset of the atomic age, many animal experiments were carried out to determine factors influencing the individual response to radiation (Wojcik and Harms-Ringdahl, 2019; Zander et al., 2019).

(148) With respect to age at exposure as a risk modifier, the results have been recently summarised (Stricklin et al., 2020). It appears in mice that the radiosensitivity during childhood is higher than during adulthood, but lower than in the elderly. The pattern is shown in Fig. 2.2, based on results of experiments on mice (Crosfill et al., 1959; Spalding et al., 1965). A simple mechanistic explanation of this pattern does not exist, but it can be assumed to result from changing balance of factors shown in Fig. 2.1.

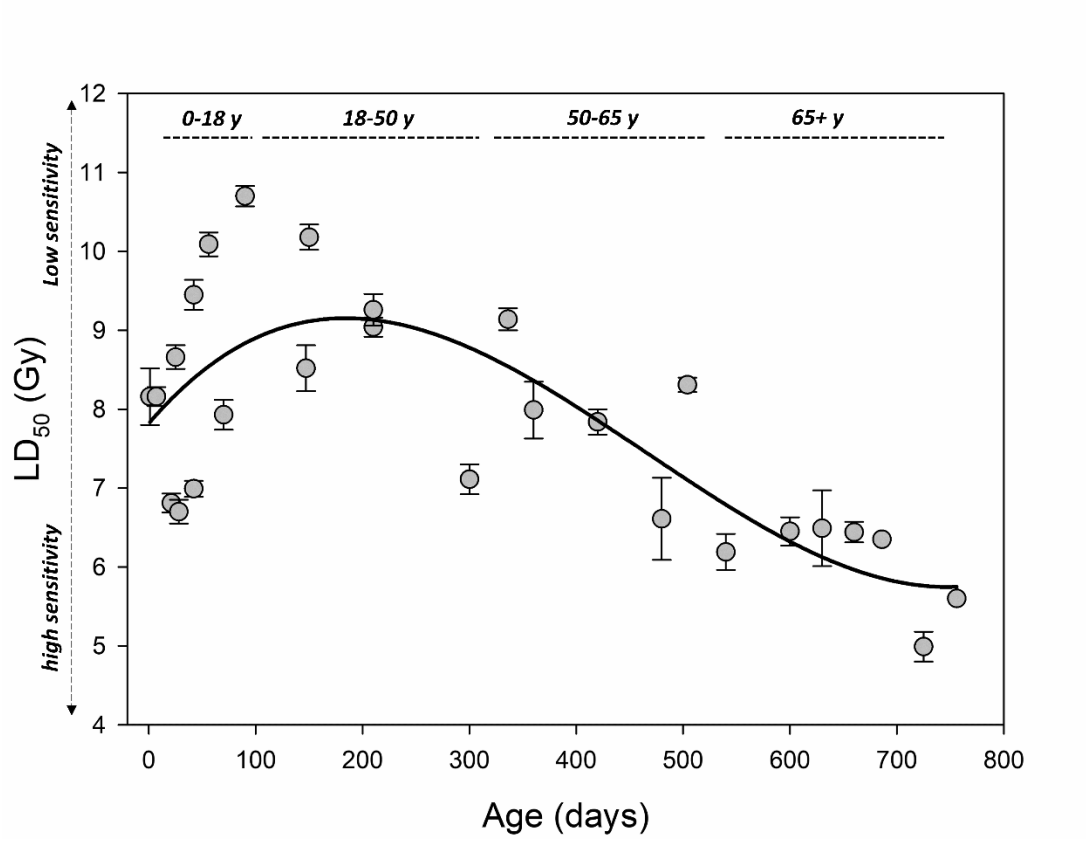

Fig. 2.2. LD_{50} in mice exposed to an acute dose of gamma radiation at different ages. A high LD_{50} is indicative of high resistance. Pooled results from Crosfill et al. (1959) and Spalding et al (1965). Results of Spalding were multiplied by 1.5 to align with results of Crosfill. Error bars represent standard errors. Numbers below the top margin indicate the respective human age in years (based on Stricklin et al., 2020). Solid line shows the fit according to the equation $LD = y+a \cdot d+b \cdot d^2+c \cdot d^3$, where y, a, b and c are fit coefficients and d is the age in days.

2.2.6.2. Early and delayed effects after medical radiation exposure.

(149) A wealth of data exists on the liklihood of developing deterministic effects in organs and tissues of adult patients receiving high local radiation doses during the course of radiotherapy (UNSCEAR, 2013). These data allow defining total doses and doses per fraction that particular organs can tolerate without developing severe late effects. Respective results are scarce for children, this being due to low number of patients and also the long time for late effects to manifest, making data acquisition and interpretation challenging, especially since no standardised protocols exist. Younger children have a higher risk for late effects than older children so observations must be stratified into age groups, further reducing the already poor statistical power of the data. Also, late effects that are assessed today result from radiotherapies carried out in times when three-dimensional treatment planning systems were not available. Consequently, significant uncertainties exist regarding doses absorbed by normal tissues where late effects occurred. Determination of tolerance for children and young people doses is therefore difficult.

(150) It is estimated that 75–100% of children undergoing radiotherapy will develop some measurable late effects (Krasin et al., 2010; Constine et al., 2019). The age at treatment has a particularly strong modifying effect on the risk of developing neurocognitive effects and

muscle and bone growth disturbances. The corresponding risk for adults is below 50%, irrespective of age at exposure (Krasin et al., 2010).

(151) An interesting question is whether all organs in paediatric patients are at a higher risk of developing late effects as compared to adults. UNSCEAR (2013) undertook the effort to summarise available information on the relative sensitivity of organs and tissues of paediatric cancer patients. The results for selected organs are shown in Table 2.4.

Table 2.4. Sensitivities relative to adults of selected organs and tissues in paediatric cancer patients of developing late effects. Grey tone marks strong level of evidence, as assessed by UNSCEAR. Source: UNSCEAR (2013).

	Sensitivity vs adult			
Organ	Less	Same	More	Effect
Bladder			X	Reduction in capacity
Bone marrow	X			Less available marrow when older
Brain			X	Neurocognitive reduction
Breast hypoplasia			X	Most severe during puberty
Cataracts			X	
Cerebrovascular			X	Stroke
Heart			X	Growth prevention, valvular abnormalities
Immune			?	
Kidney		X		
Lung	X			Capacity decreases if chest wall growth is inhibited
Musculoskeletal			X	Hypoplasia, deformity, osteochondroma
Neuroendocrine		X		Reduction in hormone secretion
Ovaries	X			
Testes			X	Sperm and hormone reduction
Thyroid autoimmune			?	
Thyroid hypofunction		X		
Thyroid nodules			X	
Uterus			X	Uterine vasculature impaired

(152) Strong evidence exists showing a high radiosensitivity of paediatric bladder, brain, heart, musculoskeletal tissue, testes and the thyroid with respect to nodule development. This effect can be explained by active maturational and organisational processes in the organs. Interestingly, no difference in radiosensitivity is evident for effects in the kidney, neuroendocrine tissue and for thyroid function. Bone marrow, ovaries and lung show an inversed age-at-exposure effect, with children being more resistant than adults. There is solid evidence for a high radioresistance of bone marrow and this could be explained by a high regenerative capacity of immune competent cells which do not form a solid tissue where organisational processes could be impaired. The evidence for high radioresistance of ovaries is weak. Metzger et al. (2013) reported that a higher dose is required for prepubertal as compared to pubertal gonadal irradiation to induce treatment-associated female reproductive and sexual dysfunction. However, no mechanistic explanation was given. In the UNSCEAR report (UNSCEAR, 2013), high radioresistance of the lung was explained by the high radioresistance of the lung by the fact that children have fewer pre-existing diseases, fewer co-morbid

conditions and better repair capability than adults. The same argument is given by Krasin et al. (2010), who at the same time points out that a pure comparison of doses that induce pulmonary effects may be misleading, because the effects and treatment-indicating disease conditions in children and adults may not be comparable. The effects among children include radiation fibrosis and alterations in pulmonary function while those in adults include radiation pneumonitis. The presence of cancer in the lung itself is uncommon among children and common among adults. Finally, diagnostic certainty of lung injury's relation to radiotherapy is high among children and moderate and at times very unclear among adults due to comorbid conditions. More generally, treatment of paediatric cancer is often different than that of adults because of the frequently aggressive nature of childhood malignancies (Constine et al., 2019). Thus, conclusions about the relative radiosensitivity of organs and tissues in children and adults based on reactions to radiotherapy are associated with large uncertainties.

(153) In conclusion, the general perception that children are more sensitive to radiation than adults is only partly true. For early tissue reactions children are more sensitive than people of advanced age, but less sensitive than middle-aged adults. The reason for this is complex and involves an interplay of various sensitising and protecting factors, the balance of which changes with age at exposure. For late tissue reactions children are more sensitive than adults, but not for all organs and tissues. The reason for this is not understood and significant uncertainties exist regarding dosimetry, quantification of effects and the possible impact of intrinsic radiosensitivity related to genetic status.

2.2.7. Modification by sex

(154) Studies published until 2011 looking at the role of sex in susceptibility to radiotherapy-induced toxicity were summarised by Borgmann et al. (2009) and in the AGIR report (AGIR, 2013). They are shown in Table 2.5 together with studies published between 2013 and 2020 that were identified via a PubMed query focusing on radiotherapy toxicity and sex, restricted to randomised trials. The study by Schuster et al. (2022) is not randomised, but was included in the Table because it is the most recent one and contains a number of analyses important for interpreting the results of earlier studies.

(155) Overall, the findings on the impact of sex on radiotherapy toxicity are mixed, with a tendency towards females showing a higher sensitivity. A number of studies investigated if cytogenetic damage and DNA repair kinetics in peripheral blood lymphocytes (PBL) from females and males differ following in vitro radiation exposure (Borgmann et al., 2009). No systematic difference could be observed. A more recent study on radiation-induced clonogenic cell survival of fibroblasts isolated from males and females showed a significantly lower SF2 value (cell survival following a dose of 2 Gy) for female fibroblasts, with large overlap between results from both sexes (Alsbeih et al., 2016). Roberts et al. (1997) noted a higher level of inter-donor variability in the level of radiation-induced cytogenetic damage of female PBL which they attributed to the action of the sex hormone progesterone. Ricoul et al. (1998) showed that the addition of progesterone to culture medium sensitises PBL to radiation-induced chromosomal aberrations and that the chromosome radiosensitivity of PBL increased during pregnancy, correlating with the level of progesterone. Krol et al. (2007) showed no difference in cytogenetic radiosensitivity of PBL collected from females at the beginning and end of the menstrual cycle when the ratio of progesterone to estrogen changed. This result suggests that the impact of variation in the physiological level of female sex hormones on radiosensitivity of PBL may not be strong. Schuster et al. (2022) observed no difference in the in vitro sensitivity of PBL collected from female and male cancer patients and healthy donors, that were analysed for cytogenetic damage and gammaH2AX focus formation.

(156) Cancer is most often treated by a combination of radiotherapy and chemotherapy, so sex specific differences related solely to radiotherapy-induced toxicities are hard to extract from clinical studies. Borgmann et al. (2009) suggested that the somewhat higher levels of toxicities observed in females may be due to differences in pharmacokinetics resulting from lower average body mass of females, higher body fat fraction, smaller plasma volume and lower average organ blood flow. A similar conclusion was reached by Schuster et al. (2022) who, in addition, noted that, if the total deposited energy from radiotherapy is calculated in relation to body weight, then 17% more energy per mass is deposited in females.

(157) In conclusion, the observation of somewhat higher level of radiochemotherapy-induced toxicities in females as compared to males appears more likely to result from differences in pharmacokinetics of chemotherapy drugs, hormone status and differences in radiation energy deposition rather than differences in intrinsic radiosensitivity.

Table 2.5. Studies comparing radiotherapy toxicity in males and females.

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Schuster et al., 2022	Rectum	710	Diarhea; nausea, appetite loss	EORTC	↑ in females	>10%	Not calculated
Diefenhardt et al., 2020	Rectum	1016	Acute haematological and diarhea	CTC	↑ in females	Not given	0.04 fo leukopenia <0.01 for diarhea
Kordzinska Cisek et al., 2019	Salivary gland	204	Early mucosa and late skin reactions	RTOG	↑ in males	Not given	0.008 for intensity of toxicity
Yock et al., 2016	Brain	59	Ototoxicity	Pediatric Oncology Group	No difference with a trend towards ↑ in females		0.08
Palassini et al., 2015	Soft tissue	321	Acute haematological and wound healing	CTC	↑ in females	OR 2.5 (95% CI, 1.4–4.6)	0.02
Wolf et al., 2013	Rectum	799	Acute haematological and organ toxicity	CTC	↑ in females	Not given	<0.001
Ris et al., 2013	Brain	110	Intellectual and academic outcomes	Pediatric Oncology Group	No difference		
Miguel et al., 2011	STS of extremities	60	Any early and late	RTOG	No difference		
Ramaekers et al., 2011	HNC	396	Xerostomia	EuroQol-5D converted to RTOG score	↑ in males	Regression coefficient 0.052; SE 0.019	0.006 (MVA)
Siala et al., 2011	Nasoph	239	Hypothyroidism	Biochemical measurement	↑ in females		
Wolff et al., 2011	Rectum	196	Acute Haematological	CTCAEv3.0/LENT	↑ in females with low BMI ↑ in females	Not given	0.001 0.04
Dehing-Oberije et al., 2010	Lung	469	Acute dysphagia	CTCAEv3.0	↑ in females	OR 1.65 [1.12–2.43]	0.011 (MVA)
Roeder et al., 2010	Lung	242	Pneumonitis	Symptoms & radiography	No difference		
Palazzi et al., 2008	HNC	149	Pain	CTCAEv3.0	↑ in females	Not given	0.02
Bhandare et al., 2007	HNC	325	Ototoxicity	Otolaryngology & audiology records	No difference		0.80 (UVA) 0.90 (MVA)
Kong et al., 2006	Lung	109	Fibrosis	RTOG / SWOG / CTCAE	↑ in females	UVA HR 4.91 [1.8–13.7]	0.0024 (UVA) ns (MVA)

(*continued on next page*)

Table 2.5. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Metzger et al., 2006	Lymphoma	461	Hypothyroidism	Biochemical measurement	↑ in females	UVA HR 1.6 [1.2–2.1] MVA HR 1.4 [1.5–4.3]	0.002 (UVA) 0.03 (MVA)
Pieters et al., 2006	Various*	53	Neurologic	Retrospective LENT	↑ in males	Not given	0.017 (MVA)
Tsujino et al., 2003	Lung	71	Pneumonitis	CTCv2	No difference		
Hernando et al., 2001	Lung	201	Pneumonitis	CTC	No difference		
Robnett et al., 2000	Lung	144	Pneumonitis	Modified RTOG	↑ in females	MVA OR 5.1	0.01 (MVA)
van der Voet et al., 1998	Glottis	383	Any late	Own scale	No difference		
Ho et al., 1999	Nasoph	294	Hearing loss	Pure tone audiogram	No difference		
Kwong et al., 1996	HNC	132	Hearing loss	Pure tone, impedance audiograms	↑ in males	Not given	0.013 (UVA) 0.018 (MVA)
Denham et al., 1995	Various	110	Erythema	Reflectance spectrophotometry	↑ in females		0.03 (UVA)
Mak et al., 1994	Rectum and rectosigmoid	224	Small bowel obstruction	Clinical diagnosis	No difference		

2.2.8. Modification by concurrent non-malignant systemic disease

(158) The relationship between systemic diseases, such as diabetes mellitus, collagen vascular disease, hypertension, inflammatory bowel disease and radiotherapy toxicity has been reviewed by Chon and Loeffler (Chon and Loeffler, 2002) and in the AGIR report (AGIR, 2013). A more recent review focusing on post-operative breast irradiation that covers diabetes was published by Batenburg et al. (2022) and a review on the impact of pro-inflammatory comorbidities was published by Lin et al. (2019). Publications summarised in the AGIR report and some more recent studies are given in Table 2.6.

(159) It is now understood that late toxicities induced by radiotherapy, such as fibrosis, are related to processes involved in wound healing (Bentzen, 2006). Thus, it can be expected that systemic diseases leading to impaired wound healing such as uncontrolled diabetes or autoimmune diseases (Avishai et al., 2017) are associated with an increased risk of toxicities.

(160) Chronic hyperglycemia leads to increased blood viscosity, poor blood circulation, hypertension and poor wound healing, microvascular occlusion, capillary hyalinisation, arteriolar obliteration, atherosclerosis and tissue hypoxia (Chon and Loeffler, 2002). As can be seen from Table 2.6 it is associated with an increased risk of toxicities, especially in the common cancers of breast and prostate. This conclusion is supported by the outcome of literature review analysis (Batenburg et al., 2022).

(161) Collagen vascular disease (CoVD) is a diverse group of systemic inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, systemic sclerosis (Butnor and Khoor, 2008). Chon and Loeffler (2002) carried out a systematic review and concluded that patients with CoVD have a significantly higher liklihood of radiotherapy-related toxicities, reaching 100% for some toxicities. The authors of a newer meta-analysis conclude that the risk of toxicities in CoVD patients is lower, being in the range 10–15% for grade 3 and <5% for grade 4 toxicities. Thus, CoVD is not an absolute contraindication to radiotherapy. In support of this, results of studies summarised in Table 2.6 indicate variable results.

(162) As can be seen from data summarised in Table 2.6, there is evidence to suggest that patients with cardiovascular disease, inflammatory bowel disease and hypertension are at a somewhat increased risk of toxicity after radiotherapy.

2170 Table 2.6. Effect of non-malignant systemic disease on radiotherapy toxicity

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Diabetesd							
Özkan et al., 2019	Gynae	129	Gastrointestinal and urinary toxicity	RTOG	↑ gastrointestinal and urinary toxicity		0.037
Alashkham et al., 2017	Postate	716	Proctitis	RTOG/EORTC	↑ toxicity	RR 2 for grade 3, RR 10 for grade 4	<0.001
Barnett et al., 2011b	Breast	1503	STAT	START LENT-SOMA EORTC BR23	↑ toxicity	0.17* [0.032–0.31]	0.016 (MVA)
Barnett et al., 2011c	Breast	1014	Breast shrinkage	Photographic assessment (START)	↑ toxicity	OR 2.08 [0.73–1.10]	0.0009 (UVA) 0.004 (MVA) 0.10 (MVA dichotomised endpoint)
Defraene et al., 2011	Prostate	512	Faecal incontinence	Incontinence of blood, mucus, or stools (requiring use of pads >2 times/wk)	↑ toxicity	D50 dose-modifying factor 0.61 [0.47–0.77] in LKB model	0.048 (MVA)
Barnett et al., 2011a	Prostate	788	Bladder and bowel	RTOG / LENT/SOMA/ RMH/ UCLA-PCI	No association		
Tucker et al., 2010	Prostate	1010	Grade ≥2 late rectal toxicity	RTOG	No association		0.91 (UVA)
Taira et al., 2009	Prostate	226	Erectile dysfunction	IIEF-6	↑ toxicity	HR 2.57 (UVA) HR 3.97 (MVA)	0.014 (UVA) 0.001 (MVA)
Valdagni et al., 2008	Prostate	1115	Acute lower GI toxicity	RTOG/EORTC and LENT/SOMA	↑ toxicity	OR 1.34	0.34 (MVA)
Lilla et al., 2007	Breast	416	Telangiectasia	RTOG/EORTC and LENT/SOMA	No association	OR 1.30 [0.61–2.76]	ns (MVA)
Mayahara et al., 2007	Prostate	287	Acute GI and GU	CTCAE v2.0	No association		
Iraha et al., 2007	Gynae	1349	Enterocolitis	Need for surgery	↑ toxicity	RR 9.02 [7.10–11.11]	<0.001 UVA <0.001 MVA
Merrick et al., 2007	Prostate	161	Late rectal function	R-FAS	↓ toxicity	Spearman's Rho = −0.17	0.03 (UVA)
Feigenberg et al., 2005	Prostate	1204	Late toxicity	Modified LEBT/SOMA	No association		
Koper et al., 2004	Prostate	199	Rectal bleeding	Questionnaires	No association		

2171 (*continued on next page*)

Table 2.6. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Diabetesd							
Akimoto et al., 2004	Prostate	52	Rectal bleeding	RTOG/EORTC	↑ toxicity	MVA RR = 2.88 [1.23–9.83]	<0.001 (UVA) <0.05 (MVA)
Jereczek-Fossa et al., 2003	Endometrium	317	Acute toxicity	RTOG / EORTC	No association		
Cozzarini et al., 2003	Prostate	154	Rectal bleeding	modified RTOG	No association		
Skwarchuk et al., 2000	Prostate	743	Gr 2/3 bleeding	RTOG / EORTC	↑ toxicity	1.8*	0.04 (MVA)
Mantz et al., 1999	Prostate	287	Erectile dysfunction	Physician reported	↑ toxicity	OR = 2.01	0.002 (MVA)
Herold et al., 1999	Prostate	944	Acute Gr 2 late GI Gr 2 late GU	RTOG RTOG/modified LENT RTOG	No association ↑ toxicity ↑ toxicity	28% *vs* 17% in non-diabetics 14% *vs* 6%,	ns 0.007 (MVA) 0.0014 (MVA)
Debus et al., 1997	Skull base	367	Brainstem	Modified RTOG scale consistent with LENT-SOMA	↑ toxicity	RR 5.7	0.04 (UVA) 0.01 (MVA)
Mak et al., 1994	Rectum / rectosigmoid	224	Small bowel obstruction	Clinical diagnosis	No association		
Kucera et al., 1987	Cervix	1304	Late	Not specified	No association		
Collagen Vascular Disease (CoVD)							
Riva et al., 2021	Various	1829	Any acute and late	CTCAEv5.0	↑ Gr 3 and higher acute toxicity no association for late toxicity	27.7 vs 2.6%	0.002
Lin et al., 2008	Various	73 cases vs matched controls	Any late toxicity	RTOG/EORTC	↑ toxicity	29% *vs* 14%	0.0010
Gold et al., 2007	Various	20	Acute & late toxicity in scleroderma patients	CTCAEv3.0	High toxicity		N/A

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Table 2.6. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Collagen Vascular Disease (CoVD)							
Pinn et al., 2008	Various	21	Acute & late toxicity in SLE patients	CTCAEv3.0	Moderate risk of toxicity	≥Gr 1 acute 42% ≥Gr 3 acute 21% ≥Gr1 late at 5 y 45% ≥Gr 1 late at 10 y 56% ≥gr 3 late at 5 y 28% ≥gr 3 late at 10 y 40%	N/A
Phan et al., 2003	Various	38 cases *vs* matched controls	Late	RTOG / EORTC	No association	Gr I 3% *vs* 7% Gr II 7% *vs* 3% Gr III 7% *vs* 7%	
Chen et al., 2001	Breast	36 scleroderma & 72 controls	Acute	RTOG / EORTC	No association	14% *vs* 8%	
			Late		↑ late toxicity in scleroderma patients	17% *vs* 3%	
Morris and Powell, 1997	Various	209	Acute & late	RTOG / EORTC	No effect for RA ↑ toxicity in non-RA disease	21% *vs* 6% late toxicity for non-RA CVD *vs* RA	0.002
Cardiovascular							
Defraene et al., 2011	Prostate	512	Rectal bleeding	Bleeding requiring laser treatment or transfusion	↑ toxicity	D50 dose-modifying factor (dmf) 0.92 [0.87–0.95] in LKB model	0.015 (MVA LKB model)
Barnett et al., 2011c	Breast	1014	Acute and late	START LENT-SOMA EORTC BR23	No association		0.067 (UVA overall toxicity)
Koper et al., 2004	Prostate	199	Rectal bleeding	Questionnaires	No association		
Mantz et al., 1999	Prostate	287	Erectile function	Physician reported	↑ toxicity	OR = 1.80	<0.001 (MVA)
Inflammatory Bowel Disease							
Riva et al., 2021	Various	1829	Any acute and late	CTCAEv5.0	↑ Gr 3 and higher acute toxicity no association for late toxicity	27.7 vs 2.6%	0.002

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Table 2.6. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Inflammatory Bowel Disease							
Barnett et al., 2011a	Prostate	788	Faecal urgency	UCLA-PCI	↑ faecal urgency	HR 3.59 [1.40–9.18]	0.008 (MVA)
Peters et al., 2006	Prostate	24	Late toxicity	CTCAE	Brachytherapy well tolerated	No Gr 3 or 4 rectal toxicity. 4 patients experienced Gr 2 late rectal toxicity	N/A
Song et al., 2001	Pelvic or abdominal tumours	24	Acute and late GI toxicity	RTOG / EORTC	Moderate prevalence of grade ≥3 toxicity	5 patients (21%) experienced ≥gr 3 acute toxicity; 2 patients (8%) had ≥Gr 3 late toxicity	N/A
Willett et al., 2000	Pelvic or abdominal tumours	28	Severe acute GI Severe late GI	Failure to complete planned course of RT Need for hospital or surgery	Moderate prevalence of severe toxicity	21% 29%	N/A
Green et al., 1999	Rectal	15	Acute and late toxicity	RTOG / EORTC	Moderate prevalence of severe toxicity	3 patients (20%) had Gr ≥3 acute toxicity, including 2 cases of Gr 3 skin toxicity and 1 case of Gr GI toxicity No long-term toxicity	N/A
Grann and Wallner, 1998	Prostate	6	Acute and late GI toxicity	Not specified	Brachytherapy well tolerated	No unusual toxicity	N/A
Hypertension							
Fodor et al., 2021	Breast	1325	late toxicities	LENT/SOMA	↑ toxicity only for fibrosis-atrophy-telangiectasia-pain	HR 2.17 [1.1–4.3)	0.025
Barnett et al., 2011a	Prostate	788	↓ urine stream	LENT/SOMA	↓ toxicity	HR 0.25 [0.09–0.71]	0.007 (MVA)
Tucker et al., 2010	Prostate	1010	Gr ≥2 rectal	RTOG	No association		0.77 (UVA)
Taira et al., 2009	Prostate	226	Erectile dysfunction	IIEF-6	↑ toxicity	HR 1.72 HR 2.06	0.047 (UVA) 0.011 (MVA)
Merrick et al., 2007	Prostate	161	Late rectal function	R-FAS	No association		
Jereczek-Fossa et al., 2003	Endometrium	317	Acute toxicity	RTOG / EORTC	No association		
Cozzarini et al., 2003	Prostate	154	Rectal bleeding	modified RTOG	No association		

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Table 2.6. (*continued*).

Reference	Cancer	n	Toxicity	Toxicity system	Finding	Effect size	*p*
Hypertension							
Eifel et al., 2002	Cervix	3,489	Bladder Small bowel	Major late complications	No association	HR 0.61 [0.33–1.10] HR 0.53 [0.28–0.99]	0.1 (MVA) 0.05 (MVA)
Mak et al., 1994	Rectum and rectosigmoid	224	Small bowel obstruction	Clinical diagnosis	No association		

2.2.9. Summary and conclusion on the range observed and main contributory modifying factors

(163) The relationships between lifestylefactors such as smoking status alcohol consumption, dietary factors/BMI and co-exposures such as chemotherapies and normal tissue sensitivity are complex, with dominating indications of either a potentiating or of no effect. If an effect is present, the point estimates of relative risk seldom exceed 2. The majority of evidence comes from studies on patients treated by radiotherapy. For smoking and alcohol consumption, there is little doubt that they potentiate the liklihood of toxicities when the oral cavity is included in the radiation field. This is explained by augmented inflammation processes. There are observations of increased clinical radiosensitivity of other tissues in smokers which may be related to their, often low, socioeconomic status. A high BMI is related to increased risk of toxicities of the breast tissue in breast cancer patients, being related to large breast size and the resulting dose inhomogeneity. For other tissues, increased sensitivity to radiation was sometimes reported in patients with low BMI, that is most probably related to undernourishment. For most organs, children show a significantly higher sensitivity than adults with respect to late effects, resulting probably from active organ maturation processes and long life expectancy. A higher level of radiotherapy-induced toxicities in women as compared to men have been reported, but they more likely result from differences in radiation energy deposition than from differences in intrinsic radiosensitivity. There is evidence to suggest that patients with such comorbidities as cardiovascular disease, inflammatory bowel disease and hypertension are at a somewhat increased risk of toxicity after radiotherapy. The underlying mechanisms are likely complex. A potentiating effect of chemotherapy on radiotherapy-induced normal tissue toxicities has been reported for some drugs. The mechanism is rather biological cooperation of the agents than cytotoxic enhancement of one by the other. This conclusion fits well with the lack of interaction of chemotherapy drugs and radiation in cell experiments and the findings that the immune system can modulate the liklihood of radiotherapy-induced toxicities. It should be noted that none of the environmental factors that may influence radiosensitivity in radiotherapy patients have been quantified in relation to the clinical CTCAE or RTOG scales.

2.2.10. Approaches to prediction – genetic and functional assays

(164) Regarding genetic factors, a significant correlation between pATMmax as part of the radiation induced ATM nucleo-shuttling (RIANS assay), SF2 and CTCAE grades has been demonstrated, thus allowing identification of patients with a significant risk of tissue effects after radiotherapy; this correlation is observed independently of age and sex (Granzotto et al., 2016; Le Reun et al., 2022). On the other hand, it seems that the radiation-induced lymphocyte apoptosis assay (RILA) may be useful in identifying patients at “low risk” of experiencing radiotherapy toxicity (Azria et al., 2024). Apart from the two assays, numerous studies have been carried out to find a correlation between toxicities and either 1) the in vitro sensitivity of their fibroblasts or lymphocytes or, 2) the SNP type. The SNP type can be analysed in a few selected genes, based on the hypothesis that the radiosensitivity phenotype is driven by a few known genes with high penetrance, or in a genome-wide association study (GWAS) approach assuming that many unknown genes of low penetrance drive the phenotype. The study design was mainly retrospective: patients who completed radiotherapy were asked for a normal tissue sample and their level of toxicity was correlated with the in vitro response or SNP type. The results have been largely inconsistent, and it is not clear how far valuable predictive tests can be established. A recent study on the level of early toxicities in patients treated by RT twice for metachronous, distally positioned tumours, showed a lack of correlation between toxicities

induced by both treatments (Caramenti et al., 2025; Gorbunova et al., 2025). This result suggests that a genetic component of radiation toxicities is low, providing an explanation for the inconsistent outcome of studies searching for a predictive test. For reviews on predictive testing see AGIR (2013), Rajaraman and coauthors (2018), Vinnikov and coauthors (2020), Kerns and coauthors (2023).

2.3. Late-developing non-cancer diseases following local or whole body irradiation

(165) Some tissue reactions, such as circulatory effects and cataracts, occur years or decades after radiation exposure. This section focuses on circulatory effects, cataracts and cognitive effects.

(166) ICRP, in its *Publication 14* (1969), described the case of death of US radiologists from cardiovascular disease. Then, ICRP, in its *Publication 41* (1984), described cardiovascular effects on the heart after fractionated radiotherapy doses of 40–60 Gy, concluding that the radiation sensitivity of heart is not high. Recognising emerging epidemiological evidence, mainly in Japanese atomic bomb survivors, ICRP, in its *Publication 118 (2012)*, first listed circulatory effects as a radiation health hazard, and recommended a nominal approximate threshold of 0.5 Gy (low-LET radiation) to the heart (for cardiovascular effects) and brain (for cerebrovascular effects) independent of dose rate and with a follow-up of >10 years after exposure, as a precaution to medical practitioner. ICRP has not yet recommended dose limits for circulatory effects.

(167) In 1950, ICRP first listed cataracts as a radiation health hazard. In 1954, ICRP first recommended occupational and public dose limits for the lens of the eye. In *Publication 118* (2012), ICRP recommended lowering threshold for vision impairing cataracts to 0.5 Gy (low-LET radiation) independent of dose rate and with a follow-up of >20 years after exposure, and also lowering occupational equivalent dose limit for the lens. Since *Publication 1* (ICRP, 1958) to date, ICRP has consistently considered that the lens, bone marrow and gonads were among the most radiosensitive tissues.

(168) ICRP has not listed cognitive impairment as a radiation health hazard, and thus has not recommended threshold and dose limits. There is some evidence in radiotherapy patients (high dose, fractionated exposures) and there is concern after high-LET exposure (astronauts in particular). Supporting information is also available from experimental animal studies. However it has been shown that such animal studies about cognitive impairment in space have involved doses and dose rates so high that they do not mimic usual space radiation and they would be lethal in humans (Krukowski et al., 2012; Restier-Verlet et al., 2021; Restier-Verlet and Foray, 2021). Much less is known about low-LET low dose or low dose rate exposure effects on cognitive impairment, considered further in Section 2.3.3.

2.3.1. Diseases of the circulatory system

2.3.1.1. Human epidemiological studies

(169) Exposure to high doses of ionising radiation, such as those experienced by patients treated for radiotherapy, has long been reported to cause damage to the heart and blood vessels, as well as elevated liklihood of various circulatory conditions in human epidemiological studies (Adams et al., 2003). More recently, mounting evidence indicates an association with diseases of the circulatory system at low levels of radiation exposure, including in patients exposed to diagnostic x-rays, for Japanese atomic bomb survivors and occupationally exposed workers (Little et al., 2023). Given the significant burden of human morbidity and mortality from

circulatory system diseases, understanding the nature of their risk following radiation exposure is of growing importance for radiological protection. More specifically, identification of potential subgroups with increased susceptibility to radiation-related cardiovascular effects could better inform protection of these groups. As with other health effects, such changes in susceptibility to circulatory diseases could be apparent on either the multiplicative or additive scale. Potential effect modifiers can be grouped into factors that are largely unchangeable (e.g., age, sex, medical comorbidities, genetics) and factors that could be more easily modified (e.g., therapeutics, obesity, exercise status, smoking, and alcohol).

(170) A recent review summarising the evidence on potential effect modifiers of radiation-related diseases of the circulatory system (DCS) indicates limited evidence for effect modification at the multiplicative scale with age at exposure, sex, and use of anthracyclines, albeit with different DCS endpoints (Little et al., 2024). Here, we briefly summarise the key studies examining risk of cardiovascular disease following radiation in various settings, and provide a detailed review of the evidence regarding potential effect modification, including assessment of potential interaction with underlying genetic variation. This section also outlines the remaining uncertainties regarding factors that may influence radiation-associated cardiovascular diseases.

(a) Overview of radiation and risk of diseases of the circulatory system

(171) The term “diseases of the circulatory system” encompasses a wide variety of specific cardiac diseases as well as vascular diseases. Specific cardiac diseases (per the 11th edition of the International Classification of Diseases, ICD-11) reported to be associated with radiation exposure include acute myocardial infarction (BA41); valvular heart disease (BC0Z); heart failure (BD1Z); cardiac arrhythmias (BC9Z); conduction disorders (BC63); acute pericarditis (BB20), coronary atherosclerosis (BA80), angina pectoris (BA40), secondary hypertension (BA04), and stroke (8B20).

(172) Most studies of circulatory system disease risk following medical exposure to ionising radiation have been conducted in populations exposed to high-dose therapeutic radiation for the treatment of cancers and other radiation-sensitive pathologies, with a smaller proportion of studies pertaining to medical imaging. Long-term studies of childhood and adult cancer survivors exposed to radiotherapy have generally indicated increased mortality and/or incidence with higher doses of radiation to critical structures for various cardiovascular late effects, including ischaemic heart disease (Armstrong et al., 2013a), angina pectoris (Aleman et al., 2007; Hooning et al., 2007), myocardial infarction (Aleman et al., 2007; Hooning et al., 2007; Boivin et al., 1992; Mulrooney et al., 2009), valvular disease (Armstrong et al., 2013a; Aleman et al., 2007; Hooning et al., 2007; Mulrooney et al., 2009; Cutter et al., 2015; Hull et al., 2003), pericardial disease (Mulrooney et al., 2009; Cosset et al., 1991), hypertension, stroke (Bowers e al., 2006; El-Fayech et al., 2017; Morris et al., 2009), arrhythmia (Morris et al., 2009; Mulrooney et al., 2020), coronary artery disease (Hull et al., 2003), and heart failure (Armstrong et al., 2013a; Aleman et al., 2007; Hooning et al., 2007; Boivin et al., 1992; Mulrooney et al., 2020; Mansouri et al., 2019; van der Pal et al., 2012; van Nimwegen et al., 2017). Results of studies of low to moderate dose therapeutic radiation following non-cancer conditions are more mixed – while some studies have observed increased risks of cardiovascular outcomes such as mortality from all diseases of the circulatory system, ischaemic heart disease, and stroke after treatment (Little et al., 2016), others have not (Little et al., 2016; Zablotska et al., 2014).

(173) In environmental or occupational settings, early indications of possible radiation-related effects on circulatory system disease at lower radiation doses came from the Life Span Study (LSS) of Japanese atomic bomb survivors, which reported possible excess relative risks

of radiation-related mortality and/or incidence from all heart disease, hypertension, stroke, valvular heart disease, hypertensive organ damage, and heart failure but showed no significant associations between radiation exposure and ischemic heart disease and myocardial infarction (Shimizu et al., 2010; Takahashi et al., 2017; Yamada et al., 2004). Elevated risk of radiation-related circulatory disease outcomes has also been reported for some, but not other endpoints/studies in occupationally exposed populations, including the International Nuclear Workers (INWORKS) study comprising over 300,000 nuclear workers reporting increased mortality risk from all diseases of the circulatory system combined; cerebrovascular disease; and ischaemic heart disease, particularly myocardial infarction (Gillies et al., 2017). Increased radiation-related risks have also been observed in chronically-exposed male and female Mayak nuclear workers for incidence (but not mortality) of all cerebrovascular disease combined (Azizova et al., 2023a) and for mortality (but not incidence) from ischemic stroke in resident men (Azizova et al., 2023b). Chronic environmental radiation exposure from the Techa river has been associated with increased mortality risks (of borderline statistical significance) from combined circulatory disease and ischemic heart disease (Krestinina et al., 2013).

(b) Assessing the potential for susceptible subgroups following radiation exposure

(174) The assessment of potential effect modifiers of radiation and cardiovascular disease risk is complicated by several considerations. For one, the term “diseases of the circulatory system” comprises a large variety of specific diseases and groupings, which likely have different specific underlying mechanisms of disease. Thus, generalisations for all circulatory disease can be misleading. On the other hand, the number of observations decreases with increasingly specific sub-groups of disease. More consequentially, the effect sizes (ERR/Gy) are quite small for diseases for the circulatory system compared to those for cancer, consequently reducing the power to detect potential effect modification on a multiplicative scale. Additionally, changes in classification of diseases over time and the variation in nomenclature used amongst studies, can make comparisons between studies conducted at different time periods challenging.

(175) With respect to radiation exposure, only a subset of studies of radiation exposure and cardiovascular disease have high-quality individual estimates of radiation dose. Of these, very few studies have a wide range of exposure doses – studies of cancer therapy typically pertain to higher doses, whereas doses in occupational and environmental studies tend to be much lower. The narrow range of some potential effect modifiers (such as age at exposure) within studies makes it more difficult both to assess the risk relationship within a study, and to compare results between studies with non-overlapping ranges. While studies of medical exposure tend to have subjects exposed at higher radiation doses and more extensive data on potential effect modifiers, cohort sizes are typically smaller. Environmentally and occupationally exposed cohorts, on the other hand, have larger cohort sizes, but lower radiation exposure doses.

(176) Despite these challenges, there is some indication of differing risk of cardiovascular disease between subgroups. The summary below is divided by intrinsic factors (such as age and sex), and extrinsic factors (such as smoking, alcohol use, and chemotherapy). The review focuses on those studies with individual estimates of radiation dose, although in settings where no studies with individual dose are available (e.g., for genetic studies), the existing limited evidence is described. For those studies that formally assessed interaction, all results with tests of interaction that reached statistical significance on the multiplicative scale ($p < 0.05$) are described. Where additive interaction is formally assessed, those estimates are included. To account for the power limitations described above, patterns of risk that are not statistically

significant (p between 0.05 and <0.2) are also noted for key studies. In those instances where there is clear indication of interaction on the additive scale, this has been described.

(c) Effect modification by intrinsic factors

Age at exposure

(177) While some studies of medical radiation exposure report increased liklihood of circulatory disease outcomes with earlier age at exposure, this has not been reported consistently across outcomes or different study settings. Breast cancer survivors treated at younger ages (age <45 yrs at breast cancer diagnosis) were reported to have higher radiation-related excess relative risk of myocardial infarction than those treated at later age (p = 0.054, borderline statistical significance) (Jacobse et al., 2019), and there appeared to be a non-statistically significant pattern of higher risk of radiation-related coronary heart disease with younger age of treatment in a Dutch Hodgkin lymphoma cohort (ERR/Gy $_{<27.5\text{years}}$, 20.0%; ERR/Gy$_{27.5–36.4\text{years}}$, 8.8%; ERR/Gy$_{36.5–50.9\text{years}}$, 4.2%; $P_{\text{interaction}}$ = 0.15) (van Nimwege et al., 2016). However, age at diagnosis did not appear to modify the effect of radiation on heart failure in a French study of childhood cancer survivors (age <20 yrs at cancer diagnosis; median age at cancer diagnosis 5 yrs; interquartile range (IQR) 2.4–9.8 yrs) (Mansouri et al., 2019) or a Dutch study of Hodgkin lymphoma survivors (treated before age 51 years; median age at treatment 28.3yrs; IQR 21.9–37.7 yrs) (van Nimwegen et al., 2017); incidence of cardiac disease (myocardial infarction, angina, heart failure, valvular diseases, cardiac arrhythmias and conduction disorders, and pericardial disease) in the Euro2K France/UK childhood cancer survivor study (<16 yrs age at cancer diagnosis) (Haddy et al., 2016); incidence of valvular heart disease in a multi-centre study of Hodgkin's lymphoma survivors (HL diagnosed at ages 15 to 41 years) (Cutter et al., 2015 ; Haddy et al., 2016), or major coronary event incidence in breast cancer survivors from Sweden and Denmark (aged 20–74 yrs at breast cancer diagnosis) (Darby et al., 2013). Similarly, no significant modification by age at first exposure was observed for overall radiation-related circulatory disease or ischaemic heart disease in a pooled study of 77,275 patients from Massachusetts and Canadian tuberculosis (TB) fluoroscopy cohorts (aged 0 to >60 years at first exposure) (Tran et al., 2017), or in a cohort of 3,719 persons treated for peptic ulcers (aged <35 to >55 years at first exposure) (Little et al., 2016).

(178) Initial mortality analyses of the atomic bomb survivor LSS data by Shimizu et al. using underlying cause of death suggested that younger age at exposure (<40 years at time of bombing) could be associated with higher risk of stroke, but the effect was not statistically significant (p = 0.23). No statistically significant effect modification by age at exposure was observed for heart disease mortality, ischaemic heart disease, or valvular heart disease (Shimizu et al., 2010; Little et al., 2012). Subsequent analyses of underlying cause of death data with an additional five years of follow up reported no statistically significant effect of age at exposure on mortality from overall heart disease, ischemic heart disease, or valvular heart disease (Takahashi et al., 2017). A re-analysis of LSS mortality data corresponding to the dataset of Shimizu et al. (2010) but using contributing as well as underlying causes of death, demonstrated a significant effect of age at exposure for all cardiovascular disease (p = 0.007), stroke (p = 0.007), and all other cardiovascular disease combined excluding stroke and heart disease (p < 0.001) (Little et al., 2012). While expanding the outcome may have increased the sensitivity of the outcome definition, it is likely to have resulted in decreased specificity, particularly given the greater misclassification observed for non-cancer outcomes in LSS participants (Ron et al., 1994). Incidence data from the Adult Health Study (AHS) clinical sub-cohort of the LSS reported no statistically significant interaction between age at time of bombing and risk of hypertension or myocardial infarction (Yamada et al., 2004).

(179) In the occupational exposure setting, the INWORKS study of nuclear workers observed no significant difference in ERR/Gy by age at exposure for mortality from all circulatory disease ($p > 0.5$), ischaemic heart disease (IHD) ($p = 0.38$) or cerebrovascular disease ($p > 0.50$) (Gillies et al., 2017); mean employment beginning and ending at 28 and 58 years respectively (Hamra et al., 2016). The Techa River environmentally exposed cohort, on the other hand, in which approximately 40% of the cohort was exposed before the age of 20 yrs (Kossenko et al., 2005), reported significant higher ERR/Gy for ischaemic heart disease mortality in those exposed at younger ages (ERR/Gy was higher for individuals aged 20 yrs [10%] than for those aged 40 yrs [2 %]; $p < 0.001$) (Krestinina et al., 2013).

Attained age

(180) A non-statistically significant trend of increasing excess relative risk of heart failure incidence with higher attained age per gray of cardiac dose was observed in a French childhood cancer study ($p = 0.12$) (Mansouri et al., 2019). While risk of radiation-related cardiac-disease increased markedly with attained age in the Euro2k cohort of childhood cancer survivors in patients who received anthracyclines (<20 years ERR/Gy 0.26; 20–29 years ERR/Gy 0.27; 30–39 years ERR/Gy 0.99; 40+ years ERR/Gy 0.87), attained age did not modify the ERR in patients who had not received anthracyclines (Haddy et al., 2016).

(181) Mortality analyses restricted to underlying cause of death in the long terms study of atomic bomb survivors (LSS) indicated no statistically significant modification by attained age on the effect of radiation on mortality of overall heart disease, stroke, ischemic heart disease, or valvular heart disease (Shimizu et al., 2010). Although there was some indication of a possible decrease in ERR for overall heart disease at attained age ≥ 60 yrs (ERR/Gy 25%. 95% CI 4–50) versus <60yrs (ERR/Gy 6%; 95% CI: −2, 15; $p = 0.11$), an analysis for finer categories of attained age showed no consistent trend ($p = 0.43$) (Takahashi et al., 2017). A re-analysis of LSS mortality data corresponding to the dataset of Shimizu et al. (2010) but using contributing as well as underlying causes of death (thus increasing the sensitivity of the outcome definition, but decreasing specificity), reported a borderline significant ($p = 0.076$) reduction in cerebrovascular disease ERR/Gy with increasing attained age, and significant reduction in ERR/Gy with increasing attained age ($p < 0.001$) for cardiovascular disease excluding heart disease and stroke, but no indications of such effects for heart disease (Little et al., 2012). While incidence analyses in the AHS clinical sub-cohort of the LSS also indicated a pattern of lower ERR/Gy for those with larger attained age for mortality from myocardial infarction, these results were not statistically significant ($p = 0.37$).

(182) The INWORKS study of nuclear workers found no significant effects of attained age on mortality for circulatory disease ($p = 0.21$), ischaemic heart disease ($p = 0.17$) or cerebrovascular disease ($p = 0.33$) (Gillies et al., 2017). Although no overall association was observed between radiation and cerebrovascular disease mortality in the Mayak nuclear workers (Azizova et al., 2022), incidence analyses indicated a significant decrease in ERR/Gy for cerebrovascular disease with increasing attained age ($p < 0.001$) (Azizova et al., 2023a), consistent with a reported reduction in ERR/Gy for ischaemic heart disease mortality from the environmentally exposed Techa River cohort ($p = 0.002$) (Krestinina et al., 2013).

Time since exposure

(183) Although only a few medical studies assessed time since exposure, pooled data from the Massachusetts and Canadian TB fluoroscopy cohorts indicate a notable reduction of relative risk for all circulatory disease and ischaemic heart disease with increasing time since last exposure (Tran et al., 2017). Decreased excess relative risk with time since exposure was also observed in a cohort of individuals treated for peptic ulcers (Little et al., 2012). Although

limited by smaller size, radiation-related excess risk of heart failure incidence was not modified by time since diagnosis in a Dutch cohort of ≥5 years survivors of Hodgkin's lymphoma (van Nimwegen et al., 2017). Potential interaction by time since exposure was not assessed/reported in the U.S. childhood cancer survivor study (Mulrooney et al., 2009), or in the Euro2k cohort (Haddy et al., 2016).

(184) Initial analyses of the atomic bomb LSS data reported no statistically significant effect modification with time since exposure on radiation-related mortality from cardiovascular disease, stroke, heart disease, or a combined category of all other cardiovascular disease apart from stroke and heart disease (Shimizy et al., 2010). A re-analysis of LSS mortality data using contributing as well as underlying causes of death also found no statistically significant effect modification with time since exposure (Little et al., 2012). With respect to occupational exposure, the INWORKS study of nuclear workers noted a borderline significant reduction in ERR/Gy for ischaemic heart disease mortality with greater time since exposure ($p = 0.06$), but no significant modification was observed for all circulatory disease or cerebrovascular disease (Gillies et al., 2017).

Biological sex

(185) No significant interaction between sex and radiation dose was observed for cardiac disease in the Euro2K childhood cancer survivors cohort (Haddy et al., 2016), or on valvular heart disease incidence, or heart failure incidence in Hodgkin Lymphoma survivors (Cutter et al., 2015; van Nimwegen et al., 2017). Effect modification of radiation-related cardiac outcomes by sex was not reported in U.S. childhood cancer survivors (Mulnoorey et al., 2020). In moderate-dose medical exposure settings, no effect modification by sex was noted for radiation-related cardiac disease mortality in the Canadian fluoroscopy study (Zablotska et al., 2014), or on the risk of radiation and cardiovascular disease, ischaemic heart disease, or cerebrovascular disease in people treated for peptic ulcers (Little et al., 2016).

(186) Analyses of LSS mortality data from the atomic bomb survivors using underlying cause of death found no statistically significant effect modification by sex on either stroke or heart disease (Shimizu et al., 2010). Although tests for interaction were not statistically significant, point estimates of risks were higher for females than males for overall heart disease mortality ($p = 0.07$) and valvular heart disease mortality ($p = 0.12$), but not for ischemic heart disease (Takahashi et al., 2017). A re-analysis of the LSS data using both underlying and contributing causes of death (thus increasing sensitivity but lowering specificity of outcome) reported higher ERR/Gy on overall heart disease mortality for females compared to males ($p = 0.02$), but no effect modification by sex for stroke or other diseases of the circulatory system (Little et al., 2012).

(187) The INWORKS study of nuclear workers observed significantly higher ERRs/Gy for females with respect to mortality from all diseases of the circulatory system ($p = 0.005$) and ischaemic heart disease ($p = 0.004$). Although not statistically significant, the pattern of risk was consistent for cerebrovascular disease mortality (Gillies et al., 2017).

(188) While the Mayak study of nuclear workers reported no statistically significant associations with external gamma-ray exposure and diseases of the circulatory system, ischaemic heart disease and cerebrovascular disease overall, or by gender (Azizova et al., 2022), incidence analyses indicate slightly higher ERR/Gy estimates for cerebrovascular disease incidence for females compared with males (0.47, 95% CI 0.31–0.66 for females; 0.37, 95% CI 0.27–0.47 for males) (Azizova et al., 2023b).

Underlying Health Conditions

(189) While cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, obesity) were directly associated with risk of various cardiac outcomes in U.S. Childhood Cancer Survivors, comparison of the relative risks of these outcomes with chest-directed radiotherapy in the absence or presence of cardiovascular risk factors indicates no clear relationship on a multiplicative scale with these underlying risk factors (Armstrong et al., 2013a). On an additive scale, survivors treated with chest-directed RT who developed two or more cardiovascular factors of which one was hypertension, demonstrated a statistically significant excess risk for development of coronary artery disease, heart failure, valvular disease, and arrythmia. No statistically significant multiplicative interaction was observed between radiation exposure and obesity for cardiovascular disease incidence in a French childhood cancer survivor study (Mansouri et al., 2019); between radiation exposure and diabetes, hypercholesterolemia, hypertension, or history of ischemic heart disease on heart failure incidence (Hooning et al., 2007; Boekel et al., 2020) or myocardial infarction (Jacobse et al., 2019) in a Dutch study of breast cancer survivors; between presence of at least one established cardiac risk factor and ischaemic heart disease in a separate cohort of Swedish/Danish breast cancer survivors (Darby et al., 2013), or by the presence of at least one cardiovascular risk factor, obesity, hypertension (end of follow-up) or hypercholesterolaemia (end of follow-up) on the relationship between radiation and valvular heart disease incidence in a multicentre study of Hodgkin lymphoma survivors (Cutter et al., 2015; van Nimwegen et al., 2016, 2017).

Genetic Factors

(190) The potential interaction of germline genetic variation on radiation-related risk of cardiovascular disease is of high interest, but few studies have examined this question. A series of studies in U.S. childhood cancer survivors and controls have examined the relationships between common genetic variants, radiation, and risk of various cardiovascular conditions, namely hypertension, cardiac fraction, cardiac dysfunction, cardiomyopathy, and stroke (Sapkota et al., 2019, 2021a, b, 2022). Whole genome sequencing data for 686 childhood cancer survivors of European ancestry from the St. Jude Lifetime Cohort (SJLIFE) indicated a genome-wide significant association between the 5p15.33 locus and stroke, with some suggestion of potential modification by chest radiotherapy dose (Sapkota et al., 2021b). A second study used 895 established blood pressure loci from the general population to calculate a polygenic risk score (PRS) within 7,995 U.S. childhood cancer survivors of European ancestry from SJLIFE and the U.S. Childhood Cancer Survivor Study (CCSS). Survivors in the top PRS decile demonstrated a more than 2-fold increase in hypertension compared to survivors in the bottom decile – this association showed some possibility of modification by exposure to hypothalamic-pituitary axis radiation (per standard deviation interaction OR 1.18; 95% CI: 1.05–1.33) (Sapkota et al., 2021a). A separate analysis from SJLIFE identified two loci associated with left ventricular ejection fraction (a marker of cardiac function) on childhood cancer survivors of African ancestry, but no clear interaction with radiation was observed (Sapkota et al., 2021b) In survivors of European ancestry from the same population, a variant near the KCNK17 gene showed genome-wide significant association with ejection fraction, as well as with increased risk of severe cardiac dysfunction – no statistically significant association was observed when this analysis was restricted to survivors unexposed to either anthracyclines or chest radiation, suggesting potential modification by radiation dose and/or chemotherapy (Sapkota et al., 2022). While these studies indicate the possibility for underlying genetic susceptibility to modify the relationship between radiation dose and circulatory disease outcomes, and methods such as the use of polygenic risk scores and

mendelian randomisation that can be used to address the question, these findings need to be confirmed by replication in other settings, with detailed consideration of radiation type, dose and other exposure-related factors.

(d) Effect modification by extrinsic factors

Chemotherapy

(191) Cancer radiotherapy studies have indicated that some chemotherapeutic agents may modify the effect of radiation on risk of cardiovascular disease. Anthracyclines are a highly effective class of chemotherapeutic agents with known toxic cardiovascular effects. A number of studies have reported a possible interaction of anthracyclines, usually detrimental, with radiation on risk of various cardiovascular outcomes including all cardiac disease incidence (Haddy et al., 2016), as well as specific cardiac events e.g., heart failure (Aleman et al., 2007; van der Pal et al., 2012; Boekel et al., 2020), coronary artery disease (van der Pal et al., 2012), and valvular disease (Aleman et al., 2007; Hooning et al., 2007). However, uncertainties remain regarding the exact nature of the interaction. For example, cohort results from the French Childhood Cancer Study indicated that 5-year survivors treated with anthracycline and a heart radiation dose >15 Gy had an increased risk of cardiac disease at a younger age than other patients. However, the overall ERR/Gy for cardiac disease was lower for those exposed to anthracycline (ERR/Gy 0.07, 95% CI 0.03–0.13) than for those who had not received anthracycline (ERR/Gy = 0.49, 95% CI = 0.26–1.3) – the lower slope for the effect of radiation in patients treated with anthracycline is associated with a higher baseline risk at a radiation dose of 0, leading to similar risks at high radiation dose with and without anthracycline. For heart failure specifically, on the other hand, use of anthracycline increased risk at a heart radiation dose of >15 Gy (Haddy et al., 2016). The later nested case-control study of Mansouri et al. in the French Childhood Cancer Study also reported a higher ERR/Gy of 0.44 (95% CI 0.18–1.12) of heart failure for those not treated with anthracycline versus an ERR/Gy of 0.09 (95% CI 0.02 to 0.22) for those treated with anthracycline (Mansouri et al., 2019). Other studies have reported no significant interaction between radiation and anthracycline for incidence of myocardial infarction in breast cancer survivors (Jacobse et al., 2019), or of valvular heart disease (Cutter et al., 2015) or heart failure (van Nimwegen et al., 2017) following radiation for Hodgkin lymphoma. Chemotherapeutic agents other than anthracycline have generally shown no consistent pattern of effect modification with radiation with respect to cardiovascular events in studies of radiotherapy following breast cancer (El-Fayech et al., 2017; Jacobse et al., 2019; Darby et al., 2013; Mansouri et al., 2019; van der Pal et al., 2013). A possible positive interaction between alkylating agents and cranial radiotherapy was reported for incidence of stroke in U.S. childhood brain cancer survivors (Bowers et al., 2006).

Smoking

(192) Despite being a typical risk factor for cardiovascular disease, smoking did not appear to be a modifier of radiation exposure in studies of cardiovascular incidence or mortality, including in patients treated for TB fluoroscopy or peptic ulcers (Little et al., 2012, 2016; Zablotska et al., 2014) and most cancer survivor studies (Cutter et al., 2015; Jacobse et al., 2019). Some studies noted that small numbers precluded the ability to formally assess the relationship. Nonetheless, potential modification needs to be examined further given reports of a possible interaction with smoking in studies of cancer survivors of myocardial infarction incidence after breast cancer treatment (Hooning et al., 2007), and cerebral vascular event incidence following cranial radiation in childhood cancer survivors (not statistically significant) (El-Fayech et al., 2017). Effect modification by smoking has not been reported in studies of

radiation exposure and circulatory disease risk in atomic bomb survivors, nuclear workers, or environmentally exposed populations.

Alcohol

(193) Literature regarding potential modification by alcohol effects is scarce. Although radiation-related cardiovascular mortality was significantly higher in Massachusetts tuberculosis fluoroscopy study participants whose reported alcohol consumption status was "unknown" (Little et al., 2016) the implications of this finding remain unclear. Effect modification by alcohol has not been reported in studies of radiation exposure and circulatory disease risk in atomic bomb survivors, nuclear workers, or environmentally exposed populations.

(e) Summary

(194) While interpretation of the data is complicated by considerations of statistical power, differences in specific disease outcomes, narrow ranges of exposure and/or potential modifiers within studies, the evidence to date suggests a possible detrimental interaction of anthracyclines with radiation on various cardiovascular outcomes, including all cardiac disease incidence, as well as specific cardiac events including heart failure, coronary artery disease, and valvular disease (Aleman et al., 2007; Hooning et al., 2007; Mansouri et al., 2019; van der Pal et al., 2012; van Nimwegen et al., 2017; Haddy et al., 2016; Boekel et al., 2020). Further studies of the effect of anthracyclines, and other chemotherapeutic agents, on the relationship between radiation risk and circulatory disease outcomes is warranted. While stratification of risk by use of chemotherapeutic agents specifically may have limited applicability to non-medically exposed populations, these findings indicate the need to consider possible interaction with other potential chemical agents.

(195) Some studies have reported increased liklihood of radiation-related cardiovascular outcomes with younger age at exposure, but this has not been consistently observed in all settings. Analyses of the LSS atomic bomb survivor study using underlying cause of death find no statistically significant effect modification by age at exposure on mortality from heart disease, ischaemic heart disease, or valvular heart disease (Shimizu et al., 2010; Takahashi et al., 2017). While a re-analysis of the same data using underlying and contributing causes of death (an outcome with lower specificity) suggests greater risk at younger at exposure for all cardiovascular disease and stroke, this was no observed for overall heart disease (Little et al., 2012). In medical settings, younger age at exposure appeared to increase liklihood of myocardial infarction and ischaemic heart disease in breast cancer survivors and Canadian TB fluoroscopy workers, respectively (Zablotska et al., 2014; Jacobse et al., 2019), but other studies of therapeutically exposed populations report no statistically significant effect modification with age at exposure on radiation-related risk of heart failure, cardiac disease, valvular heart disease, major coronary event, or cardiovascular disease (Haddy et al., 2016; Darby et al., 2013; Little et al., 2016; van Nimwegen et al., 2017; Mansouri et al., 2019; Cutter et al., 2015). No significant modification by age at exposure was noted for radiation related mortality from all circulatory disease, ischaemic heart disease, or cerebrovascular disease in the INWORKS study of nuclear workers. These discrepancies highlight the sensitivity of the results to the outcome definition. Interpretation of the age at exposure results is further complicated by limited range of age at exposure and/or small sample sizes with low power to detect effect modification.

(196) Female workers in the INWORKS nuclear worker study had significantly higher radiation-related risk mortality than males from all diseases of the circulatory system and ischemic heart disease, but not cerebrovascular disease (Gillies et al., 2017). On the other hand,

most medical exposure studies (Cutter et al., 2015; van Nimwegen et al., 2017; Little et al., 2012; Zablotska et al., 2014; Haddy et al., 2016), and analyses of underlying cause of death from diseases of the circulatory system in atomic bomb survivors (Shimizu et al., 2010; Takahashi et al., 2017), report no statistically significant modification by gender. A re-analysis of atomic bomb survivor data using both underlying and contributing causes of death (a less specific outcome) indicated higher estimates of risk for females than males for mortality from overall heart disease and valvular heart disease, but not for ischaemic heart disease (Little et al., 2012).

(197) Overall, weighing the evidence from medical, occupational, and environmental studies, there is some indication that co-exposure with certain chemotherapeutic agents (particularly anthracycline), younger age at exposure, and female sex may be associated with greater radiation-related risk of overall or specific circulatory disease outcomes. However, large uncertainties remain regarding the nature of these modifying relationships for specific disease outcomes, indicating the need for further studies examining effect modification by chemical agents, various scales of age/calendar time, gender, and potential genetic susceptibility. Large datasets with a wide range of radiation doses and types, ages, both sexes, and information on other potential effect modifiers will be particularly informative.

Table 2.7. Summary of Epidemiological Studies Assessing Effect Modification of the Relationship between Radiation and Diseases of the Circulatory System in Medical, Environmental and Occupational Settings

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
U.S. Childhood Cancer Survivor Study	Armstrong et al., 2013a	Median age at last follow-up, 34 yrs (range 11 to 59)	0 to ≥50 Gy heart dose	Incidence of coronary artery disease, heart failure, valvular disease, arrhythmia, CTCAE v4.03≥ grade 3	Hypertension, dyslipidemia, diabetes, obesity	The combined effect of radiation plus cardiovascular risk factors, especially hypertension, resulted in greater than additive (but not multiplicative) risk of major cardiac events.
U.S. Childhood Cancer Survivor Study	Bowers et al., 2006	Mean age at interview, 24 yrs among leukaemia survivors, 26 yrs among brain cancer survivors	0 to ≥50 Gy heart dose	Incidence of stroke, self-reported	Alkylating agent	Survivors of childhood brain tumours treated with an alkylating agent in addition to chest radiotherapy had increased RR of stroke.
French Childhood Cancer Survivors Study, nested case-control study	Mansouri et al., 2019	Median age at diagnosis, 5 yrs (IQR 2.4–9.8) among cases	Mean heart dose, 12.3 Gy (range 0.004–49.1) among cases	Incidence of heart failure, CTCAE v4.03	Anthracycline, attained age, age at diagnosis	The ERR of heart failure was lower in patients treated with anthracycline compared with patients unexposed to anthracycline. No significant modification by attained age or age at diagnosis.
Euro2K Childhood Cancer Survivors	Haddy et al., 2016	Age at diagnosis, <17 yrs	Mean heart dose, 7.5 Gy among all patients, 17.2 Gy among patients with cardiac disease, 19.7 Gy among patients with cardiac disease grade ≥3	Incidence and mortality of myocardial infarction, angina pectoris, heart failure, valvular diseases, cardiac arrhythmias, conduction disorders, and pericardial disease	Anthracycline, attained age, age at diagnosis, sex	The ERR of overall cardiac disease was higher in patients who had not received anthracycline. ERR of cardiac disease increased with attained age in patients without anthracycline, but not in patients with anthracycline. However, the ERR of heart failure was higher in patients who had received anthracycline. No significant interaction by age at cancer diagnosis or sex.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
Euro2K Childhood Cancer Survivors	El-Fayech et al., 2017	Age at diagnosis, 0–15 yrs	Mean dose to circle of Willis, 22 Gy for brain tumour, 13 Gy for non-Hodgkin lymphoma, 9 Gy for retinoblastoma	Incidence of all stroke, ischemic stroke, hemorrhagic stroke	Sex, follow-up time	The ERR was higher in men and increased with follow-up time for all stroke, especially ischemic stroke.
Dutch Childhood Cancer Survivor Study	van der Pal et al., 2012	Median age at the end of follow-up, 29.1 yrs (range 5.2–54.2)	Median cardiac irradiation dose (equivalent dose in 2-Gy fractions: EQD_2), 24.08 Gy to thorax (range 9.47–88.46), 26.90 Gy to abdomen (range 3.73–57.19)	Incidence of congestive health failure, ischemia, valvular disease, arryhthmia, pericarditis, CTCAE v 3.0, ≥grade 3	Anthracycline	The combined effect of anthracyclines and cardiac irradiation on cardiac diseases was stronger than the effect of anthracyclines and cardiac irradiation only, although not statistically significant.
Dutch Hodgkin Lymphoma Study, nested case-control study	van Nimwegen et al., 2017	Median age at Hodgkin lymphoma diagnosis, 28.3 yrs (IQR 21.9–37.7) among cases; median age at heart failure diagnosis, 47.9 yrs (IQR 41.2–57.7)	Average prescribed dose 30.5 Gy; average mean heart dose 20.9 Gy; average mean left ventricular dose 14.5 Gy	Incidence of heart failure, CTCAE v 3.0 and 4.0, grade≥2	Anthracyclines, splenectomy, risk factors of cardiovascular disease, sex, age at Hodgkin lymphoma diagnosis, time since Hodgkin lymphoma diagnosis	No difference in RRs of heart failure among Hodgkin lymphoma patients with mean heart dose from radiotherapy ≥26 Gy relative to 0–25Gy with respect to anthracyclines, splenectomy, at least 1 risk factor of cardiovascular disease, sex, age at Hodgkin lymphoma diagnosis, time since diagnosis.
Dutch Hodgkin Lymphoma Study, nested case-control study	van Nimwegen et al., 2015	Median age at Hodgkin lymphoma diagnosis, 32.3 yrs (IQR 24.5–39.4) among cases	Average mean heart dose 22.0 Gy among cases, 20.4 Gy among controls	Incidence of coronary heart disease, CTCAE 4.0, grade≥2	Sex, follow-up time, age at treatment, chemotherapy, risk factors of cardiovascular disease, smoking	There was a suggestion of decreased ERR of cardiovascular disease with increasing age at diagnosis, although not statistically significant. No evidence for modification by chemotherapy, sex, cardiovascular disease risk factors, and smoking.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
Dutch Hodgkin Lymphoma Study, nested case-control study	Cutter et al., 2015	Median age at diagnosis, 23.3 yrs	Mean dose to affected heart valve, 37.0 Gy among cases, 30.7 Gy among controls	Incidence of valvular heart disease, CTCAE v4.0, grade≥2	Sex, age at diagnosis, treatment period, follow-up interval, treatment center, anthracycline, vincristine, procarbazine, splenectomy, obesity at diagnosis, smoking at diagnosis, hypertension at end of follow-up, hypercholesterolaemia at end of follow-up	RR of valvular heart disease was higher among individuals with >=35 Gy compared with <35 Gy in later treatment period. There were some suggestions of increasing RR with use of anthracycline, not having splenectomy post Hodgkin lymphoma, and no obesity, although not statistically significant.
Dutch Hodgkin Lymphoma Study	Aleman et al., 2007	Median age at treatment, 25.7 yrs; Median follow-up time, 18.7 yrs in cohort	Radiotherapy yes/no	Incidence of coronary heart disease (myocardial infarction and angina pectoris), congestive heart failure, valvular disorders	Chemotherapy, anthracyclines, risk factors of cardiovascular disease (smoking, hypertension, hypercholesterolaemia, diabetes)	The HR of congestive heart failure and valvular disorders increased when radiotherapy was combined with anthracycline chemotherapy. No statistically significant interactions between radiotherapy and chemotherapy, or between treatment and risk factors cardiovascular disease.
Canadian Study Hodgkin Lymphoma Survivors, nested case-control study	Myrehaug et al., 2008	Median age at Hodgkin lymphoma diagnosis, 24–26 yrs depending on treatment	Mediastinal radiotherapy yes/no	Hospitalisation due to cardiac disease (myocardial infarction, ischemic heart disease, congestive heart failure, revascularisation procedures, other)	Doxorubicin	The HR of cardiac hospitalisation among Hodgkin lymphoma patients with radiotherapy plus doxorubicin was significantly higher than for the general population, and higher than patients with RT alone, although not statistically significant.
Netherlands-NKI-Rotterdam Breast Cancer Survivor Study, nested case-control study	Boekel et al., 2020	Median age at breast cancer diagnosis, 51.1 yrs (IQR 45.1–55.2) among cases	Median mean heart dose, 6.8 Gy (IQR 0.9–13.7) among cases, 3.9 Gy (IQR 0.9–13.4) among controls	Incidence of heart failure	Anthracycline	In breast cancer patients treated with both anthracycline and radiotherapy, RR of heart failure increased significantly. No association was observed between radiation dose and RR of heart failure in absence of anthracycline.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
Netherlands-NKI-Rotterdam Breast Cancer Survivor Study, nested case-control study	Jacobse et al., 2019	Median age at breast cancer diagnosis, 50.2 yrs (IQR 45.8–54.7) among cases	Median mean heart dose, 8.9 Gy (IQR 4.8–15.0, range 0.3–35.2) among cases, 8.5 Gy (IQR 4.3–12.2) among controls	Incidence of myocardial infarction	Age at breast cancer diagnosis, year of breast cancer diagnosis, time to myocardial infraction, chemotherapy, risk factors of cardiovascular disease, smoking	Higher ERR of myocardial infraction was observed for younger age at breast cancer diagnosis, with borderline significance. No interaction with year of breast cancer diagnosis, time to myocardial infraction, chemotherapy, risk factors of cardiovascular disease, or smoking.
Late Effects Breast Cancer Cohort – Breast Cancer Survivors from the Netherlands	Hooning et al., 2007	Median age at breast cancer diagnosis, 49 yrs	Radiotherapy yes/no	Incidence of myocardial infarction, angina pectoris, congestive heart failure, valvular dysfunction	Chemotherapy, smoking, hypercholesterolemia, hypertension, diabetes mellitus, history of ischemic heart disease, follow-up time	Radiotherapy plus chemotherapy had higher HR of congestive heart failure than radiotherapy only. Smoking and radiotherapy were associated with more than additive effect on risk of myocardial infarction. Radiotherapy-associated risk of cardiovascular disease increased with longer follow-up.
Nordic Breast Cancer Survivor, case-control study	Darby et al., 2013	Age at breast cancer diagnosis, 20–74 yrs	Average mean EQD2 dose to the heart, 3.9 Gy (range 0.1–30.4)	Major coronary event (incidence of myocardial infarction, coronary revascularisation, or death from ischemic heart disease)	Presence of at least one cardiac risk factor (history of ischemic heart disease, other circulatory disease, diabetes, chronic obstructive pulmonary disease, smoking, BMI, analgesic use), country, age at diagnosis of breast cancer, year of breast cancer diagnosis, tumour characteristics, cancer treatment	No interaction observed between % increase in the rate of major coronary event per Gy and presence of cardiac risk factor. Risk of major coronary event did not differ significantly by age at diagnosis of breast cancer or chemotherapy.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
Massachusetts Lung Cancer Survivors	Atkins et al., 2019	Median age, 65 yrs (IQR 57–73)	Mean radiation dose to heart, 12.3 Gy (IQR 5.9–19.0)	Major adverse cardiac event (cardiac death, unstable angina, myocardial infarction, heart failure hospitalisation or urgent visit, and coronary revascularisation) and all-cause mortality	Pre-existing coronary heart disease	Mean heart dose was associated with a significantly increased HR of all-cause mortality and major adverse cardiac events among patients without coronary heart disease, but not among patients with coronary heart disease.
Canadian and Massachusetts Tuberculosis Fluoroscopy Cohort	Tran et al., 2017	Mean age at first exposure, 27.66 yrs (range 1.97–80.64)	Mean cumulative lung dose, 1.12 Gy (range 0.01–27.77)	Mortality of all circulatory disease, ischaemic heart disease, cerebrovascular disease, hypertensive heart disease, other heart disease, other circulatory disease	Age at exposure, time since exposure, dose fractionation	ERR of death from all circulatory disease and ischemic heart disease decreased with increasing time since exposure. No strong modification by age at exposure or dose fractionation.
U.S. Peptic Ulcer Cohort	Little et al., 2012	Age at treatment or entry, <35 to >=55 yrs	Heart dose (also checked for thyroid, kidney, pancreas, brain dose)	Mortality for all circulatory disease, ischaemic heart disease, cerebrovascular disease, other circulatory disease	Age at exposure, time since exposure	ERR of circulatory disease mortality significantly decreased with increasing time since exposure.
Childhood Cancer Survivors (African Ancestry) – Genetic	Sapkota et al., 2021	Median age at last follow-up, 34.5 yrs (range 13.7–65.9) among African ancestry, 37.0 yrs (range 9.2–70.2) among European ancestry	Median average heart dose, 1.4 Gy (range 0–453) in African cohort, 1.2 Gy (range 0–50.5) in European cohort	Cardiomyopathy development	Genetic variants (rs6689879, rs9788776)	Among childhood cancer survivors exposed to radiotherapy, rs6689879 conferred slightly reduced effect on ejection fraction (2.4% reduction) whereas rs9788776 showed a stronger effect (8.1% reduction) – not statistically significant.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Medical exposure						
Childhood Cancer Survivors – Genetic (CCSS (+Expansion) + SJLIFE)	Sapkota et al., 2021	Median age at last contact, 41.5 yrs (IQR 12.4) in CCSS, 35.5 yrs (IQR 15.3) in SJLIFE, 30.1 yrs (IQR 8.5) in Expansion	Radiotherapy fields	Incidence of hypertension	Polygenic risk score	The association between hypertension and polygenic-risk-score appeared to be modified by exposure to hypothalamic-pituitary axis radiation – not statistically significant.
St Jude Lifetime Cohort, Childhood Cancer Survivor of European ancestry	Sapkota et al., 2019	Median age at diagnosis, 5.5 yrs (range 0–22.7); Median age at last contact, 40.4 yrs (range 12.4–64.7)	Cranial radiation therapy, 0.01–>50Gy	Incidence of stroke	Genetic variants (5p15.33 locus)	The association between radiation exposure and stroke appeared to be modified by genetic variant – not statistically significant.
Occupational exposure						
International Nuclear Workers Study (INWORKS)	Gillies et al., 2017	18–82 yrs [not mentioned in the paper]	Average cumulative equivalent dose, 25.2 mSv (median 3.4 mSv, max 1932 mSv)	Mortality of circulatory diseases (ischaemic heart disease, cerebrovascular disease)	Sex, attained age, duration of employment, socioeconomic status, age at exposure, time since exposure	The ERR of mortality from circulatory diseases was higher among females than among males, especially in ischaemic heart disease. The ERR for ischaemic heart disease was higher in white-collar workers than in blue-collar workers, while the opposite trend was observed in cerebrovascular diseases. No effect modification by age at exposure, attained age, or duration of employment.

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Occupational exposure						
Mayak Nuclear Workers	Azizova, et al., 2022	Mean age at hire, 24.9 yrs (SD 7.5)	Mean cumulative gamma-ray dose from external exposure, 0.45 Gy (SD 0.65) among men and 0.37 Gy (SD 0.56) among women; Mean cumulative alpha dose from internal exposure, 0.18 Gy (SD 0.65) among men and 0.40 Gy (SD 1.92) among women	Mortality of circulatory system disease, chronic rheumatic heart disease, arterial hypertension, ischaemic heart disease (acute myocardial infection, acute coronary failure), cerebrovascular disease (ischaemic stroke), heart failure, atherosclerosis of arteries of the extremities	Sex, attained age, age at hire, duration of employment	The ERR of ischaemic stroke increased significantly among men, but not among women.
Mayak Nuclear Workers	Azizova et al., 2022	Mean age at hire, 24.11 yrs (SD 7.13) among men and 27.32 yrs (SD 7.97) among women	Mean cumulative gamma-ray dose from external exposure, 0.45 Gy (SD 0.65) among men and 0.37 Gy (SD 0.56) among women	Incidence of cerebrovascular disease, stroke (hemorrhagic stroke, ischemic stroke)	Sex, attained age, duration of employment, age at employment, year of diagnosis	The ERR of cerebrovascular disease incidence increased among both sexes for both external and internal exposure. The ERR of external gamma dose for cerebrovascular disease significantly decreased with increasing attained age (males and females) and increasing duration of employment (females).
Environmental Exposure						
Japanese atomic bomb survivors – Life Span Study	Takahashi et al., 2017	Mean age at the time of bombing, 21.9 yrs (range 0–89)	<0.005 to ≥1 Gy	Mortality of ischemic heart disease (myocardial infraction), valvular heart disease (rheumatic and non-rheumatic), hypertensive organ damage, heart failure	Calendar time, city, sex, age at exposure, attained age	Women tended to have higher ERR than men for heart disease overall, hypertensive organ damage, heart failure and valvular heart disease. Variation across attained age was marginally significant in valvular heart disease and hypertensive organ damage (those with younger attained age had higher ERR).

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Table 2.7. (*continued*).

Subjects	Reference	Age range	Dose range	Endpoint	Variables assessed	Conclusion
Environmental Exposure						
Japanese atomic bomb survivors – Life Span Study	Shimizu et al., 2010	Age at time of bombing, 0–50+ yrs	0 to >3 Gy (86% received <0.2 Gy)	Mortality of heart disease, stroke	Sex, age at exposure, attained age, smoking, alcohol intake, education, obesity, diabetes	ERR of stroke appeared to be higher before attained age 60 than after, especially among men, and among those exposed at younger age, although not statistically significant. No significant modification of effect by sex, age at exposure, or attained age was found in heart diseases.
Japanese atomic bomb survivors – Adult Health Study	Yamada et al., 2004	Mean age at time of bombing, 30.6 yrs in Hiroshima, 24.5 yrs in Nagasaki	Mean 0.57 Sv (SD 0.94) Dose range 0–3+ Sv, 20% exposure 1+Sv	Incidence of hypertension, hypertensive heart disease, ischaemic heart disease, myocardial infarction, aortic aneurysm, stroke (I/II)	City, sex, age at exposure, age at examination, calendar time, alcohol intake, smoking	Significant quadratic dose-response relationships were observed in hypertension and myocardial infarction among survivors exposed at less than 40 years. No significant effect modification by city, sex, age at exposure, age at examination or calendar time in each disease.
Techa River Environmental Cohort	Krestinina et al., 2013	0–80+ yrs	Mean 35mGy, maximum 510mGy, 54% below 10mGy, 31% 10–50mGy, 15% exceeded 50mGy	Mortality of circulatory system disease, ischaemic heart disease	Sex, age at exposure, attained age, ethnicity, calendar period, oblast of exposure	In all diseases of the circulatory system, ethnicity was a statistically significant effect-modifying factor. In ischaemic heart disease, ERR decreased with increasing attained age and increasing age of initial exposure.

2689 2.3.1.2. Animal studies

2690 (198) Among the large number of animal studies investigating the adverse effects of
2691 radiation on the circulatory system, a few studies have actually compared the role of strain, sex,
2692 age or lifestyle factors, coexposures on the response of the circulatory (cardiovascular) system
2693 to radiation (Walls et al., 2022). The majority of such animal studies looked at cardiac function.

2694 *(a) Modification by environmental factors such as smoking status, chemotherapy, underlying*
2695 *conditions (diabetes and other comorbidities) as well as age and sex (Table 2.8)*

2696 (199) A limited number of animal studies have been undertaken to examine sex differences
2697 in the radiation response of the circulatory system. In several studies using both sexes, the
2698 number of animals was insufficient for the statistical analysis of sex differences (Unthank et
2699 al., 2019). Some studies, nevertheless, have found potential sex differences. For instance,
2700 female rats were more sensitive to radiation-related heart dysfunction than males (Andruska et
2701 al., 2023). Female mice were more sensitive to various endpoints relating to radiation-related
2702 arthrofibrosis, compared with males (Rodman et al., 2022). In-utero radiation exposure caused
2703 persistent alterations in glucose uptake, storage and antioxidant proteins in the female pups,
2704 but not in males (Nemec-Bakk et al., 2021). In apolipoprotein E-deficient ($ApoE^{-/-}$) mice which
2705 are prone to atherosclerosis, changes in macrophage content in the core of the atherosclerotic
2706 plaque occurred in females earlier than males, following local neck irradiation (Stewart et al.,
2707 2006). Sex-specific responses have also been observed for plasma triglycerides and
2708 cholesterols, and some of the pro-inflammatory markers in $ApoE^{-/-}$ mice receiving thoracic
2709 irradiation (Ramadan et al., 2021). Collectively, these studies suggest higher radiosensitivity
2710 of female mice. Nevertheless, there are some studies that found no sex difference (Ait-Aissa et
2711 al., 2022), so a firm conclusion cannot be reached.
2712 (200) For age at exposure, only a few studies have investigated the effects of in-utero
2713 irradiation. Total body exposure of pregnant mice to a low or moderate dose of radiation (0.05–
2714 1 Gy) showed no effects on cardiovascular outcomes (e.g., systemic blood pressure) in the pups
2715 (Sreetharan et al., 2019; McEvoy-May et al., 2021). Total body exposure of pregnant mice to
2716 0.02–1 Gy also altered the cardiac proteome of the male pups at the age of 6 months or the
2717 female pups at age 2 years: the significantly altered proteins were involved in mitochondrial
2718 respiratory complexes, redox and heat shock responses and the cytoskeleton (Bakshi et al.,
2719 2016). In rats exposed at age 6 weeks or 6 months, age at exposure modified radiation effects
2720 for various makers of cardiovascular disease and kidney injury (Lenarczyk et al., 2019). In
2721 atherosclerosis-prone mice, radiation exposure exhibited protective effects when exposed at
2722 age 2 months (with early-stage disease), but exhibited detrimental effects when exposed at age
2723 7 months (with late stage disease) (Mitchel et al., 2013).
2724 (201) Radiation effects may be modified by potential chemotherapeutic agents. In rats,
2725 adriamycin enhanced myocardial lesions (e.g., pericardial effusions and fibrosis) induced by
2726 local heart irradiation (Eltringham et al., 1975; Fajardo et al., 1976). Changes in cardiac
2727 mitochondrial morphology and mitochondrial permeability transition pore opening were more
2728 pronounced in rats treated both by local cardiac irradiation (9 Gy/day, 5 days) and sunitinib (a
2729 tyrosine kinase inhibitor, orally administrated for two weeks), than those treated either by
2730 irradiation or sunitinib alone; however, the combined treatment did not affect cardiac troponin
2731 I and markers of oxidative stress (Sridharan et al., 2016). Trastuzumab (an anti-HER2
2732 antibody) did not alter radiation-induced toxicity in human cardiomyocytes in vitro (Seemann
2733 et al., 2013). Neither doxorubicin (anthracycline) nor lapatinib (a tyrosine kinase inhibitor)
2734 modified radiation-related cardiac fibrosis in mice (Seemann et al., 2013). Compared with heart
2735 or thoracic irradiation alone, combination with an anti-programmed death 1 (PD-1) antibody

led to increases in mortality, myocardial injury, pro-inflammarory cytokines and immune cell infiltration in mice (Myers and Lu, 2017; Du et al., 2018; Bai et al., 2022). A transient treatment with an inhibitor of poly (ADP-ribose) polymerase (olaparib) at the time of irradiation reduced atherosclerotic stenosis induced by radiation in atherosclerosis-prone mice (Kotla et al., 2021). For other coexposures, the animal study has suggested that maternal stress (e.g., due to repeated handling and transportation) during in-utero radiation exposure may modulate potential effects in the pups (Sreetharan et al., 2019). An animal study also showed that grape seed extract reduced the effects of radiation-related oxidative stress in heart tissues (Saada et al., 2009).

(202) For comorbidity, low-dose irradiation (12.5–50 mGy every two days) of streptozotocin-induced diabetic C57BL/6J mice prevented diabetic cardiomyopathy (Zhang et al., 2016), suggesting a hormetic effect of radiation in a disease-prone model.

(b) Modification by hormonal factors, such as oestrogens over the life span

(203) Limited studies have investigated whether and how hormones contributing to CVD (e.g., endothelins, angiotensin II, thyroid hormones, growth hormone and leptin and sex hormones) modify radiation-related CVD. In rats, captopril (an inhibitor of angiotensin-converting enzyme) reduced acute myocardial injury and attenuated cardiopulmonary dysfunction induced by local heart irradiation (van der Veen et al., 2015). Also, in rats, losartan (a blocker of angiotensin II receptor) ameliorated the echocardiographic and histological evidence of left ventricular hypertrophy and fibrosis and decreased the expression of several related genes (Kovács et al., 2021).

(c) Modifications by the immune system

(204) Compared with mast cell-competent rats, mast cell-deficient rats exhibited more diastolic dysfunction and interstitial collagen III accumulation, and less myocardial degeneration, after local heart irradiation (Boerma et al., 2005). In rats deficient in T cells and B cells, loss of adaptive immune cells reduced heart function parameters such as ejection fraction and fractional shortening, but mature T cells were not necessary for the development of radiation-related cardiac injury (Schlaak et al., 2020). Cytotoxic T cells mediated enhancement of radiation-related cardiac toxicity by an anti-PD-1 antibody (Du et al., 2018).

(d) Modification by genetic and epigenetic factors/factors influencing the outcome of functional assays

(205) Deficiency of ApoE or low-density lipoprotein receptor (Ldlr) predisposes to atherosclerosis in mice, and irradiation accelerates the development of atherosclerotic lesions in such deficient mice (Stewart et al., 2006; Hoving et al., 2008; Choi et al., 2021). This potentially has implications for atherosclerosis prone individuals. Tumour-related factors may play a role in radiogenic cardiovascular effects. In mice, the transition from cardiac hypertrophy to heart failure required p53 accumulation (Sano et al., 2007), and p53 deficiency in endothelial cells led to myocardial injury and heart failure after irradiation (Lee et al., 2012). Radiation exposure exhibited protective effects in ApoE–/– mice with wild-type p53 (p53+/+), but exhibited detrimental effects in ApoE–/– mice with reduced p53 (p53+/–), and ApoE–/– p53+/– mice exhibited the accelerated progression of spontaneous and radiogenic atherosclerosis (when irradiated at a late stage of the disease) than ApoE–/– p53+/+ mice (Mitchel et al., 2013). Mice defective in p21 were prone to radiogenic myocardial injury (Lee et al., 2012; Haiyang et al., 2021). Deficiency of ataxia telangiectasia-mutated (ATM) accelerated atherosclerosis in ApoE–/– mice (Schneider et al., 2006), whilst deficiency of Wip1 phosphatase (a negative regulator of ATM-dependent signaling) prevented atherosclerosis (Le

Guezennec et al., 2012). These suggest a protective role of ATM, p53 and p21. Overexpression of CuZn-superoxide dismutase (an anti-oxidant enzyme) reduced radiation-related low density lipoprotein degradation and fatty streak formation in the murine aorta (Tribble et al., 2009, 2010). Loss of glutathione S-transferase alpha 4 (Gsta4) in mice enhanced susceptibility of cardiac mitochondria to radiation-related loss of morphology, but with cardiac function preserved (Boerma et al., 2015). Peroxisome proliferator-activated receptor alpha (PPARα) was neeed to activate the non-canonical (SMAD-independent) TGFβ signaling pathway in the murine heart (Subramanian et al., 2018). Deficiency of ras homolog family member B (RhoB–/–) enhanced cardiac radiosensitivity in femaeiving local cardiac irradiation, deficiency of interleukin-2 receptor gamma chain (IL2RG–/–) conferred protection from cardiac hypertrophy and increased heart dysfunction after single irradiation, although such differences were less evident after fractionanted irradiation (Schlaak et al., 2020).

(206) Interestingly, Apo-E has been shown to be a substrate of ATM in Alzheimer disease resulting in a severe delay of ATM nucleo-shuttling from the cytoplasm to the nucleus (Berthel et al., 2023).

Table 2.8. Animal data on the potential factors that modify radiation responses of the circulatory system.*

References	Animal model	Variable	Endpoints	Variable effect on radiation endpoints
Sex				
Sridharan et al., 2021	Adult mice, high activated protein C expressers, exposed to leg-out partial body γ-rays	Sex	Cardiac function, cardiac collagen deposition, cardiac microvascular density	Radiation endpoints differ between the sexes.
Stewart et al., 2006	Adult ApoE$^{-/-}$ mice, exposed to aortic arch and carotid artery x-rays	Sex	Number of plaques, plaque histology	No sex difference in plaque burden, some differences in plaque immune cells.
Andruska et al., 2023	Adult Dahl SS rats, exposed to local heart x-rays	Sex	Cardiac function, pericardial effusions	Endpoints more severe in female rats, but may be due to a higher volume of irradiated lung. Female pericardial effusion prevalence significantly greater than in males among irradiated rats ($p < 0.001$), but male survival significantly worse ($p < 0.01$) than females. Various cardiac output measures suggest female rats have more rapid onset of cardiac dysfunction than males.
Chmielewski-Stivers et al., 2021	Adult wild-type mice, exposed to local heart x-rays	Sex	Survival, echocardiography, histopathology of the heart	Males exhibited lower survival than females. Males showed echocardiographic and histopathological changes, but not in females.
	Adult RhoB$^{-/-}$ mice, exposed to local heart x-rays	Sex	Survival, echocardiography, histopathology of the heart	Females exhibited lower survival than males. Females showed histopathological changes, but not in males. Both sexes showed no echocardiographic changes.

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2800 Table 2.8. (*continued*).

References	Animal model	Variable	Endpoints	Variable effect on radiation endpoints
Age at exposure				
Lenarczyk et al., 2019	Male WAG/RijCmcr rats exposed to whole body x-rays at the age of 6 weeks or 6 months	Age at exposure	Blood levels of cardiovascular risk factors, perivascular fibrosis, systemic blood pressure	Different dose- and time-dependent effects on cardiovascular risk factors between young and old animals. Increasing age at exposure resulted in more strongly positive dose response for albumin (p = 0.0003), protein (p = 0.0014), AST (p = 0.0014), and alkaline phosphatase (p = 0.0003), but more negative dose response for cholesterol (p = 0.0008), HDL (p = 0.0030), triglycerides (p = 0.0333), BUN (p = 0.0068) and calcium (p = 0.0299). More severe radiation-related perivascular fibrosis and blood pressure increase in young animals.
Mitchel et al., 2013	ApoE$^{-/-}$, p53$^{+/-}$ mice, exposed to whole body γ-rays at 8 weeks or 7 months of age	Age at exposure	Vascular lesion size, lesion frequency, serum total cholesterol	p53 heterozygosity alters the effects of radiation on all endpoints. The type of modification depends on age at exposure (8 weeks vs 7 months). Higher age is associated with more severe atherosclerosis at the time of radiation.
Coexposures to chemotherapeutic agents				
Eltringham et al., 1975; Fajardo et al., 1976	Young adult New Zealand White Rabbit, exposed to local heart x-rays and Adriamycin	Anthracycline	Cardiac histopathology	Cardiac histopathology worse in combined treatment (radiation+Adriamycin) group
Myers and Lu, 2017; Du et al., 2018; Bai et al., 2022	Adult mice, thorax exposure to x-rays, pretreated with anti-PD-1 antibody or control IgG	Anti-PD-1	Animal survival, cardiac function, cardiac cytokine levels, cardiac immune cell infiltration	All outcomes are worse in combined treatment group (radiation + anti-PD-1)
Seemann et al., 2013	Adult male mice, exposed to local heart irradiation and lapatinib	Lapatinib (tyrosine kinase inhibitor)	Cardiac function, Cardiac microvascular density, cardiac immune cell infiltration, cardiac fibrosis	Lapatinib reduced immune cell infiltration. No other modification of radiation effects

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Table 2.8. (*continued*).

References	Animal model	Variable	Endpoints	Variable effect on radiation endpoints
Coexposures to chemotherapeutic agents				
Sridharan et al., 2016	Adult male Sprague-Dawley rats, exposed to local heart irradiation and sunitinib	Sunitinib (tyrosine kinase inhibitor)	Cardiac cell apoptosis, cardiac oxidative stress, mitochondrial swelling	Sunitinib reduced the effects of radiation on apoptosis, did not alter oxidative stress, and aggravated mitochondrial swelling
Kotla et al., 2021	Adult $LDLR^{-/-}$ mice on high fat diet and exposed to neck and thorax x-rays, followed by TAC and PARP inhibitor treatment	PARP inhibitor	Cardiac function, artery stenosis, artery wall thickness, perivascular fibrosis, $Mac3^{+}$ cells (macrophages) in vascular lesions	PARP inhibition reduced the effects of radiation on cardiac function, artery stenosis, and $Mac3^{+}$ cell number
Saada et al., 2009	Male albino rats, exposed to whole body irradiation and grape seed extract	Grape seed extract	Activity of enzymes involved in antioxidative defense in the serum, heart, and pancreatic tissue	Grape seed extract significantly increased ($p \leq 0.05$) the activity of serum antioxidative enzymes (released by damaged heart tissue after irradtion)

ApoE, apolipoprotein E; IgG, immunoglobulin G; LDLR, low-density lipoprotein receptor; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; TAC, thoracic aorta coarctation; AST, aspartate immunotransferase; HDL, high-density lipoprotein; BUN, blood urea nitrogen.
*Developed from Little et al., 2024.

2.3.1.3. Summary and conclusion on the range observed and main contributory modifying factors

(207) Besides obvious physical factors (e.g., dose, dose rate, radiation quality, irradiation volume), there are indications and preliminary data identifying such potential modifiers of radiation effects on the circulatory system, although no conclusions can yet be drawn. Further studies and a consensus on the evidence are needed to gain deeper insights into factors determining individual responses regarding radiation DCS and the implications for radiological protection.

2.3.1.4. Approaches to prediction – genetic and functional assays

(208) It remains unclear whether target organs/tissues for cardiovascular effects are heart, large arteries, kidneys or pancreas (Hamada, 2023). The clonogenic survival may not predict cardiovascular responses, because cell killing is unlikely the major mechanism. Markers related to oxidative stress and aging such as cellular senescence and mitochondrial dysfunction might be useful (Minamino and Komuro, 2008; Chen and Zweier, 2014). Significant efforts have been made to identify biomarkers, and association of radiogenic cardiac injury with plasma levels of circulating natriuretic peptide (atrial, N-terminal pro-B-type or brain) or troponin T has been reported (Wondergem et al., 2001; D'Errico et al., 2012; Gomez et al., 2014; Skyttä et al., 2015). Echocardiography with a new modality such as strain rate imaging or tissue velocity imaging may allow noninvasive detection of early cardiotoxic changes post radiotherapy (Erven et al., 2013; Bordun et al., 2015).

2.3.2. Cataract

(209) Cataract is a clouding of the normally transparent lens of the eye. Cataract is an age-related disease, but can also be induced by exposure to ionising radiation, and there are several other known risk factors. Cataracts have been classified as a tissue reaction, and equivalent dose limits for the crystalline lens have been recommended to prevent vision impairing cataracts (VICs) (ICRP, 2012). Since *Publication 1* (ICRP, 1959), ICRP has always considered that the lens represents one of the most radiosensitive tissues in the body.

(210) ICRP concluded in *Publication 41* (ICRP, 1984) that ocular structures other than the lens are not radiosensitive. In this regard, there is evidence for significantly increased radiation risks for several other ocular diseases in the Adult Health Study (AHS) cohort of Japanese atomic-bomb survivors, such as diabetic retinopathy (Minamoto et al., 2004) and normal-tension glaucoma (Kiuchi et al., 2013, 2019). However, an increased radiation risk for diabetic retinopathy has not been confirmed in any other cohorts. In contrast to observations of secondary glaucoma (neovascular) observed following high dose fractionated radiotherapeutic exposure (Hamada et al., 2019), an increased radiation risk of normal-tension glaucoma has been reported only in Russian Mayak workers (Azizova et al., 2022) among cohorts other than the AHS. In contrast to normal-tension glaucoma (a subtype of primary open-angle glaucoma), significantly increased risks have not been observed for high-tension glaucoma (another subtype of primary open-angle glaucoma) and primary angle-closure glaucoma in the AHS or Mayak cohorts (Kiuchi et al., 2013, 2019; Azizova et al., 2022), for self-reported glaucoma in aggregate in the AHS (Yamada et al., 2004) and the USRT cohort (Little et al., 2018b), nor for glaucoma in aggregate in Canadian nuclear workers (Villeneuve et al., 2025). Considering such emerging evidence for normal-tension glaucoma, the long-standing tenet that the lens represents the most radiosensitive ocular structure appears to remain unchanged (Hamada et al., 2020; Hamada, 2023). This section therefore focuses on cataracts with some reference to the effects on other ocular structures.

2.3.2.1. Evidence for variation in response of normal ocular tissue to radiation

(211) The results of the systematic review of relevant literature are detailed in Barnard and Hamada (2023), and an outline is given in this subsection. Tables 2.9 and 2.10 list the relevant human and experimental studies, respectively.

2.3.2.2. Human studies

(212) The most significant data of radiation-related cataract in humans come from occupational exposure studies, whether environmentally exposed or while conducting medical procedures. Interpretation is an important consideration within such studies, as outcomes can include incidence or prevalence of minor opacities, low- or high-grade cataracts, VICs, incidence of self-reported cataracts and incidence and prevalence of cataract removal surgery.

(213) The AHS cohort of atomic bomb survivors has yielded a number of significant findings, including increased radiation-related risk of cataract (particularly posterior subcapsular cataract) and cataract surgery, which appears to decrease with increasing age at exposure (Otake et al., 1992; Nakashima et al., 2006; Neriishi et al., 2013).

(214) A cohort of the US Radiologic Technologists (USRT) consisting of up to 35,000 medical workers (Little et al., 2018a, 2020a, 2020b) reported an increased liklihood of self-reported cataract with radiation dose (below 100 mGy), with greater risk with increasing age and being diabetic. Exposure to ultraviolet B light (UVB), pale skin type and smoking all increased risk of cataract.

(215) In the cohort of Russian Mayak Production Association workers, there was a significantly increased risk for incidence of radiation-related cataract at effective dose above 0.25 Sv, and such radiation risk was increased in females, diabetics, smokers, with alcohol consumption, myopia, glaucoma and attained age (Azizova et al., 2016, 2018, 2019).

2.3.2.3. Animal studies

(216) Much of the biological information regarding the induction of radiation-related cataract has come from studies involving animal exposures to radiation. Unlike epidemiological studies, controlling exposure variables is possible within laboratory-based animal studies.

(217) Mouse strain influences the response of the lens to radiation-induced damage to DNA (Barnard et al., 2018, 2022). A separate study (McCarron et al., 2022) reported significant effects of genotype and sex modifying radiation-related cataract progression (McCarron et al., 2022).

(218) Among heterogeneous stock mice from the 47 families developed using eight inbred progenitor strains, male mice were at greater risk of developing cataracts than females (Kleiman et al., 2023). Cataract risk increased with increasing number of tumours diagnosed, and was associated with Harderian gland tumours. The study, however, did not address whether modification by sex and associations with tumours differ between spontaneous cataracts and radiation-related cataracts (Kleiman et al., 2023).

2.3.2.4. In vitro studies

(219) With the limitations of human and animal studies, in vitro studies involving cultured lens cells provide a tool to study in more detail mechanistic changes within the lens following radiation exposure. A number of studies have reported significant findings most commonly using lens epithelial cell lines derived from human donors, although rodent cells have also been used. Radiation-induced DNA damage in lens epithelial cells has been reported (Baumstark-Khan et al., 2003; Markiewicz et al., 2015; Hamada, 2017; Ahmadi et al., 2022).

(220) The radiobiological characterisation of human and porcine epithelial lens cell lines showed delayed radiation induced nucleo-shuttling of ATM suggesting a strong influence of the ATM protein in radiation-induced cataractogenesis (Al-Choboq et al., 2023).

Table 2.9. Human studies on cataracts.

Author(s)	Study population	Outcome	Effect Modifier
Sex			
Azizova et al., 2019	Russian Mayak workers	Surgical removal of senile cataract	Relative risk of cataract removal surgery lower in females ($p < 0.05$)
Age			
Chylack et al., 2012	Astronauts and military aviators	Progression rate of cataract	Age and radiation dose increased progression
Otake et al., 1992	Atomic bomb survivors in Hiroshima and Nagasaki	Axial opacities, PSC changes examined	Increased relative risk with increasing age, dose and age x dose (all $p < 0.01$)

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2905 Table 2.9. (*continued*).

Author(s)	Study population	Outcome	Effect Modifier
sex			
Nakashima et al., 2006	Atomic bomb survivors	Cataract prevalence	Threshold dose point estimates 0.6 Sv (90% CI: <0.0, 1.2 Sv) and 0.7 Sv (90% CI: <0.0, 2.8 Sv) for cortical cataract and PSC opacity. Cortical cataract showed a significant dose effect ($p = 0.002$), with OR/Sv of 1.30 (95% CI: 1.10, 1.53). PSC significant dose effect ($p < 0.001$), with OR/Sv of 1.44 at age of exposure of 10 y (95% CI: 1.19, 1.73). Dose effect decreased significantly with increasing age at exposure ($p = 0.022$)
Kiuchi et al., 2019	Atomic bomb survivors	Glaucoma and retinal vascular caliber	Heterogeneity ($p < 0.01$), radiation ($p < 0.01$), NTG prevalence increased with age and dose (both $p < 0.01$), hypertension ($p = 0.02$), diabetes ($p = 0.05$)
Genetics			
Gao et al., 2022	Residents in the natural high background radiation area	Lens opacity, genomic DNA	ATM and TP53 polymorphisms modify radiation-related (cumulative lens dose of 100 mGy) cataract susceptibility (OR = 5.51, 95% CI: 1.47–20.66; OR = 2.69, 95% CI: 1.10–6.60)
Comorbidity			
Little et al., 2018a	Radiologic technologists	Cataract incidence, surgery and risk	Increased radiation dose; excess hazard ratio/mGy of 0.69×10^{-3} (95% CI: 0.27×10^{-3}, 1.16×10^{-3}, $p < 0.001$), excess hazard ratio/mGy lower in diabetics ($p = 0.002$)
Little et al., 2018b	Radiologic technologists	Glaucoma and macular degeneration	ERR/Gy for glaucoma –0.57 (95% CI: –1.46, 0.60, $p = 0.304$), macular degeneration 0.32 (95% CI: –0.32, 1.27, $p = 0.381$)
Little et al., 2020a	Radiologic technologists	Cataract incidence and surgery	Excess additive risk with age (>75 years old), diabetics (both $p < 0.001$), higher UVB exposure, white skin and smoking (all ≤0.062) and occupational exposure < 100 mGy ($p = 0.004$)
Azizova et al., 2018	Mayak workers	Senile cataract classification	Excess relative risk/Sv for cataract higher in females ($p < 0.001$), diabetics, glaucoma, high myopia (all $p < 0.05$), smoking status ($p < 0.001$), alcohol consumption ($p < 0.05$), higher attained age ($p < 0.001$)
Azizova et al., 2016	Mayak Production Association workers	Cataract incidence	RR of cataract incidence higher in workers with glaucoma (2.951, 95% CI: 2.470, 3.496) and myopia (2.073, 95% CI: 1.526, 2.749)

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2907 Table 2.9. (*continued*).

Author(s)	Study population	Outcome	Effect Modifier
Other			
Azizova et al., 2022	Mayak Production Association workers	Glaucoma incidence	Increased NTG incidence (RR = 1.88, 95% CI: 1.01, 3.51; $p = 0.047$) in exposed workers.
Kiuchi et al., 2013	Atomic bomb survivors	Glaucoma prevalence	OR at 1 Gy of 1.31 (95% CI: 1.11, 1.53, $p = 0.001$) in the case of NTG
Otake et al., 1996	Atomic bomb survivors	Linear-Linear dose response fit	N/A
Chylack et al., 2009	Astronauts and military aircrew personnel	Lens opacity, cataract incidence and classification	Cosmic radiation exposure increased PSC size ($p = 0.016$)
Little et al., 2020b	Radiologic technologists	Dose uncertainties and risk estimation	N/A
Neriishi et al., 2012	Atomic bomb survivors	Cataract surgery	The estimated threshold dose was 0.50 Gy (95% CI: 0.10, 0.95) for the ERR model and 0.45 Gy (95% CI: 0.10, 1.05) for the EAR model. The linear ERR model for a 70-year-old individual, exposed at age 20 years, showed a 0.32 (95% CI: 0.09, 0.53) [corrected] excess risk at 1 Gy. The ERR was highest for those who were young at exposure.
Minamoto et al., 2004	Atomic bomb survivors	Cataract incidence	OR/Sv was 1.07 (95% CI: 0.90, 1.27) in nuclear colour, 1.12 (95% CI: 0.94, 1.30) in nuclear cataract, 1.29 (95% CI: 1.12, 1.49) in cortical cataract and 1.41 (95% CI: 1.21, 1.64) in PSC cataract.

2908 ATM, ataxia telangiectasia mutated; CI, confidence interval; ERR, excess relative risk; N/A, not
2909 available; NTG, normal-tension glaucoma; OR, odds ratio; PSC, posterior subcapsular; RR, relative
2910 risk; UVB, ultraviolet light B.
2911
2912 Table 2.10. Experimental studies on cataracts.

Author(s)	Species	Radiation Exposure	Effect modifier
Sex			
Bigsby et al., 2009	Rats	2.5, 5, 10 and 15 Gy gamma-rays	Estradiol treatment enhanced cataract formation ($p < 0.05$), PSC fastest progressing cataract type ($p < 0.01$)
Dynlacht et al., 2008	Rats	15 Gy gamma-rays	Estrogen enhances/protects against cataract, dependent on administration time pre/post irradiation ($p \leq 0.011$)
Dynlacht et al., 2012	Rats	10 Gy gamma-rays	Ovariectomised + estrogen treatment caused faster progression of cataract ($p < 0.001$), age of exposure ($p < 0.001$)
Henderson et al., 2010	Rats	1 Gy of 600 MeV ^{56}Fe ions	Estrogen exposed male rats had significantly higher rates of cataract compared ($p = 0.025$)
McCarron et al., 2022	Mice	0–2 Gy gamma-rays	Radiation-related cataract modified by genotype, sex, dose-rate, dose and month post-exposure (all $p \leq 0.003$)

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2914 Table 2.10. (*continued*).

Author(s)	Species	Radiation Exposure	Effect modifier
Sex			
Garrett et al., 2020	Rats	2 Gy ^{56}Fe ions	Protection against cataract by estrogen dependent upon the type and ionisation density of radiation exposure
Kleiman et al., 2023	Mice	3 Gy gamma-rays, 0.4 Gy of ^{28}Si or ^{56}Fe ions	Cataracts modified by sex and Harderian gland tumours
Age			
Lehmann et al., 2016	Voles	0.01 ± 0.003 Sv (c.f., dose quantity Sv is not applicable to non-humans)	Cataract positively correlated with age (p = 0.001), home range size and predation risk
De Stefano et al., 2015	Mice	3 Gy x-rays	Cataract incidence higher in younger aged mice at time of exposure (p < 0.05), radiation (p < 0.05) and lens capsule thickness changes (p < 0.0001)
Genetics			
Barnard et al., 2018	Mice	10 and 25 mGy x-rays	DNA damage response dependent on strain of mice (p = 0.002), lens epithelia region (p≤0.001) and dose (p < 0.001)
Hall et al., 2006	Mice	0.5, 1, 2, 4 or 8 Gy x-rays, 325 mGy 1 GeV/amu ^{56}Fe ions	ATM heterozygote genotype causes susceptibility to heavy ion radiation-related cataract
Worgul et al., 2005	Mice	325 mGy – x-rays or 1 GeV/amu ^{56}Fe ions	ATM heterozygosity predisposes lens to cataract following heavy ion exposure
Kleiman et al., 2007	Mice	50 cGy x-rays	Mrad9 or ATM heterozygosity increased incidence of cataract
Barnard et al., 2022	Mice	0.5, 1 and 2 Gy gamma-rays	Radiation-induced DNA damage in the lens epithelium dependent on LEC region (p < 0.001), genotype (p = 0.002), genotype x region (p < 0.001)
Other			
Kim et al., 2015	Rats	5 Gy gamma-rays	Radiation-induced modifications to crystallins
De Stefano et al., 2016	Mice	2 Gy, 1 Gy and 0.5 Gy x-rays	Microscopic alterations in the lens following 2 Gy exposure (p < 0.05)
Markiewicz et al., 2015	Mice	0, 20, 50, 100, 250, 1000 and 2000 mGy x-rays	Time post-exposure, radiation dose and lens epithelium region affect DNA damage response and proliferation in lens epithelial cells (all p≤0.004)
Ahmadi et al., 2022	Human lens epithelial cells	0, 0.1, 0.25 and 0.5 Gy gamma-rays	Radiation-induced decreased cell viability (p > 0.001), increased ROS (p < 0.01), increased DNA damage (p < 0.05) and the induction of senescence (p < 0.01)
Markiewicz et al., 2015	FHL124 cells	0, 20, 50, 100, 250, 1000 and 2000 mGy x-rays	Early lens effects dependent upon cell region (p < 0.001), radiation dose (p < 0.001), dose x region (p < 0.001) and cell type (p≤0.003)

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Table 2.10. (*continued*).

Author(s)	Species	Radiation Exposure	Effect modifier
Other			
Fujimichi and Hamada, 2014	Human lens epithelial cells and lung fibroblasts	0.5–6 Gy x-rays	Clonogenic potential and proliferation affected by radiation exposure and cell type ($p = 0.0056$)
Hamada, 2017	Human lens epithelial cells	3.53 and 3.25 Gy x-rays	Cell growth delay ($p < 0.05$), premature senescence ($p \leq 0.02$), DNA damage ($p < 0.001$)
Baumstark-Khan et al., 2003	Bovine lens epithelial cells	X-rays and heavy ions Z = 8 (O) to Z = 92 (U)	DNA damage response increased (dose-dependent)

amu, atomic mass unit; ARC, age-related cataract; ATM, ataxia telangiectasia mutated; LEC, lens epithelial cell; LET, linear energy transfer; N/A, not available; ROS, reactive oxygen species; PSC, posterior subcapsular.

2.3.2.5. Heritability within the population

(221) Studies of heritability within human cohorts identifying genetic factors predisposing persons to radiation-related cataracts are limited. Germline mutations of certain genes (e.g., crystallins, connexins) are known to underlie congenital (childhood or juvenile) cataracts (in particular nuclear cataracts), but the relevance to radiation is not known (Hamada and Fujimichi, 2015). Greater genetic diversity and different cataract phenotypes also make the analysis of genotype-phenotype correlations more complicated in humans than within inbred mouse strains (Blakely et al., 2010). A significantly higher incidence of self-reported cataract in white skin tone persons compared to other tones has been reported in the USRT study (Little et al., 2020a). In Chinese residents of a high natural background radiation area, single nucleotide polymorphisms of ataxia telangiectasia mutated (ATM) and p53 have been reported to significantly increase radiation risk of posterior subcapsular (PSC) and cortical opacities (Gao et al., 2022).

2.3.2.6. Modification of individual radiation response of the lens

(a) Modification by lifestyle factors (e.g., smoking), environmental factors, co-exposures (e.g., chemotherapy), comorbidities (e.g., diabetes), age and sex

(222) Experimental data gathered from a limited number of animal studies suggest that the age-response for cataractogenesis varies with both dose and linear energy transfer (LET) of radiation, but in ways that are not entirely intuitive. For example, older rats exposed to low-LET ^{60}Co gamma rays showed a higher rate of increase in the development of cataracts compared to younger rats (Dynlacht et al., 2012), but the latent period was greatly reduced, and cataract incidence was much greater in younger rats. Furthermore, the progression rate of cataractogenesis was much greater in the irradiated eyes of older rats compared to younger rats exposed to high-LET iron ions, with the latent period was reduced and incidence was enhanced in the older rats (Garrett et al., 2020). Mice irradiated at younger age in comparison to those irradiated older demonstrate a higher incidence of cataract (De Stefano et al., 2015). Wild voles collected from Chornobyl with a high environmental background radiation (Lehmann et al., 2016) demonstrated cataract incidence that was positively correlated with age (Lehmann et al.,

2016), although substantial caution is needed in interpreting these results (Smith, 2020; Laskowski et al., 2022).

(223) A limited number of experimental animal studies have reported statistically significant effects of sex in relation to radiation-related cataractogenesis. Cataract incidence was significantly lower in female rats when compared to males exposed to low-LET radiation, but there was no difference in the rate of progression (Dynlacht et al., 2008). Conversely, male rats had a lower incidence of cataracts compared to females exposed to high-LET radiation, and a lower rate of progression of cataracts (Henderson et al., 2010). A significant effect of sex has not generally been identified in the current radiation epidemiological literature, although the Mayak worker study has reported a significantly higher risk of radiation-related cataracts in females than in males for all three types of cataracts (PSC cataracts in particular) but non-significantly for cataract in aggregate (Azizova et al., 2016, 2018).

(224) For cataract removal surgery in Japanese atomic bomb survivors, evaluation of potential effect modifiers showed that sex, age at exposure, and time since exposure, but not diabetes, significantly modified the radiation effect, with male sex, younger age at exposure, and shorter time since exposure having greater radiation ERRs (Neriishi et al., 2012).

(225) In the USRT cohort, there were modest, albeit non-significant reductions in radiation risk of self-reported cataract history with increasing time after exposure and age at occupational radiation exposure. There was little evidence of modification of radiation risk for the self-reported cataract or self-reported cataract surgery by sex, racial group, smoking (overall smoking status, number of cigarettes smoked, age stopped smoking), birth year, body mass index (BMI) or by cumulative UVB radiation exposure (Little et al., 2018a, 2020a). There was marked variation of excess risk by age and by diabetes status, with risk higher among persons aged ≥75 years and among those with diabetes. There were indications of increases in radiation risk among those with higher UVB, Caucasians and among those with higher levels of cigarette smoking.

(226) In Mayak workers, radiation (external gamma rays) risks for cataracts in aggregate slightly increased with adjustments for glaucoma, modestly decreased with adjustments for BMI, smoking index and hypertension, and changed little with adjustments for smoking and alcohol consumption (Azizova et al., 2016). Radiation risks for all three types of cataracts decreased with adjustments for diabetes, BMI and smoking index, increased with increasing attained age, but little changed with age at first employment (Azizova et al., 2018). In addition, radiation risk for PSC cataracts increased with adjustments for smoking and alcohol consumption, but decreased with adjustments for glaucoma and myopia; radiation risk for cortical cataracts increased with adjustments for smoking and alcohol consumption, and little changed with adjustments for glaucoma and myopia; radiation risk for nuclear cataracts changed little with adjustments for smoking and alcohol consumption (Azizova et al., 2018).

(227) Differences in diets (which may be rich or deficient in antioxidant intake) may constitute a confounding factor in epidemiological studies of radiation effects, especially at low doses. Indeed, nutritional intake has been adjusted for in a small number of epidemiological studies, including the NASA Study of Cataract in Astronauts (Chylack et al., 2009, 2012).

(b) Modification by hormonal factors (e.g., oestrogens) over the lifespan

(228) Hormonal modulation could explain some of the differences in sensitivity with age and sex. Interestingly, radiation cataractogenesis may be selectively modulated by exogenous hormone treatment if administered at different times before or after irradiation. Oestrogen administered prior to irradiation was shown to potentiate cataractogenesis in ovariectomised rats, while treatment after irradiation provided a dramatic sparing effect (Dynlacht et al., 2008).

The effect of oestrogen may also be influenced by dose, dose-rate and radiation quality, further complicating interpretation of the effect of this hormone (Henderson et al., 2010; Bigsby et al., 2009; Dynlacht et al., 2012; Garrett et al., 2020).

(229) The above evidence in rats for a role of hormonal modulation by estrogen is mirrored in studies using frogs. Irradiated-hypophysectomised (mitosis halted) frogs failed to develop lens opacities, while those with pituitary hormonal replacement (mitosis reinstated) developed cataracts following irradiation (von Sallmann et al., 1962).

(c) Modifications by the immune system

(230) Due to the lens capsule enclosing the lens, immune cells do not enter the lens, and therefore the role of cell-mediated immunity should be limited if any. Long lasting inflammation within the ocular tissue (e.g., via non-targeted mechanisms) may play a role (Hamada et al., 2011; Hamada and Fujimichi, 2015; Ainsbury et al., 2016, 2021), but there is currently no evidence supporting or refuting this possibility.

(d) Modification by genetic and epigenetic factors

(231) There is mounting evidence that mutations of oncogenes, tumour suppressor genes, DNA repair genes involved in base excision repair, nucleotide excision repair, DNA double-strand break repair, genes involved in intercellular interactions (e.g., via connexin gap junctions), and inflammation affect development of spontaneous (age-related) cataract (Graw 2009; Hamada and Fujimichi, 2015). The role of most of these genes in human radiation cataracts has not been reported, but some information is becoming available from studies in mice and human biosamples.

(232) Studies in mouse models have demonstrated increased sensitivity to radiation cataracts in mice haploinsufficient (a single or double heterozygous) for Atm, Rad9, Brca1 and Ptch1 (Worgul et al., 2002, 2005; Hall et al., 2006; Kleiman et al., 2007; Blakely et al., 2010; de Stefano et al., 2015, 2016; Tanno et al., 2022). Of these, single nucleotide polymorphisms of ATM and p53 have been reported to significantly increase radiation risk of PSC and cortical opacities in Chinese residents of a high natural background radiation area (Gao et al., 2022). The role of RAD9, BRCA1, and PTCH1 in human radiation cataract remains unknown, and a special vulnerability of the lens in a subset of radiotherapy patients has not been reported. Nevertheless, compared with cases of cataracts in Japanese atomic bomb survivors without epilation, those with epilation had a trend toward a lower threshold and a steeper slope estimate under a linear-linear threshold model, albeit differences did not reach statistical significance (Otake et al., 1996); the possibility, however, cannot be ruled out that such epilation effects may result from dose error as found for leukaemia in the LSS (Little, 2002).

(233) At present, no studies have addressed the role of epigenetic factors in radiation cataractogenesis, although there is the relevant study on UV exposure (Wang et al., 2015).

2.3.2.7. Summary and conclusion on the range observed and main contributory modifying factors

(234) Radiation is a cataractogen, with uncertainty in the dose response relationship in particular at low dose and low dose rate. In addition to obvious physical factors (e.g., dose, dose rate, radiation quality, irradiation volume), potential factors modifying individual responses for radiation cataracts include sex, age and genetics, with comorbidity and coexposures also having important roles. There are indications and preliminary data identifying such potential modifiers of radiation cataract incidence or risk, although no firm conclusions can yet be drawn. Further studies and a consensus on the evidence are needed to gain deeper

insights into factors determining individual responses regarding the different types of potentially radiation-related cataracts and the implications for radiation protection.

2.3.2.8. Approaches to prediction – genetic and functional assays

(235) Mechanisms behind lenticular radioresponsiveness remain incompletely understood. In *Publication 92* (ICRP, 2003), ICRP considered that cataract is attributable to mechanisms other than cell killing (e.g., malfunctions such as abnormal differentiation of lens epithelial cells into lens fibre cells). Prior to which time, ICRP had considered cell killing as the sole mechanism during radiation induced cataractogenesis. Indeed, clonogenic survival of human lens epithelial cells after x-irradiation showed little difference compared to human fibroblasts (Fujimichi and Hamada, 2014).

(236) Given that cell killing does not serve as the major mechanism for radiogenic cataracts, analysis of clonogenic survival or any cell death modes may not be a suitable endpoint for prediction purposes. Instead, the analysis of the vulnerability of irradiated lens epithelial cells and subsequent differentiation into lens fibre cells may be more beneficial.

(237) No biomarkers specific to radiogenic cataracts have yet been reported; however, a recent report has shown that site-specific oxidation of lens crystallin can be determined, although at present its detection is technically possible at the level of acute dose of 5 Gy (Kim et al., 2015). Experimental evidence in mice (Worgul et al., 2002) and emerging human evidence (Gao et al., 2022) also suggest that the ATM haplotype may be useful for prediction, although more extensive studies would be needed. Spatiotemporal changes in the lens opacification after radiation exposure can be monitored almost noninvasively.

2.3.3. Cognitive impairment

(238) Irradiation of the brain can occur in medical practice in the course of tumour radiotherapy or diagnostic brain imaging. The generally relative low doses used in current diagnostic imaging modalities have been shown to increase the liklihood of brain cancers (Hauptman et al., 2023), but has so far no noticeable effect on neurocognitive functions. In radiation oncology, different techniques of conformal radiotherapy are employed to deliver high doses to the tumour of cancer patients, while limiting the dose to surrounding healthy tissues in order to avoid adverse toxicities. Radiotherapy (RT) is an effective treatment modality for patients of all ages with malignant and benign brain tumours. Early and delayed effects of cranial RT are transient and reversible with conformal radiation techniques. However, late radiation effects (≥6 months post-IR) remain a significant risk, and may result in progressive cognitive impairment. Cognitive dysfunction is a symptom complex characterised by decline in full scale intelligence quotient (IQ) and/or impairment in core functional domains of attention (or vigilance), working memory, executive functioning (planning and organisation), information processing speed, visual-motor integration, or learning deficits. These core deficits can be associated with behavioural changes and can compromise social and academic performance and quality of life. In the past, potential neurocognitive morbidity after IR exposure was difficult to measure, because neurocognitive testing was often limited by the lack of standardised and validated examination methods, missing neurocognitive pre-treatment status and the reduced patient compliance.

(239) This section describes the current knowledge about the impact of IR on neurocognitive impairment. In alignment with best practices in search methodology, PubMed database was used to retrieve comprehensive sets of relevant English-language articles using combinations of search terms. The section of radiation effects in cancer-related cognitive dysfunction is based on studies published between 2000–2019, reflecting the current state of radiotherapy technology.

2.3.3.1. Evidence for variation in response of normal brain tissue to ionising radiation

(240) Evidence of the effects of IR on the developing human brain was first documented in children of atomic-bomb survivors in Japan, who were exposed prenatally (during the first and second trimesters of pregnancy) to low-to-moderate doses and revealed mental retardation (Wood et al., 1967; Otake and Schull, 1984; Schull and Otake, 1986; Yoshimaru et al., 1991; Ikenoue et al., 1993; Otake and Schull, 1993; Yoshimaru et al., 1995) (Table 2.11). However, atomic-bomb survivors exposed during their adolescence (aged ≥13 years at the time of bombings) did not show any clear deleterious effect on later-life cognitive function in adulthood (Yamada et al., 2002). Moreover, no increased risk of premature neurodegeneration was observed among a small sample of aging atomic-bomb survivors exposed in-utero or during early childhood (Yamada et al., 2009; Yamada et al., 2016; Yamada et al., 2021; Ishihara et al., 2022). These studies of atomic-bomb survivors suggest that the long-term effects of low-to-moderate radiation exposure on late-life neurocognitive function is limited (Table 2.11). Potential cognitive consequences of low-dose radiation exposure from environmental disasters, such as the Chornobyl accident, have been intensely debated over the last decades (Pasqual et al., 2021). Despite numerous publications on potential health effects during gestation, childhood and adolescence, there is no clear evidence that the low-dose fallout from Chornobyl increased the risk for neurocognitive dysfunction (Bennet, 2006; UNSCEAR, 2008). Consequences of post-natal radiation exposure were also studied in children treated by x-ray epilation for tinea capitis. Studies of the American and Israeli tinea capitis cohorts evaluating thousands of children up to 20 years after IR exposure (mean doses 1.3–1.5 Gy) demonstrated lower IQ scores with poorer school performance and higher frequencies of mental diseases compared to non-irradiated children (Albert et al., 1966; Ron et al., 1982) (Table 2.11). During 1950–1960 Swedish boys received IR for cutaneous haemangiomas before the age of 18 months and their cognitive abilities were analysed by military test scores at the age of 18 years. This large Swedish cohort study indicates that even low-level exposure of the infant brain may adversely affect the intellectual development (Hall et al., 2004). Repeated analysis of this Swedish cohort suggests that particularly the hippocampal dose is a good predictor of late cognitive side effects (Blomstrand et al., 2014) (Table 2.12). On the other hand, the very low doses generally used in diagnostic procedures do not seem to have any noticeable effect on neurocognitive function. Accordingly, IR exposure from pelvimetric examination *in-utero* had no detectable effects of children´s final primary school grades (Nordenskjöld et al., 2015). Moreover, head CT examination at the age of 6–16 years does not seem to affect later cognitive functions (Salonen et al., 2018).

Table 2.11. Atomic bomb survivors studies

Reference	Study population (location)	Sample size	Type of exposure	Age at exposure	Brain dose	Outcome	Age at outcome measurement
Wood et al., 1967	Atomic bomb survivos (Japan)	183	γ-rays and neutrons	In-utero	≤4 Gy	Small head size, mental retardation	n.s.
Otake and Schull, 1984	Atomic bomb survivos (Japan)	n.s.	γ-rays and neutrons	In-utero	≤4 Gy	Forebrain damage, mental retardation	n.s.
Schull and Otake, 1986	Atomic bomb survivos (Japan)	n.s.	γ-rays and neutrons	In-utero	≤4 Gy	Mental retardation	n.s.

(*continued on next page*)

Table 2.11. (*continued*).

Reference	Study population (location)	Sample size	Type of exposure	Age at exposure	Brain dose	Outcome	Age at outcome measurement
Otake and Schull, 1991	Atomic bomb survivos (Japan)	1673	γ-rays and neutrons	In-utero		IQ decline, lower school performance	10–11 years
Yamada et al., 2016	Atomic bomb survivos (Japan)	929	γ-rays and neutrons	In-utero	≤4 Gy	Lower school performance	n.s.
Ikenoue et al., 1993	Atomic bomb survivos (Japan)	929	γ-rays and neutrons	In-utero	≤4 Gy	Lower school performance	n.s.
Otake and Schull, 1993	Atomic bomb survivos (Japan)	1473	γ-rays and neutrons	In-utero	≤4 Gy	Small head size, mental retardation	9–19 years
Yoshimaru et al., 1995	Atomic bomb survivos (Japan)	888	γ-rays and neutrons	In-utero	≤4 Gy	IQ decline, mental retardation	15–16 years
Yamada et al., 2002	Atomic bomb survivos (Japan)	3113	γ-rays and neutrons	≥13 years	≤4 Gy	No neurocognitive dysfunction	Adulthood
Yamada et al., 2009	Atomic bomb survivos (Japan)	2286	γ-rays and neutrons	≥13 years	≤4 Gy	No increased risk of neurodegeneration	≥60 years
Yamada et al., 2016	Atomic bomb survivos (Japan)	1844	γ-rays and neutrons	≥13 years	≤4 Gy	No increased risk of neurodegeneration	60–80 years
Yamada et al., 2021	Atomic bomb survivos (Japan)	303	γ-rays and neutrons	In-utero	≤4 Gy	No increased risk of neurodegeneration	65–70 years
Ishihara et al., 2022	Atomic bomb survivos (Japan)	469	γ-rays and neutrons	≤12 years	≤4 Gy	No increased risk of neurodegeneration	≥70 years

n.s., not specified.

2.3.3.2. Clinical studies – Radiation effects on neurocognitive function in brain cancer survivors

(241) Further evidence for radiation-related cognitive impairment has come from studies on survivors of childhood, adolescent, or adult cancer. Radiotherapy (RT) is an indispensable treatment mainstay for most primary brain tumours and for brain metastases originating from extracranial tumours (Rahman et al., 2022). Brain RT is subdivided into whole-brain radiotherapy, in which the entire brain and brainstem are irradiated, and partial-brain radiotherapy, which includes treatment of the tumour or tumour bed and surrounding margin. In modern radiation oncology, different techniques of conformal radiotherapy are employed to deliver high doses to the tumour of cancer patients, while limiting the dose to surrounding

healthy tissues to avoid adverse toxicities. With intensity modulated radiotherapy (IMRT, stop-and-shoot or rotational arc techniques) multiple photon-beams from different directions and with adjusted intensities permit close shaping of radiation dose to target volumes, thereby delivering high doses to tumours while sparing healthy brain tissue. Stereotactic radiosurgery relies on precise 3-dimensional (3D) imaging and localisation to deliver ablative doses of radiation to small tumours (≤3 cm in diameter) with minimal impact on the surrounding healthy brain. In addition to these highly conformal techniques based on external photon beams, proton therapy is increasingly used, especially for treating paediatric brain tumours (Yahya and Manan, 2021). RT is an effective treatment modality for patients of all ages with malignant and benign brain tumours. Based on the clinical sequelae, radiation-related brain injury can be characterised as acute, early delayed, and late injury (even if these early side effects usually no longer occur with modern radiation techniques). Acute microvascular damage with cerebral edema can develop in hours to days after high doses (≤10 Gy, single dose) to the brain. Early delayed brain injury occurs 1–4 months post-IR and can involve structural alterations of neuronal networks and transient lesions of demyelination, followed by perturbations in the functional activity of specific brain regions. Although both early injuries can result in severe reactions, they are considered to be transient and reversible. In contrast, late brain injury is characterised by persistent damage to the grey and white matter, with extensive demyelination and ultimately necrosis. These severe parenchymal defects are accompanied and exacerbated by vascular damage leading to impaired perfusion, and usually begin to occur 4–6 months post-IR. Late brain injury can develop progressively even years after IR exposure and the organic damage with correspondingly different neurocognitive deficits is generally irreversible (Kosmin and Rees, 2022).

Table 2.12. Studies of medically exposed children

Reference	Study population (location)	Sample size	Type of exposure	Age at exposure	Brain dose	Outcome	Age at outcome measurement
Albert et al., 1966	tinea capitis (New York)	1908	X-ray RT	mean: 8y	mean: 1.3 Gy	mental disorders, psychosis	21y
Ron et al., 1982	tinea capitis (Israel)	10842	X-ray RT	range: 1–15y, mean: 7y	range: 0.7–1.6 Gy, mean: 1.5 Gy	IQ decline, lower school performance	24y
Hall et al., 2004	cutaneous haemangioma (Sweden)	2816	X-ray RT	range: 0–18m, mean: 7m	range: 0–2.8 Gy, mean: 0.02 Gy	neurocognitive dysfunction ≥0.25 Gy	18y
Blomstrand et al., 2014	cutaneous haemangioma (Sweden)	3030	RT (different IR qualities)	range: 0–18m, median: 5m	range: 0–1.1 Gy, median: 0.02 Gy	hippocampus ≥0.25 Gy → lower verbal skills	18y
Nordenskjöld et al., 2015	maternal X-ray pelvimetry (Sweden)	1612	diagnostic x-ray	in-utero	estimated fetal dose: 0.0015 Gy	no effect on school performance	15y
Salonen et al., 2018	CT scan (Sweden)	147	diagnostic head CT	range: 6–16y, mean: 11y	estimated dose: 0.03–0.05 Gy	no cognitive dysfunction	18y

(242) Cognitive dysfunction is a symptom complex characterised by decline in full scale intelligence quotient (IQ) and/or impairment in core functional domains of attention (or

vigilance), working memory, executive functioning (planning and organisation), information processing speed, visual-motor integration, or learning deficits. These core deficits can be associated with behavioural changes and can compromise social and academic performance and quality of life. In the past, potential neurocognitive morbidity after IR exposure was difficult to measure because neurocognitive testing was often limited by the lack of standardised and validated examination methods, missing neurocognitive pre-treatment status assessment and reduced patient compliance. Only in more recent studies comprehensive neurocognitive and quality of life assessments were conducted at baseline and at follow-up.

(243) Childhood cancer survivors frequently experience cognitive dysfunction, commonly months to years after treatment for paediatric brain tumours or acute lymphoblastic leukaemia (ALL) (Mulhern et al., 2004; Castellino et al., 2014). In childhood brain tumours, most reports derive from survivors of low-grade gliomas or medulloblastoma, the most frequently observed brain tumours in children with high survival rates (Merchant et al., 2009; Padovani et al., 2012). Children receiving radiotherapy for their cancer demonstrate greater impairment than those who undergo surgery and/or chemotherapy without IR (Packer, 2002). Dose and field of cranial irradiation are highly associated with subsequent development of cognitive dysfunction (Meadows et al., 1981; Duffner, 2010). Limiting use and reducing dose and volume of cranial IR while intensifying chemotherapy has improved survival and reduced the severity of cognitive dysfunction (Duffner, 2004; Mabbott et al., 2005). Due to these treatment modifications prevalence and severity of cognitive dysfunction in survivors of childhood cancer has declined over the last decades (Castellino et al., 2014). Younger age at treatment is the most important patient-related risk factor, explained by the concurrence of radiation-related injury with vulnerable periods of brain development (Broadbent et al., 1981; Danoff et al., 1982; Mulhern et al., 1992; Radcliffe et al., 1994, Skowrońska-Gardas, 1999; Edelstein et al., 2011; Stadskleiv et al., 2022) (Table 2.13).

(244) After introduction of prophylactic whole brain RT in pediatric patients with leukaemia, it became apparent that radiation leads to reductions in IQ, particularly in younger children (Meadows et al., 1981; Twaddle et al., 1983; Ladavas et al., 1985; Said et al., 1989; Chessells et al., 1990; MacLean et al., 1995; Iuvone et al., 2002; Reinhardt et al., 2002) (Table 2.14). With evidence that the use of whole-brain RT in ALL was causally related to IQ decline, the dose was systematically reduced from 24 Gy in the 1980s to abandonment of cranial RT for the majority of children with leukaemia in the current era (Pui and Howard, 2008; Richards et al., 2013). A meta-analysis of children and adolescent survivors of ALL demonstrated clinically significant differences in cognitive functions, with lower scores for total IQ, verbal and performance IQ compared to healthy controls (Mavrea et al., 2021). Moreover, recent studies suggest that adult survivors of childhood cancer treated with prophylactic whole-brain RT have a higher liklihood of developing dementia later in life (Armstrong et al., 2013b). Aging survivors of ALL who received 24 Gy (but not 18 Gy) whole-brain RT revealed an early-onset memory loss with reduced ability to recall verbal associations and to reproduce visual patterns (Armstrong et al., 2013b). Functional neuroimaging of these survivors with cognitive impairment demonstrated reduced structural integrity of anatomical regions established for memory formation (Armstrong et al., 2013b). Longitudinal studies of adult survivors of childhood medulloblastoma suggest that RT causes not only neurocognitive late effects throughout the lifespan of children and adolescents but may even progress for decades after treatment has been completed (Edelstein et al., 2011). According to this study, RT is associated with the progressive decline in working memory at different ages throughout adulthood lifespan, reflecting a common sign of cognitive aging (Edelstein et al., 2011). Collectively, these findings suggest that survivors of childhood cancer who received cranial RT with higher doses may experience early onset of cognitive aging.

Table 2.13. Childhood cancer survivor studies

Reference	Study population	Sample size	Type of exposure	Age at exposure	Dose	Outcome	Age at outcome
Broadbent et al., 1981	medulloblastoma (UK)	8	60Co RT (neuroaxis)	1–12y	tumour: 43–50Gy	mental retardation, younger children (≤2y) more affected	n.s.
Danoff et al., 1982	primary brain tumours (USA)	38	60Co RT	1–16y	tumour: 40–65Gy	mental retardation, younger children (≤3y) more affected	n.s.
Mulhern et al., 1992	primary brain tumours (USA)	544	RT (local/whole brain)	1–18y	n.s.	IQ decline, younger children (≤4y) more affected	1–21y after RT
Radcliffe et al., 1994	medulloblastoma (USA)	24	cranial RT	1–20y	n.s.	IQ decline, younger children (≤7y) more affected	2–4y after RT
Skowrońska-Gardas, 1999	CNS tumours (Poland)	52	photon RT (neuroaxis)	3–19y	tumour: 50Gy; neuroaxis: 30Gy	mental retardation, younger children (≤3y) more affected	5y after RT
Edelstein et al., 2011	medulloblastoma (Canada)	46	photon RT	3–21y	tumour: 50Gy; neuroaxis: 23Gy	IQ decline, younger children (≤7y) more affected	≤40y after RT
Yock et al., 2016	medulloblastoma (USA)	59	proton RT (neuroaxis)	3–21y	tumour: 54Gy; neuroaxis: 23Gy	IQ decline	7y after RT
Ventura et al., 2018	primary brain tumours (USA)	65	photon RT (local)	2–17y	n.s.	IQ decline	4–18y after RT
Tso et al., 2019	germ cell tumours (Hong Kong)	25	cranial RT	7–18y	tumour: 30–54Gy	IQ decline	1–12y after RT
Stadsleiv et al., 2022	medulloblastoma (Norway)	50	photon RT (neuroaxis)	5–51y	tumour: 44–56Gy	IQ decline	19y after RT

n.s, not specified.

Table 2.14. Prophylactic Whole Body Radiotherapy studies

Reference	Study population	Sample size	Type of exposure	Age at exposure	Brain dose	Outcome	Age at outcome measurement
Meadows et al., 1981	children with ALL (USA)	41	WBRT	2–15y	24Gy, fractionated	IQ decline; younger children more affected	1–3y after RT
Twaddle et al., 1983	children with ALL (England)	23	WBRT	1–8y	24Gy, fractionated	IQ decline; younger children more affected	1–3y after RT
Ladavas et al., 1985	children with ALL (Italy)	21	WBRT	2–9y	24Gy, fractionated	IQ decline; younger children (<5y) more affected	1–3y after RT
Said et al., 1989	children with ALL (Australia)	106	WBRT	1–8y	18–24 Gy, fractionated	IQ decline; younger children more affected	1–13y after RT
Chessells et al., 1990	children with ALL (England)	136	WBRT	1–12y	18–24 Gy, fractionated	IQ decline, younger children (≤2y) more affected	1–5y after RT
MacLean et al., 1995	children with ALL (USA)	74	WBRT	3–7y	18 Gy, fractionated	neuropsychological deficits	1y after RT
Iuvone et al., 2002	children with ALL (Italy)	21	WBRT	1–12y	18–24 Gy, fractionated	age at WBRT not relevant	4–12y after RT
Reinhardt et al., 2002	children with AML (Germany)	38	WBRT	0–18y	12–18 Gy, fractionated	learning & deficits, younger children more affected	4–11y after RT

(245) Adulthood cancer survivors: Brain tumour survivors irradiated as adults may also experience progressive deterioration in cognitive functioning and accelerated cognitive decline (Scoccianti et al., 2012). High-grade gliomas account for 50% of all primary brain tumours in adults, but due to their poor prognosis with early tumour progression most patients do not experience neurocognitive impairment from RT. Most studies evaluating the relationship between RT and cognitive impairment are based on patients with low-grade gliomas. Findings from the literature propose that treatment variables, such as total and fractional dose, extent of target volume, and irradiation technique define the potential risk of radiotherapy-related neurotoxicity (Olson et al., 2000; Surma-aho et al., 2001; Postma et al., 2002; Correa et al., 2008; Douw et al., 2009). However, prospective trials indicate that neurocognitive deficits in patients with brain tumours usually have a multifactorial genesis (Armstrong et al., 2002; Klein et al., 2002; Brown et al., 2003; Laack et al., 2005). RT may contribute to the neurocognitive deterioration, but the causes of cognitive decline generally include tumour-related factors (tumour localisation, tumour size and histology, disease progression), other treatment-related factors (neurosurgery, use of anti-epileptic drugs, parenteral or intrathecal chemotherapy) and patient-related factors (age at treatment, pre-existing co-morbidities). Brain tumour patients deal with significant neurological symptoms that severely impact cognitive function and quality of life. Surgical resection of brain tumours is often required to provide histopathological

specimens and to reduce tumour burden. Tumour location determines extent of resection and risk for complications. While total resection increases the chance of long-term survival, the benefits of aggressive resection must be weighed against risks of disability. In the last twenty years, the use of 3D-conformal radiotherapy resulted in reduced amount of brain tissue treated to high-dose levels. In this context, results of most prospective trials argue for limited damage from focal RT and support the hypothesis that cognitive impairment in adult cancer survivors is mainly due to tumour relapse.

(246) Whole-brain RT in adult tumour patients is used to prevent or delay the spread of cancer cells to the brain. Prophylactic cranial radiotherapy was the standard care for patients with small-cell lung cancer, showing complete response to front-line chemotherapy. However, recent clinical trials suggest that prophylactic whole-brain RT did not provide survival benefits, but an increased risk of neurocognitive decline that can affect quality of life (Halthore et al., 2018). Allogeneic bone marrow transplantation for haematological malignancies generally requires total-body irradiation to eradicate malignant cells (in sanctuary organs that are not reached by chemotherapeutic drugs) and to induce immunosuppression to prevent the rejection of donor marrow. Clinical studies with neuropsychological testing of adult patients indicate that total-body irradiation with doses ≥12 Gy can lead to cognitive deficits in long-term survivors (Harder et al., 2006).

2.3.3.3. Animal studies

(247) The genesis of radiation-related brain injury with the development of neurocognitive decline is highly complex with multiple molecular and cellular mechanisms interacting at different levels in various brain compartments. Accumulating evidence from animal models suggests that cognitive decline following IR exposure involves radiation-induced damage in multiple cell populations, causing structural and functional alterations simultaneously in different neuronal lineages, in supporting glial cells, as well as in cerebral microvasculature. Injury-related processes set in motion soon after IR exposure may interact and synergize to alter the signalling environment in stem cell niches in the brain, specifically in the hippocampus, a structure critical to memory and cognition. Neurophysiological disturbances may progressively alter neuronal stem cell niches and changed niche conditions may lead to reduced neurogenesis with pathophysiological effects on cognitive function (Negredo et al., 2020). Overall, this multifactorial scenario with neurovascular and neuroinflammatory responses may result in the depletion and long-term dysfunction of neurons, and consequently in permanent cognitive impairment.

(248) In the central nervous system (CNS), multiple subtypes of neurons are interconnected to maintain the functionality of the complex mammalian brain. Glial cells, categorised into lineages of microglia, astrocytes, and oligodendrocytes, collectively support neuronal viability and functionality. Originally considered as non-functional glue for neurons, decades of research have highlighted the importance and diverse functions of different glial populations in the brain under both physiological and pathological conditions. Astrocytes, the most numerous cell type within the brain, perform a variety of tasks, from energy delivery to neurons, axon guidance and synaptic support, to the control of the blood-brain barrier (Santello et al., 2019). Microglia, originating from mesodermal cells, are specialised immune cells of the brain with phagocytic and antigen-presenting capabilities. Microglia are specialised for the uptake and removal of pathogens, apoptotic cells and cellular debris (Song and Colonna, 2018). Activated microglia undergo morphological changes along with changes in protein expression and secretion, releasing pro- and anti-inflammatory mediators. The main function of oligodendrocytes is the formation of myelin sheets around neuronal axons, thereby facilitating fast conduction of signals along the axons. In the brain, outside of stem cell niches, the majority

of cycling cells are oligodendrocyte precursor cells, which can undergo apoptosis within days after IR exposure, followed by progressive demyelination months later (Kuhn et al., 2019). Collectively, it is increasingly appreciated over the last years that the diverse and dynamic functions of glial cells orchestrate essentially all aspects of nervous system formation and function, from neuronal birth and migration, formation of dendrites and axons, up to circuit assembly into the neuronal network. As neural circuits mature, distinct glia cells fulfil key roles in synaptic communication, plasticity, and homeostasis, thereby controlling physiological and pathological brain functions. Notably, not only the cell phenotype but also the differentiation stage can predispose the fate of affected cells. Indeed, proliferating cells are generally more sensitive to radiation damage and undergo apoptosis at lower doses compared to terminally differentiated parenchymal and vascular cells.

(249) Evidently, the pathogenesis of radiation-related brain disease is multifactorial and depends on the latency of cell responses and the dynamics of radiation-related structural and functional alterations, which determine the temporal course and finally the severity of organic brain injury. In the context of the above considerations, there are three main pathophysiological concepts to explain the complex mechanisms underlying the age-dependent radiation-related brain disease. One of these is based on the pathogenic mechanism of hippocampal neurogenesis, and the others are focused on the neurovascular and neuroinflammatory etiology of the disease.

(250) Age-dependent effects of IR exposure on hippocampal neurogenesis: The hippocampal formation is a crucial structure for memory processing, learning, spatial navigation, and emotions (Chauhan et al., 2021). The hippocampus is divided into the dentate gyrus (DG) and different subregions of the cornu ammonis. In the subgranular zone (SGZ) of the DG neural stem cells continuously self-renew and differentiate into neurons in a process called adult neurogenesis (Toda and Gage, 2018). Depending on the chronological age of the individual, new neurons are generated from asymmetrical division of progenitor radial glial cells in the SGZ, a narrow layer of cells located between the granule cell layer (GCL) and the hilus of the DG. During their post-mitotic maturation these neuroprogenitors of the SGZ migrate into adjacent GCL where they establish their mature morphological and functional characteristics with the outgrowth of axons and dendrites, thereby integrating themselves into established neuronal networks (Götz et al., 2016). An increasing amount of evidence indicates that adult neurogenesis is tightly controlled by environmental conditions in the neurogenic niche, which consists of glia cells such as microglia and astrocytes.

(251) Increasing insights from rodent models indicate that IR exposure (even in the moderate and low dose range) impairs hippocampal neurogenesis by eliminating radiosensitive neuroprogenitors and suppressing the differentiation of neuroprogenitors into mature neurons (Monje et al., 2002). The age-dependent sensitivity of the developing brain is correlated with the number and vulnerability of neuroprogenitors in the hippocampal stem cell niche (Fukuda et al., 2005). Proliferating neuroprogenitors are inherently more radiosensitive than post-mitotic neurons and IR exposure reduces or ablates hippocampal neurogenesis as the result of massive death of proliferating neuroprogenitor cells. Reduced hippocampal neurogenesis following prenatal irradiation in moderate and low dose ranges is associated with lower cognitive performance as evaluated by behavioral testing (Casciati et al., 2016; Verreet et al., 2016).

(252) According to radiobiological principles that dividing cells are more likely to go into apoptosis after radiation damage, the developmental stage of the brain at the time of IR exposure plays an important role in determining radiation-related neurocognitive changes (Fukuda et al., 2005). In different rodent models, specific biological effects were observed at different developmental stages of the brain, suggesting that the biological mechanisms may differ depending on the timing of IR exposure. Following prenatal IR, proliferating neuroprogenitors in the embryonic brain are highly sensitive to radiation-induced apoptosis, at

doses on the order of 10 mGy (Saha et al., 2014). After in-utero IR of mouse embryos, apoptosis is one of the main mechanisms of radiation-induced neurodevelopmental dysfunction (Nowak et al., 2006; Etienne et al., 2012; Verreet et al., 2016). To investigate the influence of low doses of radiation on brain development, mice were exposed prenatally (E11 develpmental stage) to IR doses ranging between 0.1–1.0 Gy and brain structures and functions were characterised by magnetic resonance (MR) imaging and behavioral testing at 12 weeks of age (Verreet et al., 2015). Microcephaly with reduced total and regional brain volumes was apparent at doses ≥ 0.3 Gy. Altered brain functions could be verified by behavioral testing at doses ≥ 0.5 Gy (Verreet et al., 2016). Neural progenitors are characterised by specific DNA damage responses and the deleterious effects of IR increase with the proportion of actively proliferating neural progenitors, which are more prone to cell cycle arrest, apoptosis, or premature differentiation (Roque et al., 2012; Mokrani et al., 2020). This proportion of proliferating neuropogenitors varies in terms of both developmental stage and specific brain region, and thus explains the increased radiosensitivity of circumscribed stem cell niches in the brain. Prenatal IR can also alter the fate of neural progenitors by inducing premature neurogenesis, thus reducing the pool of proliferating precursors (Eom et al., 2016). For perinatal IR exposure, defects in adult neurogenesis were detectable even several months after brain IR and associated with long-term consequences on learning and memory (Daynac et al., 2013; Pineda et al., 2013; Kempf et al., 2015). During postnatal hippocampus development, some long-term alterations (increased apoptosis, alterations in neurogenesis, mitochondrial homeostasis, and altered protein expression involved in synaptic plasticity) were observed at doses of 0.1 Gy (Casciati et al., 2016). Daily low-dose irradiation (5x, 10x, 15x, 20x fractions of 0.1 Gy) of juvenile and adult mice revealed an accumulation of radiation-induced DNA damage, leading to the progressive decline of hippocampal neurogenesis with decreased numbers of stem/progenitor cells and reduced complexity of dendritic architectures, clearly more pronounced in the immature brain of young animals (Schmal et al., 2019). In addition, these investigations showed a pronounced shift in the differentiation process of stem/progenitor cells from neurogenesis to gliogenesis (Schmal et al., 2021). Further evidence supporting the role of neuroprogenitor loss in cognitive dysfunction following IR exposure comes from studies showing that cognitive functions can partially be rescued by neural stem cell transplantation (Killer et al., 2021).

(253) Radiation-induced microvascular damage and neuroinflammation altering the microenvironment of the stem cell niche is another possible explanation for the mode of IR action in the hippocampus region. Dysregulated signalling in the hippocampal microenvironment may disturb complex differentiation processes and may suppress the physiological maturation of progenitor cells to their neuronal phenotype (Eom et al., 2016). In the hippocampal microenvironment, the control of cellular survival and proliferation is dependent on balanced networks of neural signals, being a prerequisite for ordered tissue development and maintenance (Zhang et al., 2018; Antonelli et al., 2021). The transcription factor cAMP response element-binding (CREB) plays critical roles in proliferation, survival and differentiation of neuronal stem/progenitor cells (Merz et al., 2011). In response to genotoxic insults, CREB activation leads to the expression of various neuroprotective factors, thereby contributing to the protection and survival of newborn neurons (Hladik et al., 2020). Disturbance of CREB functions in the brain can contribute to the development and progression of neurodegeneration.

(254) Increasing research evidence indicates that radiation effects on brain parenchyma cells are aggravated by the associated damage to the microvascular endothelium, potentially leading to cerebrovascular inflammation and breach of the blood-brain barrier (Gorbunov and Kiang, 2021). The blood-brain barrier sustains brain tissue homeostasis by regulating the molecular trans-endothelial transport between brain parenchyma and blood circulation and by restricting the translocation of peripheral immune cells. This well-structured barrier system is composed

of endothelial cells, pericytes, and astrocyte end-feet that form tight junctions and support endothelial vesicular transport. In the acute setting, radiation-induced vascular damage is characterised by membrane destabilisation of endothelial cells (detachment from basement membranes) and their induction of apoptosis leading to vascular leakage (Rubin et al., 1991; Li et al., 2003). Radiation damage to the microvascular endothelium can promote cerebrovascular inflammation. The endothelial pro-inflammatory phenotypes are characterised by the expression of cytokines, chemokines, and adhesion molecules, that facilitate the recruitment and homing of immune cells to sites of tissue injury (Pena et al., 2000). Disruption of the blood-brain-barrier results in the passage of systemic immune and inflammatory cells; their infiltration of the brain parenchyma enhances neuroinflammation (Allen and Limoli, 2022). In terms of mechanisms of late endothelial damage, inadequate repair of damaged endothelial cells and blood-brain barrier disruption may contribute to tissue hypoxia and the impairment of metabolic homeostasis (Allen and Limoli, 2022). After radiation-related brain damage, the structural and functional integrity of neurovascular networks may decline gradually within weeks through years' post-IR and this may foster long-term cerebrovascular complications such stroke. Even repetitive low-dose irradiation (20 × 0.1Gy) of juvenile and adult mice induced long-lasting inflammatory responses, most pronounced in the hippocampal region of juvenile brain, with an increased local blood flow and vascular permeability, as measured by MR imaging (Schmal et al., 2021).

(255) Neuroinflammation is a multifaceted immune response involving numerous cell types (both within the CNS and in the peripheral circulation) with the aim of clearing the brain parenchyma from damaged cells or infectious agents. Microglia and astrocytes are considered key players in initiating the inflammatory response following injury to the CNS (Dong et al., 2015). Dying or damaged cells within irradiated brain areas release cellular debris into the microenvironment, thereby priming local microglia and astrocytes to initiate an inflammatory cascade. Microglia cells reveal a large degree of heterogeneity in structure and shape, depending upon their activation state. While resting or surveilling microglia cells have highly branched morphologies, activated microglia cells acquire de-ramified or amoeboid forms. Microglia cells remove dying cells and cellular debris through phagocytosis, and together with astrocytes secrete inflammatory cytokines, chemokines, reactive oxygen and nitrogen species (Osman et al., 2020). Reactive astrocytes can acquire hypertrophic morphologies after injury, involving extension of processes and swelling of cell bodies (Schmal et al., 2021). These pleiotropic responses of glia cells have shown to facilitate both inflammation resolution and exacerbation, and ultimately, these responses determine the extent of damage and subsequent regeneration. Persistent activation of microglia and astrocytes are hallmarks of chronic neuroinflammation (Schmal et al., 2021) and their prolonged activation leads to a vicious circle, where secretion of pro-inflammatory cytokines and other neurotoxic agents leads to further neuronal damage, thereby promoting neurotoxicity and neurodegeneration. Collectively, emerging evidence identifies neuroinflammation as a critical mediator of the adverse effects of RT on neurocognitive function.

(256) Overall, research in pre-clinical rodent models provides basic insights for the pathophysiology of radiation-related brain injury and the development of neurocognitive impairment. Overall, the developing and immature brain is particularly vulnerable to the damaging effects of IR. The high content of progenitor cells, and that IR induces both the acute loss of neuroprogenitors through apoptosis and the perturbed microenvironment in stem cell niches, leading to disturbed proliferation and differentiation of neuroprogenitors, are fundamental mechanisms that explain the increased radiosensitivity of the immature brain. The extent of radiation damage is directly dependent on the developmental stage of neurogenesis and age-related increased cell loss of radiosensitive neuroprogenitors subsequently leads to pronounced neuroinflammatory and neurovascular responses. However, multiple factors are

implicated in the etiology of radiation-related cognitive impairment. Apart from the main causes presented above, there are other neurobiological processes such as impaired neuronal network connectivity, neurotransmitter imbalance, altered brain metabolism, etc. that may contribute to pathogenesis of radiation-related brain injury. Elucidation of these complex relationships in the pathophysiology of radiation-related brain injury are only at an early stage.

2.3.3.4. Range and distribution within the population

(257) Apart from as a result of possible serious nuclear accidents, reduction in cognitive performance in humans as a result of radiation-related brain damage is only conceivable in the context of radiation treatment. Radiotherapy-related neurocognitive impairment is a major clinical problem in neuro-oncology, especially in the treatment of brain tumours in children. Protective strategies aimed at minimising the injury to the proliferative regions of the brain may greatly reduce the adverse side effects and improve the quality of life of the growing number of children who survive their malignancies. Improved precision in terms of dose distribution of recent technological developments in RT has the potential to reduce the radiation dose to critical brain regions that contribute the most to the development of cognitive impairment. In recent years inverse planning and dose modulation with intensity-modulated radiation therapy have allowed for more precise targeting and sparing of critical structures in the brain. Image guidance during radiation delivery has further refined radiotherapy treatment, and additional improvements in precise dose distribution are explored with particle therapies, such as those using protons or carbon ions (Grosshans et al., 2018). Nevertheless, even RT procedures with stereotactic precision, produce scattered radiation to normal brain tissue outside the target areas, presenting an ongoing challenge in the radiation treatment of children (Auerbach et al., 2023). However, using modern techniques of conformal radiotherapy with conventionally fractionated doses and limited volumes, the expected liklihood of pronounced neurotoxicity for adult brain tumour survivors should be reasonably low. Nevertheless, optimising radiation parameters is always a beneficial approach to reduce neurotoxicity and improve neurocognitive outcome. Given that high-dose fractional and total doses are likely to result in cognitive disability, it is recommendable to use conventional fractionation and the lowest efficient total dose according to evidence-based literature. When possible, IR volume must be limited using highly conformal techniques, such as IMRT. When whole-brain RT is necessary, IMRT with hippocampal avoidance is expected to decrease the likelihood of severe adverse effects. Despite immense improvements in precision radiotherapy, there is an ongoing need for effective therapeutics in mitigating and treating radiation-related brain injury. Therapies targeting CNS injuries must consider the multifaceted nature of cellular responses (e.g., by harnessing protective or reparative effects of inflammatory responses while simultaneously dampening their deleterious effects), so that the progression and exacerbation of radiation-related neuroinflammation can potentially be controlled. Therefore, a greater understanding of the precise mechanisms governing radiation-related brain injury will aid in the development of better therapeutics for the neurocognitive sequelae of cerebral RT.

2.3.3.5. Modification of the radiation response of brain tissue

(258) Treatment-, tumour- and patient-associated factors decisively influence the liklihood of radiation-related impairment of neurocognitive function, as previously discussed. In addition to the outstanding importance of the individual age, additional patient-related factors may influence the extent of radiation-related brain damage as discussed below.

(a) Modification by genetic and epigenetic factors

(259) In recent years genome-wide association studies (GWAS) have successfully identified single nucleotide polymorphisms (SNPs) associated with radiation toxicity in patients with different tumour entities. These genetic studies of radiation-related adverse responses generally focused on candidate genes involved in DNA repair, DNA damage signalling, cell cycle control, and inflammatory response, but many of them had limited sample sizes and suffered a lack of independent replication. A recent prospective clinical trial (GARTP, Genetic Architecture of the Radiotherapy Toxicity and Prognosis) identified genetic variants in the centrosomal protein CEP128 that conferred increased risk of radiation-related brain injury in nasopharyngeal carcinoma patients (Wang et al., 2019). CEP128 is a key regulator of ciliation and plays important roles in coordinating cellular signalling pathways in neuronal cells, thereby regulating cell migration and differentiation. GWAS identified different alleles of the apolipoprotein E (APOE) gene (involved in lipoprotein metabolism) to increase the risk of developing age-related cognitive decline (particularly in women) and Alzheimer's disease characterised by accumulation of pathological protein aggregates (amyloid-β peptide plaques, neurofibrillary tangles). To determine potential effects of APOE isoform and sex on radiation-related cognitive impairments, the brain of male and female mice with defined APOE genotype were irradiated and their cognitive performance was assessed 3 months after IR exposure. The experimental results of behavioral testing indicate that the effects of radiation on cognitive performance are dependent on sex- and APOE isoform (Villasana et al., 2006). However, in a recent clinical phase III trial the search for baseline biomarkers associated with CNS injury after radiotherapy for single brain metastasis revealed that the APOE genotype was not associated with neurocognitive decline (Huntoon et al., 2022).

(b) Modification by underlying conditions

(260) Vascular structural and functional abnormalities due to underlying comorbidities may be associated with an increased liklihood of radiation-related CNS damage. However, there are no experimental or clinical studies showing that cardio-vascular comorbidities (such as arterial hypertension, diabetes mellitus and hypercholesterolemia) increase the likelihood of radiation-related neurocognitive impairment due to increased vascular damage. The crosstalk between the nervous and immune systems has gained increasing attention for its emerging role in neurological disorders. So far, however, there are no studies on whether an altered immune system may influence radiation-related neurocognitive decline. Experimental and clinical studies are warranted to investigate potential modifications of radiation-related CNS damage by underlying comorbidities.

(c) Modification by life-style factors

(261) In human clinical trials smoking was the only life-style factor associated with an increased likelihood of the development of radiation-related leukoencephalopathy (Terziev et al., 2021). Systematic studies on the importance of other lifestyle factors (obesity, healthy diet, regular exercise) regarding radiation-related cognitive impairment have not yet been carried out. Experimental studies in rodents showed that forced running exercise appears to mitigate radiation-related cognitive deficits e.g., by stimulating hippocampal neurogenesis (Ji et al., 2014; Zhang et al., 2020).

2.3.3.6. Summary and conclusion on the range observed & main contributory modifying factors

(262) Multiple treatment-, tumour- and patient-related factors influence the extent of radiation-associated brain damage with potential impairment of neurocognitive functions. The chronological age of the organism at the time of IR exposure is a decisive factor influencing individual radiation sensitivity. This important fact is already considered as far as possible in the radiation treatment of children, even if there are no dedicated regulations within the framework of the official radiation protection legislation. There are indications of genetic, epigenetic and lifestyle factors, such as smoking affecting the risk of neurocognitive outcomes after exposure but the available evidence base is small and likely incomplete.

2.3.3.7. Approaches to prediction – genetic and functional assays

(263) An optimised prediction framework to assess the risk of radiation-related brain injury following radiotherapy constitutes an important aspect of precision medicine (Sultana et al., 2020). Identifying individual patients or subsets of patients at risk of developing late effects prior to treatment using predictive biomarkers may improve the outcome of radiotherapy. Identification by predictive biomarkers of patient cohorts who might experience such late effects as brain injury could enable exclusion of radiosensitive patients from radiotherapy, or dose escalation to the tumour in less sensitive patients, and thus result in overall better treatment outcome (Prasanna et al., 2014).

The identification of potential biomarkers of radiation-related brain injury is challenging, because it is not possible to routinely and/or repetitively biopsy the brain and also because neurocognitive deficits occur several months after IR exposure, requiring long-term studies in patient populations with poor prognosis. Potential biomarkers were identified based on cellular and molecular mechanisms associated with pathologic changes leading to functional deficits, including the key processes mitotic death of proliferating progenitor cells, endothelial damage and neuroinflammatory response. Emerging evidence suggests that, following radiation-related brain damage, various biochemical indicators of tissue breakdown (neuronal and glia markers) are rapidly released into biofluids (cerebrospinal fluid or blood serum), making them strong candidate biomarkers for assessing radiation-related brain injury and/or late occurring neurocognitive functional deficits. So far, however, validated biological biomarkers for the practical application in the clinical routine could not be established. The development and refinement of biochemical indicators combined with structural and functional imaging modalities will probably be the future research direction of biomarker application. In addition to predicting, research and development of biomarkers could also bring great benefits for early detection and diagnosis of brain injury, as well as for monitoring subsequent health outcomes after treatment. Although the practical application of biomarkers is still relatively new, it is expected that the translation of this research advance to radiation oncology will help stratify patients for optimised treatment, minimize side effects, and improve therapeutic efficacy and quality of life.

3. CANCERS

3.1. Overview

3.1.1. Importance for radiological protection and medical uses of radiation

(264) Radiation-related cancer historically observed by pioneers of IR research and later in various medical cohorts and the atomic bomb survivors can also result from exposures to moderate to high doses of IR as secondary cancers following external beam radiotherapy (Wakeford, 2004). Various epidemiological studies indicate an association between the appearance of cancers and exposure to IR even at low doses. Although these studies do not establish a link of causality between the exposure to IR and the cancer, the consistency of the observation across settings, and the existence of a dose-effect relationship favour a probable link.

(265) There is substantial evidence that cancer results mostly from DNA insults and subsequent mutations from various origins (genetic, environmental, medical and lifestyle). Normal cells evolve progressively in time to a neoplastic state in three classical consecutive steps (initiation, promotion and progression) by acquiring a succession of hallmarks corresponding to lesions which provide sustained proliferative signalling, evading growth suppression, resisting cell death, enabling replicative immortality, inducing angiogenesis, escaping immunologic surveillance, reprograming of energy metabolism activating invasion and metastasis (Hanahan and Weinberg, 2011). A cancer may result from a combination of DNA lesions/mutations disturbing normal cellular homeostasis, where a minimum of 10 lesions seems necessary (Bernstein et al., 2013) or possibly less when one oncogene is activated.

(266) The medical use of IR for both diagnosis and treatment is governed by three considerations; justification, optimisation and limitiation. The repetition of dose (mostly due to the repetition of examinations) should be carefully considered since the total cumulated dose can reach 100mGy which is the currently accepted lower limit at which significant epidemiological associations have been reported between IR exposures and cancer. Medical screening, e.g., of breast cancer by X ray mammography, is performed in individuals who are not patients and deliver repeated intentional exposures raising ethical and legal responsibilities. Such exposures still require justification, optimisation and limitation. Notheless, it remains desirable to know which persons may present an abnormal response to IR in such a way that they are prioritised for Magnetic Resonance Imaging or other non-ionising radiation diagnostic imaging modalities.

3.1.2. Risk Metrics

(267) In Section 1.4 some basic definitions of the terms absolute and relative risk are provided, and here we consider these and related topics in greater depth in relation to their use in studies of radiation cancer risk, particularly in human populations.

(268) Risk models for incidence or death from a disease of interest (e.g., cancer) that describe the outcomes seen in studies of people exposed to radiation are the starting point for the calculation of estimates of radiation detriment and for modifying these calculations so that they can be transported from exposed populations followed through epidemiological studies to predict radiation detriments or risk in other populations. Two widely used models to describe the incidence or mortality from a disease of interest are the excess additive risk (EAR) model and the excess relative risk (ERR) model. Both models can be used to describe the incidence or mortality rate of the disease of interest at given age. Here “incidence rate at a given age”

means the chance of having the outcome at that age assuming that the person has survived up to that age, this incidence rate is also known as the hazard rate, or just hazard.

(269) At its simplest, the EAR model describes the hazard of disease at a given age in terms of the sum of two terms: the background incidence (or mortality) rate in unexposed individuals plus the absolute increase in incidence or mortality rate that is due to exposure to radiation at a given dose. We can write this mathematically as:

$$\text{Hazard of Disease} = \text{Baseline\_Hazard} + \text{Excess\_Absolute\_Risk},$$

where the Excess_Absolute_Risk refers to the excess due to radiation exposure.

(270) A relative risk RR model describes the same data but using a different emphasis, this time on the risk due to radiation as a multiplier of the baseline risk. For example, suppose that a person exposed to a certain dose is 1.1 times more likely to get (a particular) cancer at a given age than is an otherwise similar person without radiation exposure, this person has a relative risk of cancer equal to 1.1 compared to an unexposed person. Another way of saying the same thing is to note that the risk of disease in the exposed person is 10 percent greater than in the unexposed person so that this person has a 10 percent excess relative risk. An ERR model describes this excess risk directly. In other words, this can be expressed as follows:

$$\text{Hazard of Disease} = \text{Baseline\_Hazard} \times (1 + \text{Excess\_Relative\_Risk}).$$

(271) It is important to realize that ERR models and EAR models can yield identical descriptions of the risk of disease in an exposed population. For example, an EAR model can be transformed by division to an ERR model:

$$\text{Hazard of Disease} = \text{Baseline\_Hazard} \times \left(1 + \frac{\text{Excess\_Absolute\_Risk}}{\text{Baseline\_Hazard}}\right),$$

and vice-versa.

(272) The hazard of disease is not however a fixed quantity, it varies with an individual's age and is often influenced by other factors such as sex, age at exposure, race/ethnicity, and year of birth (often reflective of changes in time of unmeasured risk factors). To account for this each of the terms in the EAR and ERR models, (Baseline_Hazard, Excess_Absolute_Risk, and Excess_Relative_Risk) can have modifiers so that Baseline_Hazard may depend upon age, sex, and year of birth, while the Excess_Absolute_risk or Excess_Relative_Risk portions, may typically depend upon age, sex, and year of exposure, and for protracted exposures, on dose rate. Because of the flexibility of both EAR and ERR models in allowing for dependence upon modifiers such as age, sex, etc., generally speaking both models "fit the data" equally well. One model may be more complicated than another (depending on more modifiers) but both give similar descriptions of the disease rates in the population being studied, and using either description results in very similar detriment calculations, for the population under study.

3.1.3. Transfer of Risk

(273) It is well known that incidence and mortality rates of many diseases vary by population. For example, the (baseline) rate of stomach cancer has historically been much higher in Japan (and in the LSS) than in European or U.S. populations and the reverse is true for breast cancer. Calculation of excess incidence due to radiation in a population for which the baseline rate of disease is very different depends upon whether risk calculations assume an ERR or EAR model. For example, consider using an EAR versus an ERR model fitted to the Japanese (LSS) data to compute the excess number of cases of stomach cancer due to radiation

exposure in a European or U.S. population. Letting E and J denote the Japanese and European populations:

(274) Using ERR model for transfer from J to E, so that the ERR is kept the same in the two populations we have

$$\mathrm{EAR(E)} = \mathrm{baseline(E)} * \mathrm{ERR(J)}.$$

(275) Using the EAR model for transfer gives:

$$\mathrm{EAR(E)} = \mathrm{EAR(J)} = \mathrm{baseline(J)} * \mathrm{ERR(J)}.$$

(276) Since baseline(J) is greater than baseline(E) the excess absolute risk is greater when using an EAR model for transfer than when using the ERR model. Therefore, the radiation detriment for stomach cancer that is transferred from J to E, will also be greater using the EAR model than the ERR.

(277) Similar considerations apply when considering baseline risk factors. For example, consider transferring the radiation excess for lung cancer from a largely non-smoking population, NS, to one with a high rate of smoking, S. Therefore:

$$\mathrm{EAR(S)} = \mathrm{baseline(S)} * \mathrm{ERR(NS)}$$

when using an ERR model and

$$\mathrm{EAR(S)} = \mathrm{EAR(NS)} = \mathrm{baseline(NS)} * \mathrm{ERR(NS)}.$$

(278) So that the radiation detriment will be higher using the ERR model than the EAR.

3.1.4. Genetics

(279) As stated by the US National Cancer Institute, cancer is a genetic disease caused by changes in genes that control the way cells grow and multiply (https://www.cancer.gov/about-cancer/causes-prevention/genetics). Hanahan and Weinberg have defined the hallmarks of cancer as 'acquired functional capabilities that allow cancer cells to survive, proliferate, and *disseminate'* (Hanahan and Weinberg, 2011; Hanahan, 2022).

(280) Some types of cancer are more likely to be hereditary or at least to have a hereditary component. Below (Table 3.1) is a list of common cancers, and the most common genes that have been linked to increased risk for each (https://www.facingourrisk.org/info/hereditary-cancer-and-genetic-testing/genes-by-cancer-types).

(281) Nevertheless, there recently has been considerable new information discovered about risk due to genetic variation using the genome-wide association study (GWAS) approach. For the major cancers and other diseases, hundreds of relatively common risk alleles each with a relatively small effect have been discovered and are beginning to be used in composite (as genetic risk scores) to predict genetic risk. These genetic risk scores are beginning to explain a significant fraction of genetic heritability as measured by familial relative risks (e.g., relative risk due to having a near relation with the disease). These scores are already being promoted for individual risk prediction by genotyping companies such as 23 and Me (www.23andme.com/en-gb/) and Ancestry.com (https://www.ancestry.com/). Moreover, these scores may explain some of the differences between ancestry groups in baseline risk which as seen above is a key aspect of the transfer of excess risk between populations for the purpose of detriment calculations. The existence of reasonably informative genetic risk scores raises the

question about whether these predictors of baseline risk can be incorporated into excess risk and detriment calculations. The same issues are involved as above. If an ERR model is used for estimating the excess risk due to radiation exposure, then our improved knowledge of baseline risk (e.g., the genetic risk score) will influence the estimate of excess risk due to radiation whereas the calculations from the EAR model would be immune from these considerations.

Table 3.1. Common cancers and the most common genes linked to increased risk.

Cancer	Genes
Breast cancer in women	ATM, BARD1, BRCA1, BRCA2, CHEK2, CDH1, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
Breast cancer in men	BRCA1, BRCA2, CHEK2, PALB2
Colorectal cancer	APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, PMS2, CHEK2, POLE, PTEN, SMAD4, STK11, TP53, PUTYH
Endometrial cancer	BRCA1n EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11
Fallopian tube, ovarian, primary peritoneal cancer	ATM, BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D,
Gastric cancer	APC, CDH1, STK11, EPCAM, MLH1, MSH2, MSH6, PMS2
Melanoma	BAP1, BRCA2, CDK4, CDKN2A, PTEN, TP53
Pancreatic cancer	ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PMS2
Prostate cancer	ATM, BRCA1, BRCA2, CHEK2, HOXB13, EPCAM, MLH1, MSH2, MSH6, PMS2

(282) Four genome-wide associations studies (GWAS) evaluated the effects of treatment-related radiation exposure and large numbers of single nucleotide polymorphisms (SNP) on the risk of subsequent malignancies in exposed populations.

(283) In the Childhood Cancer Survivor Study (CCSS), Morton et al. (2017) identified one SNP which was statistically significantly associated with breast cancer among childhood cancer survivors who received a breast dose of 10 Gy or more. The study concludes that germline genetic variants other than those related to high-risk syndromes can modify the effect of radiation exposure on breast cancer risk after childhood cancer.

(284) Sapkota et al. (2019) identified polymorphisms in a specific gene (HTR2A) associated with subsequent basal cell carcinoma among irradiated participants of the CCSS. The associations were validated in a separate cohort of irradiated childhood cancer survivors.

(285) Opstal-van Winden et al. (2019) identified 9 SNPs interacting with radiation exposure on breast cancer risk in a case-only design with breast cancer patients after chest radiotherapy for Hodgkin lymphoma (HL) and first primary breast cancer patients. A score composed of these SNPs was associated with breast cancer among chest-irradiated HL survivors, as well as a previously developed polygenic risk score for breast cancer in the general population. The results indicate that previously observed associations between genetic polymorphisms and breast cancer hold among radiation-exposed subjects and that there may be polymorphisms specifically associated with radiotherapy-related breast cancer risk.

(286) A further study of the risk of second cancers arising in childhood cancer survivors (Gibson et al, 2024) found that the cumulative incidence of subsequent cancer by age 50 years was increased for those with high versus low polygenic risk scores, specifically for cancers of the breast, thyroid and skin (melanoma and squamous cell carcinoma). No association was found in relation to colorectal cancer. The findings of this extensive study of some 11,220 cancer survivors suggest a degree of shared genetic etiology for the above malignancies in the general population and survivors, which remains evident in the context of strong radiotherapy-related risk.

(287) In summary, the evidence available so far on radiation-gene interactions and subsequent malignancies is limited and lacks replication but could be a promising approach. The results do currently not provide strong evidence that radiation effects differ by genetic variants, nor can variant-specific radiation effects be estimated. There is hope for the future as larger cohorts are established and followed, including both diagnostically and medically exposed individuals. Ultimately these findings could result in individual risk/detriment prediction.

3.2. Evidence for variation in response to radiation carcinogenesis

3.2.1. Modification by age and sex

3.2.1.1. Human

(288) In this section, and the following related human epidemiology sections, we focus on evidence obtained from investigations of the Japanese atomic bombing survivor cohorts, notably the Life Span Study. These studies remain the main source of evidence used in the evaluation of health effects. The issue of modification of risk by biological sex is covered in more detail in Section 4 and Annex A.

(289) The Life Span Study (LSS) cohort of Japanese atomic-bomb survivors provides the primary source of information to evaluate the health effects from external exposure to ionising radiation as well as the variation of the radiation effects by other factors, such as sex, age at exposure and attained age. The main body of information is obtained from follow-up studies of the mortality and cancer incidence in the LSS cohort of about 120,000 subjects who were exposed to atomic-bomb radiation of doses ranging 0–4 Gy.

(290) In the latest report of the LSS cancer mortality follow-up, among 86,611 eligible subjects who were in the cities of Hiroshima and Nagasaki at the time of bombing and have DS02 doses estimated, 58% (50,620) died during the follow-up period from1950 to 2003, of which 22% (10,929) were from solid cancer (Ozasa et al., 2012). The radiation-associated increases were examined for mortality from all solid cancer as a group as well as 17 site-specific cancers (esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung, breast, uterus, ovary, prostate, bladder, kidney parenchyma, renal pelvis and ureter, and other solid). For each of these cancer endpoints, the radiation-associated risk was systematically evaluated using a standard form of the excess risk; $\beta d \cdot \exp\{\gamma_1(e-30)/10\}(a/70)^{\gamma_2}(1+\gamma_3 s)$, where each of the effect modifying factors [$\mathrm{sex}(s) = -1/+1$, age at exposure (e) and attained age(a)] was assumed to proportionally affect the linear non-threshold function of dose (d) in both ERR and EAR models. With this form, β is interpreted as the sex-averaged excess risk per unit dose (Gy) at age 70 after exposure at age 30 (with which we present risk estimates in the following unless otherwise noted). The estimated risks and effect modifications for the major cancer sites are presented in Table 3.3.

(291) For mortality from all solid cancers combined, the sex-averaged ERR at age 70 after exposure at age 30 was 0.42 (95%CI: 0.32, 0.53) per 1 Gy while EAR was 26.4 (20.3, 32.8) per 10,000 person-year-Gy. These risks were significantly larger for females than males, with a female to male ratio (F:M ratio) of 2.1 in ERR, but the ratio was much smaller (1.1) and insignificant when considering the EAR. The radiation related risks for all solid cancers combined significantly decrease as the age at exposure increases, with 29% and 19% decreases per a decade increase of age at exposure in ERR and in EAR, respectively. ERR exhibits a significant descrease with increasing attained age proportionally to age to the power −0.86, whilst EAR tends to increase with age to the power 3.40.

(292) The mortality risks among those individuals exposed in utero to atomic bomb radiation in Hiroshima or Nagasaki in August 1945 were analyzed for associations with mother's uterine dose. During the follow up between 1950 and 2012, a total of 339 deaths (including 137 from solid cancer) were observed among 2463 subjects. Among males, the ERR/Gy was significant for noncancer disease mortality (1.22, 0.10–3.14), but not for solid cancer mortality (−0.18, <−0.77–0.95). Among females, the unadjusted ERRs/Gy were increased for solid cancer (2.24, 0.44–5.58). The ERRs/Gy did not change appreciably for solid cancer mortality by adjustment for potential mediators including head size, birth weight, and parents' survival status.

(293) The cancer incidence data in the LSS were analysed by Preston et al. based on a follow-up between 1958 and 1998, during which 17,448 first primary cancers were identified from 105,427 subjects with individual DS02 dose estimates available. The radiation-associated increase in incidence of all solid cancer was examined using the standard risk function in both ERR and EAR models (Table 3.2). With the linear dose response model, the sex-averaged ERR was estimated to be 0.47 (95%CI: 0.40, 0.54) per 1 Gy at age 70 after exposure at age 30, and the corresponding EAR was 52 (43, 60) per 10,000 person-year-Gy. These risks significantly varied by sex, with a female to male ratio of 1.6 and 1.4 in ERR and EAR, respectively, and decreased significantly with increasing age at exposure, by −17% and −24% per a decade increase of age at exposure in ERR and in EAR, respectively. ERR significantly decreased with increasing attained age, in proportion to age to the power −1.65, whilst EAR increased, in proportion to age to the power 2.38. Overall, the observed characteristics of the risk and the effect modification in the incidence data of all solid cancer were fairly similar to those for the mortality data.

(294) As noted in the opening paragraph of this section, the main focus here is the LSS; the LSS and environmental radiation exposure studies tend to include a wider age range of exposed persons as occupational and medical exposure studies are limited to specific groups of working age or in the age range where specific medical conditions present. Nonetheless, the impact of age-at-exposure has been considered in occupational studies, such as the INWORKS cohort (Daniels et al, 2024). The findings of Daniels et al do indicated some age-dependancy, but for some cancer types younger ages are at lower risk than older persons. However, this study uses <35 years of age as the youngest group, and as an occupational cohort, in effect is 18–35. Age-at-exposure has been considered in environmental exposure studies, such as those if the Techa river population (e.g., Krestinina et al, 2013). While a more representative range of ages is included in this study, age dependence is variable by leukaemia type.

(295) Grant et al. updated the LSS solid cancer incidence analysis by extending the follow-up by 11 years up to year 2009 (Grant et al., 2017). With a total of 22,538 eligible first primary incident cancers diagnosed from 105,444 study subjects with the updated DS02R1 dose estimates available (Cullings et al., 2017), the radiation-associated increase in incidence of all solid cancers as a group was examined with adjustment for smoking. There was evidence for a significant sex difference in the ERR dose response shape; for females, the dose response was consistent with linearity, with an ERR of 0.64 per Gy (95% CI: 0.52, 0.77) at age 70 after exposure at age 30, while for males, a significant upward curvature was observed, which resulted in ERRs of 0.20 (95% CI: 0.12, 0.28) at 1 Gy and 0.010 (95% CI: −0.0003, 0.021) at 0.1 Gy. As observed in the previous studies, females' risks for incidence of all solid cancers combined appeared to be larger than males' risks, and, due to the curvature in males, the sex ratio of ERR was also variable, e.g., F:M ratio was 3 at 1 Gy and 6 at 0.1 Gy. ERR tended to decrease with increasing age, and the decrease was significantly more rapid in males compared to females. ERR was also found to decrease by 22% per a decade increase of age at exposure. As in the ERR model, the upward curvature was significant in the EAR dose response. The sex-specific EARs were estimated to be 54.7 and 42.9 excess cases per 10,000 person-year-Gy

(95% CI: 44.7 to 65.3) for females and males, respectively. The EAR increased with increasing attained age for both males and females but the sex difference was only marginally significant and decreasing with attained age.

(296) To further investigate the sex difference in the dose response curvature observed in the solid cancer incidence data analysis (Grant et al., 2017), additional analyses were conducted by excluding individual cancer sites or groups of sites from all solid cancers (Cologne et al., 2019) Curvature among males disappeared after excluding a few sites, which have unique features in age-specific background incidence that are not captured by a background-rate model fit to all solid cancers combined, leading the authors to conclude that misspecification of background rates can cause bias in inference about the shape of the dose response, so heterogeneity of background rates might explain at least part of the all solid cancer dose-response difference in curvature between males and females. To further investigate the sex-difference in the dose response relationship, all solid cancer mortality and incidence data were analyzed in parallel under a similar condition (e.g., with a follow-up in 1958 to 2009, DS02R1 doses, not-in-city (NIC) subjects included) (Brenner et al., 2022). Fitting sex-specific ERR models, upward curvature was suggested for solid cancer mortality among both males (p = 0.06) and females (p = 0.01) with no significant sex difference (p > 0.7), while the curvature was significant only among males (p = 0.01) with a significant sex difference (p = 0.01) for solid cancer incidence. It was also indicated that the strength of evidence for the upward curvature likely depend on the composition of sites for all solid cancer, age at exposure or calendar period.

Table 3.2. Parameter estimates and 95% confidence intervals for the preferred ERR and EAR risk models for all solid cancer mortality and incidence in the LSS cohort of Japanese atomic-bomb survivors (significant effects are in bold). ERR and EAR parameters are for the risk at attained age 70 after exposure at age 30.

ERR model

	ERR per Gy					
	Male	female	sex-averaged	FM ratio	age at exposure*	attained age (power)
Mortality 1950–2003	**0.27**	**0.57**	**0.42** **(0.32,0.53)**	**2.1** **(1.4, 3.1)**	**−29%** **(−41, −17)**	**−0.86** **(−1.60, −0.06)**
Incidence 1958–1998	**0.36**	**0.58**	**0.47** **(0.40, 0.54)**	**1.6** **(1.31, 2.09)**	**−17%** **(−25, −7)**	**−1.65** **(−2.1, −1.2)**
Incidence 1958–2009	linear: 0.094 (<0.02, 0.23) quadratic: **0.11** **(0.04, 0.19)**	**0.64** **(0.52, 0.77)**	**0.42** **at 1Gy** **0.037** at 0.1 Gy	**3.1** **at 1Gy** **6.1** at 100 mGy	**−22%** **(−30, −13)**	male: **−2.70** **(−3.58, −1.81)** female: **−1.36** **(−1.86, −0.84)**

EAR model

	EAR per 10,000 person-years-Gy					
	Male	female	sex-averaged	FM ratio	age at exposure	attained age (power)
Mortality 1950–2003	**25.1**	**27.7**	**26.4** **(20.3, 32.8)**	**1.10** **(0.80, 1.74)**	**−19%** **(−31, −7)**	**3.40** **(2.7, 4.1)**
Incidence 1958–1998	**43**	**61**	**52** **(43, 60)**	**1.40** **(1.10, 1.79)**	**−24%** **(−32, −16)**	**2.38** **(1.9, 2.8)**
Incidence 1958–2009	linear: 21.7 (<−1.7, 47.7) quadratic: **21.2** **(6.8, 37.6)**	**54.7** **(44.7, 65.3)**	**48.8** **at 1Gy** **3.93** **at 0.1 Gy**	**1.3** **at 1Gy** **2.3** **at 100 mGy**	**−30%** **(−37, −22)**	**2.89** **(2.14, 3.68)** **2.07** **(1.64, 2.53)**

*Change in % per a 10-year increase in age at exposure.

(297) Ozasa et al. analyzed the site-specific cancer mortality of the LSS cohort in 1950–2003 (Ozasa et al., 2012). The risk increased significantly for most major cancer sites, including stomach, lung, liver, colon, breast, gallbladder, oesophagus, bladder and ovary. Table 3.3 exhibits the estimates for the excess risk as well as effect modifications for major cancer sites. ERR significantly varied by sex for stomach (with an FM ratio of 3.7) and lung (2.7), by age at exposure for breast (by −45% per a decade increase in age at exposure), and by attained age for colon (in proportion to age to the power −5.8). With the EAR model, there was no significant sex difference observed for any endpoint, while the risk varied significantly by age at exposure for breast (by −51% per a decade increase in age at exposure), and increased with attained age for stomach (in proportion to age to the power 2.0), colon (3.2), liver (6.0), lung (6.2), breast (3.0) and bladder (7.5).

(298) Preston et al. (2007) analysed the LSS cancer incidence data from a follow-up from 1958 to 1998 for cancers at 19 sites (oral cavity, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, lung, non-melanoma skin, female breast, uterus, ovary, prostate, renal cell, bladder, brain/CNS, thyroid and other solid). Table 3.3 shows the parameter estimates for major cancer sites. ERR significantly varied by sex for stomach (with an FM ratio of 2.3), lung (4.8) and bladder (3.1). As in analysis for all solid cancers, ERR decreased with increasing age at exposure for most sites and, in particular, significantly for non-melanoma skin (by −73% per a decade increase in age at exposure) and thyroid (−31%), while it increased significantly for lung cancer (by 20%). ERR significantly decreased with attained age for stomach (in proportion to age to the power −1.5), lung (−1.94), breast (−2.3) and thyroid (−1.5). EAR significantly varied by sex for all solid (with a F:M ratio of 1.4), colon (0.2), liver (0.3), lung (1.5) and thyroid (3.6), by age at exposure for all solid (with a −24% change per 10 yr increase), colon (−56%), skin (−61%), breast (−37%), thyroid (−46%), by attained age for all solid (with a power of 2.38), stomach (1.9), colon (6.9), lung (4.2), skin (4.4), breast (1.7) and bladder (6.3).

(299) Furukawa et al. (2013) analysed the LSS thyroid cancer incidence in 1958–2005. With a linear non-threshold dose–response model, the gender-averaged ERR and EAR at age 60 after exposure at age 10 were estimated to be 1.28 (95% CI: 0.59, 2.70) per 1 Gy and 29.5 (13.8, 49.6) cases per 100,000 person-year-Gy, respectively. Both the ERR and EAR significantly and rapidly decreased with increasing age-at-exposure by 53% and 70%, respectively, per decade increase in exposure age. Allowing for the modifying effect of age-at-exposure, the ERR tended to decrease and the EAR to increase with increasing attained age, in proportion to age to the power 1.27 and 1.03, respectively. The EAR for women was significantly higher than that for men, with a female:male ratio of 6.3, while the ERR sex ratio was smaller and not statistically significant.

(300) Sugiyama et al. (2014) analysed the LSS skin cancer incidence by histological types with a follow-up between 1958 and 1996. A significant excess relative risk (ERR) of basal cell carcinoma (BCC) was estimated to be 0.74 at 1 Gy (95% CI: 0.26, 1.6) at age 70 after exposure at age 30 based on a linear-threshold model with a threshold dose of 0.63 Gy (95% CI: 0.32, 0.89) and a slope of 2.0 (95% CI: 0.69, 4.3). The risk increased 11% with each one-year decrease in age at exposure, but with no significant sex difference.

(301) Sugiyama et al. (2020) analysed the LSS colorectal cancer incidence by anatomical site (1958–2009). Radiation effects on colorectal cancer rates, adjusted for smoking, alcohol intake and frequency of meat consumption and body mass index (BMI) by anatomical subsite (proximal colon, distal colon and rectum) were examined in a cohort of 105,444 atomic bomb survivors. Significant linear dose–responses were found for total colon (sex-averaged ERR/Gy for 70 years old exposed at age 30 = 0.63, 95% CI: 0.34, 0.98), proximal (ERR/Gy = 0.80, 95% CI: 0.32, 1.44) and distal colon cancers (ERR = 0.50, 95% CI: 0.04, 0.97), but not for rectal cancer (ERR = 0.023, 95% CI: −0.081, 0.13). The ERR decreased with attained age for total

colon, but not for proximal colon cancer, and with calendar year for distal colon cancer. The ERRs and EARs did not vary by age at exposure, except for decreasing trend in EAR for proximal colon cancer. The ERR for proximal cancer persists over time, but that for distal colon cancer decreases.

(302) Sakata et al. (2019) analysed incidence of upper digestive tract cancers (oral cavity/pharyngeal, esophageal, and stomach cancers) in the LSS 1958–2009. While the radiation-associated risk of oral cavity/pharyngeal cancer, other than salivary gland, was not significant, that of salivary gland cancer exhibited a strong and significant linear dose response with an estimated ERR of 2.54 per Gy (95%CI: 0.69 to 6.1), which tended to decrease with increasing age at time of exposure (–66% per decade, 95% CI: –88% to –32%). The dose response for esophageal cancer was statistically significant and better described by a linear-quadratic model with evidence for a sex difference (female > male, $p = 0.02$). Adjustment for lifestyle factors (smoking, alcohol consumption) had almost no impact on the radiation effect estimates.

(303) Sadakane et al. (2019) analysed LSS incidence of liver, biliary tract, and pancreatic cancers (1958–2009). Radiation dose was significantly associated with liver cancer risk (ERR per Gy: 0.53, 95% CI: 0.23, 0.89; EAR per 10,000 person-year Gy: 5.32, 95% CI: 2.49, 8.51). ERRs by age-at-exposure categories were significantly increased among those who were exposed at 0–9, 10–19 and 20–29 years, but not significantly increased after age 30 years. Radiation ERRs were little affected by adjustment for smoking, alcohol consumption or BMI. Examined effect modification by sex, age at exposure and attained age and joint effects of radiation with smoking, alcohol consumption and BMI. The radiation-associated risk for pancreatic cancer was significant among women (ERR per Gy: 0.70, 95% CI: 0.12, 1.45) but not among men.

(304) Brenner et al. (2020) evaluated radiation risks of brain/central nervous system cancers (glioma, meningioma, schwannoma, and other or not otherwise specified tumours) in the LSS cohort. With a total of 285 cases diagnosed among 105,444 subjects, ERR/Gy was 1.67 (95% CI: 0.12, 5.26) for glioma, 1.82 (95% CI: 0.51, 4.30) for meningioma, 1.45 (95% CI: −0.01, 4.97) for schwannoma and 1.40 (95% CI: 0.61, 2.57) for all CNS tumours as a group. For each tumour type, the dose–response was consistent with linearity and appeared to be stronger among males than among females, particularly for meningioma.

(305) The risks of urinary tract cancer (UTC) and kidney cancer incidence were analyzed with 90 UTC and 218 kidney cancer cases diagnosed in the LSS cohort during the period between 1958–2009, Adjusted for smoking, there was a strong linear radiation dose response for UTC, with an ERR 1.4 per Gy. The risk for females was greater than that for males by a factor of 3.4 (95% CI: 1.4 to 8.6), but with no significant effect modification by age at exposure or attained age. There was no significant association of kidney cancer with radiation exposure, although sex-specific dose responses were found to be statistically different.

(306) The radiation-associated risk of ovarian cancer between 1958 and 2009 among 62,534 female survivors in the LSS cohort was analysed (Utada et al., 2021). Based on 288 first primary cases, the radiation-associated risk of total ovarian cancer was positive but not significant (ERR/Gy = 0.30, 95%CI: −0.22 to 1.11). There was no significant evidence for the ERR varying with time since exposure or age at exposure.

(307) Prostate cancer incidence among males of the LSS was analyzed, with 851 incident cases of prostate cancer diagnosed among 41,544 male subjects during the period between 1958 and 2009 (Mabuchi et al., 2021). More than half of the total cases were diagnosed among those who were 20 years or younger at the time of bombing. A significant linear dose response was observed with an estimated ERR per Gy of 0.57 (95% CI: 0.21, 1.00), with a suggestive decrease with increasing age at exposure ($p = 0.09$).

Table 3.3. Parameter estimates and 95% confidence intervals for the ERR and EAR risk models for site-specific solid cancer mortality and incidence in the LSS cohort of Japanese atomic-bomb survivors (significant effects are shown in bold). ERR and EAR paratemers are for the risk at age 70 after exposure at age 30.

cancer site	ERR*/Gy	FM ratio	age at exposure	attained age	EAR	FM ratio	age at exposure†	attained age
LSS cancer mortality 1950–2003								
esophagus	**0.60**	4.3	35%	−3.70				
	(NA,1.64)	(0.54, >100)	(−28, 184)	(−9.6, 1.0)				
stomach	**0.33**	**3.7**	−18%	−0.74	**4.1**	1.80	18%	**2.00**
	(0.17,0.52)	**(1.3, .100)**	(−47, 20)	(−2.5, 1.2)	**(2.1, 6.7)**	(0.66, 32)	(−18, 62)	**(1.0, 3.6)**
colon	**0.34**	1.4	−3%	**−5.80**	**1.6**	0.98	−30%	**3.20**
	(0.05,0.74)	(0.39, 6.6)	(−51, 63)	**(−10.4, 2.2)**	**(0.5, 3.0)**	(0.34, 4.5)	(−58, 2)	**(1.3, 5.3)**
liver	**0.38**	1.6	−8%	0.02	**3.4**	0.69	−25%	**6.00**
	(0.11,0.62)	(0.43, 7.9)	(−62, 42)	(−2.8, 4.2)	**(0.7, 5.9)**	(0.19, NA)	(−66, 15)	**(3.2, 12)**
gallbladder	**0.48**	0.42	−27%	−1.90				
	(0.12,1.02)	(0.001, 2.4)	(−76, 40)	(−6.6, 7.8)				
lung	**0.75**	**2.7**	−7%	−0.04	**6.5**	0.78	−16%	**6.20**
	(0.51,1.03)	**(1.3, 6.8)**	(−35, 29)	(−2.2, 2.6)	**(4.3, 9.0)**	(0.40, 1.8)	(−37, 6)	**(4.5, 8.2)**
female breast	**0.90**		**−45%**	−0.17	**2.3**		**−51%**	**3.00**
	(0.30,1.78)		**(−67, −17)**	(−2.7, 2.3)	**(1.0, 3.8)**		**(−68, −30)**	**(1.7, 4.7)**
ovary	**0.20**		−22%	−4.10				
	(NA,1.30)		(−96, 218)	(−33, 1.9)				
bladder	**1.19**	1.7	−2%	0.49	**1.2**	0.40	−1%	**7.50**
	(0.27,2.65)	(0.2, 9.0)	(−62, 92)	(−3.6, 6.1)	**(0.3, 2.4)**	(0.0, 5.3)	(−65, −80)	**(3.1, 15)**
LSS cancer incidence 1958–1998								
stomach	**0.34**	**2.3**	−13%	**−1.50**	**9.5**	1.00	−2%	**1.90**
	(0.22,0.47)	**(1.2, 4.5)**	(−35, 15)	**(−2.7, −0.3)**	**(6.1, 14)**	(0.5, 2.1)	(−26, 29)	**(0.8, 3.1)**
colon	**0.54**	0.5	1%	−2.68	**8**	**0.20**	**−56%**	**6.90**
	(0.30,0.81)	(0.17, 1.01)	(−36, 45)	(−5.1, 0.4)	**(4.4, 12)**	**(0.06,0.52)**	**(−74, −34)**	**(4.5, 10)**
liver	**0.30**	0.9	3%	−2.70	**4.3**	**0.30**	−21%	3.60
	(0.11, 0.55)	(0.16, 2.4)	(−37, 68)	(−5.8, 0.5)	**(0.2, 7.2)**	**(0.10, 3.2)**	(−57, 378)	(−3.5, 6.1)
lung	**0.81**	**4.8**	**20%**	**−1.94**	**7.5**	**1.50**	2%	**4.23**
	(0.56, 1.1)	**(2.6, 12)**	**(−7, 54)**	**(−3.7, −0.2)**	**(5.1, 10)**	**(0.82, 3.9)**	(−20, 28)	**(2.8, 5.7)**
non-melanoma skin	**0.17**	2.2	**−73%**	0.27	**0.35**	0.80	**−61%**	**4.36**
	(0.003, 0.55)	(0.93, 5.7)	**(−85, −55)**	(−1.4, 1.9)	**(0.0, 1.1)**	(0.43, 1.7)	**(−75, −42)**	**(2.4, 6.5)**

(*continued on next page*)

Table 3.3. (*continued*).

cancer site	ERR*/Gy	FM ratio	age at exposure	attained age	EAR	FM ratio	age at exposure†	attained age
LSS cancer incidence 1958–1998								
female breast	**0.87**		0%	**−2.30**	**9.2**		**−37%**	**1.70**
	(0.55, 1.3)		(−19, 24)	**(−3.5, −1.1)**	**(6.8, 12)**		**(−48, −24)**	**(1.0, 2.5)**
bladder	**1.23**	**3.1**	−3%	0.33	**3.2**	0.70	−19%	**6.30**
	(0.59, 2.1)	**(0.17, 1.0)**	(−42, 56)	(−2.8, 4.4)	**(1.1, 5.4)**	(0.21, 10)	(−54, 41)	**(3.2, 10.2)**
thyroid	**0.57**	1.3	**−31%**	**−1.50**	**1.2**	**3.60**	**−46%**	0.60
	(0.24, 1.1)	(0.56, 3.9)	**(−59, 4)**	**(−2.9, 0.0)**	**(0.48,2.2)**	**(1.78, 9.5)**	**(−68, −12)**	(−0.58, 1.8)
other solid	**0.91**	1.5	−26%	−0.79	5	0.70	−19%	2.80
	(0.50, 1.4)	(0.70, 3.3)	(−51, 4)	(−2.4, 1.0)	(2.7, 7.7)	(0.37,1.58)	(−44, 9)	(1.3, 4.7)

EAR, excess absolute risk.

*Excess absolute risk per 10,000 person-year-Gy.

†Change in % per a 10-year increase in age at exposure.

3965 3.2.1.2. Animal studies

3966 *(a) Age at exposure*

3967 (308) Although there is no straightforward way to relate ages between species, attempts of
3968 cross-species comparison have been made based on the developmental and ageing processes
3969 (Table 3.4) (Sengupta, 2013; Dutta and Sengupta, 2016). With these comparisons in mind,
3970 following terms are adopted to describe rodent ages: prenatal, <0 days; neonatal, 0–1 week;
3971 juvenile, 1–5 weeks; young adult, 0.1–0.5 years; maturity, 0.5–1.5 years; aged, >1.5 years. For
3972 dogs, we follow the terms in the original literature.
3973
3974 Table 3.4. Comparison of ages between human and rodents (Sengupta, 2013; Dutta and
3975 Sengupta, 2016).

Event	Human age	Rodent age
Birth	0 year	0 day
Weaning	0.5 year	3–4 weeks
Puberty	11.5 year	5–6 weeks
End of skeletal growth	20 year	7 months*
Reproductive senescence	51 year	15–20 months
Death	80 year	2–3 years

3976 *Age for rat.
3977
3978 (309) Age at exposure. In general, young animals are more susceptible than fetuses and
3979 adults when risks of all malignancies are analyzed collectively (Covelli et al., 1984; Benjamin
3980 et al., 1991; Sasaki, 1991; Sasaki and Fukuda, 2005). Individual organs nevertheless exhibit
3981 specific age-at-exposure dependence. Exposure during short time windows spanning the
3982 prenatal and neonatal periods is associated with the highest incidence/mortality of radiation-
3983 related pituitary tumour of wild-type animals (Sasaki, 1991) as well as medulloblastoma of
3984 *Ptch1*$^{+/-}$ mice (Pazzaglia et al., 2006, 2009; Tsuruoka et al., 2016) and renal tumours of
3985 *Tsc2*$^{Eker/+}$ rats (Kokubo et al., 2010). In most organs, susceptibility is high in the prenatal or
3986 neonatal period and continues to be high until various postnatal ages ranging from neonatal to
3987 young adult stages, as in liver cancer (Vesselinovitch et al., 1971; Di Majo et al., 1990; Sasaki,
3988 1991; Maisin et al., 1996) and thymic (Sunaoshi et al., 2015) and other malignant lymphoma
3989 (Vesselinovitch et al., 1971; Sasaki, 1991) of wild-type mice, skin cancer of wild-type rats and
3990 *Ptch1*$^{+/-}$ mice (Burns et al., 1993; Mancuso et al., 2006), small intestine and colon tumours of
3991 *Apc*$^{Min/+}$ mice (Okamoto and Yonekawa, 2005; Ellender et al., 2006; Sasatani et al., 2023),
3992 thyroid cancer of dogs (Benjamin et al., 1997), ovarian tumours in wild-type mice and rats
3993 (Vesselinovitch et al., 1971; Knowles, 1985; Sasaki, 1991; Sasaki and Fukuda, 2008) and bone
3994 malignancies of mice and dogs (Luz et al., 1979, 1985; Nilsson et al., 1980; Sasaki, 1991;
3995 Lloyd et al., 1999). In contrast, a small number of organs show low susceptibility in early life.
3996 Adults are more susceptible regarding induction of Harderian gland tumours (Vesselinovitch
3997 et al., 1971; Sasaki, 1991) and myeloid leukaemia (Sasaki, 1991) of mice. Regarding the breast,
3998 studies on wild-type rats (Bartstra et al., 1998a,b; Imaoka et al., 2013, 2017, 2019) indicate
3999 high susceptibility during the peripubertal ages and lower susceptibility before and after the
4000 period, as supported by a recent retrospective analysis (Imaoka et al., 2023). Results on lung
4001 tumours should be viewed with caution, as most lung tumours in rodents occur as non-fatal
4002 diseases late in life at a small incidence and results are thus likely to be affected by other causes
4003 of death. Although more mice were found with lung tumour at death after irradiation at prenatal
4004 to juvenile stages than other periods (Vesselinovitch et al., 1971; Sasaki, 1991), the age-

specific rate of death with lung tumour was higher after irradiation as juveniles and young adults than neonates (Yamada et al., 2017). Detailed information is summarised in Table 3.5.

Table 3.5. Experiments on the effect of age at exposure on radiation-related carcinogenesis.

Age range examined*	Radiation	Animal	Outcome	Period of high susceptibility	Reference
Overall					
Juvenile – maturity (day 35–365)	γ rays	Mouse	All tumours	Juvenile (day 35)	Doi et al., 2020
Prenatal – maturity (E17–day 365)	γ rays	Mouse	All solid tumours	Neonatal – juvenile (day 0–35)	Sasaki and Fukuda, 2005
Prenatal (E14 and E17)	γ rays	Mouse	All solid tumours	Constant (E14–17)	Uma Devi and Hossain, 2000
Neonatal – juvenile (day 7 and 21)	X rays	Mouse	All malignant neoplasms	Constant (day 7 and 21)	Maisin et al., 1996
Neonatal – juvenile (day 7 and 21)	Neutrons	Mouse	All malignant neoplasms	Juvenile (day 21)	Maisin et al., 1996
Prenatal – young adult (E8–day 365)	γ rays	Dog	All fatal malignancies	Perinatal (E55–day 2)	Benjamin et al., 1991
Young adult – maturity (3–14 mo)	X rays	Rat	All malignant tumours	Constant (3–14 mo)	Anisimov and Prokudina, 1986
Prenatal –aged (E17–19 mo)	X rays	Mouse	All tumours	Young adult (3 mo)	Covelli et al., 1984
Prenatal (E12–E18)	X rays	Mouse	All tumours	Prenatal (E16–18)	Sasaki et al., 1978b
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant epithelial neoplasms	Young adult (3 mo)	Castanera et al., 1971
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant non-epithelial neoplasms	Juvenile (1 mo)	Castanera et al., 1971
Pituitary					
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Pitutary tumour	Prenatal (E 17)	Sasaki, 1991
Brain					
Prenatal – neonatal (E14–day 10)	γ rays Neutrons	Mouse, *Ptch1*$^{+/-}$	Medulloblastoma	Prenatal – neonatal (E17–day 1)	Tsuruoka et al., 2016; Tsuruoka et al., 2021
Neonatal – juvenile (day 1–10)	γ rays	Mouse, *Ptch1*$^{+/-}$	Medulloblastoma	Neonatal (day 1–4)	Pazzaglia et al., 2009
Neonatal – juvenile (day 1 or 10)	X rays	Mouse, *Ptch1*$^{+/-}$	Medulloblastoma	Neonatal (day 1)	Pazzaglia et al., 2006
Kidney					
Prenatal – young adult (E15–7 wk)	γ rays	Rat, *Tsc2*$^{Eker/+}$	Renal tumour (adenoma, adenocarcinoma)	Prenatal – neonatal (E15–day 5)	Kokubo et al., 2010
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant kidney neoplasm	Juvenile and young adult (1–3 mo)	Castanera et al., 1971

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4011 Table 3.5. (*continued*).

Age range examined	Radiation	Animal	Outcome	Period of high susceptibility	Reference
Liver					
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Liver tumour	Neonatal (day 0–7)	Sasaki, 1991
Prenatal –aged (E17.5–19 mo)	X rays	Mouse	Liver tumour	Prenatal – young adult (E17.5–3 mo)	Di Majo et al., 1990
Prenatal –aged (E17.5–19 mo)	Neutrons	Mouse	Liver tumour	Prenatal (E17.5)	Di Majo et al., 1990
Prenatal – juvenile (E17–5 wk)	X rays	Mouse	Hepatocellular tumour	Neonatal (day 0)	Sasaki et al., 1978a
Neonatal – juvenile (day 1–42)	X rays	Mouse	Hepatoma	Neonatal (day 1)	Vesselinovitch et al., 1971
Lymphoma					
Neonatal – young adult (1–7 wk)	γ rays	Mouse	Precursor B cell lymphoma	Constant (1–7 wk)	Tachibana et al., 2020
Neonatal – young adult (1–4, 4–7, 8–11 wk)	X rays	Mouse	Thymic lymphoma	Constant (1–4, 4–7, 8–11 wk)	Sunaoshi et al., 2015
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Malignant lymphoma, lymphocytic	Juvenile (day 35)	Sasaki, 1991
Juvenile – young adult (1–3 mo)	γ rays	Mouse	Lymphoma	Juvenile (1 mo)	Gorelik et al., 1984
Neonatal – juvenile (day 1–42)	X rays	Mouse	Malignant lymphoma	Constant (day 1–42)	Vesselinovitch et al., 1971
Skin					
Neonatal – young adult (day 3–60)*	X rays	Mouse, *Ptch1*$^{+/-}$	Skin basal cell carcinoma	Neonatal (day 3, anagen)	Mancuso et al., 2006
Juvenile – maturity (day 28–182)	Electrons	Rat	Skin cancer	Constant (day 28–182)	Burns et al., 1993
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant skin neoplasm	Juvenile and young adult (1–3 mo)	Castanera et al., 1971
Intestine					
Prenatal – juvenile (E7–day 35)	X rays	Mouse, *Apc*$^{Min/+}$	Intestinal adenoma	Neonatal (day 2–10)	Ellender et al., 2006
Neonatal – young adult (2–48 days)	X rays	Mouse, *Apc*$^{Min/+}$	Intestinal tumour, small intestine	Neonatal – juvenile (day 2–24)	Okamoto and Yonekawa, 2005
Neonatal – young adult (2–48 days)	X rays	Mouse, *Apc*$^{Min/+}$	Intestinal tumour, colon	Neonatal – juvenile (day 2–10)	Okamoto and Yonekawa, 2005
Neonatal – young adult (1–61 days)	γ rays	Mouse, *Apc*$^{Min/+}$, chromosome 13 consomic	Intestinal tumour, small intestine	Juvenile (day 11–21)	Sasatani et al., 2023
Thyroid					
Prenatal – young adult (E8–1 y)	γ rays	Dog	Thyroid neoplasms	Neonatal – juvenile (day 2–70)	Benjamin et al., 1997

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4013

4014 Table 3.5. (*continued*).

Age range examined	Radiation	Animal	Outcome	Period of high susceptibility	Reference
Mammary					
Juvenile – young adult (1 – 15 wk)	γ rays	Rat	Mammary cancer	Young adult (7 wk)	Imaoka et al., 2023
Juvenile – young adult (3–13 wk)	γ rays	Rat	Mammary cancer	Constant (3–13 wk)	Imaoka et al., 2019
Juvenile – young adult (3–7, 7–15 wk)	γ rays, chronic	Rat	Mammary cancer	Juvenile (3–7 wk)	Imaoka et al., 2019
Neonatal – young adult (1–7 wk)	Neutrons	Rat	Mammary cancer	Young adult (7 wk)	Imaoka et al., 2017
Prenatal – young adult (E14–15 wk)	Carbon ions	Rat	Mammary cancer	Young adult (7 wk)	Imaoka et al., 2013
Prenatal – young adult (E14–15 wk)	γ rays	Rat	Mammary cancer	Neonatal – young adult (1–7 wk)	Imaoka et al., 2013
Neonatal – young adult (1–15 wk)	X rays	Rat	Mammary cancer	Juvenile – young adult (5–15 wk)	Yamada et al., 2017
Juvenile – young adult (3–7 wk)	γ rays	Rat	Mammary cancer	Young adult (7 wk)	Imaoka et al., 2011
Juvenile – young adult (2–10 wk)	X rays	Mouse, *Apc*$^{Min/+}$	Mammary tumour	Young adult (7–10 wk)	Imaoka et al., 2006
Young adult – maturity (8–64 wk)	γ rays	Rat, estradiol-treated (for ~1 y)	Mammary cancer	Young adult (8–15 wk)	Bartstra et al., 1998b
Young adult – maturity (8–64 wk)	γ rays	Rat	Mammary cancer	Young adult – adult (8–36 wk)	Bartstra et al., 1998a
Ovary					
Prenatal –aged (E17–day 550)	γ rays	Mouse	Ovarian tumour	Neonatal and juvenile (day 0–35)	Sasaki and Fukuda, 2008
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Ovarian tumour	Neonatal – young adult (day 0–105)	Sasaki, 1991
Neonatal – juvenile (day 5–30)	X rays	Rat	Ovarian tumour	Neonatal (day 5)	Knowles, 1985
Prenatal (E11–E16)	X rays	Mouse	Ovarian tumour	Prenatal (E14–16)	Schmahl and Kriegel, 1980
Neonatal – juvenile (day 1–42)	X rays	Mouse	Ovarian tumour	Juvenile (day 15–42)	Vesselinovitch et al., 1971
Bone/muscle					
Juvenile – maturity (3 mo – 5 y)	^{239}Pu, ^{226}Ra	Dog	Skeletal malignancies	Young adult (6 mo)	Lloyd et al., 1999
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Bone tumour	Juvenile (day 35)	Sasaki, 1991
Juvenile – maturity (3–60 mo)	^{226}Ra	Dog	Osteosarcoma	Constant (3–60 mo)	Bruenger et al., 1991
Juvenile – maturity (3–60 mo)	^{239}Pu	Dog	Osteosarcoma	Young adult (18 mo)	Bruenger et al., 1991
Juvenile – young adult (4–10 wk)	^{227}Ac or ^{227}Th	Mouse	Bone osteosarcoma	Constant (4–10 wk)	Muller et al., 1990
Juvenile – maturity (1–12 mo)	^{227}Th	Mouse	Bone osteosarcoma	Juvenile (1 mo)	Luz et al., 1985

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Table 3.5. (*continued*).

Age range examined	Radiation	Animal	Outcome	Period of high susceptibility	Reference
Bone/muscle					
Juvenile – maturity (day 25–300)	$^{90}Sr(NO_3)_2$	Mouse	Bone osteosarcoma	Young adult (day 75)	Nilsson et al., 1980
Juvenile – maturity (1 and 5–6 mo)	^{224}Ra or ^{227}Th	Mouse	Bone osteosarcoma	Constant (1–6 mo)	Luz et al., 1979
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant bone neoplasm	Juvenile (1 mo)	Castanera et al., 1971
Juvenile –aged (1–21 mo)	Neutrons	Rat	Malignant skeletal muscle neoplasm	Juvenile (1 mo)	Castanera et al., 1971
Harderian gland					
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Harderian gland tumour	Juvenile – young adult (day 35–105)	Sasaki, 1991
Neonatal – juvenile (day 1–42)	X rays	Mouse	Harderian gland tumours	Juvenile (day 15)	Vesselinovitch et al., 1971
Leukaemia					
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Myeloid leukaemia	Young adult (day 105)	Sasaki, 1991
Juvenile – young adult (5–10 wk)	X rays	Mouse	Leukaemia	Constant (5–10 wk)	Robinson and Upton, 1978
Lung					
Neonatal – young adult (1–15 wk)	X rays	Rat	Lung cancer	Juvenile – young adult (5–15 wk)	Yamada et al., 2017
Young adult – maturity (day 84 and 450)	$^{239}PuO_2$	Rat	Lung cancer	Young adult (day 84)	Lundgren et al., 1995
Prenatal – maturity (E17–day 365)	γ rays	Mouse	Lung tumour	Prenatal – neonatal (E17–day 7)	Sasaki, 1991
Young adult – maturity (day 70–450)	$^{144}CeO_2$	Mouse	Lung cancer	Young adult (day 70)	Lundgren et al., 1980
Neonatal – juvenile (day 1–42)	X rays	Mouse	Lung adenoma	Constant (day 1–42)	Vesselinovitch et al., 1971

E, embryonic day; wk, week; y, year.
*Focus on hair cycle (anagen vs. telogen) rather than age itself.

(310) Mechanistic evidence suggests that the above-mentioned variation among tissues is associated with the age-related change in the biology of both individual tissues and the systemic environment. The perinatal high susceptibility period coincides with the presence of specific cell types that might be vulnerable to carcinogenic insults, at least in the models of hereditary medulloblastoma and renal tumours (Pazzaglia et al., 2006; Kokubo et al., 2010). The high activity of crypt fission in the intestine coincides with the peak in the susceptibility to intestinal tumorigenesis induced either by radiation or via conditional knockout of a driver gene (Sasatani et al., 2023). The peak in the susceptibility of neonatal wild-type mice to radiation-related intestinal and liver tumours is associated with the refractoriness of the normal tissue cells in this period to radiation-induced apoptosis and cell cycle arrest, possibly leading to survival and proliferation of cells with mutations (Miyoshi-Imamura et al., 2010; Shang et al., 2017). A transplantation experiment suggests that the high susceptibility of young mice to induction of thymic lymphoma is associated with systemic environment rather than the intrinsic nature of

the lymphocytic lineage (Utsuyama and Hirokawa, 2003), whereas the fluctuation in susceptibility during young life (neonatal to pubescent) may be related to the preference of the proliferation signal of the immature lymphocytes (Sunaoshi et al., 2022). Refractoriness of prenatal and neonatal rats to mammary carcinogenesis induced by whole-body high dose exposure is related to induction of premature ovarian failure and resulting alterations in the hormonal milieu (Mazaud Guittot et al., 2006; Imaoka et al., 2013). Nevertheless, neonatal rats are also resistant to tumour induction by local thoracic irradiation sparing the ovary (Yamada et al., 2017), suggesting other mechanisms such as the high radiosensitivity in the clonogenicity of mammary cells during neonatal and juvenile periods (Shimada et al., 1994). The refractoriness of young animals to induction of lung tumours and myeloid leukaemia is associated with low susceptibility of the lung tissue to radiation-induced inflammation (Johnson et al., 2010) and resistance of bone marrow cells to radiation-induced reproductive cell death (Ariyoshi et al., 2014), which may lead to persistence of hematopoietic cell clones with chromosomal aberrations (Nakano et al., 2014).

(311) Attained age/time since exposure. Analysis of the effect of these time factors on radiation disease requires mathematical modelling, but only a few animal studies attempted such analysis. Even in the small number of studies that took the approach, the risk models therein very often adopt time-independent formulation, with assumption of proportional radiation-related increase to the baseline risk (e.g., Cox's proportional hazard model). As a result, it is difficult to see animal experiments as a rich source of information on the effect of attained age or time since exposure. An exceptional study by Sasaki and Fukuda (2005) indicated an increasing trend of EAR and a decreasing trend of ERR with attained age as a power function. Other studies generally indicated the same trend (Table 3.6). Re-analyses of past animal studies are thus warranted to clarify if attained age/time since exposure modify radiation-related cancer risk in manners observed in humans.

Table 3.6. Effect of attained age/time since exposure on radiation-related carcinogenesis in animals.

Method	Radiation	Animal	Outcome	Trend with attained age/TSE	Reference
Time[*]					
Qualitiative	γ rays (20 mGy/day)	Mouse	All tumours	ERR, decrease EAR, peak at 400–500 days	Tanaka et al., 2017
Qualitative	γ rays	Mouse	Thymic lymphoma[†]	EAR, peak at TSE 60–90 days	Dange et al., 2007
Attained age					
Model analysis	γ rays	Mouse	All solid	ERR, decrease (power of −1) EAR, increase (power of 1–2)	Sasaki and Fukuda, 2005
Model analysis	Electron, Ar ions	Rat	Skin cancer [b]	EAR, increase (power of 2)	Burns et al., 1993
Qualitative	γ rays	Mouse	All tumours	EAR, increase	Sasaki, 1991
Model analysis	^{239}Pu, ^{226}Ra	Dog	Osteosarcoma	EAR, increase (exponential)	Bruenger et al., 1991
Qualitative	X rays	Mouse	All tumours	EAR, increase	Sasaki et al., 1978b
Model analysis	X rays	Rat	Lung cancer	ERR, increase (spline)	Yamada et al., 2017
Model analysis	γ rays	Rat	Mammary cancer	ERR, decrease (power of −0.7) EAR, increase (power of 0.6)	Imaoka et al., 2023

[*]Attained age is equivalent to time since exposure because of fixed age at exposure.
[†]Incidence is interpreted as EAR because of the negligible baseline incidence. TSE, time since exposure.

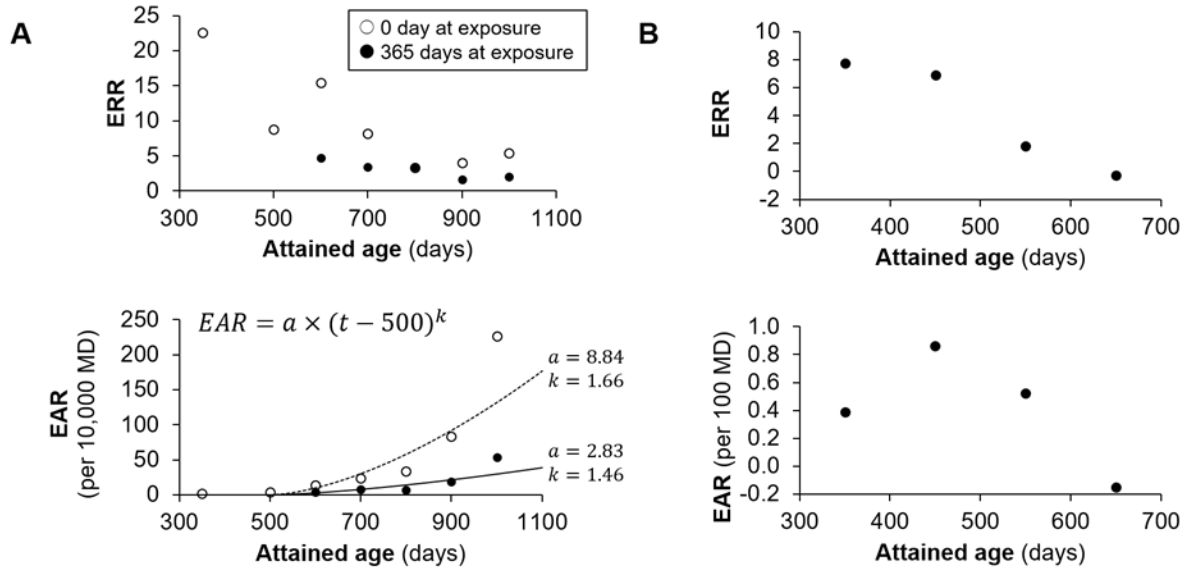

Fig. 3.1. Examples of the effect of attained age in animal carcinogenesis studies. A. Mortality from all tumours in B6C3F1 mice acutely γ-irradiated at 1.9 Gy (Sasaki and Fukuda, 2005). B. Incidence of all tumours in B6C3F1 mice chronically γ-irradiated at a cumulative dose of 8 Gy (Tanaka et al., 2017). MD, mouse day. Data in original studies have been reanalyzed.

(312) A number of animal experiments have clarified the sex-specific effects of radiation on various tissues (Table 3.7). Sex was treated as an effect modifier in the statistical analysis of the results on very rare occasions (Muggenburg et al., 1996; Chernyavskiy et al., 2017). Some quantitative studies treated sex for adjustment but not as an effect modifier (Zander et al., 2020; 2021). Some studies did not directly compare the effect of radiation between sexes, but they analyzed the dose response and provided sex-specific parameters of fitted equations (Ullrich and Storer, 1979; Coggle, 1988; Grahn et al., 1992; Di Majo et al., 1996; Suzuki et al., 2022) Most of other studies qualitatively compared the data between the sexes. In general, these studies agree with higher susceptibility of females to all solid tumours, higher susceptibility of males to myeloid leukaemia and liver tumours; the results differ among studies regarding lymphoma and lung, which is probably due to the difference in the strains used. Only small amounts of data are available regarding other tumours.

Table 3.7. Effect of sex on radiation-related carcinogenesis in animals

Measure	Animal	Radiation	Major results	Reference
Sex ratio (M:F) (95% CI)*	Mouse	γ rays	Solid cancer: 0.50 (0.34, 0.73) Lymphoma: 0.56 (0.38, 0.84)	Chernyavskiy et al., 2017
		Fe ions	Solid cancer: 0.78 (0.51, 1.18) Lymphoma: 0.79 (0.47, 1.32)	
		Si ions	Solid cancer: 0.63 (0.41, 0.97) Lymphoma: 0.73 (0.44, 1.22)	
Sex ratio (M:F) (95% CI)	Dog	$^{238}PuO_2$	Lung 1.34 (0.74, 2.42) Bone 1.02 (0.67, 1.57) Liver 0.78 (0.34, 1.78)	Muggenburg et al., 1996

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4085 Table 3.7. (*continued*).

Measure	Animal	Radiation	Major results	Reference
EAR/Gy (M vs. F) (mean ± SE)[†]	Mouse	γ rays	Tumours (except ovary): 6.27 ± 0.84 vs. 8.60 ± 0.94 Lymphoreticular tumour: 7.36 ± 1.08 vs. 3.65 ± 1.13 Vascular tumour: 6.67 ± 1.21 vs. 5.54 ± 1.03 Lung tumour: 5.35 ± 0.87 vs. 12.30 ± 1.43 Liver tumour: 2.24 ± 0.96 vs. 7.46 ± 1.11 Harderian gland tumour: 8.24 ± 0.70 vs. 9.69 ± 0.88	Grahn et al., 1992
Dose response (M vs. F) (mean ± SE)[‡]	Mouse	X rays	Myeloid leukaemia: 28.7 ± 12.3 vs. no induction Malignant lymphoma: 4.91 ± 3.62 vs. no induction Harderian gland tumour: 9.23 ± 1.46 vs. 13.2 ± 2.63 Life lost with tumour: 24 ± 3 vs. 56 ± 4	Di Majo et al., 1996
		Neutrons	Myeloid leukaemia: 67.0 ± 21.4 vs. no induction Malignant lymphoma: 55.7 ± 25.8 vs. no induction Harderian gland tumour: 373.5 ± 68.7 vs. 168.8 ± 42.5 Life lost with tumour: 570 ± 159 vs. 480 ± 4	
Dose response (M vs. F) (mean ± SE)[§]	Mouse	X rays Neutrons	Lung tumours 10.15 ± 2.71 vs. 6.01 ± 2.34 47.26 ± 13.40 vs. 51.63 ± 7.33	Coggle, 1988
Dose response (M vs. F)[¶]	Mouse	γ rays	Thymic lymphoma: 6.9/Gy vs. 120/Gy^2 Myeloid leukaemia: 6.5/Gy vs. 1.4/Gy	Ullrich and Storer, 1979a
Dose response (*D*, dose in Gy)	Mouse	γ rays	Harderian gland tumour: M: $1.5 + 0.3D + 1.3D^2$ F: $1.2 + 1.5D + 2.2D^2$ Pituitary: M: Too low to warrant analysis F: $6.3 + 0.8D + 1.3D^2$	Ullrich and Storer, 1979b
ERR/Gy (M vs. F)	Mouse	γ rays	Lung adenocarcinoma: 1.05 vs. 1.24	Suzuki et al., 2022
Qualitative	Mouse	γ rays	Mortality from neoplasms: F > M (prevalence: lymphoma F > M, liver M > F, adrenal, F > M, pituitary F > M, lung M > F, hemangiosarcoma M > F, soft tissue F > M)	Tanaka et al., 2007
Qualitative	Mouse	Neutrons	Breast: F only Fibrosarcoma: M > F Liver tumour: M > F Lung carcinoma: M > F Osteosarcoma: F only Other epithelial tumours: F > M Reticulum cell sarcoma: F > M	Storer and Fry, 1995
Qualitative	Rat	γ rays	All neosplasms: F > M	Gross et al., 1988

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Table 3.7. (*continued*).

Measure	Animal	Radiation	Major results	Reference
Qualitative	Mouse	X rays	Thymic lymphoma: M = F Liver tumour: M > F Lung tumour: F > M Pituitary tumour: F > > M Harderian gland tumour: F > M Vascular tumour: F > M	Sasaki and Kasuga, 1981
Qualitative	Rat	X rays	All neoplasms: F > M	Gross and Dreyfuss, 1979
Qualitative	Mouse	X rays	Hepatoma: M > F Lung tumour: M = F Harderian gland tumour: M = F	Vesselinovitch et al., 1971
Qualitative	Rat	X rays	All neoplasms: M = F	Anisimov and Osipova, 1993
Qualitative	Dog	γ rays	All cancer: F > M	Lao, 1998
Qualitative	Mouse	X rays	Myeloid leukaemia: M > F	Yoshida et al., 1993
Qualitative	Mouse	X rays	Thymic lymphoma: M = F	Okumoto et al., 1989
Qualitative	Mouse	γ rays	B cell lymphoma: M = F	Tachibana et al., 2020
Qualitative	Dog	^{226}Ra	Bone tumour: M = F	Polig et al., 2004
Qualitative	Mouse	^{224}Ra	Bone tumour: F > M	Muller et al., 1978
Qualitative	Mouse, *Apc*$^{1638N/+}$	X rays	Desmoid tumour: F > M	van der Houven van Oordt et al., 1997; van der Houven van Oordt et al., 1999
Qualitative	Mouse, *Apc*$^{1638N/+}$	γ rays	Intestinal tumour: M > F	Trani et al., 2013
Qualitative	Mouse, *Mlh1*$^{-/-}$, DSS-treated	X rays	Intestinal tumour: M = F (juvenile) M > F (young adult)	Morioka et al., 2015
Qualitative	Mouse	Neutrons	Liver tumour: M > F	Ito et al., 1992
Qualitative	Mouse	γ rays, neutrons	Liver tumour: M > F	Takahashi et al., 1992
Qualitative	Mouse	X rays	Liver cancer: M > F	Sasaki et al., 1978a
Qualitative	Rat	$^{239}PuO_2$	Lung tumour: M = F	Lundgren et al., 1995
Qualitative	Rat	$^{144}CeO_2$ inhalation	Lung tumour: M = F	Hahn and Lundgren, 1992
Qualitative	Mouse, NNK-treated	X rays	Lung tumour: F > M	Miller et al., 2013

F, female; M, male; DSS, dextran sodium sulfate; NNK, 4-(methylnitrosoamino)−1-(3-pyridyl)−1-butanone.

*Cox regression fitting of models supported significant intereaction between sex and radiation.

†Per 10^4 mouse-days per Gy at attained age 800–999 days, single γ ray exposure.

‡Cumulative percentage of animals (age-adjusted) or life lost (days) with tumour per Gy.

§Cumulative percentage of animals with tumour at attained age 12 months was fitted to $A + B \times \text{dose}^2 \times e^{-\alpha \times \text{dose}}$, and the value of B is shown.

¶Cumulative percentage of animals (age-adjusted) was fitted to $A + B \times$ dose (myeloid leukaemia) or $A + B \times \text{dose}^2$ (thymic lymphoma), and the value of B is shown.

3.2.2. Modification by lifestyle factors such as smoking, alcohol consumption, BMI, reproductive history/hormonal factors

3.2.2.1. Human

(313) Solid cancer incidence data in 1958–2009 was analysed by Grant et al. (2017) with adjustment for smoking. Smoking adjustment improved the fit over the unadjusted models, and an additive ERR model for the joint effect of radiation and smoking fit the data better than a multiplicative model. Due to the sex difference in smoking prevalence, the additive model, where the radiation-associated ERR was relative to the rate for non-smokers, lowered the radiation ERR estimate for males compared to the non-adjusted models and the multiplicative model, where the radiation effect was relative to the risk for people of comparable smoking habits. Otherwise, smoking adjustment had little impact on the estimates of ERR and its modification by attained age or age at exposure. Similarly, other lifestyle factors, including alcohol consumption, educational background, reproductive history, medical history and dietary intake, also had little impact on the ERR/Gy estimates.

(314) The joint effects of radiation and smoking on the lung cancer incidence in the LSS cohort were firstly studied by Pierce et al. (2003). Furukawa et al. (2010) fitted several radiation-smoking interaction models that generalised simple additive and multiplicative models to the data from follow-up in 1958–1999 to find that the radiation associated risk varying by the smoking status (smoking intensity) in a rather complicated manner. Most recently, Cahoon et al. (2017) analyzed the incidence of lung, laryngeal and other cancers of the respiratory system in the LSS with an extended follow-up period in 1958–2009. In this study, for non-smokers, the sex-averaged excess relative risk per Gy for lung cancer (at age 70 after radiation exposure at age 30) was estimated as 0.81 (95% CI: 0.51, 1.18) with a female-to-male ratio of 2.83. Similar to the study by Furukawa et al., the ERR/Gy for lung cancer was significantly higher for low-to-moderate smokers than for heavy smokers, with little evidence of any radiation-associated excess risk in heavy smokers. Egawa et al. (2012) evaluated the radiation-smoking joint effects by histological type (adeno, squamous cell and small cell carcinomas) to find that the nature of the joint effect of smoking and radiation might be similar among different histological types, despite a considerable variation in the estimated magnitude of smoking and radiation effects.

(315) In the LSS, adenocarcinoma was the most common lung cancer diagnosed in non-smokers, but was significantly associated with both smoking and radiation (Egawa et al., 2012). Castelletti et al. constructed a molecular mechanistic model based on molecular pathways identified from published genomic data and applied it to the lung adenocarcinoma incidence data of the LSS (Castelletti et al., 2019). The best fitted model suggested that smoking and radiation act on different pathways; one unique to transmembrane receptor-mutant patients that displayed robust signatures of radiation exposure and one shared between submembrane transducer-mutant patients and patients with no evident driver mutation that carried the signature of smoking. There was no strong indication of biological interaction between radiation and smoking.

(316) Brenner et al. (2018) analysed the LSS female breast cancer incidence in 1958–2009. The ERR was estimated to be 1.12 per Gy (95% CI: 0.73, 1.59) for females at age 70 after exposure at age 30 and tended to decrease with increasing attained age while the EAR tended to increase with attained age up to age 70. Age at menarche was a strong modifier of the radiation effect; for a given dose, both the ERR and EAR significantly decreased with increasing age at menarche. Age-at-exposure effects on ERR and EAR differed before and after menarche, with highest risks for exposures around menarche. Persistently increased risk

of female breast cancer after radiation exposure and its modification pattern suggests heightened breast sensitivity during puberty.

(317) Utada et al. (2018) studied the incidence of uterine cancer during 1958–2009 among 62 534 female LSS subjects. ERR models were fitted to the incidence of cervical cancer and corpus cancer with adjustment for several lifestyle and reproductive factors. While an overall significant association between radiation dose and risk of corpus cancer (ERR/Gy = 0.73, 95%CI: 0.03, 1.87) was found, the elevated risk was strong and significant for women exposed to radiation between ages 11 and 15 years (ERR/Gy = 4.10, 95% CI: 1.47, 8.42) and no indication of a radiation effect for exposures before or after this exposure-age range. There was no evidence of radiation risk modification for cervical or corpus cancer or by any of reproductive factor, BMI, or smoking. There was no significant evidence for the radiation-associated risk of cervical cancer.

(318) Adjustment for lifestyle factors (such as smoking and alcohol consumption) was considered in analyses of other recent site-specific cancer incidence data in the LSS. It had, however, little impact in estimation of the radiation-associated risks at any sites other than lung, including upper digestive tract cancers (oral cavity/pharyngeal, esophageal, and stomach) (Sakata et al., 2019), liver (Sadakane et al., 2019), and prostate (Mabuchi et al., 2021).

(319) A nested case-control study in AHS examined the modifying effect of postmenopausal estradiol level on radiation-associated breast cancer risks (Grant et al., 2018). The results indicated that estradiol level might be more like a mediator of radiation-associated breast cancer risk and radiation increase directly the breast cancer risk or indirectly by increasing estradiol levels.

(320) Aside from the LSS, few epidemiological studies had sufficient information for lifestyle factors (e.g., smoking behavior, alcohol consumption, BMI and physical activity) to thoroughly examine the roles of such factors as modifiers to radiation-associated cancer risks. Even if some informaiton is available, studies for populations with low-dose and low-dose-rate exposures are generally limited by design and exposure circumstance to have sufficient statistical power to examine possible effect modifications.

(321) Several studies have examined the modification of radiation effects by smoking, but the evidence for interactions between radiation and smoking is less consistent. While observations in the LSS indicate a complex interaction between smoking behaviour and radiation dose for lung cancer, studies of radiotherapy patients mostly support multiplicative or supermultiplicative interactions.

(322) Studies of Hodgkin lymphoma patients in the US have shown increased lung cancer risk with increasing dose from radiotherapy in analyses with adjustment for chemotherapy and smoking. Analysis supported a multiplicative interaction of radiation exposure and smoking, while the interaction of radiation exposure and chemotherapy was more consistent with an additive relationship (Travis et al., 2002; Gilbert et al., 2003).

(323) A case-control study in breast carcinoma survivors in the US examined the combined effects of thoracic radiotherapy and cigarette smoking on lung cancer incidence and reported a supramultiplicative interaction effect between smoking and radiotherapy on lung cancer incidence (Ford et al., 2003). The study did not include quantitative information on either radiation exposure or smoking habits and did not consider possible modification of the risks by latency.

(324) A nested case-control study in a cohort of Danish females treated for breast cancer in 1982–2007 examined the risk of second primary lung cancer from postoperative radiotherapy. Using models adjusting for smoking status and systemic adjuvant treatment, ERR/Gy was highest and significant among ever-smokers (ERR/Gy = 0.173, 95% CI: 0.045, 0.54) while it was low and insignificant in the group of non-smokers and those with unknown smoking status

combined (ERR/Gy = 0.006, 95% CI: −0.020, 0.163). However, the difference between groups was not statistically significant (p = 0.08) (Grantzau et al., 2014).

(325) A study in the cohort of United States Radiologic Technologists (USRT) with a follow up between 1983–2012 evaluated the lung cancer mortality risk associated with protracted low-dose occupational radiation exposures and smoking behaviours (Velazquez-Kronen et al., 2020). Overall, lung dose was not associated with lung cancer mortality (ERR/100mGy = −0.02, 95% CI: <0, 0.13). The interaction between radiation and smoking appeared to be sub-multiplicative with an ERR per 100 mGy of 0.41 (95% CI: 0.01, 1.15) for those who smoked <20 pack-years and −0.03 (95% CI: <0, 0.15) for those who smoked ≥20 pack-years.

(326) A cohort study of Japanese nuclear workers followed up mortality of the 71,733 male nuclear workers in Japan through 2010 (Kudo et al., 2018). With all cancers other than leukaemia (2,636 deaths), a positive association of external dose was observed, with ERR/Sv estimated to be 1.26 (95% CI: −0.27, 3.00), while ERR/Sv was 0.29 (95% CI: −0.81, 1.57) among those with self-reported smoking. With 319 observed lung cancer deaths, the ERR/Sv for lung cancer was 1.94 (90% CI: −0.56, 5.26) and 0.94 (90% CI: −1.24, 3.90) without and with adjustment for smoking, respectively.

(327) An analysis of Mayak workers (who were initially hired from 1948–1982 and followed for at least 5 years between 1953–2008) examined the radiation-associated lung cancer risk (Gilbert et al., 2013). The average absorbed lung dose was 0.12 Gy from internal sources, and 0.40 Gy from external sources. With a linear model adjusted for age, calendar period, birth cohort, and smoking status, ERR/Gy from internal exposure at age 60 was 7.4 (95% CI: 5.0, 11; n = 446) for males and 24 (95% CI: 11, 56; n = 40) for females. However, ERR/Gy from external exposure for both sexes combined was 0.13 (95% CI: −0.04, 0.38). The relationship between plutonium exposure and smoking was best described as greater than additive (p < 0.001). Based on a generalised multiplicative model, ERR/Gy for non-smokers was about four times that for smokers. When the plutonium risk was allowed to depend on smoking, the female to male ratio of the risk reduced from 3.3 to 1.0.

(328) A nested case-control study of a pooled cohort of nuclear workers in Belgian, French, and United Kingdom (followed up in 1946–2003) comprised 533 lung cancer deaths and 1,333 controls matched by age, sex and facility (Grelier et al., 2017). The average cumulative dose to the lung from alpha emitters was 8.13 mGy (n = 1,721), with 5.09 mGy (n = 711) for plutonium and 6.45 mGy (n = 1,409) for uranium. The median external dose was 33 mGy (n = 1,783). The excess odds ratios per Gy were 11 (90% CI: 2.6, 24), 50 (90% CI: 17, 106), and 5.3 (90% CI: −1.9, 18) for total alpha, plutonium and uranium doses, respectively, adjusting for external dose. No significant dose–response relationship was found for external radiation dose. There was no evidence for effect modification by smoking (p = 0.35) and other covariates tested.

(329) Radon is known as the second leading cause of lung cancer after cigarette smoking among smokers and the leading cause among non-smokers. Epidemiological evidence for the association between radon exposure and lung cancer has been reported mostly from studies of occupational and residential exposure. In addition to being a confounder, smoking could modify the effect of radon on lung cancer risk, and the joint effects of smoking and radon exposure have been investigated in several epidemiological studies.

(330) Among residential studies, a pooled analysis of 13 European case-control studies found no significant heterogeneity in relative risks due to residential radon exposure between smoker and non-smokers (Darby et al., 2005). A case-control study nested within Czech cohorts (Tomásek et al., 2013) reported an increased risk associated with residential radon for never-smokers compared to ever-smokers [the ERRs = 0.73 (90% CI: 0.02, 1.90) and 0.14 (90% CI: 0.02, 0.30) per 100 Bq m^{-3}, respectively]. A Danish study of a prospective cohort (Brauner, et al, 2012) observed a similar pattern with an increased risk (incidence rate ratio)

for never-smokers, however, with much wider confidence intervals, suggesting no significant risk nor effect modification. A case-control study of non-smokers in Spain (Torres-Duran et al, al., 2014) reported an increased radon-associated lung cancer risk by exposure to environmental tobacco smoke.

(331) In studies of occupational radon exposure of miners, sub-multiplicative joint effects, which imply larger risks per unit exposure for non-smokers (on the multiplicative scale), were favoured in a combined analysis of three European nested case-control studies of uranium miners (Lauraud et al., 2009, Hunter et al., 2013) and the Colorado Plateau uranium miners cohort (Schubauer-Berigan et al., 2009). In the Newfoundland fluorspar miners study (Villeneuve et al., 2013), the ERRs per working level month (WLM) were not significantly different between never- and ever- smokers but tended to increase with the amount of cigarettes smoked. In the German Wismut study, a sub-cohort of uranium miners hired in 1960 or later indicated a sub-multiplicative interaction between smoking and radon (ERR/WLM = 0.022 for non/light smokers vs. 0.013 for moderate/heavy), while a supra-multiplicative interaction was suggested when a geometric mixture model was fitted (Kreuzer et al., 2018). A nested case-control study of the Czech cohort (Tomásek et al., 2013) reported that the interaction between smoking and radon was more additive than multiplicative based on fitting a geometric mixture model (with mixing parameter of 0.2).

3.2.2.2. Animal studies

(332) Cigarette smoke has been shown to reduce removal of radioactive particulates of $^{239}PuO_2$ from lung in mice (Talbot et al., 1987) and rats (Finch et al., 1998). A large set of experiments using rats have revealed that the interaction of $^{239}PuO_2$ aerosol and cigarette smoke on induction of lung cancer are significantly larger than additivity and beyond the level that is explained by the increased retention of $^{239}PuO_2$ by the cigarette smoke (Mauderly et al., 2010). Other studies found that cigarette smoke and its components increase the number of animals dead with cancer in rats and dogs exposed to internal and external radiation, with a controversial study indicating an antagonistic interaction (Table 3.8).

Table 3.8. Experiments on the effect of cigarette on radiation-related carcinogenesis.

Modifying factor	Period of exposure	Radiation	Animal	Outcome	Modification	Reference
Cigarette smoke	Pre-radionuclide + throughout life	^{239}PuO2	Rat	Lung cancer	Supra-additive	Mauderly et al., 2010
Cigarette smoke	Concommitant with radionuclide + throughout life	Mixture of ^{222}Rn, its daughters and uranium ore dust	Dog	Nose and lung cancers	Antagonism	Cross et al., 1982
Cigarette smoke	Post-radionuclide	^{222}Rn and its daughters	Rat	Lung cancer	Increase	Chameaud et al., 1982
Cigarette tar	Post-irradiation	β rays (^{90}Sr)	Rat	Skin cancer	Increase	McGregor, 1976
Cigarette smoke condensate	Post-irradiation	β rays (^{90}Sr)	Rat	Skin cancer	Non-significant increase	McGregor, 1982

(333) Very few studies have been reported in relation to alcohol. A study reports that risk of Am-241-induced liver malignancies in beagles is enhanced by long-term ethanol treatment (Taylor et al., 1992).

(334) In general, evidence suggests that obesity and overweight increase, whereas dietary restriction decreases, radiation-related carcinogenesis in some animal models (Karabulutoglu

et al., 2019). Forced restriction of the amount food intake decreases incidence (need check) of all tumours in rats (Gross and Dreyfuss 1984, 1990) and of lymphoid leukaemia in mice (Gross and Dreyfuss, 1986). Calorie restriction (by ~30%) reduces mortality from myeloid leukaemia in mice (Yoshida et al., 1997) and various neoplasms including liver cancer, lung cancer, Harderian gland tumour, hemangioma, intestinal tumour and late developing lymphoma whereas it did not affect development of early-developing lymphoma (Shang et al., 2014; Morioka et al., 2021). High fat diet (20% lard) increases mammary cancer of rats (Silverman et al., 1980), which seems related to body weight gain and metabolic changes rather than the diet itself (Imaoka et al., 2016). Radiation and high corn oil diet (23.5%) display supramultiplicative interaction on mammary cancer of rats (Imaoka et al., 2023) (Table 3.9).

Table 3.9. Experiments on the effect of obesity/overweight on radiation-related carcinogenesis

Modifying factor	Body weight	Period under diet	Radiation	Animal	Outcome	Modification	Reference
Carbohydrates*	+30–40%	Post-irradiation	X rays	Mouse	Liver and lung cancer, late-onset lymphoma, all tumours	Increase (apparently multiplicative)	Shang et al., 2014
Carbohydrates	+20%	Post-irradiation	X rays	Mouse	Intestinal tumour	Increase	Yoshida et al., 2006; Morioka et al., 2021
Carbohydrates	+30%	Post-irradiation	X rays	Mouse	Myeloid leukaemia	Increase	Yoshida et al., 2006
Carbohydrates	+20%	Pre-irradiation	X rays	Mouse	Myeloid leukaemia	Non-significant increase	Yoshida et al., 1997
Carbohydrates	+40%	Post-irradiation	X rays	Mouse	Myeloid leukaemia	Increase	Yoshida et al., 1997
Carbohydrates	+40%	Pre- and post-irradiation	X rays	Mouse	Myeloid leukaemia	Increase	Gross and Dreyfuss, 1986
Food intake†	N.D.	Post-irradiation	γ rays	Mouse	Leukaemia	Increase	Gross and Dreyfuss, 1990
Food intake	+100%	Post-irradiation¶	γ rays	Rat	All tumours (benign and malignant)	Increase	Gross and Dreyfuss, 1984
Food intake	N.D.	Post-irradiation¶	X rays	Rat	All tumours (benign and malignant)	Increase	Silverman et al., 1980
Fat	+16%§	Pre- and post-irradiation	X rays	Rat	Mammary cancer	Increase	Imaoka et al., 2016
Fat	+12%	Post-irradiation	γ rays	Rat	Mammary cancer	Increase (supra-multiplicative)	Imaoka et al., 2023
Fat-induced obesity‡	+25%	Pre- and post-irradiation	γ rays	Rat	Mammary cancer	Acceleration	Shang et al., 2014

N.D., no data reported.

*Modification is interpreted as the effect of ad libitum feeding compared to calorie-restricted feeding (i.e., body weight control through reducted dietary carbohydrates including dextrose), with the former showing the indicated percentage of additional maximum BW.

†Modification is interpreted as the effect of ad libitum feeding compared to restricted feeding.

‡Animals fed on the same high-fat diet showing different proneness to obesity.

[§]Difference not significant.
[¶]Not explicitly mentioned in the original report and likely to be post-irradiation dietary control.

(335) A large number of studies have been addressing whether various dietary ingredients affect radiation-related carcinogenesis. Feeding of natural and synthetic antioxidants of various kinds are reported to reduce radiation-related cancers in various models (Sanders and Mahaffey 1983; Inano et al., 1999, 2000a; Inano and Onoda, 2002; Rabin et al., 2005, Dange et al., 2007; Kennedy et al., 2008, 2011; Mitchell et al., 2012; Miller et al., 2013)). The mechanism ofaction of the natural antioxidant curcumin may include reduction of circulating prolactin levels (Inano et al., 1999) and antioxidant activity (Inano and Onoda, 2002). Natural ingredients like soybean protease inhibitor (Evans et al., 1992; Kennedy et al., 2008, 2011) and sugar beet fiber (Ishizuka et al., 1999; Nagai et al., 2000) meadowsweet extract (Bespalov et al., 2017) and potato extract (Kim et al., 1994) reduce the incidence of radiation-related tumours in various tissues. The mechanism of action of protease inhibitor may include inhibition of protease activity and/or downregulation of expression of protooncogenes (Kennedy, 1994). Regarding minerals and vitamins, diet excessive or deficient in iodine increases thyroid adenoma in rats (Boltze et al., 2002). Iron increases myeloid leukaemia in irradiated mice via oxidative stress (Chan et al., 2021). Vitamin A reduces lymphoma in mice (Przybyszewska, 1985) and increases lung cancer (Mian et al., 1984), whereas a diet low in vitamin D3 increases the incidence of radioiodine-induced parathyroid adenoma (Wynford-Thomas et al., 1983) (Table 3.10).

Table 3.10. Experiments on the effect of dietary factor on radiation-related carcinogenesis

Modifying factor	Period of treatment[†]	Radiation	Animal	Outcome	Modification	Reference
Antioxidant						
Curcumin	Post-irradiation	γ rays	Rat, DES-treated	Mammary tumour (benign and malignant)	Decrease	Inano et al. (1999)
Curcumin	Short time covering exposure period	γ rays	Rat, DES-treated	Mammary tumour (benign and malignant)	Decrease	Inano et al. (2000a), Inano and Onoda (2002)
Ascorbic acid	Post-radionuclide (1 year)	^{239}Pu	Rat	Lung cancer	Decrease	Sanders and Mahaffey (1983)
Ascorbic acid	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Non-significant decrease	Dange et al. (2007)
Eugenol	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Non-significant decrease	Dange et al. (2007)
Curcumin	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease	Dange et al. (2007)
Mixture of antioxidants[*]	Pre- and post-irradiation	Proton, Fe ions	Mouse	Malignant lymphoma	Decrease	Kennedy et al. (2008)
Mixture of antioxidants[*]	Pre- and post-irradiation	Proton, Fe ions	Mouse	Harderian gland tumour	No effect	Kennedy et al. (2011)
Tempol	Post-irradiation	Not indicated	Mouse	All neoplasms	Decrease	Mitchell et al. (2012)

(*continued on next page*)

4320 Table 3.10. (*continued*).

Modifying factor	Period of treatment†	Radiation	Animal	Outcome	Modification	Reference
Antioxidant						
NAC	Short time covering exposure period	X rays	Mouse, NNK-treated	Lung tumour	Decrease	Miller et al. (2013)
Natural ingredient						
Bowman-Birk protease inhibitor	Pre- and post-irradiation	X rays	Mouse	Thymic lymphoma	Decreae of tumour grade	Evans et al. (1992)
Bowman-Birk protease inhibitor	Pre- and post-irradiation	Proton, Fe ions	Mouse	Malignant lymphoma	Decrease	Kennedy et al. (2008)
Bowman-Birk protease inhibitor	Pre- and post-irradiation	Proton, Fe ions	Mouse	Harderian gland tumour (large tumours)	Decrease	Kennedy et al. (2011)
Sugar beet fiber	Pre- and post-irradiation	γ rays	Rat, treated with immune-suppressant	Colonic abberant crypt foci	Decrease	Nagai et al. (2000)
Sugar beet fiber	Pre- and post-irradiation	γ rays	Rat	Colonic abberant crypt foci	No effect	Ishizuka et al. (1999)
Meadowsweet extract	Post-irradiation	γ rays	Rat	Mammary cancer	Decrease	Bespalov et al. (2017)
Potato extract	Post-irradiation	γ rays	Rat, DEN-treated	Liver foci	Decrease	Kim et al. (1994)
Mineral/vitamin						
Low iodine	Pre- and post-irradiation	X rays	Rat	Thyroid tumour	Apparent synergism	Boltze et al. (2002)
High iodine	Pre- and post-irradiation	X rays	Rat	Thyroid tumour	Apparent synergism	Boltze et al. (2002)
Sodium selenite	Post-irradiation	Electrons	Rat	Cutaneous tumours	No effect	Zackheim et al. (1993)
Calcium	Post-irradiation	^{131}I	Rat	Thyroid C cell tumour	No effect	Triggs and Williams (1977)
Iron	Post-irradiation	γ rays	Mouse	Myeloid leukaemia	Increase	Chan et al. (2021)
Vitamin A	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Apparent decrease	Przybyszewska (1985)
Vitamin A	Pre- and post-irradiation	γ rays	Mouse	Lung adenoma	Increase	Mian et al. (1984)
Vitamin D3	Post-irradiation	^{131}I	Rat	Parathyroid adenoma	Decrease	Wynford-Thomas et al. (1983)

4321 DES, diethylstilbestrol (a synthetic estrogen); NAC, N-acetylcysteine; NNK, 4-(methylnitrosoamino)−1-(3-
4322 pyridyl)−1-butanone (a chemical carcinogen); Tempol, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.
4323 *L-selenomethionine (0.06 mg/kg diet), N-acetylcysteine (171.4 mg/kg diet), α-lipoic acid (85.7 mg/kg diet),
4324 vitamine E succinate (71.4 mg/kg diet), coenzyme Q10 (27.9 mg/kg diet), and ascorbic acid (142.8 mg/kg).
4325 †Treatments are performed for lifetime unless otherwise mentioned.

(336) Parity reduces mammary cancers in rats irradiated with γ rays before, but not after, puberty in a manner that does not depart from either additivity or multiplicativity (Takabatake et al., 2018; Imaoka et al., 2023). Exposure during pregnancy, lactation and the post-lactation period impose similar risks of mammary cancer in otherwise non-treated rats (Holtzman et al., 1982), whereas exposure during lactation results in highest mammary cancer development if the rats are treated with a synthetic estrogen diethylstilbestrol (DES) after exposure (Inano et al., 1996). There was no significant difference in the susceptibility to mammary cancer in the estrous cycles of DES-treated rats (Inano et al., 1992). In addition, pregnancy reduces radiostrontium-induced bone tumours via reduction in the retention of radiostrontium in bone (Nilsson et al., 1967; Nilsson, 1967) (Table 3.11).

Table 3.11. Experiments on the effect of reproductive status/history on radiation-related carcinogenesis

Modifying factor	Timing	Radiation	Animal	Outcome	Modification	Reference
Parity	Pre-irradiation	X rays	Rat	Mammary cancer	No effect	Holtzman et al. (1982)
Estrous cycle	At the time of irradiation	γ rays	Rat, DES-treated	Mammary cancer	No effect	Inano et al. (1992)
Pregnancy	At the time of irradiation	γ rays	Rat, DES-treated	Mammary cancer	Increase	Inano et al. (1996)
Pregnancy	At the time of irradiation	X rays	Rat	Mammary cancer	No effect	Holtzman et al. (1982)
Lactation	At the time of irradiation	γ rays	Rat, DES-treated	Mammary cancer	Increase	Inano et al. (1996)
Lactation	At the time of irradiation	X rays	Rat	Mammary cancer	No effect	Holtzman et al. (1982)
Parity	Post-irradiation	γ rays	Rat	Mammary cancer	Decrease (no departure from additivity or multiplicativity, prepubertal irradiation); no effect (postpubertal irradiation)	Takabatake et al. (2018), Imaoka et al. (2023)
Parity	Post-irradiation	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Decrease	Nilsson (1967)

DES, diethylstilbestrol (a synthetic estrogen).

(337) Long-term treatment of irradiated rats with various estrogenic hormones synergistically enhances mammary carcinogenesis, which is attributed to increased prolactin secretion (Shellabarger et al., 1976, 1978, 1982, 1983; Segaloff and Pettigrew, 1978; Holtzman et al., 1979; Blankenstein et al., 1981; Bartstra et al., 1998a,b, 2000), which may be suppressed by progesterone (Segaloff, 1973). On the contrary, ovariectomy (Clifton et al., 1985), long-term treatment with anti-estrogens (such as tamoxifen) and estrogens with weak activity (such as estriol) reduces the risk (Welsch et al., 1981; Lemon et al., 1989). Hyperprolactinemia accelerates rat mammary carcinogenesis (Clifton et al., 1985). Many studies were excluded from consideration as they lacked pathological classification of mammary tumours (Cronkite et al., 1960; Shellabarger et al., 1960, 1962; Inano et al., 1995, 1996; Yamanouchi et al., 1995). Besides mammary cancer, the promoting effect of an estrogen on 90Sr-induced bone cancer is

well documented as well as the inhibiting effect of a glucocorticoid (Nilsson and Rönnbäck, 1973; Nilsson and Broomé-Karlsson, 1976; Haraldsson and Nilsson, 1988) (Table 3.12).

Table 3.12. Experiments on the effect of hormonal treatments on radiation-related carcinogenesis

Modifying factor	Period of treatment	Radiation	Animal	Outcome	Modification	Reference
DES	Pre- and post-irradiation	Neutrons (0.43 MeV)	Rat, ACI	Mammary cancer	Apparent synergism	Shellabarger et al. (1983)
	Post-irradiation	Neutrons (0.43 MeV)	Rat, ACI	Mammary cancer	Apparent synergism	Shellabarger et al. (1983)
	Pre- and post-irradiation	X rays and neutrons (0.43 MeV)	Rat, ACI	Mammary cancer	Apparnt synergism	Shellabarger et al. (1982)
	Pre- and post-irradiation	X rays	Rat	Mammary cancer	Increase	Holtzman et al. (1981)
	Pre- and post-irradiation	X rays	Rat	Mammary cancer	Supra-aditivity	Holtzman et al. (1979)
	Pre- and post-irradiation	Neutrons (0.43 MeV)	Rat, ACI	Mammary cancer	Supra-additivity	Shellabarger et al. (1978)
	Pre- and post-irradiation	X rays	Rat, ACI	Mammary cancer	Apparent synergism	Segaloff and Pettigrew (1978)
	Pre- and post-irradiation	Neutrons (0.43 MeV)	Rat, ACI	Mammary cancer	Apparent synergism	Shellabarger et al. (1976)
Estradiol*	Pre- and post-irradiation	γ rays	Rat	Mammary cancer	Apparent supra-multiplicativity	Bartstra et al. (1998a), Bartstra et al. (1998b)
	Pre- and post-irradiation	γ rays	Rat	Mammary cancer	Apparent multiplicativity	Bartstra et al. (2000)
Induced hyperprolactinamia	Post-irradiation	γ rays	Rat	Mammary cancer	Acceleration	Clifton et al. (1985)
Progesterone in the presence of DES	Pre- and post-irradiation	X rays	Rat, ACI	Mammary cancer	Decrease	Segaloff (1973)
Removal of ovary	Pre- and post-irradiation	γ rays	Rat	Mammary cancer	Decrease	Clifton et al. (1985)
Tamoxifen†	Post-irradiation	γ rays	Rat	Mammary cancer	Marked decrease	Lemon et al. (1989)
	Short time covering the irradiation period	γ rays	Rat	Mammary cancer	Decrease	Welsch et al. (1981)
	Short time after irradiation	γ rays	Rat	Mammary cancer	Decrease	Welsch et al. (1981)

(*continued on next page*)

Table 3.13. (*continued*).

Estriol (E_3)[‡]	Post-irradiation	γ rays	Rat	Mammary cancer	Decrease	Lemon et al. (1989)
Ethinylestriol (EE_3)[§]	Post-irradiation	γ rays	Rat	Mammary cancer	Decrease	Lemon et al. (1989)
Melatonin	Pre- and post-irradiation	γ rays	Rat, DMBA-treated	Mammary cancer	No effect	Mockova et al. (2000)
Polyestradiol phosphate[¶]	Pre- and post-irradiation	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Acceleration	Nilsson and Ronnback (1973)
	Short time covering the irradiation period	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Increase	Haraldsson and Nilsson (1988)
	Pre- and post-irradiation	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Increase	Nilsson and Broome-Karlsson (1976)
Methylprednisolone[**]	Short time covering the irradiation period	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Decrease	Haraldsson and Nilsson (1988)
	Short time after irradiation	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Decrease	Nilsson and Broome-Karlsson (1976)
Nortestosterone[††]	Short time after irradiation	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	No effect	Nilsson and Broome-Karlsson (1976)
4-methyl-2-thiouracil[#]	During and after irradiation	^{131}I	Hamster	Ovarian tumour	Decrease	Christov and Raichev (1973)

DES, diethylstilbestrol (a synthetic estrogen); DMBA, 7,12-dimethylbenz(a)anthracene (a tumour initiator).
[*]The most potent natural estroge.
[†]Synthetic estrogen receptor blocker.
[‡]A natural estrogen with weak activity.
[§]Synthetic estrogen.
[¶]Prodrug of estradiol.
[**]Synthetic glucocorticoid.
[††]Anabolic steroid (androgen).
[#]antithyroid drug.

3.2.3. Modification by underlying conditions (e.g., diabetes, collagen vascular diseases, chronic inflammation)

3.2.3.1. Human

(338) A nested case-control study with AHS participants of Atomic-bomb survivors suggested that radiation highly and significantly increased the liklihood of diffuse-type gastric cancer without CAG (chronic atrophic gastritis) while the risk was not significant with CAG positive or intestinal-type gastric cancer. CAG is a condition where inflammation of the gastric mucosa continues long due to infection with H. pylori, by which the functions of the mucous membrane of the stomach are weakened (Ueda et al., 2020).

(339) A nested case-control study within the AHS has found a statistically significant, supermultiplicative interaction between radiation and infection to Hepatitis C virus (HCV) on

the prevalence of hepatocellular carcinoma (HCC) based on 238 HCC cases and 894 controls (Sharp et al., 2003). Among subjects without cirrhosis, the relative risk of HCC for subjects with HCV infected was 58.0 (95% CI 1.99–Inf, $p = 0.01$) compared to those without HCV, while such an interaction was not found among subjects with cirrhosis ($p = 0.67$). No evidence for interaction between Hepatitis B virus (HBV) and radiation on the risk of HCC was observed, regardless of cirrhosis status ($p = 0.58$). Another nested case-control study using sera stored before HCC diagnosis in the AHS has shown that radiation exposure and HBV and HCV infections are associated independently with increased risk of HCC (Ohishi et al., 2011). In particular, radiation exposure appeared to increase the risk of HCC without HCV nor HBV with no apparent confounding by alcohol consumption, BMI, or smoking habit.

3.2.3.2. Animal studies

(340) As far as we have ascertained, no animal studies have reported on the effect of diabetes on radiation-related carcinogenesis, excluding some studies using diet-induced obesity models (*see above*).

(341) As far as we have asertained, no animal studies have reported so far on the effect of collagen vascular diseases on radiation-related carcinogenesis.

(342) Although evidence is very limited, a few studies suggest that experimentally-induced inflammation increases carcinogenesis in radiation-related models. Experimental induction of inflammation increases radiation induction of soft-tissue tumours in rats (Eltze et al., 2006), myeloid leukaemia in mice (Yoshida et al., 1993) and colon cancer in *Mlh1*$^{-/-}$ mice (Morioka et al., 2015). Anti-inflammatory agents reduce radiation-related colon carcinogenesis of rats (Northway et al., 1990) (Table 3.13).

Table 3.13. Experiments on the effect of inflammation on radiation-related carcinogenesis

Modifying factor	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Gastritis, allogenic antigen-indcued	Pre-irradiation*	X rays	Mouse	Stomach cancer	Increase	Hirose et al. (1976)
Inflammation, implant-induced	Pre-irradiation*	X rays	Mouse	Mandibular gland carcinoma	Increase	Eulderink and van Rijssel (1972)
	Post-irradiation	X rays	Mouse	Mandibular gland carcinoma	Increase	Eulderink and van Rijssel (1972)
Piroxicam (anti-inflammatory agent)	Short time covering irradiation	X rays	Rat	Colon neoplasms	Decrease	Northway et al. (1990)
Inflammation, implant-induced	Post-irradiation	X rays	Mouse	Myeloid leukaemia	Increase (male), non-significant increase (female)	Yoshida et al. (1993)
	Pre-irradiation*	X rays	Mouse	Myeloid leukaemia	No change	Yoshida et al. (1993)
Skin fibrosis, implant-induced	Pre-irradiation*	Electron	Rat	Soft tissue tumours	Non-significant increase	Eltze et al. (2006)
Colitis, DSS-induced	Post-irradiation	X rays	Mouse, *Mlh1*$^{-/-}$	Colon neoplasms	Non-significant increase	Morioka et al. (2015)

DSS, dextran sodium sulfate.

*Note that inflammation lasts after treatment.

3.2.4. Modification by other environmental factors (e.g., UV/sunlight exposure, chemical exposure, chemotherapy treatments)

3.2.4.1. Human

(343) While ultraviolet radiation (UVR) is an established risk factor for non-melanoma skin cancer (NMSC), interaction between exposures to ionising radiation and UVR is still uncertain. The available data suggest that ERRs may be lower for sites exposed to sunlight, whereas EARs may be higher for such sites.

(344) In analysis of non-melanoma skin cancer incidence of atomic-bombing survivors in the LSS, comparison of the risks between body parts showed some indication of the interaction between ionising radiation and ultraviolet radiation (UVR) exposures. The ERR for face or neck (more likely to be exposed to UV) basal-cell carcinoma (BCC) was 0.6 (95% CI: < 0, 2.1) Gy^{-1} while the ERR for BCC on the rest of the body was 2.3 (95% CI: 0.61, 6.7) Gy^{-1}. There was no conclusive evidence on whether the interaction between ionising radiation and UVR is additive or multiplicative (Sugiyama et al., 2014)

(345) A case-control study of residents in New Hampshire observed the radiotherapy-associated skin cancer risk was significantly increased in subjects with no sunburn experience while the risk in those with sunburn experience was not. (Karagas et al., 2007)

(346) A study to follow up 2,224 children given x-ray therapy for tinea capitis (ringworm of the scalp) for up to 50 years, along with a control group of 1,380 tinea capitis patients given only topical medications, observed higher risks of BCC on the sunexposed margin of the scalp (EAR = 21/100 cm^2 Gy) compared with the relatively sun-shielded scalp (EAR = 4.7/100 cm^2 Gy). (Shore et al., 2002)

3.2.4.2. Animal studies

(347) A very few studies suggest positive interaction between radiation exposure and UV/sunlight exposure. Significant correlation has been reported between solar dermatosis and skin malignancies (hemangiosacroma and squamous cell carcinoma) in beagle dogs, suggesting positive interaction (Nikula et al., 1992). Although x-ray exposure itself is weak in inducing squamous cell carcinoma of the skin in hairless mice, it has been associated with significantly faster development of carcinomas in mice exposed to simulated solar radiation either before or after X rays (Lerche et al., 2013).

(348) Among most studied are the effects of combined treatments with radiation and genotoxins including DNA alkylating agents and adduct-forming agents. Some studies indicate significant departure of the combined effects from the sum of the individual effects (Mandybur et al., 1985; Peraino et al., 1986; Kakinuma et al., 2012; Iwata et al., 2013; Imaoka et al., 2023) whereas some indicate their additivity (Vesselinovitch et al., 1972; Iwata et al., 2013). Very few studies assess their departure from multiplicativity (Imaoka et al., 2023). Mechanisms of the interaction of radiation and these chemicals may include radiation-related clonal expansion of chemically-initiated cells (Yamauchi et al., 2008; Kakinuma et al., 2012; Imaoka et al., 2014). Some evidence suggests their antagonistic interactions (Knowles, 1982; Schmahl and Kriegel, 1985; Hasgekar et al., 1986; Kakinuma et al., 2012). Modification of radiation effects by other classes of chemicals (DNA base analogue, liver toxicants, mitogens, particulate materials and chemotherapeutics) also ranges from antagonism to apparent supra-additivity (Table 3.14).

Table 3.14. Experiments on the effect of chemical carcinogens (including chemotherapeutics) on radiation-related carcinogenesis

Chemicals	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Genotoxin (alkylating agent)						
BHP	Post-irradiation	X rays	Rat	Lung cancer	Additivity to supra-additivity (depending on exposure age)	Iwata et al. (2013)
DEN	Pre-irradiation	γ rays	Rat	Liver foci	No effect	Kim et al. (1994)
	Post-irradiation	γ rays	Rat	Liver foci	Apparent increase	Kim et al. (1994)
	Pre- or post-irradiation	X rays	Mice	Liver foci	No effect	Maisin et al. (1993)
	Post-irradiation	γ rays	Rat	Liver foci	Supra-additivity	Peraino et al. (1986)
DMH	Post-irradiation	γ rays	Rat	Colon tumour	Apparent supra-additivity	Sharp and Crouse (1989)
	Post-irradiation	X rays	Rat	Colon tumour	Apparent supra-additivity	Sharp and Crouse (1989)
ENU	Simultaneous	X rays	Mouse	Thymic lymphoma	Apparent supra-additivity	Hirano et al. (2013)
	Post-irradiation	X rays	Mouse	Thymic lymphoma	Supra-additivity (high dose) or decrease (low dose)	Kakinuma et al. (2012)
	Simultaneous	γ rays	Rat	Schwannoma	Decrease	Hasgekar et al. (1986)
	Post-irradiation	X rays	Rat	All causes of death	Apparent supra-additivity	Mandybur et al. (1985)
	Post-irradiation	X rays	Rat	Barin tumours	Decrease	Schmahl and Kriegel (1985)
	Pre-irradiation	X rays	Rat	Nervous system tumour	Decrease	Knowles (1982)
MNNG	Post-irradiation	X rays	Rat	Gastric cancer	No effect	Fujii et al. (1980)
MNU	Post-irradiation	γ rays	Rat	Mammary cancer	Additivity	Imaoka et al. (2014)
	Post-irradiation	γ rays	Rat	Mammary cancer	Apparent additivity	Imaoka et al. (2005)
	Pre-irradiation	X rays	Rat	Mammary cancer	Apparent supra-additivity	Kantorowitz et al. (1995)
	Pre-irradiation	X rays	Rat	Intestinal cancer	Increase	Morishita et al. (1993)

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Table 3.14. (*continued*).

Chemicals	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Genotoxin (adduct-forming agent)						
2AA	Post-irradiation	β rays (^{90}Y)	Rat	Skin tumour	Apparent supra-additivity	Myers and McGregor (1982)
AAF	Post-irradiation	X rays	Rat	Liver foci	Apparent supra-additivity	Mori et al. (1990)
DAAF	Pre-irradiation	Neutrons (fission)	Rat	All neoplasms	Apparent supra-additivity	Vogel and Zaldivar (1971)
	Pre- or post-irradiation	X rays	Rat	Liver tumour	Apparent supra-additivity	Nagayo et al. (1970)
DMBA	Pre-irradiation	β rays (^{90}Y)	Mouse, mezerein-treated	Skin tumour	Increase	Mitchel and Trivedi (1992)
	Pre-irradiation	X rays	Hamster	Cheek pouch cancer	Increase	Lurie and Rippey (1987)
	Pre-irradiation and simultaneous	X rays	Hamster	Cheek pouch tumour	No effect	Lurie (1982)
	Simultaneous and post-irradiation	X rays	Hamster	Cheek pouch tumour	Increase	Lurie (1977)
	Simultaneous	X rays	Hamster	Lnguial cancer	No effect	Lurie and Cutler (1979)
	Post-irradiation	X rays	Rat	Lung cancer	Increase	Gross et al. (1969)
MAM	Pre-irradiation	X rays	Rat	Intestinal cancer	Apparent supra-additivity (male)	Tanaka et al. (1993)
	Post-irradiation	X rays	Rat	Intestinal cancer	Apparent increase (male)	Tanaka et al. (1993)
MCA	Pre- or post-irradiation	Neutrons (fission)	Rat	Mammary cancer	Apparent additivity	Shellabarger and Straub (1972)
4NQO	Post-irradiation	β rays (^{90}Y)	Mouse	Malignant skin tumour	Apparent supra-additivity	Hoshino and Tanooka (1975)
	Pre- or post-irradiation	β rays (^{90}Y)	Mouse	Skin tumour	Apparent supra-additivity	Hoshino et al. (1968)
PhIP	Post-irradiation	γ rays	Rat	Mammary cancer	Additivity	Imaoka et al. (2014)
Urethane	Simultaneous	X rays	Rat	All tumours	Apparent sub-additivity	Myers (1976)
	Post-irradiation	X rays	Mouse	All neoplasms	Apparent additivity	Goldfeder (1972)

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Table 3.14. (*continued*).

Chemicals	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Genotoxin (adduct-forming agent)						
Urethane	Pre- or post-irradiation	X rays	Mouse	Lymphoma	Additivity	Vesselinovitch et al. (1972)
	Post-irradiation	X rays	Mouse	Lung tumour	Apparent additivity	Cole and Foley (1969)
Genotoxin (DNA base analogue)						
BrdU	Pre-irradiation	X rays	Rat	All malignant tumours	Increase	Anisimov and Osipova (1993)
Liver toxicant						
Carbon tetrachloride	Post-irradiation	Neutrons	Mouse	Liver cancer	Increase	Habs et al. (1983)
Chloroform	Post-irradiation	Neutrons	Mouse	Liver cancer	No effect	Habs et al. (1983)
DL-ethionine	Pre- and post-irradiation	X rays	Rat	Benign mammary tumour	No effect	Telles and Ward (1969)
Mitogen						
Mezerein	Simultaneous	β rays (^{90}Y)	Mouse, DMBA/TPA-treated	Skin tumour	Decrease	Mitchel and Trivedi (1992)
Phorbol	Post-irradiation	X rays	Rat	Mammary cancer	No effect	Shellabarger et al. (1979)
TPA	Simultaneous	β rays (^{90}Y)	Mouse, DMBA-treated	Skin tumour	Decrease	Mitchel and Trivedi (1992)
	Post-irradiation	β rays (^{90}Y)	Mouse, MNNG-treated	Skin tumour	Increase	Mitchel and Trivedi (1992)
Particulate						
Asbestos (chrysotile)	Post-irradiation	X rays	Rat	Intestinal tumour	No effect	Donham et al. (1984)
Asbestos	Simultaneous	$^{239}PuO_2$	Rat	Malignant lung tumour	Decrease	Sanders (1975)
Quartz (SiO_2) dust aerosols	Pre-radionuclide	^{228}Th (Thorotrast)	Rat	Lung cancer	Apparent supra-additivity	Spiethoff et al. (1992)
Zircotrast (ZrO_2)	Pre-irradiation	Neutrons, 14 MeV	Rat	Liver tumour	No effect	Spiethoff et al. (1992)
Other						
MNU and PhIP analyzed collectively	Post-irradiation	γ rays	Rat	Mammary cancer	Multiplicativity	Imaoka et al. (2023)
Doxorubicin	Post-irradiation	γ rays	Mouse	Sarcoma	Apparent decrease	Zietman et al. (1991)

2AA, 2-aminoanthracene (CAS no. 613–13–8); AAF, 2-acetylaminofluorene (CAS no. 53–96–3) 304–28–9; BHP, N-nitrosobis(2-hydroxypropyl)amine (CAS no. 53609–64–6); BrdU, ; 5-bromo-2'-deoxyuridine (CAS no. 59–14–3); DAAF, 2,7-diacetamidofluorene (CAS no. 304–28–9); DEN, diethylnitrosoamine (CAS no. 55–18–5); DMBA, 7,12-dimethylbenz[a]anthracene (CAS no. 57–97–6); ENU, 1-ethyl-1-nitrosourea (CAS no. 759–73–9); MAM, methylazoxymethanol acetate (CAS no. 592–62–1); MCA, 3-methylcholanthrene (CAS no. 56–49–5);

MNNG, 1-methyl-3-nitro-1-nitrosoguanidine (CAS no. 70–25–7); MNU, 1-methyl-1-nitrosourea (CAS no. 684–93–5); mezerein (CAS no. 34807–41–5); 4NQO, ; 4-Nitroquinoline N-oxide (CAS no. 56–57–5); PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (CAS no. 105650–23–5); TPA, 12-*O*-tetradecanoylphorbol-13-acetate (CAS no. 16561–29–8).

(349) A wide variety of radioprotectors and radical scavengers administered shortly before irradiation are protective against carcinogenesis of various tissues (Table 3.15). Some agents are effective after post-irradiation administration (Kempf et al., 1994a, 1994b; Ueno et al., 2009) presumably because some of them accelerate removal of damaged cells (Kempf et al., 1994a). Effects of feeding natural antioxidants and other food ingredients are summarised above.

Table 3.15. Experiments on the effect of radioprotectors and cancer-preventive chemicals on radiation-related carcinogenesis

Chemicals	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Radioprotector/radical scavenger						
Amifostine (WR-2721)	Pre-irradiation	γ rays	Mouse	Hematopoietic neoplasms	Decrease	Cook et al. (2018)
	Pre-irradiation	γ rays	Rat, DES-treated	Mammary cancer	Decrease	Inano et al. (2000b)
	Pre-irradiation	Neutrons (fission)	Mouse	All neoplasms	Decrease	Carnes and Grdina (1992)
	Pre-irradiation	γ rays	Mouse	All tumours	Decrease	Grdina et al. (1991a)
	Pre-irradiation	γ rays	Rat	Liver foci	Decrease	Grdina et al. (1985)
	Pre-irradiation	γ rays	Mouse	Sarcoma	Decrease	Milas et al. (1984)
	Pre-irradiation	X rays	Mouse	Lung tumours	Decrease	Yuhas and Walker (1973)
Amifostine + zinc aspartate	Pre-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease	Floersheim et al. (1992)
WR-151327	Pre-irradiation	Neutrons (fission)	Mouse	All tumours	Decrease	Grdina et al. (1991b)
AD-20	Pre-irradiation	X rays	Mouse	Thymic lymphoma	Decrease	Buc-Calderon et al. (1989)
Mixture of radioprotectors* or AET alone	Pre-irradiation	X rays	Mouse	Thymic lymphoma, lung cancer, myloid leukaemia, all carcinoma, liver tumour	Decrease	Maisin et al. (1978)
Cysteamine	Pre-irradiation	γ rays	Rat, DES-treated	Mammary cancer	Non-significant decrease	Inano et al. (2000b)
	Pre-irradiation	X rays	Mouse	Leukaemia	Decrease	Nelson et al. (1971)
Hydrogen	Pre-irradiation	γ rays	Mouse	Thymic lymphoma	Non-significant decrease	Zhao et al. (2011)

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Table 3.15. (*continued*).

Orientin†	Pre-irradiation	γ rays	Mouse	Tumours (ovary, spleen, total)	Decrease	Uma Devi and Satyamitra (2004)
Vicenin†	Pre-irradiation	γ rays	Mouse	Tumours (ovary, liver, spleen, others, total)	Decrease	Uma Devi and Satyamitra (2004)
$DMPGE_2$	Pre-irradiation	γ rays	Rat, DEN-treated	Liver foci	Decrease	Kim et al. (1994)
Bismuth nitrate‡	Pre-irradiation	X rays	Mouse	Thymic lymohoma	Decrease	Kagimoto et al. (1991)
Nitric oxide scavenger/inhibitor						
DETC	Short time covering irradiation	γ rays	Rat, DES-treated	Mammary cancer	Decrease	Inano and Onoda (2003)
1,4-PB-ITU	Short time covering irradiation	γ rays	Rat, DES-treated	Mammary cancer	Decrease	Inano and Onoda (2003)
PBN	Pre-irradiation	γ rays	Rat, DES-treated	Mammary cancer	Non-significant decrease	Inano and Onoda (2005)
1400W	Post-irradiation	γ rays	Rat, DES-treated	Mammary cancer	Non-significant decrease	Inano and Onoda (2005)
TMG	Immediately after irradiation	X rays	Rat, DES-treated	Mammary cancer	Non-significant decrease	Ueno et al. (2009)
	Immediately after irradiation	X rays	Rat, DES-treated	Pituitary tumour	Decrease	Ueno et al. (2009)
Oxidising agent						
TCDO	Post-irradiation	γ rays	Rat	Leukaemia	Decrease	Kempf et al. (1994a)
	Post-irradiation	γ rays	Rat	All malignant neoplasms	Decrease	Kempf et al. (1994b)
Miscelleneous						
DFMO	During irradiation (lifetime)	β rays	Mouse	Malignant skin tumours	Decrease	Ootsuyama and Tanooka (1993)

1,4-PB-ITU, S,S'-(4-phenylene-bis-(1,2-ethanedinyl))bis-isothiourea (an inhibitor of inducible nitric oxide synthase [iNOS]); 1400W, N-(3-(aminomethyl)-benzyl)-acetamide (an iNOS inhibitor); 5HT, hydroxytryptamine; AD-20, (ortho-methoxyphenylacetyl)-dehydroalanine (a radical-scavenging agent); AET, 2-(2-aminoethyl)isothiourea dihydrobromide; DEN, diethylnitrosoamine (a tumour initiator); DES, diethylstilbestrol (a synthetic estrogen); DETC, diethyldithiocarbamate (a nitric oxide scavenger); DFMO, α-difluoromethylornithine (an inhibitor of putrescine synthesis); DMPGE2, dimethylprostaglandin E2 (a prodrug of prostaglandin E2 and a radioprotector); PBM, phenyl-N-tert-butylnitrone (an iNOS inhibitor); TCDO, tetrachlorodecaoxygen (an oxidising agent); TMG, 2-(α-D-glucopyranosyl)methyl-2,5,7,8-tetramethylchroman-6-ol (a scavenger of free radicals and nitric oxide).

*Include glutathione, cysteine, AET, cysteamine and 5HT.

†Plant flavonoid with radical-scavenging activity.

‡Inducer of methallothionein, a radical scavenger.

3.2.5. Modification by other biological factors (e.g., DNA repair capacity, immune system)

3.2.5.1. Human

(350) Several rare, autosomal recessive diseases involving mutations in high penetrance genes such as *ATM*, *NBS, BLM* and *ERCC* are associated with a a high overall risk of both spontaneous and ionising radiation-related cancers (ICRP 1998). The capacity of DNA damage repair is influenced by a large number of genes and some SNP variants in these genes have been found in normal tissues of cancer patients, suggesting that they may be responsible for increased susceptibility to some cancer types (Alberg et al., 2013). However, the effect size is generally below 2 and results have generally not been independently replicated (Vineis et al., 2009). A recent meta-analysis showed that a better identification of cancer susceptible individuals is achieved with the help of phenotypic/ functional tests (Wu et al., 2022). The effect size of the test results appears higher than of the genetic tests and they characterise a larger number of cancer types (Wu et al., 2022). The results come from comparative analyses of DNA repair capacity in tissues from healthy donors and cancer patients, without identifying the cause of cancer. How far the polymorphisms in DNA repair genes or a low DNA repair capacity are responsible for an increased susceptibility to radiation-related cancer is not clear. Most relevant results come from studies of patients who developed second primary cancers (SpC) following radiotherapy of a primary cancer or who were exposed to diagnostic radiation and developed a primary cancer. Several studies focused on mutations in the *BRCA1* and *BRCA2* genes that code proteins involved in the repair of DNA double strand breaks. Mutations in these genes are not rare and significantly enhance the risk of spontaneous breast cancer (Chen and Parmigiani, 2007). The authors of a recent review note conflicting results of relevant investigations and conclude that there is no proof for an association between exposure to ionising radiation and an increased risk of developing cancer in carriers of mutations in the *BRCA* genes (Gonçalves et al., 2022). However, Colin et al., showed a significant increase and lasting increase of DNA DSBs assessed by γH2AX assay in mammary cells from women with family risk of breast cancer exposed to 2mGy (the standard dose of mammography), suggesting that these women are at increased risk of DNA insults that may pave the way to oncogenesis (Colin et al., 2011). More convincing, but also controversial evidence for increased susceptibility to radiotherapy-induced SpC exists for carriers of mutations in the *RB* gene, that codes for a protein controlling the cell cycle (Fabius et al., 2021).

(351) The role of the immune system in cancer surveillance is demonstrated by the increased risk of some cancers among organ transplant recipients who receive immusupressive drugs, as compared to the general population (Huo et al., 2020). Evidence for the impact of immunomodulation on the risk of radiation-related cancers could come from studies on patients receiving radiotherapy and immunosupressive drugs. However, we were not able to find relevant investigations. A systematic review on the outcome of radiotherapy in kidney transplant recipients concludes that, notwithstanding scarcity of available studies, immunosuppression has no impact on overall patient survival (Lancellotta et al., 2022). Relevant information may come from analysing the risk of radiotherapy-induced cancers in patients receiving both immune checkpoint inhibitor therapy and radiotherapy. However, no results are yet available.

3.2.5.2. Animal studies

(352) Animal studies enable the investigation of the consequences of alteration in specific genes on radiation-related carcinogenesis. Among the most extensively studied is the gene for

catalytic subunit of DNA-dependent protein kinase (*Prkdc*), the defect of which diminishes the activity of non-homologous end joining and leads to either positive or negative modification of the radiation effect depending on the experimental system (Table 3.16). A small number of studies has been performed on mouse models of hereditary diseases showing cancer susceptibility or radiation sensitivity such as ataxia telangiectasia, Fanconi anemia, hereditary breast and ovarian cancer syndrome and Lynch syndrome, as well as models harbouring genetic defects in DNA damage response and repair (Table 3.16), in general indicating increased risk or absence of modifying effect.

Table 3.16. Experiments on the effect of DNA repair capacity on radiation-related carcinogenesis

Modifying factor	Radiation	Animal	Outcome	Modification	Reference
NHEJ					
Prkdc$^{scid/scid}$	γ rays	Mouse	Thymic lymphoma	Increase	Gurley et al. (1998)
Prkdc$^{scid/+}$	γ rays	Mouse	Thymic lymphoma	No effect	Ishii-Ohba et al. (2007)
Prkdc$^{scid/scid}$	γ rays	Mouse	Thymic lymphoma	Increase	Ishii-Ohba et al. (2007)
Prkdc$^{scid/+}$	γ rays	Mouse	Solid tumours	No effect	Ishii-Ohba et al. (2007)
Prkdc$^{scid/scid}$	γ rays	Mouse	Solid tumours	No effect*	Ishii-Ohba et al. (2007)
Prkdc$^{-/-}$	X rays	Mouse, *Ptch1*$^{+/-}$	Medulloblastoma	Decrease	Tanori et al. (2019)
BALB/c variant of *Prkdc*	X rays	Mouse, *Apc*$^{Min/+}$	Mammary tumour	Antagonism	Haines et al. (2015)
BALB/c variant of *Prkdc*	X rays	Mouse, *Apc*$^{Min/+}$	Intestinal tumour	Increase	Haines et al. (2015)
HR					
Rad54$^{-/-}$	X rays	Mouse, *Ptch1*$^{+/-}$	Medduloblastoma	Increase	Tanori et al. (2019)
Xrcc2$^{+/-}$ (FA)	X rays	Mouse, *Apc*$^{Min/+}$	Mammary tumour	Increase	Haines et al. (2015)
Xrcc2$^{+/-}$ (FA)	X rays	Mouse, *Apc*$^{Min/+}$	Intestinal tumour	No effect	Haines et al. (2015)
Brca1$^{+/-}$ (HBOC)	γ rays	Mouse	Ovarian tumour	Increase†	Jeng et al. (2007)
Brca1$^{+/-}$ (HBOC)	γ rays	Rat	Mammary cancer	Increase	Nakamura et al. (2022)
Other repair systems					
Mlh1$^{-/-}$ (mismatch repair, LS)	X rays	Mouse, DSS-treated	Colon neoplasms	Increase	Morioka et al. (2015)
Parp1$^{-/-}$ (base excision repair, NF-κB pathway)	γ rays	Mouse	Thymic lymphoma	No effect‡	Bock et al. (2013)
DNA damage responses					
Atm$^{-/-}$ (AT)	Fe ions	Mouse	All neoplasms	No effect†	Yamamoto et al. (2011)
Atm$^{+/-}$ (AT)	Fe ions	Mouse	All neoplasms	No effect†	Yamamoto et al. (2011)
Atm$^{+/-}$ (AT)	X rays	Mouse	Mammry cancer, lymphoma	No effect	Umesako et al. (2005)

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Table 3.16. (*continued*).

Modifying factor	Radiation	Animal	Outcome	Modification	Reference
DNA damage responses					
Atm$^{+/-}$ (AT)	X rays	Mouse, Trp53$^{+/-}$	Mammry cancer, lymphoma	No effect[‡]	Umesako et al. (2005)
Trp53$^{+/-}$	X rays	Mouse	Mammry cancer, lymphoma	No effect[‡]	Umesako et al. (2005)
Trp53$^{S389A/+}$, *Trp53*$^{S389A/S389A}$	X rays	Mouse	Thymic lymphoma	No effect[§]	Hoogervorst et al. (2005)
Cdkn1a$^{-/-}$	γ rays	Mouse	All solid cancer	Increase[§]	Jackson et al. (2003)
Nucks1$^{+/-}$	X rays	Mouse, *Trp53*$^{+/-}$	Thymic lymphoma	Increase[§]	Yue et al. (2016)
Repair phenotype					
Capacity to rapidly diminish γH2AX foci (strain difference)	γ rays	Mouse	Lung cancer	Decrease	Ochola et al. (2019)

AT, ataxia telangiectasia; DSB, double strand break; DSS, dextran sulfate sodium; FA, Fanconi anemia; HBOC, hereditary breast and ovarian cancer syndrome; HR, homologous recombination; LS, Lynch syndrome; NHEJ, non-homologous end joining.
[*]Potential bias from small number of mice surviving thymic lymphomas which are early-onset ;
[†]Potential bias from partial lack of pathology data;
[‡]The repair defect increases spontaneous tumours whereas radiation had no effect;
[§]Unirradiated controls lacking.

(353) There is consistent evidence that development of thymic lymphoma induced by repeated acute radiation exposure is supressed by interventions that promote recovery from the radiation-related immunological suppression (Gorelik et al., 1984; Elgebaly et al., 1985; Boniver et al., 1989; Datta, 1996; Humblet et al., 1997; Martina et al., 2003) (Table 3.17). Regarding cancers of other tissues, most studies failed to prove the modulatory effect of immunological interventions (Table 3.17).

Table 3.17. Experiments on the effect of immunological status on radiation-related carcinogenesis.

Modifying factor	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Stimulation of immune system						
BMT	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease[*] (via recovery of radiation-depressed NK and NC cells)	Datta (1996)
	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease[*] (NK cell activity is not relevant)	Gorelik et al. (1984)
	Post-innoculation	X rays	Mouse, inoculated with preleukemic cells	Thymic lymphoma	Decrease	Humblet et al. (1997)

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4569 Table 3.17. (*continued*).

Modifying factor	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Poly I:C treatment	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease* (via recovery of radiation-depressed NK and NC cells)	Datta (1996)
	Pre- and post-irradiation	NR	Mouse	Thymic lymphoma	Decrease	Ball and McCarter (1971)
Interferon γ, TNFα or both	Post-irradiation	X rays	Mouse	Thymic lymphoma	Decrease	Boniver et al. (1989)
TBZ and DNFB	Post-irradiation	γ rays	Mouse	Thymic lymphoma	Decrease (via stimulation of T-cell development)	Elgebaly et al. (1985)
	During and after irradiation	γ rays	Mouse	Thymic lymphoma	Decrease	Elgebaly et al. (1985)
Immunisation with MuLV	Pre- and post-irradiation	X rays	Mouse	Thymic lymphoma	Decrease*	Peters et al. (1977)
Immunisation with normal rat serum	Post-irradiation	X rays	Mouse	Thymic lymphoma	Decrease*	Ferrer et al. (1973)
	During and after irradiation	X rays	Mouse	Thymic lymphoma	Decrease*	Ferrer et al. (1973)
Immunisation with *Salmonella tyohosa* endotoxin	Pre-irradiation	X rays	Mouse	Thymic lymphoma	No effect	Pollard and Matsuzawa (1966)
Anti CD3ε antibody treatment	Pre-irradiation	γ rays	Mouse, *Prkdc*$^{scid/scid}$	Thymic lymphoma	Decrease* (via recovery of *scid*-affected T cells)	Martina et al. (2003)
Interferons	Post-radionuclide injection (lifetime)	^{239}Pu	Mouse	Bone osteosarcoma	No effect	Taylor et al. (1984)
Immunisation with BCG	Post-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	Decrease*	Nilsson et al. (1965)
Glucan	Post-radionuclide	^{90}Sr injection	Mouse	Osteosarcoma	Decrease (stimulation of mononuclear phagocyte system)	Walinder et al. (1992)
	Post-radionuclide	^{90}Sr injection	Mouse	Malignant lymphoma	Increase	Walinder et al. (1992)
	Post-radionuclide	^{90}Sr injection	Mouse	Other tumours	No effect	Walinder et al. (1992)

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Table 3.17. (*continued*).

Modifying factor	Timing of treatment	Radiation	Animal	Outcome	Modification	Reference
Suppression of immune system						
Cyclosporin A treatment	Post-irradiation	γ rays	Mouse	Lymphoma (thymic, B-cell)	Apparent synergy	Hattori et al. (1988)
Absence of T cells in nude mice	Lifetime	γ rays	Mouse	Urethan-induced lung cancer	No effect or decrease[†]	Kobayashi et al. (1996)
THX, neonatal	Pre-irradiation	PuO_2	Rat	Lung cancer	No effect	Nolibe et al. (1981)
THX, adult	Pre-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	No effect	Bierke and Nilsson (1989)
	Pre-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Lymphoreticular and extraskeletal tumours	No effect	Bierke and Nilsson (1990)
ALG treatment	Post-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	No effect	Bierke and Nilsson (1989)
	Post-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Lymphoreticular and extraskeletal tumours	No effect	Bierke and Nilsson (1990)
THX and ALG treatment	Pre- and post-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Bone tumour	No effect	Bierke and Nilsson (1989)
	Pre- and post-radionuclide	$^{90}Sr(NO_3)_2$	Mouse	Lymphoreticular and extraskeletal tumours	No effect	Bierke and Nilsson (1990)

ALG, antilymphocyteglobulin; BMT, bone marrow transplantation; DNFB, 1-fluoro-2,4-dinitrobenzene; MuLV, murine leukaemia virus; NC, natural cytotoxic; NK, natural killer; NR, not reported; poly I:C, polyinosinic polycytidillic acid; TBZ, thiabendazole; THX, thymoectomy; TNF, tumour necrosis factor.
[*]Unirradiated controls lacking.
[†]Decrease only at a specific radiation dose (2 Gy).

3.2.6. Modification by genetic factors and epigenetic factors

3.2.6.1. Human

(354) The quantification of human radiation cancer sensitivity, i.e., radiation induced cancer proneness, is quite difficult for the following reasons:

- Radiation cancer sensitivity cannot be clinically described, nor can radiation induced cancers be distinguished from others through genetic or other analyses. Consequently, the relative risk (RR) or the excess of relative risk (ERR) calculated from epidemiological studies are currently the only parameters to express cancer risk / incidence after exposures to IR. Furthermore, epidemiological studies cannot establish causation which is only suspected if the risk of cancer significantly increases as a function of dose at the population level.
- Unless specifically designed to consider modification of radiation risks, epidemiological studies do not generally take into account any individual predispositions to specific

malignancies, because the individuals constituting the cohorts are considered as equal in terms of sensitivity. More dedicated studies addressing the issues are necessary.

- There is no generally agreed mathematical model that describes cancer incidence (which would be similar to the LQ model for cell survival) or its risk as a function dose. LNT does not fit all situations of cancers.
- At the molecular or cellular level, the quantification of cancer proneness is still made difficult by the uncertainties about the intrinsic mechanisms of carcinogenesis. However, should suitable biomarkers/bio-indicators be identified and validated, this situation could change.

(355) Basically, the question of human radiation cancer sensitivity, and its prediction has not been definitively resolved so far; it is, however, an important issue given the numbers of people treated with radiotherapy annually. El Nachef et al., showed recently significant correlations between the hyperrecombination rate quantified by plasmid assay and the proliferation capacity assessed by flow cytometry, and the excess of relative cancer risk (ERR) (El Nachef et al., 2024). Progress could be made in epidemiology with the help of biomarkers to identify potentially susceptible subgroups (e.g., Pernot et al., 2012).

(a) Breast cancer and radiation sensitivity

(356) The issue of breast cancer (BC) and IR needs to be addressed because it is a good example to highlight the problem of radiation cancer sensitivity.

(357) Worldwide BC is the most frequent cancer in women as one woman in eight will develop such a cancer, mostly after the age of 50. Mammography screening programs starting at the age of 50 are proposed to women to make an early diagnosis of BC and are justified by the reality that early detection is beneficial to the women because the cancer is less likely to have metastasised and still be in early stages of development. Consequently, the treatments are not so aggressive, the secondary effects are less, quality of life is better preserved and crucially, mortality decreases. Because the incidence of BC is increasing and the age of onset decerases, mammography examinations are increasingly frequently used at younger ages (Seely et al., 2024; Sung et al., 2024, 2025; Zhao et al., 2023), there are concerns of an increase in occurance of radiation-related BC.

(358) Risk of BC evaluation of digital mammography giving a glandular dose of 5 mGy from a 2-view breast image led to a ratio of induced incidence rate over base line incidence rate of about 1.6% for biennial screening in women aged 50–74 years (Pauwels et al., 2016). Similar values were obtained by Yaffe and Mainprize (2011) and De Gelder et al. (2011). This carcinogenic risk is indeed small in comparison with the benefit of early detection of BC, but there could be an argument women the with a family BC history should be directed towards non-IR screening technologies.

(359) Given one in eight women with BC may be considered to be at risk due to familial factors, i.e., at least one woman from the family has developed a BC, with a significant risk before the age of 50. Additionally, 20 to 30% of BC develop in women with a family risk of cancer (INCa 2019). Therefore, worldwide, millions of women are potentially affected by a familial history of BC. Furthermore, the susceptibility gene of a family BC, e.g., BRCA, is only known in about 20% of those family cases. Consequently, most women with a family risk of BC cannot be identified before BC has developed enough to be identified by screening.

(360) Colin et al. studied breast epithelial cells obtained by biopsy samples from low-risk women with no family history of BC and high-risk women with a family history of BC (Colin et al., 2010). Cells were irradiated with low energy X rays to mimic the mean glandular dose of mammography. DNA DSBs were evaluated with γ-H2AX and micronucleus assays. The

authors concluded that :1–10 min after irradiation DNA damage was significantly higher in high-risk women than in low-risk women at 10 min and remained at 24 h, and that the repetition of dose at 3 min to mimic a second view exacerbated the effects in comparison to one double dose.

(361) Hernandez et al. studied the deleterious effects of mammography screening in young and old breast epithelial cells with γ-H2AX assays (Hernandez et al., 2013). This study showed an age effect: aged cells had a diminished capacity of DNA damage response with an accumulation of irreparable DSBs in comparison with young cells. The Immunology Study of the Japanese atomic-bomb survivors have provided some evidence for possible gene-exposure interactions on cancer risks based on blood samples collected from participants to the Adult Health Study, a clinical subcohort of the LSS, in 1981–2006. Genetic or epigenetic factors that have been suggested to possibly affect the radiation-associated cancer risk include immunosuppression-related IL-10 haplotype in the gastric cancer risk (Hayashi et al., 2013), CD14 and IL18 gene polymorphisms in the colorectal cancer subsite risk (Hu et al., 2015) and the EGFR pathway in the risk of lung adenocarcinoma (Yoshida et al., 2009).

3.2.6.2. Animal studies

(362) The strain of experimental animals is a well-known factor that affects susceptibility to radiation-related cancer. As different tumours develop in different strains, researchers have intentionally used various strains to study carcinogenesis for different tissues. Although such genetic influences are thought to be governed by multiple polymorphisms of genes, it is not generally easy to delineate the gene(s) determining the susceptibility. As described in the section of DNA repair capacity, a polymorphism in the gene Prkdc in the BALB/c strain of mice is a factor identified as a determinant of the susceptibility of the strain (Okayasu et al., 2000b). Studies have considered a number of genetic factors and mechanisms influencing the strain difference in the susceptibility to thymic lymphoma induced by four weekly fractionated irradiations (Table 3.18). Evidence suggests Rbbp8 (also known as CtIP, a gene for DNA double strand break repair) as a determinant of the strain-dependent susceptibility to radiation-related myeloid leukaemia in mice (Darakhshan et al., 2006; Patel et al., 2016) and polymorphisms related to Mtf1 and Cdkn2a for thymic lymphoma (Tamura et al., 2005; Mori, 2010). Strain difference of susceptibility to other cancers has been approached by a number of studies, yet the genes governing the susceptibility remain to be identified (Table 3.18).

Table 3.18. Experiments on the effect of background strains on radiation-related carcinogenesis

Outcome	Modification by strain*	Radiation	Animal	Susceptibility allele/ mechanism	Reference
Thymic lymphoma	S: C57BL/6 R: SEG/Pas	γ rays	Mouse	*Cd274* (expressed in stroma, with polymorphisms affecting inducibility of apoptosis), *Anxa1* (expressed in stroma, with a polymorphism affecting its activity)	Santos et al. (2009), Santos et al. (2010), Boulton et al. (2001)
	S: C57BL/6 R: C3H	X rays	Mouse	Low IL9R and downstream signal	Shang et al. (2008)

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Table 3.18. (*continued*).

Outcome	Modification by strain*	Radiation	Animal	Susceptibility allele/ mechanism	Reference
Thymic lymphoma	S: BALB/c R: MSM	X rays	Mouse	D2Mit15 (BALB/c), D4Mit12 (with *Mtf1* polymorphism of BALB/c), D5Mit4-D5Mit315 (MSM)	Okumoto et al. (1995), Saito et al. (2001), Kodama et al. (2004), Tamura et al. (2005)
		γ rays	Mouse, *Tp53*$^{+/-}$	D19Mit5-D19Mit123 (MSM)	Ochiai et al. (2003)
	S: C57BL/6 R: SPRET/Ei	γ rays	Mouse	D19Mit32-D19Mit71 (C57BL/6)	Santos et al. (2002)
	S: C57BL/10 R: C3H	γ rays	Mouse	Microenvironment can alter resistance	Kamisaku et al. (2000)
	S: C57BL/10 R: STS	γ rays	Mouse	Resistance is intrinsic to T cells	Kamisaku et al. (2000)
	S: BALB/c R: STS	X rays	Mouse	A region containing *Tyrp1, Ifna1* and D4Mit302–D4Mit144 (with *Cdkn2a* polymorphism of BALB/c), D4Mit17 (BALB/c), D16Mit34 (BALB/c), co-existence of D16Mit34 and D16Mit5 (STS)	Okumoto et al. (1989), Okumoto et al. (1990), Okumoto et al. (1995), Mori et al. (2000), Mori (2010)
	S: C57BL/6 R: Swiss Webster	γ rays	Mouse, CsA-treated	N/A	Hattori et al. (1988)
	S: C57BL/6 R: A/J, CBA/J	γ rays	Mouse	N/A	Gorelik et al. (1984)
	S: BALB/c R: A/J	γ rays	Mouse	N/A	Gorelik et al. (1984)
Myeloid leukaemia	S: CBA, 129Sv2 R: C57BL/6	X rays	Mouse	Possible relevance of *Rbbp8*	Patel et al. (2016)
	S: RFM, C3H, LP, SJL, CBA/Ca, CBA/H, BALB/c (in this order) R: DBA/2, AKR, A, NOD, NON, C57BL/6	X rays	Mouse	*Rbbp8* (chromosome 2 aberration)	Darakhshan et al. (2006)
	S: CBA/H R: C57BL/6	X rays	Mouse	D1Mit150, D6Mit384	Boulton et al. (2003), Boulton et al. (2001)
	CBA/H†	X rays, ^{224}Ra	Mouse	Intrastrain polymorphism of interstitial telomere-like sequence	Silver and Cox (1993)
B-cell lymphoma	S: Swiss Webster R: C57BL/6	γ rays	Mouse, CsA-treated	N/A	Hattori et al. (1988)

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4676 Table 3.18. (*continued*).

Outcome	Modification by strain*	Radiation	Animal	Susceptibility allele/ mechanism	Reference
Lymphoma	S: Wild-type R: T190/tf	γ rays	Mouse	Chromosomal translocation t(1;17)190Ca	Wlodarska (1988)
	S: C57BL/10 R: A/J	γ rays	Mouse	Linkage with polymorohism of *Ly6* and *Ly11*	Meruelo et al. (1981)
	S: B10.D2/n R: B10.D2/o	X rays	Mouse	N/A	Kaliss et al. (1974)
	HS/Npt†	γ rays, Si ions, Fe ions	Mouse	N/A	Chernyavskiy et al. (2017)
Mammary cancer	S: ACI R: Sprague-Dawley	Neutrons	Rat, DES-treated	N/A	Shellabarger et al. (1978)
	S: Sprague-Dawley R: ACI, F344, Wistar	Carbon ions	Rat	N/A	Imaoka et al. (2007)
	S: Sprague-Dawley R: Copenhagen (Quasi-multiplicative interaction)	γ rays	Rat	N/A	Nishimura et al. (2021), (Nishimura et al. 2022)
	S: Sprague-Dawley R: Fischer-344, Wistar-Lewis	Neutrons	Rat	N/A	Vogel and Turner (1982)
	S: BALB/c R: SPRET/EiJ	X rays	Mouse	TGFβ pathway signal in microenvironment	Zhang et al. (2015)
	S: BALB/c R: DBA2	γ rays	Mouse, *Trp53*$^{+/-}$	N/A	Backlund et al. (2001)
	S: BALB/c R: C57BL/6	γ rays	Mouse	An epithelium-intrinsic mechanism (effect on mammary dysplasia assessed as a surrogate)	Ullrich et al. (1996)
Intestinal adenoma	S: BALB/c R: C57BL/6	X rays	Mouse, *Apc*$^{Min/+}$	Relevance of 5 loci (Mrip1–5)	Degg et al. (2003), Elahi et al. (2009)
	S: C3H (supra-additive) R: A/J (subadditive)	X rays	Mouse, *Apc*$^{1638N/+}$	N/A	van der Houven van Oordt et al. (1999)
Medulloblastoma	S: CD1, C57BL/6J R: C57BL/6N	X rays	Mouse, *Ptch1*$^{+/-}$	N/A	Pazzaglia et al. (2009), Ishida et al. (2010)
Lung cancer	S: A/J R: C57BL/6	Rn and its progeny	Mouse	N/A	Groch et al. (1997)
	S: F344 R: Wistar	$^{239}PuO_2$	Rat	N/A	Sanders and Lundgren (1995)
	S: 2•4, 4•22 R: 15•16, 87•20	^{210}Po	Hamster	N/A	Little et al. (1973)

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Table 3.18. (*continued*).

Outcome	Modification by strain*	Radiation	Animal	Susceptibility allele/ mechanism	Reference
Skin tumour	S: Car-S R: Car-R	X rays	Mouse, *Ptch1*$^{+/-}$	N/A	Pazzaglia et al. (2004)
	S: Car-S R: Car-R	X rays	Mouse	N/A	Pazzaglia et al. (2002b)
Lymphoma, myelocytic tumours, lung tumours	S: BALB/c R: STS	Not specified	Mouse	D5Mit143 (BALB/c)	Szymanska et al. (1999)
Liver tumour	S: C3H R: C57BL/6	Neutrons	Mouse	N/A	Ito et al. (1992)
	S: F344 R: Sprague-Dawley	γ rays	Rat	GST-P^{+} foci affected	Lee et al. (1998)
Solid tumours	S: C3H R: C57BL/6	γ rays, limb localised	Mouse	N/A	Edmondson et al. (2015)
	HS/Npt†	γ rays, Si ions, Fe ions	Mouse	N/A	Chernyavskiy et al. (2017)

*S, susceptible; R, resistant.

†A genetically heterogeneous stock of mice descended from matings of eight inbred founder strains (A/J, AKR/J, BALB/cJ, C3H/HeJ, C57BL/6J, CBA/J, DBA/2J and LP/J).

(363) Technologies of genetic manipulation in experimental animals have enabled research on the influence of specific genetic variations on the susceptibility to radiation-related cancer. As listed in Table 3.19, modified models of a number of tumour suppressor genes (Sfpi1, Hip2k, Mt1, Mt2, Cdkn1a, Pten, Apc, Ptch1, Pax6, Trp53, and Nf1) have been devised and used for radiation carcinogenesis experiments, supporting the influence of germline mutations of these genes. The tissue specificity of the genetic influence may in some cases depend on the primary role of the gene (e.g., Sfpi1, Apc, Ptch1), but it may reflect the exposure regimen and the genetic background of the model used in other cases (e.g., thymic lymphoma after 4 weekly fractionated exposures in C57BL strains).

Table 3.19. Experiments on the effect of genetic modifications on radiation-related carcinogenesis.

Outcome	Gene modification	Radiation	Animal	Background	Modification	Reference
Myeloid leukaemia	*Sfpi1*$^{+/-}$	γ rays	Mouse	B6;129, (CBA×B6;129)F_1	Increase (via LOH of *Sfpi1*)	Genik et al. (2014b)
Thymic lymphoma	*Hip2k*$^{+/-}$	γ rays	Mouse	ND	Increase	Mao et al. (2012)
	Mt1$^{-/-}$ *Mt2*$^{-/-}$	X rays	Mouse	B6	Increase	Shibuya et al. (2008)
	Cdkn1a$^{-/-}$	γ rays	Mouse, *Trp53*$^{-/-}$ or *Trp53*$^{+/-}$	B6	Increase	De la Cueva et al. (2006)
	Pten$^{+/-}$	γ rays	Mouse	Backcross of *Mus spretus* on 129	Increase	Mao et al. (2003)
	Trp63$^{+/-}$	γ rays	Mouse	ND	No effect	Perez-Losada et al. (2005)
	Trp73$^{+/-}$	γ rays	Mouse	ND	No effect	Perez-Losada et al. (2005)

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Table 3.19. (*continued*).

Outcome	Gene modification	Radia-tion	Animal	Background	Modification	Reference
Lymphoma	*Pim1* transgenic (with *Igh* Eμ enhancer)	X rays	Mouse	B6	Increase	van der Houven van Oordt et al. (1998)
Mammary tumour	$Apc^{Min/+}$	X rays	Mouse	B6	Increase	Imaoka et al. (2006)
Medulloblastoma	$Ptch1^{+/-}$	X rays	Mouse	CD1	Increase	Pazzaglia et al. (2002a)
Sarcoma	$Ptch1^{+/-}$	X rays	Mouse	CD1	Increase in background*	Pazzaglia et al. (2002a)
Digestive tract tumour	$Pax6^{+/-}$	γ rays	Mouse	C3H	Increase	Nitta et al. (2007)
Intestinal tumour	$Apc^{1638N/+}$	X rays	Mouse	B6	Increase	van der Houven van Oordt et al. (1997)
All neoplasms	$Trp53^{+/-}$	γ rays	Mouse	B6;129	Increase (additive)	Carlisle et al. (2010)
	$Trp53^{+/-}$	γ rays	Mouse	NIH;129	Increase	Kemp et al. (1994)
	$Trp53^{-/-}$	γ rays	Mouse	NIH;129	Increase and acceleration	Kemp et al. (1994)
	$Trp53^{R193P}$ or $Trp53^{A135V}$ transgenic	γ rays	Mouse	CD1	Increase	Lee et al. (1994)
	$Nbn^{+/-}$	γ rays	Mouse	B6;129	Increase in background*	Dumon-Jones et al. (2003)
	$Cdkn1a^{+/-}$	γ rays	Mouse	B6;129	Antagonistic	Martin-Caballero et al. (2001)
	$Nf1^{+/-}$	γ rays	Mouse	B6;129	Increase	Choi et al. (2012), Nakamura et al. (2011)

ND, not described.
*Increased spontaneous, but not radiation-related, carcinogenesis.

(364) Little evidence exists concerning epigenetic difference among individuals. Because epigenetic alterations are common in cancer, epigenetic drugs (inhibitors of enzymes such as DNA methyltransferase and histone acetyltransferase) are used for cancer treatment. It is of note that an inhibitor of DNA methyltransferase, zebularine, is reported to suppress incidence of radiation-related thymic lymphoma of mice (Herranz et al., 2006). A review paper has discussed the possibility of the use of food components which affect epigenetics (e.g., methyl donor nutrients, polyphenols, selenocompounds) in prevention of radiation-related cancer (Imaoka et al., 2016a).

3.3. Summary and conclusion on the range observed and main contributory modifying factors

3.3.1. Age

(365) The risk of radiation-related cancer in humans depends on the age at exposure, although patterns of risk vary by cancer site. As a general pattern observed in the Life Span

Study of Japanese atomic-bomb survivors, radiation related relative risks are higher for those exposed as children and in adolescence than as adults and tend to increase with increasing age at exposure for leukaemia and most site-specific solid cancers. For breast cancer in females, the most sensitive age is the peri-pubertal period.

(366) Young animals are in general more susceptible than fetuses and adults regarding radiation-related risk of all cancers. In most organs, susceptibility is high in the prenatal or neonatal animals and continues to be high until postnatal ages ranging from neonatal to young adult stages. The breast is most susceptible during the peri-pubertal ages in rats; human and animal studies are consistent in this finding. Mechanistic evidence suggests that the variation among tissues is associated with the age-related change in the biology of individual tissues and the systemic environment.

(367) In humans, the likelihood of developing radiation-associated cancer changes over time after exposure; the risk of leukaemia starts increasing relatively soon after exposure, in a few years, while solid cancers can take years or decades to develop. For many cancers, the relative risk tends to decrease and the absolute risk to increase as the baseline rate increases with age. In the case of leukaemia, absolute risk is higher at younger ages. Very little evidence from animal studies exists regarding attained age.

3.3.2. Sex

(368) Evidence from the LSS and other epidemiological studies (see Section 4 and Annex A) generally indicates that the radiation related relative risk is higher for females than for males for all solid cancers combined, and for some individual cancer sites (e.g., stomach, liver, lung, bladder) but not others (e.g., colon, brain/CNS). Animal studies in general agree with higher susceptibility of females to all solid tumours and higher susceptibility of males to myeloid leukaemia and liver tumours, whereas the results for other tissues are inconsistent or scarce. See further discussion in Section 4.

3.3.3. Lifestyle factors

(369) Both epidemiological and experimental animal evidence suggest that smoking increases the risk of radiation cancer in the lung. In humans, the nature of the interaction effect of radiation and smoking on cancer is still inconclusive. Evidence from the LSS indicates presence of a complicated smoking-radiation interaction for the risk of lung cancer incidence; the radiation-associated lung cancer risk may be higher among light to moderate smokers than heavy smokers after adjustment for the total amount of smoking. A large animal experiment has revealed a supra-additive interaction between exposures to $^{239}PuO_2$ aerosol and cigarette smoke on induction of lung cancer in rats, with supportive evidence from a few other studies. The interaction is beyond the level explained by the smoking-induced increase in the retention of radioactive particulates in the lung.

(370) Very few studies have been reported concerning the impact of alcohol cpnsumption on radiation cancer risk.

(371) Diet-induced overweight increases—and underweight decreases—radiation-related carcinogenesis of various organs in animal models. A study suggests a supra-multiplicative interaction between radiation and a high-fat diet in animals.

(372) Many plant-derived chemicals are shown to reduce radiation-related tumours of various animal models; some evidence suggests modification by iodine, iron, and vitamins.

(373) Parity reduces radiation-related breast cancer in rats depending on the age at exposure, whereas the reproductive status at the time of exposure has no modifying effect. Long-term oestrogen treatment enhances radiation-related breast cancer risk while ovariectomy, anti-oestrogens and weak oestrogens reduce the risk in rats. Animal studies suggest that parity

reduces ^{90}Sr-induced bone tumours by reducing the retention of the radionuclide in bone, whereas oestrogen increases the risk. Cancers of the breast and endometrium in atomic bomb survivors demonstrate distinct patterns that could associated with hormonal factors, with highest excess breast cancer risk for individuals exposed around the time of menarche, and highest radiation-related endometrial cancer risk with exposure just before the onset of puberty.

3.3.4. Underlying conditions

(374) A supra-multiplicative interaction between radiation and infection to Hepatitis C virus (HCV) on the risk of hepatocellular carcinoma (HCC) among atomic-bomb survivors.

(375) No animal studies have reported in relation to the impact of diabetes and collagen vascular disease on radiation cancer risk.

(376) Limited evidence suggests increased radiation-related carcinogenesis by experimental inflammation.

3.3.5. Other environmental factors

(377) Some epidemiological studies including the LSS indicate that the relative risk of non-melanoma skin cancer might be lower for sites exposed to sunlight, whereas the absolute risk might be higher for such sites. A few animal studies suggest positive interaction between radiation and sunlight exposures on skin cancer.

(378) Radiation and genotoxic chemicals act generally additively while some evidence indicates significant departure from additivity, with very few studies assessing departure from multiplicativity. Possible mechanisms of the interaction include radiation-related clonal expansion of chemically initiated cells. Interactions of radiation and other classes of chemicals ranges from antagonism to apparent supra-additivity. Radioprotectors and radical scavengers administered shortly before radiation exposure are protective against carcinogenesis.

3.3.6. Other biological factors

(379) Capacity to repair γH2AX foci is related to low risk of radiation-related lung cancer among various mouse strains. Defect in NHEJ either positively or negatively modifies the risk of radiation-related cancer depending on the experimental system, whereas a defect in HR often increases the risk, although evidence is limited.

(380) Development of thymic lymphoma in mice induced by repeated acute radiation exposure is supressed by interventions that promote recovery from immunological suppression. Most studies failed to prove the modulatory effect of immunological interventions on other cancers.

3.3.7. Genetic factors and epigenetic factors

(381) The strain of experimental animals affects susceptibility to radiation-related cancer, with only a few genetic loci (e.g., *Rbbp8*, *Mtf1* and *Cdkn2a*) proven to be responsible. Germline mutations in many tumour suppressor genes increase radiation carcinogenesis, with their tissue specificity seemingly governed by the primary role of the gene. Evidence is lacking as to whether these interactions are additive or multiplicative.

(382) Little evidence exists on the impact of epigenetic modifications on radiation cancer risk.

3.4. Approaches to prediction – genetic and functional assays

(383) Survivors of childhood cancers have been found to be at greater risk of second primary cancers than the population in general (Meadows et al., 2009). This can be explained by the fact that many childhood cancer patients suffer from DNA repair disorders associated with enhanced cancer predisposition (Sharma et al., 2020). Except for rare syndroms caused by mutations in high penetrance genes like *ATM*, the predispositions are organ-specific, manifesting by cancers arising in particular anatomic sites or tissues (Imyanitov et al., 2023). It is currently not clear how far these syndromes increase the susceptibility to radiogenic cancers. What is clear is that homozygous patients with syndromes resulting from mutations in high penetrance genes including ataxia telangiectasia, ligase IV deficiency and Nijmegen breakage syndrome show strongly elevated radiosensitivity resulting in severe reactions to radiotherapy and possibly radiogenic cancers (AGIR, 2013). But these patients show a strong phenotype. A comparative study on phenotypically normal Hiroshima and Nagasaki survivors who developed only a first primary cancer and both first and second primary cancers showed a similar dose-response relationship for cancer risk in both survivor groups indicating that survivors with multiple cancers were not more susceptible to radiogenic cancer than those with one cancer (Li et al., 2010). A meta-analysis of the risk of developing second primary cancer after radiotherapy showed that the ERR per unit dose estimated for the seven second primary cancer sites (haematopoietic and lymphoid malignancies, sarcoma, breast cancer, lung cancer, gastrointestinal cancer, thyroid cancer, and brain cancer) is generally lower than those reported by other radiation epidemiological studies on nonradiotherapy exposures, also suggesting that phenotypically normal people who develop cancer after radiotherapy do not show a higher level of radiosensitivity compared with healthy people who develop radiogenic cancers (UNSCEAR, 2024). Because there is some weak evidence for increased radiogenic cancer susceptibility among carriers of known low penetrance cancer predisposition genes like *BRCA1* and *BRCA2* (UNSCEAR, 2024), it appears possible to find assays predicting the susceptibility to radiogenic cancers.

(384) A number of cell-based assays have been identified with some prospects of being developed into assays predictive of elevated radiation cancer risk. In a recent review article (Gomolka et al., 2020) identified four types of assay in various stages of development/validation: (i) radiation-induced chromosomal aberrations (e.g., G2 assay, micronucleus assay), (ii) radiation-induced DNA damage and repair (e.g., g-H2AX assay), (iii) candidate genetic variants (e.g., in DNA damage recognition and repair genes, cell cycle genes etc.), (iv) Genome-wide variant approaches (e.g., GWAS, exploratory studies). In addition, it was found that three classes of assay may have predictive potential: (i) radiation-induced gene expression profiling, (ii) tests for acquired cancer susceptibility (circulating clonal mutations) and (iii) imaging markers (computer-based radiology image analysis/radiomics).

(385) There are therefore prospects of the development of predictive assays for radiation cancer susceptibility and some identified genetic factors that indicate elevated risk. However, there remains no clinically validated universal assay for radiation cancer susceptibility.

3.5. Possibilities of modulating the risk

(386) Cancer originates from mutations in the DNA that can result from lesions induced by external factors such as ionising radiation and by intrinsic biological processes such as oxidative stress and replication errors. The lifetime risk of cancer, averaged over both sexes, is approximately 50% (Sasieni et al., 2011). Estimates exist suggesting that about 40% of cancers

are preventable because they are caused by such factors as smoking, viruses, carcinogens in food and the environment, sun light and obesity (Golemis et al., 2018). Carcinogens can act as initiators and promoters of cancer. When two carcinogens act together, the question arises if they act independently, in an additive manner of if they interact in a multiplicative manner. In principle, two carcinogens can only interact if one is an initiator and the other a promoter. Many carcinogens have both functions. An example is ionising radiation that can initiate cancer by inducing DNA damage and promote cancer by killing cells, triggering repopulation. Obesity induces cancer by oxidative stress and promotes cancer by triggering cell division via production of growth hormones. Under conditions of combined exposure, carcinogens potentiate each other. Elimination of one carcinogen reduces the action of the other. The magnitude of interaction is often difficult to assess because risk estimates in humans are based on epidemiological studies where exposure levels to factors of interest are not experimentally controlled. Nevertheless, evidence provided in this publication demonstrates that external factors do influence the level of radiogenic cancer.

(387) The uncertainty in the mode of interaction between carciongens is reflected in ICRP´s recommendations on the strategy of transferring cancer risk between populations (ICRP, 2007). The incidence of different types of cancers varies between countries, often by a factor of around 10. Genetic differences cannot explain these differences because when people migrate, they acquire the cancer incidence of their adopted country (Golemis et al., 2018). The question remains when risk of radiation-related cancer is estimated in a population of one country and predictions are made on the cancer incidence among potentially exposed people in another country, should the risk estimate be based on a multiplicative or additive model? The former approach assumes that radiation interacts with other present carcinogens and the latter – that it does not. In view of the uncertainty regarding the mode of interaction, ICRP recommends that, for most cancers, the transfer is done by applying the average risk from relative and absolute risk models. Interestingly, BEIR VII recommends, for most cancers, applying a ratio of 70% relative risk and 30% absolute risk model (National Research Council BEIR VII, 2006). Whichever strategy is adopted, the underlying assumption is that the risk of radiation-related cancer is potentiated by the presence of other carcinogens. Conversely, this risk can be diminished by reducing or eliminating exposure to other carcinogens. Here, it is important to note that an interaction between two carcinogens does not require their simultaneous presence. For example, cigarette smoking potentiated the lung cancer risk in Japanese people exposed to radiation from atomic bombs irrespectively of whether they began smoking before or after the exposure (Furukawa et al., 2010). Obviously, the risk of radiation-related cancer can be diminished if exposure to a co-carcinogen is reduced or eliminated after the combined exposure. This means that the individual risk of radiation-related cancer is not pre-determined, but can be modulated by changing the life-style following exposure. Like all risks, the risk of radiation-related cancer is conditional and depends, to some degree, on actions taken by the exposed person after the exposure.

4. THE ROLE OF BIOLOGICAL SEX IN MODIFICATION OF RESPONSES TO RADIATION (HUMAN STUDIES)

4.1. Introduction

(388) This publication has considered the role of biological sex in modification of responses to radiation for specific endpoints within preceding sections. Given the potential importance of, and interest in biological sex as a modifier of radiation-related health effects in human studies, this section presents a summary of a large systematic review of the topic, considering both cancers and late-developing non-cancer endpoints. A more complete description of the review and its findings is provided as an annex to this publication (Annex A).

4.2. Approach

(389) A systematic review search protocol was published in the PROSPERO registry in 2020 under CRD42020207563. The focus of the search was on human, animal, and tissue/cell studies. Outcomes that were sought included cancer, circulatory diseases, cognitive effects, and cataracts. Full inclusion and exclusion criteria can be found in the registry. Full details of the search strings, approach to risk of bias assessment and screening approach are provided in the Annex. The initial searches identified 9678 unique papers to which an additional 20 were added having been identified from other sources. While animal and in vitro studies were captured as part of the search, this publication prioritised the analysis and synthesis of human studies given the significant time needed to address such a large search scope. Screening of human study reports resulted in 110 papers for consideration for synthesis in the review. The main source of information is the Life Span Study of the survivors of the 1945 Japanese atomic bombings. In addition, informative environmental, occupational and medical exposure studies were identified. Tabulation of the studies considered, and relevant findings are included in the Annex, the following paragraphs provide a brief summary of the findings. Papers relevant to each of the major late developing health outcomes were identified; most in relation to cancers, but also ciriculatory diseases, cataract and cognitive impairment.

4.3. Summary of findings

4.3.1. Cancers

(390) The strongest evidence for sex differences in cancer risk comes from the LSS studies (mostly cohort studies, sound dosimetry, demonstration of a dose-response). In addition, women were well represented in the study population (as compared to many occupational cohorts). For both mortality and incidence from all solid cancers combined, women are observed to have higher ERR compared to men, including from in utero exposures and for secondary cancers. However, this does not extend to the EAR, where no sex differences are observed. Preston et al. (2007) explained that the EAR, which is not influenced by spontaneous background rates, is likely a better indicator of sex differences. Sex differences in the shape of the all-solid cancer dose-response are likely explained by age at exposure, the differences in the spontaneous background rates, and the composition of the case series (Cologne et al., 2017; Brenner et al., 2022). Similarly, differences between the ERR and EAR for urinary tract cancer incidence can be explained by the different spontaneous background rates (Grant et al., 2017).

Further follow-up and site-specific analyses will be necessary to better understand these findings.

(391) Sex differences in radiation-related cancer incidence and mortality are observed at different sites. Males have a statistically significant higher risk estimate compared to women for meningioma (ERR), esophageal cancer incidence (ERR), malignant lymphoma mortality (ERR), leukaemia, acute lymphoblastic leukaemia and non-Hodgkins lymphoma incidence (EAR), whereas, females have a significantly higher estimate for esophageal cancer mortality (ERR), stomach cancer (ERR), thyroid cancer incidence (EAR), multiple myeloma mortality (ERR), and chronic myeloid leukaemia (EAR). For the studies evaluating stomach and thyroid cancer, the ERR and EAR values were not consistent. For stomach cancer, only the ERR varied by sex, not the EAR (Sakata et al., 2019), and the opposite was observed for thyroid cancer where only the EAR varied by sex (Furukawa et al., 2013).

(392) With regards to the Environmental Exposures study category, the evidence was weak as many of the studies are ecological in design. Overall, there was a suggestion that women were generally more at risk of developing cancer compared to men for thyroid and solid cancer; and men more at risk of leukaemia, lung, and esophageal cancer; however, the weight of evidence did not support the existence of sex differences.

(393) Many of the occupational cohorts are largely made up of men with the exception of those occupationally exposed in the medical field (e.g., radiologic technologists). This results in studies that restrict their analyses to men or do not allow for a robust evaluation of sex differences.

(394) Among several studies that reported ERR estimates in the occupationally exposed, no statistically significant sex differences were observed. Importantly, this included the higher ranked studies (e.g., Zablotska et al., 2014, Cardis et al., 2007). Studies on the Mayak workers suggest that women have a higher risk of lung cancer incidence and mortality (Stram et al., 2021 and Labutina et al., 2013), however important dosimetry uncertainties for this cohort exist (especially for plutonium). The US Nuclear Power Plant Workers cohort estimate for lung cancer incidence (ERR/100 mGy), while larger in women, was not statistically significant (Boice et al., 2022).

(395) Overall, the identified studies on patients undergoing medical treatment (tinea capitis, diagnostic imaging/fluoroscopic interventions, thorotrast, and radiotherapy) suggest that women are more at risk compared to men for radiation related thyroid cancer (excess absolute risk, Shore et al., 1985), secondary cancers (relative risk, Wang et al., 2019), and solid cancer: (excluding brain) (incidence rate ratio and excess incidence rate, Mathews et al., 2013), but the weight of evidence does not support a significant sex difference.

(396) In line with the weight of evidence, pooled studies did not observe sex differences for radiation related thyroid cancer from childhood exposures (LSS+Medical: excess relative risk: Veiga et al., 2016, relative risk: Lubin et al., 2017), or for lung cancer (Occupational+Medical: excess relative risk: Boice et al., 2018).

4.3.2. Circulatory diseases

(397) According to the ICRP, cardiovascular disease, which is currently considered to be a tissue reaction, has a nominal threshold dose of 0.5 Gy. This is chiefly informed by epidemiological data, including that from the LSS (ICRP, 2012). Given that the LSS provides evidence for increased risk of cardiovascular disease at less than 5 Gy and with a mean dose of <0.5 Gy and that the form of the dose response <0.5 Gy is uncertain, the magnitude of risks of at low doses (<100 mGy) remain uncertain. To add to the uncertainty, there are many confounders that are associated with these diseases that are very common in the general population (Gillies et al., 2017).

(398) Risk of heart disease did not substantially vary by sex in the LSS cohort. Both a narrative and a systematic review on cardiovascular disease in the LSS cohort support this conclusion (Ozasa et al., 2017, Little et al., 2023).

(399) Important limitations and lack of consistency between the environmental exposure studies identified do not permit a firm conclusion regarding sex differences.

(400) The higher ranked evidence for occupational exposures indicates that women are at a higher risk of circulatory disease and ischemic heart disease mortality. While the sex difference was considered statistically significant, large uncertainties remain (female representation, large confidence intervals, low female cumulative dose, lack of high dose information) (Gillies et al., 2017, Cha et al., 2020).

(401) While several medical studies were included in Little et al. (2023), the searches carried out for this publication identified only a few studies that considered both sexes. This can be explained partly by the fact that the present study did not include one sex-specific studies (e.g., women treated for breast cancer), or studies where patients received chemotherapy. Identified studies did not offer strong evidence for significant sex differences. There seems to be a suggestion that males are more at risk for carotid stenosis and ischemic attacks, however, important uncertainties remain (Yang et al., 2017, Chang et al., 2009).

4.3.3. Cataract

(402) According to ICRP, cataracts are considered to be tissue reactions with a threshold of 0.5 Gy for low linear transfer radiation (ICRP, 2012). This threshold for acute exposure was chiefly determined by LSS studies on cataracts and cataract surgery (Nakashima et al., 2006, Neriishi et al., 2007), whereas the threshold for fractionated or protracted exposures was determined by a study on Chornobyl clean-up workers (Worgul et al., 2007, Hamada et al., 2020).

(403) While not numerous or consistent, there is evidence that exists for sex differences. Both the LSS and Mayak worker studies observed statistically significant higher cataract risk for females compared to males (Nakashima et al., 2006, Azizova et al., 2020). In the case of the Mayak workers, for all three types of cataracts (cortical, nuclear, posterior subcapsular), the ERRs/Sv were 2–4 times higher in females than in males ($p < 0.001$). No sex differences in the EAR were found however in the US Radiologic Technologist cohort (Little et al., 2020).

4.3.4. Cognitive effects

(404) The symptoms of radiation-related cognitive impairment include decreased verbal memory, spatial memory, attention, and novel problem-solving ability, and rarely dementia (Greene-Schloesser and Robbins, 2012). Only one identified study fits this narrow definition (Farjam et al., 2015). It demonstrated sex differences at very high doses, however, further studies are needed to draw more robust conclusions. This search excluded radiotherapy studies that evaluated neurocognitive functioning based on the fact that they included patients that had undergone chemotherapy (possible confounder).

5. RECOMMENDATIONS FOR FURTHER RESEARCH

(405) It is clear from the extensive reviews undertaken in the course of writing this publication that the evidence base relating to the factors that govern individual response to radiation for all the endpoints considered is incomplete. Here we suggest areas for further research that are judged to be of most importance for practical radiation protection, especially in medicine.

(406) In the future, it would be very helpful to maintain comprehensive patient treatment databases containing the exact treatment regimen and dosage, as well as individual dose distributions of radiotherapy. These databases can improve future treatments, especially for children with cancer, who typically have an excellent prognosis and will experience their late neurocognitive side effects. It is recognised that such data collection and collation systems would have significant resource and cost implications, including appropriate medical and scientific staff, as well as appropriate IT capacity.

(407) There would be benefits to a more systematic approach to collection of data and biological samples on the frequency of severe normal tissue reactions following cancer radiotherapy. Collation at an international level would be beneficial but great care will be needed to ensure that there is consistency in the recording and reporting of radiation dose information and assessment of the severity of normal tissue reactions.

(408) The ability to reliably predict normal tissue response at the individual level has the potential to 'tailor' radiotherapy at the individual level. A relatively small number of promising predictive assays have been reported, some being prospective in nature. However, few if any of these assays are in use across multiple treatment centres within one country, and none internationally. Further work to develop and validate such assays could lead to significant patient benefits; in principle genetic testing approaches are likely to be most reliable, though currently the best developed assays are cellular.

(409) Of the diseases considered in this publication, there is most information available in relation to the factors that govern individual response to radiation in terms of the development of cancers. The data are notably robust for age-at-exposure and sex, although patterns vary by cancer site. Having similarly robust evidence available for the non-cancer endpoints of cataract, circulatory diseases and cognitive impairment could be beneficial.

(410) Notwithstanding the above, continued follow up of large epidemiological cohorts remains important, both in terms of refining risk estimates for cancers, but also identification of cancer risk modifying factors. Studies informative on risk to females and to the full age range remain somewhat under-represented currently, and therefore furter such studies would be beneficial. Inclusion of radiation exposure into broader studies considering multifactorial cancer risk modification would be useful in determining the relative impact of radiation in comparison to other agents/factors.

(411) With the identification of factors modifying radiation risk through population and/or clinical studies, there will be a requirement to gain mechanistic insights through experimental animal and/or cellular investigations.

6. ASSESSMENT OF UNCERTAINTIES AND CONFIDENCE IN CONCLUSIONS

(412) Based on the literature review, the uncertainty regarding the impact of factors that influence individual response is presented in the tables below according to the guidelines developed by the Intergovernmental Panel on Climate Change (Mastrandrea et al., 2010). Uncertainty is presented as the level of confidence among the authors regarding the impact of a factor or statement. Confidence is expressed using five qualifiers: "very low," "low," "medium," "high," and "very high" and is a vector of the collective agreement among the authors of this publication and evidence found in the published literature. The relationship between agreement and evidence and the resulting level of confidence are best depicted in the form of a matrix (Fig. 6.1). There is some flexibility in this relationship, as for a given evidence and agreement statement, different confidence levels could be assigned. However, a high level of evidence and degree of agreement correlates with high confidence (Mastrandrea et al., 2010). A conclusion describes the direction of the risk modulating effect along with a generalised statement on how much is known.

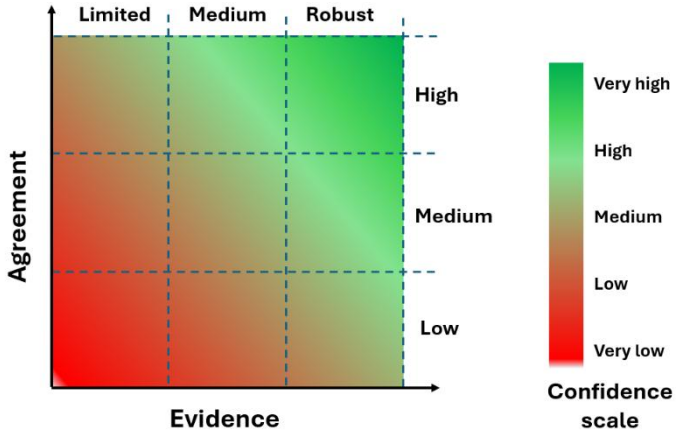

Fig. 6.1. A matrix representing the relationship between evidence and agreement and the resulting confidence. Evidence is most robust when there are multiple, consistent, independent observations published in peer-reviewed journals. Agreement reflects the level of consistency in opinions expressed by the authors of the publication.

5075 Table 6.1. Factors modulating tissue reactions in patients exposed to radiotherapy.

Factor	Evidence	Agreement	Confidence	Conclusion
Monogenic diseases (e.g., Ataxia telangiectasia)	Robust	High	Very high	Monogenic diseases involving DNA damage response pathways potentiate toxicities
SNP and other, likely polygenic, factors	Medium	Medium	Medium	SNP in numerous low penetrance loci, including some in DNA damage response pathways, have been shown to correlate with risk of toxicities.
Smoking	Limited	High	Medium	May potentiate toxicities
Alcohol	Limited	Low	Low	May potentiate toxicities
Chemotherapy	Robust	High	Very high	Potentiates toxicities
BMI	Limited	High	Medium	No generalisation possible regarding the direction of interaction
Immune system	Limited	High	Medium	The role of the immune system in modulating toxicity is not well understood
Age	Robust	High	Very high	Adults show highest resistance to toxicities with children being most sensitive and elderly intermediate
Sex	Limited	High	Medium	No clear differences between sexes
Comorbidities	Robust	High	Very high	Cardiovascular disease, diabetes, inflammatory bowel disease and hypertension potentiate the risk

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5077 Table 6.2. Factors modulating the risk of radiation-related diseases of the circulatory system.

Factor	Evidence	Agreement	Confidence	Conclusion
Age at exposure	Medium	High	High	Age at exposure has no clear effect on radiation-related risk; weak indication of increased risk with younger age at exposure but not consistent across outcomes or exposure settings.
Attained age	Limited	High	Medium	Attained age has no clear effect on risk; effect is not consistent across outcomes or exposure settings
Biological sex	Medium	High	High	Sex has no clear effect on risk; weak indication of increased risk in females but not consistent across outcomes or exposure settings
Comorbidities	Limited	High	Medium	Impact of comorbidities on risk not clear
Genetic factors	Limited	High	Medium	Impact of genetic factors on risk not clear
Chemotherapy	Medium	High	High	Anthracyclines likely interact with radiation in potentiating the risk. Not clear for other drugs.
Smoking	Limited	High	Medium	Impact of smoking on risk not clear
Alcohol	Limited	High	Medium	Impact of alcohol on risk not clear

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5079 Table 6.3. Factors modulating the risk of radiation-related cataract.

Factor	Evidence	Agreement	Confidence	Conclusion
Age at exposure	Limited	High	Medium	Weak indication for decreasing risk with age at exposure
Attained age	Limited	High	Medium	No clear impact of attained age
Biological sex	Limited	High	Medium	No clear impact of sex, but weak indication for higher risk in females
Comorbidities	Limited	High	Medium	No clear impact of comorbidities, except increased risk in diabetics
Genetic factors	Limited	High	Medium	Impact of genetic factors on risk not clear. Most evidence available from animal studies
Smoking	Limited	High	Medium	Impact of smoking on risk not clear
Alcohol	Limited	High	Medium	Impact of alcohol on risk not clear

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Table 6.4. Factors modulating the risk of radiation-related cognitive effects.

Factor	Evidence	Agreement	Confidence	Conclusion
Age at exposure	Robust	High	Very high	Higher risk in children as compared to adults
Attained age	Medium	High	High	No clear impact of attained age
Biological sex	Limited	High	Medium	No clear impact of sex
Comorbidities	Limited	High	Medium	No clear impact of comorbidities
Genetic factors	Limited	High	Medium	Impact of genetic factors on risk not clear
Smoking	Limited	High	Medium	Impact of smoking on risk not clear
Alcohol	Limited	High	Medium	Impact of alcohol on risk not clear

Table 6.5. Factors modulating the risk of radiation-related cancer.

Factor	Evidence	Agreement	Confidence	Conclusion
Age at exposure	Robust	High	Very high	For all solid cancer sites combined, higher risk in for younger age at exposure but effects of age at exposure vary between individual sites.
Attained age	Robust	High	Very high	Attained age decreases ERR and increases EAR of all solid cancers. For all solid cancer sites combined, lower risk with increasing attained age, but effects of attained age vary between individual sites
Biological sex	Robust	High	Very high	For all solid cancer sites combined, higher ERR in women but variation between individual sites. EAR measures do not vary between sexes.
Comorbidities	Limited	High	Medium	No clear impact of comorbidities
Genetic factors	Medium	High	High	Impact of genetic factors on risk not clear
Smoking	Robust	High	Very high	Smoking potentiates the risk of lung cancer and possibly of other cancers
Alcohol	Limited	High	Medium	Impact of alcohol on risk not clear. Some animal data and limited data from Life Span Study
Obesity	Limited	High	Medium	Impact of obesity on risk not clear
Female sex hormones	Medium	Medium	Medium	Hormonal variability impacts risk at some sites. Animal data indicate that estrogen increases, and progesterone decreases risk. Emerging human data suggest increased susceptibility around the age of puberty to radiation cancers of the breast and uterine corpus.

Table 6.6. Prospects for prediction of individual risk of deterministic and stochastic radiation effects.

Effect	Evidence	Agreement	Confidence	Conclusion
Tissue effects (deterministic)	Medium	Medium	Medium	Apart from some special circumstances where there are strong DNA repair defects, and assay results are consistent, generally it is not possible to predict tissue effects reliably.
Cancer (stochastic)	Limited	Low	Low	Possibility to predict cancer risk not clear.

(413) On the basis of the considerations above, and to summarise the analysis of uncertainties, a number of broad points can be made:

- There is robust evidence for the severity of normal tissue reactions to radiotherapy being influenced by genetic factors (inherited monogenic disorders), concurrent chemotherapy, comorbidies (cardiovascular disease, diabetes, inflammatory bowel disease and hypertension), and age; additionally, some evidence supports a role of smaller genetic changes (single nucleotide polymorphisms) in some genes. Prediction of normal tissue reactions using cellular and other assays has been reported, but it remains unclear if prediction is possible.

- For circulatory diseases, concurrent chemotherapy with anthracyclins may influence risk, convincing evidence in relation to other factors is lacking, although age and sex may influence the liklihood of certain circulatory disease outcomes; investigation of the prediction of individual response has not been conducted.
- Only limited evidence is available in relation to cataract risk, some evidence suggests that concurrent diabetes increases risk; investigation of the prediction of individual response has not been conducted.
- For cognitive effects, there is robust evidence for age at exposure influencing risk, with those exposed at younger age being at greater risk; investigation of the prediction of individual response has not been conducted.
- In terms of radiogenic cancers, robust evidence indicates that risk is influenced by age-at-exposure (younger ages at elevated risk, but with variation between cancer sites), biological sex (in terms of excess relative risk females are at greater risk, but with variation between cancer sites), and smoking (notably radon lung cancer risk higher in smokers); some evidence exists for genetic factors and female sex hormones influencing risk; prediction of radiation cancer risk by means of simple tests has not been convincingly demonstrated.
- Overall, only limited robust evidence is available on the influence of specific factors on responses to radiation exposure. The most secure evidence is in relation to age and biological sex, particularly with respect to radiation-related cancer. The ability to predict responses at the individual level remains a challenge.

7. GENERAL CONCLUSIONS

What is the impact of age, sex, and other determinants on normal tissue reactions?

(414) There is some evidence that sex, increasing age, rheumatoid arthritis, prior surgery and chemotherapy increase the frequency of normal tissue reactions.

(415) Smoking generally increases the frequency of normal tissue reactions but in the lung protects against radiation-related normal tissue reactions.

(416) There is suggestive evidence that genetic factors, collagen vascular diseases, alcohol consumption and microbiome may modulate the frequency of normal tissue reactions.

What is the impact of age, sex, and other determinants on non-cancer diseases following radiation exposure?

Cataract

(417) The risk of cataract tends to be higher in females after radiation exposure, and in those of younger age at the time of exposure. Animal studies and limited human studies have indicated that genetic factors play a role, with some DNA repair related genes modifying risk. Some evidence indicates that co-morbidities (e.g., diabetes) and co-exposures (UV, antioxidants) modify risk. However, no firm conclusions can yet be drawn.

Diseases of the circulatory system (DCS)

(418) There is some suggestive evidence that concurrent chemotherapeutic exposure (particularly anthracycline) increases the liklihood of radiation induced DCS, with the majority of evidence coming from fractionated high dose radiotherapy studies. Less consistent evidence indicates a possible increased risk of DCS with younger age at radiation exposure, although this depends on specific DCS outcome.

Cognitive impairment

(419) Current knowledge indicates a clear age dependency of radiation-related brain injury associated with cognitive dysfunction that can be explained by the higher radiosensitivity of numerous proliferating precursor cells in the developing brain. Other factors (such as sex, lifestyle and environmental factors) have no or significantly less influence on the development of neurocognitive disorders after exposure of the brain to ionising radiation.

What is the impact of age, sex, and other determinants on incidence of cancers following radiation exposure?

(420) Epidemiological and animal data indicate that younger age at exposure and female sex are associated with a higher relative risk for most solid cancers. However, there is variation between cancer sites. For example, radiation-related risk appears to be higher in females for cancers of the stomach, liver, lung, bladder, and thyroid, but higher in males for cancers of the brain/CNS and colon. For female breast cancer, the most sensitive age is the peri-pubertal period; human and animal studies are consistent in this finding.

(421) In the case of leukaemia, absolute risk is higher at younger ages at exposure and in males.

(422) Both epidemiological and some experimental animal evidence suggest that smoking increases the relative and absolute risk of radiation cancer in the lung.

(423) Animal studies provide some indication that excess body weight is associated with increased solid cancers and leukaemias.

(424) For breast cancer in animal studies hormonal factors (long-term estrogen exposure) increases risk.

(425) Animal studies provide some evidence that co-exposure to chemical agents is generally additive to radiation cancer risk, and radioprotectors and free radical scavengers reduce radiation cancer risk

(426) Variation in cancer risks in inbred strains provides good evidence that genetic factors modify radiation cancer risks. The use of genetically modified mouse strains indicates that deficiencies in genes that modify background cancer incidence also modify radiation cancer incidence.

What is the contribution of genetics to individual normal tissue responses with respect to adverse reactions to varying doses such as given during radiotherapy?

(427) There is clear evidence that rare homozygous mutations in some genes, such as ATM, have a large effect on normal tissue radiosensitivity. The combined effect of multiple common mutations will be smaller; while the heritability of intrinsic cellular radiosensitivity is known to be high, around 70%, the heritability of radiotherapy-related normal tissue reactions is expected to be more modest. There is an ongoing search to identify the genes that contribute to the common genetic risk of normal tissue reactions, and there is likely to be different genes contributing to the different specific tissue reactions, and not only those involved in DNA damage response.

Would predictive tests contribute to a better radiation protection of radiotherapy patients without compromising cancer cure rates?

(428) Yes, in principle but there are no internationally validated assays available despite promise being shown for some specific assays. There is a need for multi-centre international intercomparison studies to standardise and validate specific assays.

What is the contribution of genetics and epigenetic factors to tissue radiation response with respect to cancer induction at relevant doses and dose rates?

(429) A significant majority of the evidence relating to this question comes from studies at moderate to high doses of radiation delivered at high dose rates.

(430) Inbred mouse strains show different susceptibility to radiation cancer, indicating a role of genetics in determining radiation cancer risk. Genetically modified mouse strains where genes affecting spontaneous cancer frequencies have been knocked out, generally also show modified radiation cancer frequencies. The search for genetic determinants of radiation cancer risk in humans has been challenging, requiring very large genome-wide association studies. The development of methods in this area would be beneficial.

(431) Evidence from twin studies of spontaneous cancer risk in humans indicate that the genetic contribution to variability in risk is around 30–40%.

(432) There is currently little evidence relating to epigenetic factors.

What is the evidence that modifiable factors can affect individual risk of radiation-related cancer, tissue reactions, and other non-cancer diseases?

(433) It is clear that smoking effects the liklihood of cancer and normal tissue reactions after radiation exposures. There is currently no evidence on the modification of radiation-related cataract or circulatory disease by smoking.

(434) Experimental animal studies indicate that diet affects radiation cancer risk, with high fat and high carbohydrate diets and elevated body weight being associated with higher risk.

(435) Alcohol consumption affects risk of normal tissue reactions after radiotherapy, but there is limited evidence in other settings.

(436) Experimental animal studies provide evidence that radioprotectors and free radical scavengers administered before exposure can reduce the risk of radiation-related cancer. There are no supporting human studies.

What are the ways to quantify the potential impact of individual response to radiation on the incidence of cancers, non-cancer diseases, and normal tissue reactions?

(437) This is currently possible on a population basis rather than on an individual basis, though tests are being investigated.

(438) In rare exceptions, such as in the case of ataxia telangiectasia patients and other rare genetic syndromes, genetic tests can be informative. Such genetic testing may become more informative in the future when better knowledge of the contributory genetic factors is available.

(439) Cellular tests are capable of detecting rare highly sensitive individuals, such as those with AT and other genetic syndromes. The availability of specialised regional centres to conduct such testing, even though it would be needed only infrequently, would be beneficial. There are nonetheless ethical issues associated with such testing that would have to be addressed before wide implementation.

What are the ways to modulate individual risk?

(440) The occurrence of radiation-related cancers is known to be inherently stochastic in nature, and as such individual risk is not rigidly predetermined, nor can it be reliably predicted in routine practice. Like all risks, the risk of radiogenic cancer is conditional and may be modulated by changing life-style factors such as smoking that can have a considerable impact.

ANNEX A. SYSTEMATIC REVIEW OF RADIATION-RELATED HEALTH EFFECTS MODIFIED BY BIOLOGICAL SEX (HUMAN STUDIES)

(A 1) This publication has considered the role of sex in modification of responses to radiation for specific endpoints within preceding sections. Given the potential importance of, and interest in biological sex as a modifier of radiation-related health effects in human studies, this section presents a summary of a large systematic review of the topic, considering both cancers and late-developing non-cancer endpoints.

A.1. Approach

(A 2) The search protocol was published in the PROSPERO registry in 2020 under CRD42020207563.

(A 3) The focus of the search was on human, animal, and tissue/cell studies. Outcomes that were sought included cancer, circulatory diseases, cognitive effects, and cataracts. Full inclusion and exclusion criteria can be found in the registry.

(A 4) The MEDLINE search string included the following:

(A 5) (TI ((sex* based) OR (gender* based) OR (gender* dependent) OR ("sex dependent") OR ("sex-dependent") OR (gender* specific) OR ("m#n vs wom#n") OR (m#n N2 wom#n) OR (sex* N3 role*) OR (sex* N3 identit*) OR (sex* N3 determination*) OR (sex* N3 differentiation*) OR (sex* N3 factor*) OR (masc* N2 fem*) OR ("masc* and fem*") OR ("male* versus female*") OR (male* N2 female*) OR (sex* N3 characteristic*) OR (gender* N3 differen*) OR (sex* N3 differen*) or (sex* N3 dimorphism*) OR ("m#n versus wom#n") or ("m#n and wom#n") OR (m#n N2 wom#n)) OR AB ((sex* based) OR (gender* based) OR (gender* dependent) OR ("sex dependent") OR ("sex-dependent") OR (gender* specific) OR ("m#n vs wom#n") OR (m#n N2 wom#n) OR (sex* N3 role*) OR (sex* N3 identit*) OR (sex* N3 determination*) OR (sex* N3 differentiation*) OR (sex* N3 factor*) OR (masc* N2 fem*) OR ("masc* and fem*") OR ("male* versus female*") OR (male* N2 female*) OR (sex* N3 characteristic*) OR (gender* N3 differen*) OR (sex* N3 differen*) or (sex* N3 dimorphism*) OR ("m#n versus wom#n") or ("m#n and wom#n") OR (m#n N2 wom#n)) OR ((MH "Sex Differentiation") OR (MH "Sex Factors") OR (MH "Sex Characteristics") OR (MH "Sex") OR (MH "Sex Distribution") OR (MH "Sex Ratio")))

(A 6) AND

(A 7) TI ((radiation N2 expos*) OR (radiation N2 expos*) OR ("nuclear weapon*") OR ("chernobyl") OR ("body irradiation") OR ("low dose radiation") OR ("low-dose radiation") OR ("radiosusceptibility") OR ("atomic bomb survivor*") OR ("nuclear bomb survivor*") OR ("hydrogen bomb survivor*") OR ("radiation effect*") OR ("radiation-induced") OR (radiation dos*) OR (radiation N2 exposure) OR (radiation N3 (tumo?r* OR neoplas* OR carcinoma* OR malignan*)) OR (ioni#ing N2 radiation) OR (radiation N2 cancer*)) OR AB ((radiation N2 expos*) OR (radiation N2 expos*) OR ("nuclear weapon*") OR ("chernobyl") OR ("body irradiation") OR ("low dose radiation") OR ("low-dose radiation") OR ("radiosusceptibility") OR ("atomic bomb survivor*") OR ("nuclear bomb survivor*") OR ("hydrogen bomb survivor*") OR ("radiation effect*") OR ("radiation-induced") OR (radiation dos*) OR (radiation N2 exposure) OR (radiation N3 (tumo?r* OR neoplas* OR carcinoma* OR malignan*)) OR (ioni#ing N2 radiation) OR (radiation N2 cancer*)) OR ((MH "Chernobyl Nuclear Accident") OR (MH "Radiation Injuries") OR (MH "Radiation, Ionizing") or (MH "Radiation Effects") OR (MH "Whole-Body Irradiation") OR (MH "Dose-Response Relationship, Radiation") OR (MH "Nuclear Warfare") OR (MH "Nuclear

Warfare") OR TI ("nuclear war*") OR AB ("nuclear war*") OR (MH "Radiation Exposure") OR (MH "Nuclear Weapons") OR (MH "Neoplasms, Radiation-Induced") OR (MH "Atomic Bomb Survivors"))

(A 8) The SCOPUS search string included the following:

(A 9) ((TITLE-ABS-KEY(("sex* based" OR "gender* based" OR "sex dependent" OR "sex-dependent" OR "gender* dependent" OR "gender* specific*"))) or (TITLE-ABS-KEY((men OR man OR male* OR masc*) W/2 (women OR woman OR female* OR fem*))) or (TITLE-ABS-KEY(sex* W/3 (differen* OR characteristic* OR dimorphism* OR factor* OR determination* OR role* OR identit*))) or (TITLE-ABS-KEY(sex* W/2 (distribution* OR ratio*))) or (TITLE-ABS-KEY(gender* W/3 differen*))) AND ((TITLE-ABS-KEY(radiation W/2 (induc* OR cancer* OR tumor* OR tumour* OR neoplas* OR carcinoma* OR malignan*))) or (TITLE-ABS-KEY(nuclear W/2 weapon*)) or (TITLE-ABS-KEY(respon* W/2 dos* W/2 radiation)) or (TITLE-ABS-KEY("nuclear war*")) or (TITLE-ABS-KEY(("atomic bomb survivor*" OR "nuclear bomb survivor*" OR "hydrogen bomb survivor*"))) or (TITLE-ABS-KEY(("whole-body irradiation" or "body irradiation" or "low dose radiation" or radiosusceptibility))) or (TITLE-ABS-KEY(chernobyl nuclear)) or (TITLE-ABS-KEY(radiat* W/2 (expos* OR effect OR effects OR injur OR ion*))))

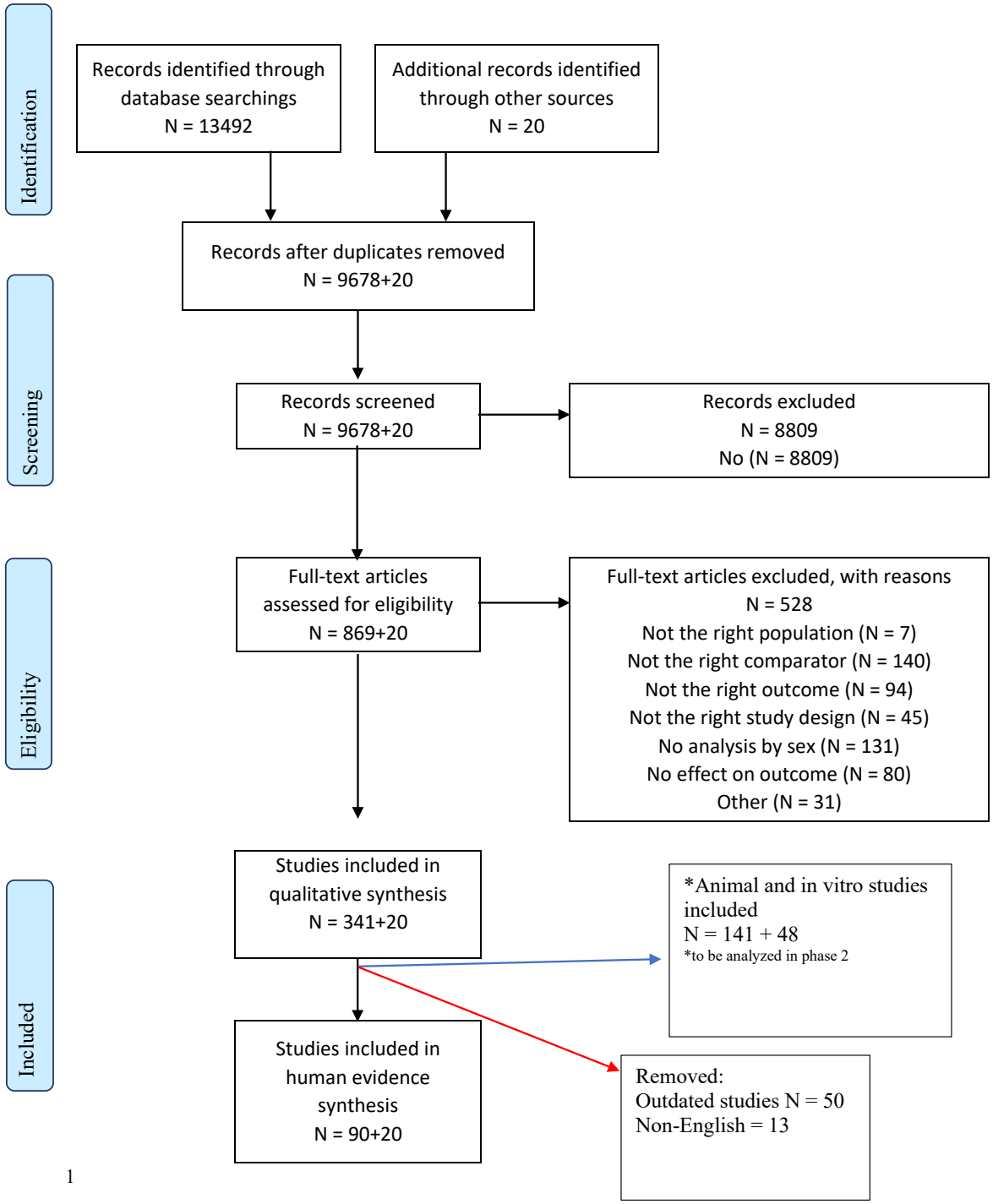
(A 10) Risk of bias assessment was conducted following data extraction (tool modified from Office of Health Assessment and Translation).

(A 11) Title/abstract screening, full text screening, data extraction and risk of bias assessment were conducted by two independent reviewers.

(A 12) Superceeded studies were replaced by their updated versions, and key references that had not been identified in the original search were added at the synthesis stage. Non-English studies were not included in the synthesis stage.

(A 13) To draw conclusions from the collected evidence the synthesis was based on the GRADE-informed UNSCEAR approach (UNSCEAR, 2017).

A.2. Results



1

Fig. A.1. PRISMA flow diagram of literature selection for the systematic review. Additions to the original PRISMA Flow Diagram, Copyright © 2021, Evidence Partners Inc., All Rights Reserved.Adapted from "Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097."

(A 14) After removing duplicates and conducting title/abstract screening (level 1), full-text screening (level 2) and risk of bias assessment, 153 human studies were identified. Of the 153,

the evidence from 90 plus an additional 18 records were synthesised. Superceeded and non-English records were left out (total: 63 studies).

(A 15) The dose from the included studies varied from very low to high dose (very low: <10 mGy, low: >10–100 mGy, moderate: >100 mGy–1 Gy and high: >1 Gy). The estimated individual radiation dose for the LSS cohort ranged up to around 4 Gy, but about 38,500 had an estimated weighted absorbed colon dose of less than 5 mGy (Ozasa et al., 2017). The studies on environmental exposures consisted of very low doses to low doses. With regards to occupational exposures, they vary from low to moderate doses, however, the median annual dose is generally very low to low. In the case of the Mayak workers, the mean cumulative liver absorbed dose for gamma was 0.43 Gy and 0.25 Gy for alpha (plutonium) (Azizova et al., 2023). The medical exposures generally are high, where radiotherapy, the largest contributor to dose, can consist of several Grays for the treatment of tinea capitis, or even higher doses for the treatment of cancer. Diagnostic imaging however typically involves low doses.

A.2.1. Cancer incidence and mortality

A.2.1.1. Lifespan Study

(A 16) The Life Span Study (LSS) of atomic bomb survivors describes the cancer risks observed amongst Japanese survivors of the Hiroshima and Nagasaki bombings in 1945. The cohort consists of 105,444 subjects where 40.4% are male and 59.8% are female. Given the sex distribution, important information about radiation induced sex differences can be ascertained.

(a) All solid cancer mortality and incidence

(A 17) Studies on the solid cancer incidence and mortality of atomic bomb survivors have indicated differences in how male and females respond to radiation. In an earlier study on cancer incidence, the authors observed that the ERR and EAR estimates were significantly higher for adenocarcinomas in females (ERR/Gy: 0.62(90%CI 0.50 to 0.75); EAR 10,000/person-year (PY) Gy: 40 (90%CI 33 to 48)) compared to males (ERR/Gy: 0.31(90%CI 0.22 to 0.40); EAR 10,000/PY Gy: 22(90%CI 15 to 31)). The ERR/Gy estimate for sarcomas of 0.76 (90%CI 0.08 to 2.3) for men was non-significantly higher than that of 0.20 (90%CI 0.02 to 0.8) for women. However, the EAR (10,000/PY Gy) for men of 0.60 (90%CI 0.10 to 1.7) was significantly higher than for women (0.19 (90%CI 0.03 to 0.67)), with a female:male ratio of 0.31 (90%CI 0.05 to 0.99) (Preston et al., 2007). Additional sex differences were observed in a more recent study where that the shape of the dose response was significantly different among male and females (p = 0.02). For females, the dose response was consistent with linearity (ERR/Gy = 0.64 (95% CI: 0.52 to 0.77) and for males, the linear quadratic model (ERR = 0.20 (95% CI: 0.12 to 0.28) at 1 Gy and an ERR = 0.010 (95% CI: 0.0003 to 0.021) at 0.1 Gy) (Grant et al., 2017). Similarly, a study on cancer mortality, noted that the female ERR/Gy was about 2 times higher than males (0.30 (95%CI 0.24 to 0.35) vs 0.15 (95% CI 0.52, 0.80). ERRs for most cancer sites were also higher in females. Notably, the cancer of the gallbladder and renal pelvis/ureter was increased in males, but not in females, and cancer of the stomach, rectum and other digestive diseases were increased in females, but not in males (in all cases, not significantly, Cis overlapped). Interestingly, there were no sex differences in EAR for all solid cancer or specific types. The authors explained that this was a result of differences in the background mortality rates where the background mortality rates of cancer were much higher in men than in women (Ozasa et al., 2012). Indeed, the heterogeneity of background rates seem to explain part of the sex differences in the ERR (Cologne et al., 2019).

(A 18) The dose-response findings were further refined recently by comparing all solid cancer mortality and incidence (Brenner et al., 2022). In this study, the model was adjusted for the "high dose" effect to minimize the influence of individuals that had received >4 Gy. This resulted in an increase in the magnitude of the upward curvature for both males and females. Over the entire range of doses, the cancer mortality dose response for males exhibited an upward curvature ($p = 0.062$), and a significant upward curvature for females ($p = 0.10$). Like the 2017 study, for solid cancer incidence, males exhibited a significant upward curvature ($p = 0.001$), but not among females. Their findings indicate that the upward curvature in all solid cancer is neither specific to males nor to incidence data. The authors suggest that this result depends on composition of case series (i.e. contribution of sex-specific cancers) and age at exposure or time. Further analysis is warranted to confirm the emerging trend.

(A 19) For the individuals exposed in utero, a significant ERR in females for solid cancer mortality was observed (ERR/Gy = 2.51 (95% CI: 0.53, 6.28)), but not in males [−0.07 (95% CI: <−0.82, 1.37)] (Sugiyama et al., 2021). Similarly, females exposed in utero or in childhood had a larger ERR and EAR estimates for solid cancer incidence compared to males. The ERR Female:Male ratio was 1.7(95%CI 0.9 to 3.8) ($p = 0.13$) and the EAR F:M was 2.1(1.1 to 4.7) ($p = 0.02$) (Preston et al., 2008).

(A 20) The ERRs of first and second primary solid tumour incidence were larger among women (ERR/Gy = 1.09; 95% CI, 0.94–1.24 and ERR/Gy = 1.03; 95% CI, 0.64–1.49, respectively) compared with men (ERR/Gy = 0.51; 95% CI, 0.40–0.63 and ERR/Gy = 0.37; 95% CI, 0.11–0.70, respectively). Some caution is recommended when interpreting these results because of the relative rarity of second primary cancers and therefore the limited statistical power of the study (Li et al., 2010).

(b) Site-specific cancer incidence and mortality studies

(A 21) The most recent update for the study on the incidence of central nervous system tumours (Brenner et al., 2020) indicate that the dose response is stronger in males than among females for each tumour type, but only significantly for meningioma (ERR/Gy Male: 5.54 (95%CI 1.32, 17.09); Female: 0.99 (95% CI <−0.15, 3.13; $p = 0.045$). A suggestion that sex modified the ERR for all CNS tumours combined was found ($p = 0.053$).

(A 22) Grant et al. (2021) found that for urinary tract cancer incidence, the ERR/Gy was significantly increased for both males and females, however, the estimate for females was 3.4 times greater than males (95% CI: 1.4–8.6). The EAR point estimates at 70 years were 4.4 (95%CI 0.70–8.8) for males and 3.7 (95%CI 2.0–5.8) for females per 10,000 person-year-Gy. The different pattern between ERR and EAR values indicate that the ERR sex differences are likely due to different background rates. No strong association between kidney cancer and radiation was observed, however, the female dose response (linear ERR 0.62/Gy (95% CI: –0.20 to 2.1;) was significantly different compared to the male dose response (linear ERR −2.1/Gy and quadratic ERR 1.2/Gy2, ind. CIs) ($p = 0.04$). The authors suggest that the non-intuitive shape of the male dose response and the small numbers of cases mean that the findings do not represent a real sex-based difference in radiation sensitivity. Further follow-up is required to confirm.

(A 23) For colorectal cancer incidence, no sex differences were observed (Sugiwama et al., 2020).

(A 24) A sex difference in linear ERRs for esophageal cancer incidence was not statistically significant; however, when the dose-response shape was allowed to vary by sex, statistically significant curvature was found among males, but not for females (Sakata et al., 2019). However, Ozasa et al. (2012) observed that the ERR/Gy for mortality was significant in females (1.1(0.04 to 3.0), $p = 0.04$), but not in males (0.39(−0.006 to 0.97), $p = 0.054$). Females

have a higher risk for stomach cancer incidence (ERR/Gy F/M = 2.20, 95%CI 1.15–4.80, p = 0.02), however the EAR showed no sex differences (p = 0.29) (Sakata et al., 2019).

(A 25) A study by Sadakane et al. (2019) observed a statistically significant increased risk of pancreatic cancer incidence among females (ERR/Gy 0.70, 95%CI 0.12–1.45), but not in males (ERR/Gy 0.07, 95%CI −0.29 to 0.63). However, the tested sex difference was not significant (p = 0.193). The same study did not observe sex differences for liver cancer (p = 0.371), or biliary tract cancer (including gallbladder, and other parts of the biliary tract) (p = 0.284).

(A 26) A study looking at lung, laryngeal and other respiratory cancer incidence found a non-significant risk of lung cancer in females (ERR/Gy Female: 1.20 (95% CI 0.74, 1.75); Male: 0.42 (95% CI 0.16, 0.84)). There was no evidence of a sex-dependent curved dose-response. The other cancer types were not associated with radiation exposure (Cahoon et al., 2017).

(A 27) Exposure to radiation during adulthood leads to an increase in thyroid cancer incidence in females and a decrease in males. These results are not statistically significant given that the confidence intervals overlap (Females: ERR/Gy = 0.70 (90% CI = 0.20, 1.46); Males: ERR/Gy = −0.25 (90% CI = <0, 0.35)). The increased risk seems to be lower for those exposed to radiation in adulthood vs childhood (Richardson 2009). In a more recent study assessing those exposed in childhood, the EAR (100,000 person-years-Gy) for females was significantly higher than that for males, with a female:male ratio of 6.3 (p = 0.001), while the ERR/Gy sex ratio was smaller and not statistically significant (2.0; p = 0.30) (Furukawa et al., 2013). The observation that the thyroids of younger children are more sensitive to radiation exposure is further supported by a study measuring the prevalence of thyroid nodules, however, no sex differences were observed (p > 0.17) (Imaizumi et al., 2015).

(A 28) In addition, sex differences were observed for lymphoid and hematopoietic malignancies mortality where males only had significant increases for malignant lymphoma and females only for multiple myeloma (ERR/Gy 0.7 (95%CI 0.08 to 1.7), p = 0.02 and 0.86 (95% CI 0.02 to 2.5), p = 0.04) (Ozasa et al., 2012). However, a more recent analysis provides a more complex picture for the incidence of leukaemia, lymphoma and multiple myeloma (see Table A.1). Sex differences could be observed in the EAR model (but not for the ERR model) of several types of blood cancer. All estimates, but for chronic myeloid leukaemia, were larger for males. The small number of cases of HL, ALL, CLL and ATL limit the statistical power.

(A 29) A study by Little et al. compared breast cancer mortality and incidence between male and females. Males have a significant increased risk (p < 0.01) for cancer mortality (ERR/Sv 8.88, 95%CI 0.60–92.34 vs Female: 1.56, 95%CI 0.96–2.34) and incidence (ERR/Sv 19.41, 95%CI 1.53–761.30 vs Female: 1.50, 95%CI 1.12–1.95). Females nevertheless have larger EAR/104 person year/Sv values for both cancer incidence and mortality, indicating that the background rate for breast cancer is influencing the result. A degree of caution is recommended in interpreting these results given the important limitations including a small male sample size (large confidence intervals), and lack of consideration to lifestyle risk factors (Little et al., 2017).

(A 30) A case-control study measuring standardised incidence rates of salivary gland tumours suggest that exposed males are at great risk. High risk of bias is likely given the study limitations (small number of male cases, confounding/modifying factors not considered, no individual dose measurement) (Takeichi et al., 1976).

Table A.1. Hsu et al. (2013) summary on incidence of lymphoid and hematopoietic malignancies.

Type of lymphoid and hematopoietic malignancy	Main findings	ERR/Gy	EAR
Leukaemia other than CLL or ATL	EAR estimates for women were about 66% of those for men.	No indication that ERR varied significantly with sex ($p = 0.29$)	Statistically significant sex difference ($p = 0.08$). F: 0.70 (0.13 to 1.53) M: 1.06 (0.16 to 2.42) F/M ratio: 0.66 (0.41 to 1.04)
Acute Myeloid Leukaemia	No sex differences.	N/A	N/A
Acute Lymphoblastic Leukaemia	ERR for women ~40% of that of men. Significant sex difference in the EAR model, where men are more at risk.	F: 0.95(0.23 to 3.37) M: 2.40 (0.63 to 7.90)	F: 0.09(0.03 to 0.25) M: 0.23(0.07 to 0.58) Significant sex difference $p = 0.05$, Female:Male EAR ratio = 0.4
Chronic Myeloid Leukaemia	Significant sex dependent attained age effect, where women are more at risk.	No sex difference in ERR by sex $p > 0.5$	Sex dependent attained age effect on EAR model $p = 0.01$. EAR for women significantly increases with attained age (2.10 (0.48 to 4.21, $p = 0.009$), whereas there is little variation for men (−0.20(−1.03 to 0.66, $p > 0.5$).
Chronic Lymphocytic Leukaemia	N/A	N/A	N/A
Adult T cell Leukaemia	No dose response, no statistically significant sex differences	M: 0.88 (−0.60 to 4.532, $p = 0.28$)	N/A
Non Hodgkin lymphoma	Only a suggestion of elevated ERR in men, however the EAR is statistically significant	M:0.46(−0.08 to 1.29), $p = 0.11$ F: 0.02(<−0.44 to 0.64, $p > 0.5$)	M: 0.54(0.09 to 1.32, $p = 0.003$) F: ~0 (−0.02 to 0.3), $p > 0.5$)
Hodgkin lymphoma	No dose response	N/A	N/A
Multiple myeloma	No statistically significant dose response.	No statistically significant variation by sex ($p > 0.5$)	No statistically significant variation by sex ($p = 0.5$)

A.2.1.2. Environmental Exposures

(A 31) The references captured under environmental exposures include studies of residents living near nuclear facilities, residents exposed to nuclear contamination, and residential radon exposures.

(A 32) While no sex differences were observed in studies looking at cancer incidence in populations living in the vicinity of Nuclear Power Plants (Desbiolles et al., 2018, Lane et al., 2013), a study on residents affected by the Three Mile Island accident did suggest an increased relative risk in leukaemia among the 5 mile radius male residents (maximum and likely gamma: RR = 1.15, 95% CI = 1.04, 1.29 and RR = 1.36, 95% CI = 1.08, 1.71, respectively). This finding, which was not observed in females (maximum and likely gamma: RR = 0.90, 95% CI = 0.69, 1.15 and RR = 0.85, 95% CI = 0.53, 1.38, respectively), needs to be further investigated (Han et al., 2011).

(A 33) Cancer incidence in counties in Sweden contaminated by the Chornobyl accident was found to be higher in women compared to men in rural and non-rural residencies and tended to increase in both sexes at higher exposures (Incidence Rate Ratio: non-rural: F = 1.18 (95% 1.16–1.19), rural: F = 1.1 (95% 1.08–1.14); M = reference) (Alinaghizadeh et al., 2016). Similarly, Magnanti et al. (2009) reported a non statistically significant trend where women had a higher risk than men. With regards to thyroid cancer in children from Belarus or Bryansk Oblast exposed to I-131 after the Chornobyl accident, no significant statistical difference between sexes was observed (EOR/Gy males = 2.01 (95% <−0.03, 156); EOR/Gy females = 2.26 (95% 0.36, 14.6); $p = 0.94$) (Zablotska et al., 2015) (girls 0–4 years ERR/Gy 45.3 (5.2, 9953) with internal control, and 28.8 (4.3, 2238) with external control; boys 0–9 years ERR/Gy 68.6 (10.0, 4520) with internal control, and 177.4 (−276, 106) with external control) (Ivanov et al., 2006). For Ukrainian children, it was suggested that females had a higher risk of developing thyroid cancer compared to males. The age-adjusted incidence rate of females of the high-exposure regions increased from 3.34 to 10.99 per 100,000, while in females of the low-exposure regions, it increased from 2.51 to 5.69 per 100,000 (Males: high exposure region: 0.87 to 2.64/100,000; low exposure region: 0.87 to 1.37/100,000) (Fuzik et al., 2011). For leukaemia incidence in Ukrainian children, no sex differences were observed (Rate Ratio females = 2.7 (95% 0.6–8.6), males = 2.3 (95% 1.6–4.7)) (Noshchenko et al., 2001).

(A 34) No sex differences in solid cancer incidence was observed in the cohort consisting of residents that lived near the Techa River where radioactive material was released as a result of the Mayak plutonium production (female:male ERR/100 mGy ratio 1.5; $p > 0.5$) (Davis et al., 2015). Similarly for leukaemia incidence (non-CLL), sex did not significantly modify radiation risk (ERR/100mGy: F:M ratio 1.0, 95%CI 0.14–6.7; $p > 0.5$), (Krestinina et al., 2013).

(A 35) With regards to residential radon exposures, conflicting evidence exists regarding sex differences for leukaemia. In addition, only a few studies suggest that men are more at risk of developing lung and esophageal cancer when exposed to radon (see Table A.2).

Table A.2. Residential Radon studies.

Study	Main finding	Endpoint
Leukaemia incidence		
Oancea et al., 2017	A significant interaction between gender and radon exposure was observed (M > F; $p = 0.009$).	Number of CLL cases per 10^6
Teras et al., 2016	A statistically significant difference between sexes was observed (F > M, $p = 0.002$).	Adjusted Hazard Ratio
Lung cancer		
Barbosa-Lorenzo et al., 2015	Statistically significant correlation between male SMR and lung cancer ($p = 0.023$)	Standard Mortality Ratio
Wang et al., 2022	No statistically significant difference between sexes ($p = 0.62$)	Excess Odds Ratio
Pisa et al., 2001	No statistically significant difference between sexes (confidence intervals overlap). However, an association was observed in males exposed to 40 to 76 Bq (confidence intervals >1.0).	Odds Ratio
Esophageal cancer		
Ruano-Ravina et al., 2014	Statistically significant correlation observed in men, but not women ($p < 0.001$).	Relative Risk

5490 A.2.1.3. Occupational exposures

5491 (A 36) The studies identified in this group can be categorised into three: Medical, Nuclear
5492 and Various. The Medical category includes the US Radiologic Technologists (~27% men) and
5493 Chinese Medical x-ray workers (~75% men). The Nuclear category includes studies on nuclear
5494 workers, which consist mainly of men (~75–97% of the study population). The Various
5495 category includes larger scope gender-balanced occupational studies. Many of the included
5496 studies below contain large dosimetry uncertainties, and limited statistical power (Table A.3).
5497
5498 Table A.3. Summary of Occupational Studies.

Study	Cohort name	Main finding	Endpoint
Medical			
Little et al., 2014	US Radiologic Technologists	No effect by sex on the chromosome translocation rates in relation to occupational and personal -diagnostic-medical doses (p = 0.7166).	Regression analysis
Sigurdson et al., 2003	US Radiologic Technologists	Risk of all solid tumours in females was higher than in males (1.06 (95%1.02–1.10) vs 0.92 (95%0.85– 0.98)).	Standard Incident Rate
Sun et al., 2016	Chinese Medical X-ray Workers	No sex differences in solid cancer incidence were observed for the ERR/Gy for both the colon dose and badge dose risk models. Both male (colon dose: 0.82 (95%0.46 to 1.32), badge dose: 0.29 (95%0.16 to 0.46) and females (colon: 0.93 (0.35 to 1.84), badge dose: 0.32 (0.12 to 0.64) had similar statistically significant increases in the ERR.	Excess Relative Risk
Boice et al., 2023	US Medical Radiation Workers	The ERR for lung cancer was 0.16 (0.01, 0.32) among the 55,218 male workers and 0.09 (–0.19, 0.36) among the 53,801 female workers; a difference that was not statistically significant (p = 0.23)	Excess Relative Risk / 100 mGy
		Nuclear	
Zablotska et al., 2014	Canadian Nuclear Energy Workers (part of 15 Country Study)	Solid cancer mortality risks per unit dose for all other Canadian workers (not early AECL workers) remained negative and did not vary by sex (p > 0.5).	Excessive Relative Risk per Sv
Cardis et al., 2007	15 Country Study	The mortality estimates for women (All cancers excluding leukaemia, lung cancer, leukaemia excluding CLL) were lower than for men, but confidence intervals were very wide and there was no statistical difference between sexes (p = 0.41, 0.73 and 0.68, respectively).	Excessive Relative Risk per Sv
Muirhead et al., 2009	UK third analysis of the National Registry for Radiation Workers	No statistically significant sex differences were observed for all malignant neoplasms. Unadjusted SMR (95% CI) Men: 84 (82–86) Women: 81 (73–90) p = 0.36 (χ^2 for heterogeneity) Social class adjusted Men: 82 (80–84) Women: 84 (76–93) p = 0.17 Fewer than 10% of all workers were female and have lower mean lifetime doses.	Standard Mortality Ratio

5499 (*continued on next page*)
5500

5501 Table A.3. (*continued*).

Study	Cohort name	Main finding	Endpoint
Medical			
Schubauer-Berigan et al., 2015	US Nuclear Workers	No significant effect modification by sex was observed for any cancer mortality outcome (p values range from 0.39 to 0.97). Cohort consisted of ~80% men, ranging from 74.7 to 99.6% for each sub-cohort.	Excess Relative Risk / 10 mGy
Boice et al., 2008	Grants Uranium Miners and Millers	Statistically significant increases are reported for males for lung cancer (1.66 (95%1.37 to 1.99)) and all malignant neoplasms (1.22 (95%1.07 to 1.39)) (both $p <$ 0.05). This was not observed in females (Lung cancer: 1.27 (95%0.26 to 3.72); All malignant neoplasms: 1.18 (95%0.59 to 2.11)).	Standard Mortality Ratio
Richardson et al., 2013	Oak Ridge National Laboratory Workers	Hourly-paid males had more deaths due to cancer of the pleura (SMR = 12.09, 95% CI: 4.44, 26.32), and cancer of the bladder (SMR = 1.89, 95% CI: 1.26, 2.71). Female workers also had more deaths than expected from cancer of the bladder (SMR = 2.20, 95% CI: 1.20, 3.69) and leukaemia (SMR = 1.64, 95% CI: 1.09, 2.36).	Standard Mortality Ratio
Boice et al., 2022	US Nuclear Power Plant Workers (part of the Million Person Worker Study)	Significant SMR for males were observed for mortality of all malignant neoplasms (1.03), all solid cancers (1.04), pleura/peritoneum/mesothelioma (5.69), and bronchus/trachea/lung (1.05). The only significant SMR for females was for smoking related cancers (1.31). There was no radiation associated statistically significant increase for lung cancer for both sexes (ERR/100mGy M: −0.06(95%−0.11 to 0.01), F: 0.63(95%−0.91 to 2.17), p = 0.37). The small number of females means that the sex specific differences could not be thoroughly evaluated.	Standard Mortality Ratio and Excess Relative Risk
Azizova et al., 2018	Mayak workers (skin cancer)	No significant differences between sexes were observed for the incidence of malignant skin neoplasms. Melanoma incidence with cumulative dose from external gamma-rays: ERR/Sv of 0.22 (95% CI: −0.29, 1.46) ERR/Sv 95% CI melanoma Males: −0.06 (95% CI: n/a. 0.82) Females: 2.18 (95% CI: n/a, 15.22) Non-melanoma skin cancer Males: 0.70 (95% CI 0.28, 1.41) Females: 0.22 (95% CI −0.09, 0.77)	Excess Relative Risk per Sv

5502 (*continued on next page*)
5503

5504 Table A.3. (*continued*).

Study	Cohort name	Main finding	Endpoint
Medical			
Stram et al., 2021	Mayak workers (lung cancer)	Sex differences were observed according to plutonium dose, where women were at higher risk for cancer mortality compared to men ($p < 0.001$). External dose ERR/Gy (95% CI): Male: 0.164 (95% CI 0.043, 0.284) Female: 0.550 (−0.101–1.201), $p = 0.246$ Plutonium dose ERR/Gy (95% CI): Male: 3.472 (95% CI 2.342, 4.602) Female: 8.910 (95 % CI 3.420–14.402) $p =< 0.001$	Excess Relative Risk per Gy
Sokolnikov et al., 2015	Mayak workers (solid cancer mortality)	There was no evidence that the linear dose-response effect for external exposure differed by sex ($p > 0.5$). Solid cancer mortality, other than lung/liver/bone ERR/Gy males = 0.15 (90% CI 0.06–0.27) ERR/Gy females = 0.17 (90% CI 0.02–0.35)	Excess Relative Risk per Gy
Labutina et al., 2013	Mayak workers (lung, liver, bone cancer incidence)	The relative risk (RR) for lung cancer incidence was statistically significant between males and females ($p < 0.05$), where females had a higher risk of developing lung cancer in relation to accumulated internal plutonium lung dose. The ERR/Gy was higher in women, but this was not statistically significant (Males 0.22 Gy: 24.1 (95% < 14.3;936.2); Females 0.39 Gy: 33.4 (95% < 21.9; 72.0); $p > 0.5$). The study reported a significant internal plutonium dose response for all histological types of lung cancer evaluated (adenocarcinoma, squamous-cell, and other epithelial) for men only. ERR/Gy for adenocarcinoma was the largest (ERR/Gy = 32.5; 95% CI: 16.3; 71.9). While large estimates were observed for females, they were not significant. Malignant neoplasms of liver There was no evidence of a difference in RR between males and females ($p > 0.5$). There was no statistically significant difference in RR between sexes from malignant neoplasms of bone and associated connective tissue ($p > 0.5$).	Excess Relative Risk and Relative Risk
Various			
Lope et al., 2006	Swedish Occupational Cohort	Female workers exposed to high intensities and probabilities of ionising radiation registered a marked excess risk 1.85 (95%1.02–3.35). This trend was not in evidence among the men.	Relative Risk
Ashmore et al., 1998	Canadian National Dose Registry	Males have a significant risk of developing all cancers and lung cancer (all cancers = 3.0 (1.1–4.9); lung cancer = 3.6 (0.4–6.9)) (Cis >0). This finding was not observed in females (all cancers = 1.5 (−3.3 to 6.3) Lung cancer = 0.0 (−2.2 to 2.2)).	Excessive Relative Risk per 10 mSv

A.2.1.4. Medical Exposures

(A 37) Several studies on patients receiving x-rays for scalp epilation for the treatment of tinea capitis do not report any sex differences for different cancer sites (total cancer, thyroid, brain, and skin) (Table A.4, Tinea capitis). Doses received as part of this procedure varies, but it ranges from several Grays to the scalp/bone marrow/brain, to 0.1–0.5 Gy to the face and neck, 0.05 to 0.5 Gy to the thyroid, and 0.016 Gy to the breast (Antunes et al., 2020).

(A 38) No consistency in the findings of the diagnostic/fluoroscopic interventions studies were observed (thyroid, leukaemia, brain cancer and all cancers) (Table A.4, Diagnostic Imaging and Fluoroscopic Interventions). Study design limited conclusions on the radiation dose-response. Similarly, identified studies of patients exposed to thorotrast (thorium dioxide), a contrasting agent used in procedures like cerebral angiography, did not show any consistent sex differences for all cancer and leukaemia.

(A 39) Identified radiotherapy studies, which typically involve high doses, generally suggest that women are more sensitive to radiation compared to men, however, this can vary according to cancer site. There is no strong evidence for overall significant sex differences (Table A.4, Radiotherapy).

Table A.4. Summary of Medical Studies (cancer).

Study	Cohort name	Main finding	Endpoint
Tinea capitis			
Antunes et al., 2020	Tinea capitis (Portugal)	No statistically significant differences between sexes (Cis overlap). Some suggestion that females are more radiosensitive given that the there was an increased risk at higher doses (not observed in males) Total cancers: Males: 1.65 (95% 1.43–1.89) Females: 1.35 (95% 1.17–1.55) for ≥630 R, females: 2.00 (95% 1.21–3.13) for 325–475 R, females: 1.30 (95% 1.11–1.51)	Standard Incidence Ratio
Sadetzki et al., 2006	Tinea capitis (Israel, thyroid)	No statistical significant difference between the sexes. Males: 17.3 (95% 3.6, 46.8) Females: 21.1 (95% CI 11.5, 35.6) ERR: males vs. females $p = 0.7$	Excess Relative Risk / Gy
Sadetzki et al., 2005	Tinea capitis (Israel, brain)	No evidence for interaction between radiation and gender. Benign Meningiomas Males = 4.97 (1.91–14.20) Females = 4.37 (1.82–10.97) ERR/Gy for Malignant Brain Tumours Males = 2.11 (0.56–6.45) Females = 1.79 (0.25–7.03)	Excess Relative Risk / Gy
Flint-Richter et al., 2011	Case control study on Tinea capitis patients (Israel, brain, smoking)	Among women, significant differences in the effect of smoking between irradiated and nonirradiated subjects were observed. A significant protective effect was observed for smokers among the nonirradiated women ($p < 0.01$) and a non significant increased risk was observed in the irradiated women group ($p = 0.10$).	Odds Ratio
Ron et al., 1991	Tinea capitis (Israel, skin cancer)	No statistically significant difference between sexes. BCC of the Head and Neck among Irradiated and Comparison Subject Male: 5.4 (95% 3.4–9.5) Female: 5.8 (95% 3.7–10.1)	Relative Risk

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Diagnostic Imaging and Fluoroscopic Interventions			
Shao et al., 2019	Case control Taiwanese National Health Insurance Beneficiaries CT Study	The elevated risk in thyroid cancer and leukaemia in association with medical CT was stronger in women than men. Thyroid cancer: Female: OR: 2.76 (95% 2.53 to 3.02)* aOR: 2.75 (95% 2.52 to 3.01)* Male: OR: 2.04 (95% 1.75 to 2.37) aOR: 2.03 (95% 1.74 to 2.37) Leukaemia: Female: OR: 1.82 (95% 1.60 to 2.07)* aOR: 1.81 (95%1.59 to 2.06)* Male: OR: 1.39 (1.25 to 1.55) aOR: 1.38 (1.24 to 1.54) * = significant, Cis don't overlap between sexes	Adjusted Odds Ratio
Mathews et al., 2013	Australian Childhood CT	For brain cancer, leukaemias and myelodysplasias, other lymphoid and haematopoietic cancers, and all cancers combined, neither the IRR nor the EIR differed significantly between the sexes. The authors suggest that for solid cancers other than brain cancer, the risk was significantly greater in female patients than in male patients (IRR = 1.23 (95% 1.16 to 1.31) vs 1.14 (1.07 to 1.22), $p = 0.07$). The EIR was significantly greater in female patients vs. male patients (7.59 (95% 5.35 to 9.82) vs 3.57 (95% 1.76 to 5.37), $p = 0.006$). However, for both the IRR and EIR, the confidence intervals overlapped. The possibility of reverse causation cannot be ruled out.	Incidence Rate Ratio and Absolute Excess Incidence Rate (per 100,000 PY)
Memon et al., 2010	Case Control Study on dental x-rays in Kuwait	No significant difference in the risk of thyroid cancer between genders. Males = 2.4 (95% 1.0–5.6) Females = 2.0 (95% 1.2–3.3)	Odds Ratio

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Diagnostic Imaging and Fluoroscopic Interventions			
Infante-Rivard et al., 2003	Case Control study on diagnostic x-rays in Quebec (ALL)	A higher OR for Acute Lymphoblastic Leukaemia (ALL) is observed in exposed girls (not observed in exposed boys), however, the confidence intervals overlap. Girls 2 + x rays: 1.67 (95% 1.01–2.74) Boys 2+ x rays: 1.41 (95% 0.99 to 2.01)	Odds Ratio
Wei et al., 2016	Case Control Taiwanese Cardiac Fluoroscopic Interventions	Gender subgroup analyses showed that men had a higher risk of leukaemia incidence compared with control ($p < 0.005$), compared to women vs control ($p > 0.005$) for the group with most procedures (>3). However, confidence intervals overlap between sexes. Leukaemia: OR: Male >3: 2.118(1.238–3.622) ($p < 0.005$) aOR: Male >3: 1.849(1.073–3.187) ($p < 0.005$) OR: Female >3: 1.086(0.251–4.707) aOR: Female >3: 0.826(0.189–3.605)	Adjusted Odds Ratio
Ryan et al., 1992	Case Control Risk of brain and meninges tumours in Australians receiving amalgam fillings	No differences between sexes for glioma were observed. Exposed males had an increased risk of developing meningioma compared to control. This was not observed in females. Glioma adjusted for age and sex, was 0.42 (95% 0.24–0.76, $p = 0.004$). Sex specific analyses (adjusted for age) showed no substantial heterogeneity (data not shown). Meningioma adjusted for age and sex, was 1.37 (95% 0.68–2.73, $p = O.38$). Female: 0.86 (95% 0.40 to 1.85, $p = 0.69$) Male: N/A (all males with meningioma had been exposed to dental xrays, preventing estimation of the adjusted RR). 10 of 10 male meningioma subjects compared with 106 of 176 (60%) male controls had been exposed (Fisher's exact $p = 0.01$; lower limit of exact 95% C.I. = 1.42).	Relative Risk
Bithell et al., 1975	Case control study on prenatal irradiation and childhood malignancy (UK)	No statistically significant differences in the risk of all malignant tumours between sexes were observed. males = 1.52 females = 1.45 $\chi^2 = 0.23$ (no confidence intervals provided)	Relative Risk

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Diagnostic Imaging and Fluoroscopic Interventions			
Carpeggiani et al., 2015	Cancer risk in cardiovascular disease patients having undergone medical radiation exposure (Italy)	The dose response relationship was similar in male and female patients. An interaction term between sex and radiation exposure was added to the model and it was not statistically significant (p = 0.117 for primary cancer onset and p = 0.056 for cancer mortality).	Multivariable analysis
Thorotrast			
Travis et al., 2003	Thorotrast cohort (cerebral angiography, Denmark/Sweden/US)	Differences between males and females are not statistically significant. Denmark and Sweden Cancer incidence: all cancers males = 3.6 (95% 2.8–4.8) all cancers females = 3.3 (95% 2.6–4.2) USA cancer mortality all cancers, males = 3.9 (95% 2.0–8.2) all cancers, females = 4.1 (95% 2.1–8.7)	Relative Risk
Nyberg et al. 2002	Thorotrast cohort (cerebral angiography, Sweden)	No statistically significant differences between sexes for all cancer types (Cis overlap).	Standard Incidence Ratio
Becker et al., 2008	Thorotrast exposed patients (German) and cancer risk	Statistically significant difference in the mortality risk of malignant neoplasms between sexes (M > F) was observed. Malignant neoplasms Males: 3.7 (95% 3.1–4.3) Females: 2.3 (95% 1.7–3.0)	Relative Risk
Travis et al., 2001	Mortality after cerebral angiography with or without radioactive thorotrast (Denmark, Sweden and US)	No statistically significant difference in leukaemia risk between sexes. Cancer (including leukaemia) Females: 2.8 (95% CI 2.4–3.3) Males: 2.9 (95% CI 2.3–3.7	Relative Risk

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Radiotherapy			
Wang et al., 2019	SEER	For all primary malignancies combined, no differences were observed in the incidence of second malignancies between males that received radiotherapy and those that did not ($p = 1.000$). However, significant increases were observed in females with RT ($p < 0.001$) Males: patients who received RT had statistically significant lower cumulative incidence of second malignancies for CNS and orbits ($p < 0.001$), head and neck ($p = .05$), thorax ($p < .001$), and abdomen ($p < 0.001$) primaries and higher cumulative incidence of second malignancies for pelvis ($p < 0.001$) primaries. Females: RT resulted in a statistically significant lower cumulative incidence of second malignancies for CNS and orbits ($p = 0.003$), abdomen ($p = 0.001$), and pelvis ($p = 0.007$) primaries and a higher cumulative incidence of second malignancies for head and neck ($p < 0.001$) and thorax ($p < 0.001$) primaries.	Relative Risk
Vinchon et al., 2011	French Pediatric Neurosurgical Longitudinal Study	The study reported a higher cumulated radiation induced tumours (RIT) incidence in males ($p = 0.005$) and a higher cumulative cavernoma incidence in males ($p = 0.002$). Limitations of this study include its retrospective nature, and its underestimation of cancers due to only recently implemented sensitive diagnostic technologies. M/F ratio for RIT = 1.80 (27 males/15 females) $p = 0.005$ (log rank) Cumulative incidence of RIT (%): Male cavernoma (5 years: 2.9) (10 years: 11.6) (20 years: 35.5) Female cavernoma (5 years: 0.8) (10 years: 2.1) (20 years: 8.7) $p = 0.002$	M/F Ratio for RIT and Cumulative Incidence of RIT
Adams et al., 2010	Hempelmann Cohort (thyroid cancer incidence as a result of chest RT)	No significant difference between males and females. Male: 4.4 (95% 1.4–15.8) Female: 2.6 (nf-nf) nf-boundary not found	Excess Relative Risk/Gy

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Radiotherapy			
Schneider et al., 1993	RT for benign conditions of the head and neck at University of Illinois (thyroid cancer and nodules)	No statistically significant difference between sexes. ERR/cGy Thyroid cancer Males: 0.036 Females: 0.028 $p = 0.78$ No Cis provided RR: females compared to males is 1.4 (95% 1.1 to 1.7) for cancer; 1.7 (95% 1.4 to 2.0) for benign nodules and 1.7 (95% 1.1 to 1.9) for all nodules	Excess Relative Risk/cGy and F/M Relative Risk
Furst et al., 1988	RT for skin hemangioma: cancer incidence (Sweden)	Overall, exposed females were at an increased risk of developing cancer compared to males. However, confidence intervals overlap. In the radium-226 treated or orthovoltage x-ray treated group: males: 1.08 (95% 0.65 to 1.69) and not significant females: 1.21 (95% 1.04–1.40) ($p < 0.05$) [confidence intervals overlap] Analyzed by treatment period: 1920–1939 -not significant males = 1.08 (95% 0.65 to 1.69) females = 1.36 (95% 1.09–1.66) 1940–1959 – not significant Males: 1.09 (95% 0.72 to 1.57) Females: 1.08 (95% 0.86 to 1.34)	Relative Risk

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Table A.4. (*continued*).

Study	Cohort name	Main finding	Endpoint
Radiotherapy			
Asal et al., 1988	Case control study on US renal carcinoma patients that received diagnostic and therapeutic radiation	Statistical significant increase in risk in females who received RT was observed, however, male and female confidence intervals overlap. Diagnostic for kidney or bladder: Males = 1.3 (95% 0.6–2.8) for 23 cases and 15 controls Females = 2.0 (95% 0.9–4.8) for 13 cases and 9 controls Any therapy: males = 1.3 (95% 0.6–2.9) for 19 cases and 11 controls females = 2.9 (95% 1.3–6.4) (p = 0.01) for 20 cases and 9 controls	Odds Ratio
Darby et al., 1987	UK Ankylosing spondylitis patients treated with x-rays	No statistical significant difference between sexes was observed.	Observed/expected ratio
Shore et al., 1985	US thymus irradiation in infancy (thyroid tumours)	The absolute excess risk associated with radiation was two to three times as great among females as among males. Regression coefficients: For thyroid cancers the absolute-risk coefficients were 5.25± 1.52 per 10^6 PY-rad for females and 2.05±0.75 for males. The coefficients for thyroid adenomas were 7.7±1.9 for females and 3.6±1.3 for males.	Excess Absolute Risk (per 10^6PY rad)

A.2.1.5. Pooled studies (Medical, LSS, Occupational)

(A 40) Two pooled studies that included LSS and various radiotherapy cohorts evaluated the risk of thyroid cancer following childhood exposure (one focused on lower doses). Neither observed sex differences (ERR/Gy by sex $p = 0.35$ (Veiga et al., 2016); RR/0.2Gy by sex: $p = 0.35$ (Lubin et al., 2017)).

(A 41) Similarly, a pooled study that included radiation workers and TB Fluoroscopy patients did not observe sex differences in the risk of lung cancer mortality (Boice et al., 2018).

A.2.2. Circulatory diseases

A.2.2.1. Lifespan Studies

(A 42) Looking at the larger LSS cohort, Ozasa et al. (2012) observed a significant increase in the ERR/Gy for circulatory disease mortality in females (0.14 (95%CI 0.06 to 0.23), $p < 0.001$), but not in males (0.07(95%CI −0.001 to 0.16, $p = 0.053$)). However, no sex differences were observed in other studies reporting on mortality from heart diseases overall (ERR/Gy M: 0.06 (95%CI −0.05 and 0.18), F: 0.21(0.10 to 0.33), $p = 0.07$), ischaemic heart disease (ERR/Gy M: 0.07 (95%CI −0.09 to 0.26), F: −0.01 (−0.15 to 0.17), $p > 0.5$) and valvular heart disease (ERR/Gy M: 0.06 (95%CI NA to 0.68), F: 0.64 (0.22 to 1.19), $p = 0.12$) (Takahashi et al., 2017) (%ERR/Gy M: 7 (95% −4–20), F: 20 (95% 8–34), $p = 0.14$) (Shimizu et al., 2010). Another study focusing only on the Hiroshima Atomic Bomb Survivors and using either initial radiation dose or exposure distance as a surrogate for radiation dose, found that males (initial radiation: 0 to 9; distance: 0 to 9, 20 to 29, and 30 years and over ATB) and older females (distance: 30 years and over ATB) near the hypocenter had a high excess risk of mortality ($p < 0.05$) (Hara et al., 2016). Further investigation is required to clarify these findings.

(A 43) A study analyzing aging and radiation impact on blood pressure of survivors found no significant difference between males and females [systolic: $\chi(16)^2 = 16.5$, $p = 0.42$; diastolic: $\chi(8)^2 = 8.5$, $p = 0.39$]. Some caution in interpretation is warranted given the lack of consideration to confounding factors such as salt intake, which is high in Japan, as well as psychological factors (Sasaki et al., 2002). Yamada et al. (2004) also reported no sex differences in the relative risk estimate (RR 1 Sv: Males: 1.03, Females: 1.02, $p = 0.65$, LQ model).

(A 44) Sex differences were observed in a study that measured cholesterol levels ($\chi^2 = 11.86$ on 6 df, $p = 0.065$; $\chi^2 = 10.91$ on 4 df, $p = 0.028$, after stepwise reduction). Radiation effects were significant for males ($\chi^2 = 13.32$ on 6 df, $p = 0.038$; $\chi^2 = 6.39$ on 2 df, $p = 0.041$, after stepwise reduction) and for females ($\chi^2 = 44.75$ on 6 df, $p < 0.0001$; $\chi^2 = 43.55$ on 4 df, $p < 0.0001$, after stepwise reduction). The maximum predicted cholesterol increase after 1 Gy exposure for women occurred at 52 years of age for the 1930 cohort [2.5 mg/dl (95% CI 1.6–3.3 mg/dl) for Hiroshima and 2.3 mg/dl (95% CI 1.5–3.1 mg/dl) for Nagasaki], whereas, for men it occurred at age 29 years for the 1940 cohort [1.6 mg/dl (95% CI 0.4–2.8) for Hiroshima and 1.4 mg/dl (95% CI 0.3–2.6) for Nagasaki]. While statistically significant, there was still considerable overlap in the individual growth curves of the irradiated vs unirradiated subjects (Wong et al., 1999).

(A 45) For cerebrovascular disease of those exposed as teens in Hiroshima, no significant risk was detected for males, but for females, the initial dose influenced the hazard ratio significantly for those exposed between 10 and 19 years of age (1.51, $p < 0.001$) (Matsuba et al., 2016). However, a prospective study differentiating between ischaemic and hemorrhagic stroke observed that for men the risk of hemorrhagic stroke increased from 11.6 to 29.1 per 10,000 person-years as doses increased from <0.05 to >2Gy ($p = 0.009$), and for women the

risk increased only after reaching doses of 1.3 to 2.2 Gy (13.5 to 20.3 per 10,000 person-years, $p = 0.002$). Nonetheless, the number of hemorrhagic events was insufficient to allow for careful assessment. For both sexes, dose was unrelated to ischaemic stroke (Takahashi et al., 2012).

A.2.2.2. Environmental Exposures

(A 46) A study on the residents impacted by the Three Mile Island accident provided evidence of negative association between gamma exposure and heart disease for both sexes (M: $p = 0.03$, F: $p < 0.0001$) (Talbott et al., 2003).

(A 47) For residents in the contaminated areas of the Chornobyl Nuclear Power Plant, cardiovascular mortality rates were found to be sex-dependent. Mortality was significantly higher in men than in women (circulatory system, hypertensive disease, ischemic HD, pulmonary HD, other forms of HD, cerebrovascular disease, diseases of arteries/arterioles) (Buzunov et al., 2013). However, a follow-up study indicated the opposite trend, where women were more at risk of circulatory system diseases (congestive HD, cerebrovascular disease, other cerebrovascular diseases, arteries/arterioles/capillaries diseases, vein/lymph vessels/ nodes disease) (Buzunov et al., 2018).

(A 48) Blood pressure in exposed Israeli immigrants from areas affected by the Chornobyl accident was significantly higher compared to the unexposed. This finding was dependent on age and sex, where generally older males had higher blood pressures rates than females (Cwikel et al., 1997).

(A 49) Large uncertainties around dosimetry and the fact that key lifestyle confounding factors were not considered warrants caution in the interpretation of the results of the Chornobyl studies.

A.2.2.3. Occupational Exposures

(A 50) A study on the mortality from circulatory disease among nuclear workers in France, UK and US (INWORKS) reported significant increases in ERR/Sv for females compared to males for circulatory disease (4.22 (90% 1.72 to 7.21) vs 0.20 (90% 0.07 to 0.36), $p = 0.005$), and ischemic heart disease (6.17 (90% 2.44 to 10.92) vs 0.16 (90%−0.01 to 0.34), $p = 0.004$). While these estimates are significant, large uncertainties exist. Female cumulative doses were low (4.7 mSv) and there was little information on higher doses, which is important given that 7 circulatory disease deaths occurred above 200 mSv (Gillies et al., 2017).

(A 51) Cha et al. (2020) reported significant evidence of differences between men and women medical workers in ERR/100 mGy estimates for all circulatory diseases (male −0.07 (95%−0.76–0.76), female 4.21 (0,30–9.92), $p = 0.03$), and circulatory disease except cerebrovascular disease and others (Male: −0.27 (95% −1.01 to 0.66), Female: 5.53 (−0.03 to 15.84), $p = 0.04$), with women having a higher ERR/100 mGy than men, although the confidence intervals on their estimates were large.

(A 52) Another medical worker study, with a cross-sectional design, reported a significant difference in blood pressure between male and females (M > F, $p < 0.001$). Male blood pressure for 2A (0.40 mSv/year) and 2D (0.17 mSv/year) were higher than 2E (1.96 mSv/year) ($p < 0.01$); for female 2E is higher than 2A and 2D ($p > 0.05$). No statistical association of abnormal heart rate between sexes was found ($p > 0.05$), as well as for abnormal heart electrocardiogram ($p > 0.05$) (Wang et al., 2017).

(A 53) For Canadian radiation workers, no significant differences between sexes were observed (Zielinski et al., 2009).

(A 54) Hypertension incidence in Mayak workers did not depend on sex [ERR per unit dose (95% CI) Males: 0.15 (95% CI 0.09, 0.22) Females: 0.14 (95% CI 0.05, 0.24), $p > 0.50$] (Azizova et al., 2019). A recent analysis of the dose rate effect on mortality from ischemic

heart disease in Mayak workers did not observe a statistically significant sex difference (Azizova et al., 2023).

(A 55) No significant differences in the radiation dose response of circulatory disease [heart (HD) and coronary heart disease (CHD)] between male and female Chornobyl clean up workers were reported even though the dose to male workers was twice as high as in females. HD, CHD, and their comorbidity were more often diagnosed in women vs men. The cumulative incidence rate of HD was higher in women age 53–75 years compared to men ($\chi 2 = 4.298$, $p = 0.038$). HD developed at a younger age in male workers compared to female workers and controls. The cumulated CHD morbidity rate in males was highest for the 23–74- and 25–53-year-old categories. Myocardial infarction morbidity rate was higher in male workers in comparison to females (Bilyi et al., 2018).

A.2.2.4. Medical exposures

(A 56) Few studies were identified that analyzed both sexes for radiation-related circulatory disease in the medical setting. There is a suggestion that a higher degree of carotid stenosis (narrowing of the carotid artery) and ischemic attack (cerebrovascular) exists in men compared to women, however, some caution is recommended when interpreting the results because of the important limitations of the studies (e.g., cross-sectional design, and no adjusting for key risk factors) (Table A.5).

Table A.5. Summary of Medical Exposures Studies (circulatory diseases).

Study	Description	Main finding	Endpoint
Thorotrast			
Travis et al. 2001	Mortality after cerebral angiography with or without radioactive thorotrast (Denmark, Sweden and US)	No statistically significant difference in CV risk between sexes. Females: 1.8 (95% 1.3–2.5) Males: 1.4 (95% 1.0–2.0)	Relative Risk
Radiotherapy			
Yang et al. 2017	Cross sectional study on radiation induced carotid stenosis in patients treated for neck tumours with RT (China)	Higher degree of stenosis in male patients (64.6%) than female patients (36.1%) ($p = 0.004$). Higher occurrence of transient ischemic attack (cerebrovascular event) in men (23.7%) vs women (12.5%) ($p = 0.012$)	Degree of stenosis / occurrence of cerebrovascular events
Chang et al. 2009	Cross sectional study on radiation induced carotid stenosis in patients treated for neck tumours with RT (Taiwan)	RT had a significantly smaller effect on stenosis in women than men. with RT, males as reference: females Beta = −1.940 (95% −3.380, −0.500) ($p < 0.05$) Without RT Male as reference Female Beta = −0.315 (95% −1.399, 0.768) $p > 0.05$	Bilateral Carotid Score / Multiple Regression Analysis

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Table A.5. (*continued*).

Study	Description	Main finding	Endpoint
Thorotrast			
Reinders et al. 1999	Ischemic heart disease after irradiation for Hodgkin's (Netherlands)	No statistically significant difference between sexes. Cardiac death Male: O/E = 10/1.7 SMR 6.0 (2.8, 10.6) Female: O/E = 2/0.6 SMR 3.7 (0.4, 13.2) Hospital admissions Male: O/E = 20/7.0 RR 2.8 (1.7, 4.4) Female: O/E = 5/2.2 2.2 (0.7, 5.2)	Standard Mortality Ratio

A.2.3. Cataract

A.2.3.1. Lifespan studies

(A 57) Cataract studies of atomic bomb survivors are few. The most recent study of cataract incidence in atomic bomb survivors reported a significant sex difference in the odds ratio for cortical cataracts [F/M: 1.69 (95%CI 1.28 to 2.23), $p < 0.001$] and a suggestive difference for posterior sub-capsular opacities (F/M: 1.39 (95%CI 0.98 to 1.98), $p = 0.063$) (Nakashima et al., 2006).

A.2.3.2. Occupational exposures

(A 58) In a study of US radiologic technologists evaluating cataract incidence, no sex differences were reported in the EAR/10,000 PYGy (M = 144.3 (95% 70.17 to 224.3); F = 77.45 (95% 27.43 to 129.1), $p = 0.080$) (Little et al., 2020).

(A 59) For Mayak workers, a significantly higher ERR/Sv for posterior subcapsular cataract and cortical cataract was observed for women compared to men (Males: PSC: 0.46 (95% 0.27, 0.72), CC: 0.42 (95% 0.30, 0.56), NC: 0.36 (95% 0.23, 0.51); Females: PSC: 1.74 (95% 1.21, 2.46) $p < 0.001$, CC: 1.07 (95% 0.82, 1.38) $p < 0.001$; NC: 0.68 (95% 0.46, 0.95) $p = 0.018$) (Azizova et al., 2018).

A.2.3.3. Medical Exposures

(A 60) In Allodji et al. (2016), no statistically significant sex differences were observed in the risk of cataract after nonretinoblastoma solid cancer in childhood radiation. Importantly, no risk measure was used to tie sex and radiation dose (Hazard Ratio), nor was the type of cataract identified.

A.2.4. Cognitive effects

A.2.4.1. Environmental exposures

(A 61) A cross-sectional study on depression after chronic low dose rate exposure from contaminated buildings reported no statistical difference between sexes, however, exposed men had a significant increased risk compared to control ($p < 0.05$). This increase was not observed in women (Yen et al., 2014). Limitations of this study include the inherent limitations

of the cross-sectional design, the potential for self-selection bias, and the dosimetric uncertainties.

(A 62) A cross-sectional study done on the rural Kazakhstani population exposed to contamination from the Semipalatinsk Nuclear Test Site observed a significant sex difference in mental distress which was evaluated by several tools to assess depression, anxiety, somatic distress and fatigue. For the exposed group compared to unexposed, an association between male gender and somatic distress was established (PHQ-15: $p = 0.047$). In addition, in the unexposed group compared to exposed, a marginal association between male gender and general fatigue (MFI GF: $p = 0.049$) and significant associations between male gender and reduced motivation (MFI RM: $p = 0.04$), as well as mental fatigue were observed (MFI MF: $p = 0.001$) (Semenova et al. 2019).

A.2.4.2. Medical exposures

(A 63) In Farjam et al. (2015), radiation induced alterations in hippocampal vascular properties of patients undergoing brain radiotherapy were analyzed as an injury surrogate marker. Late delayed neurocognitive decline was further assessed by tests such as Controlled Oral Word Association, revised Hopkins Verbal Learning Test and Trail Making Tests. It was found that radiation induced hippocampal vascular injury and the subsequent neurocognitive decline was age and sex dependent (F > M), where the dose response was more pronounced in older females ($p < 0.0007$).

A.3. Summary

(A 64) All references included in the evidence tables (most up to date study versions) following data extraction are described above. Using a weight of evidence approach to formulate the conclusions below, the higher ranked evidence was mainly considered.

A.3.1. Cancers

(A 65) The strongest evidence for sex differences in cancer risk comes from the LSS studies (mostly cohort studies, sound dosimetry, demonstration of a dose-response). In addition, women were well represented in the study population (as compared to many occupational cohorts). For both solid cancer mortality and incidence, women are observed to have higher ERR compared to men, including from in utero exposures and for secondary cancers. However, this does not extend to the EAR, where no sex differences are observed. Preston et al. (2007) explained that the EAR, which is not influenced by spontaneous background rates, is likely a better indicator of sex differences. Indeed, sex differences in the all-solid cancer dose-response are likely explained by age at exposure, the differences in the spontaneous background rates, and the composition of the case series (Cologne et al., 2017; Brenner et al., 2022). Similarly, differences between the ERR and EAR for urinary tract cancer incidence can be explained by the different spontaneous background rates (Grant et al., 2017). Further follow-up and site-specific analyses will be necessary to confirm these findings.

(A 66) Cancer incidence and mortality sex differences are observed at different sites. Males have a statistically significant higher estimate compared to women for meningioma (ERR), esophageal cancer incidence (ERR), malignant lymphoma mortality (ERR), leukaemia, acute lymphoblastic leukaemia and non-Hodgkins lymphoma incidence (EAR), whereas, females have a significantly higher estimate for esophageal cancer mortality (ERR), stomach cancer (ERR), thyroid cancer incidence (EAR), multiple myeloma mortality (ERR), and chronic myeloid leukaemia (EAR). For the studies evaluating stomach and thyroid cancer, the ERR

and EAR values were not consistent. For stomach cancer, only the ERR varied by sex, not the EAR (Sakata et al., 2019), and the opposite was observed for thyroid cancer where only the EAR varied by sex (Furukawa et al., 2013).

(A 67) With regards to the Environmental Exposures category, the evidence was weak as many of the studies are ecological in design. Overall, there was a suggestion that women were generally more at risk of developing cancer compared to men for thyroid and solid cancer; and men more at risk of leukaemia, lung, and esophageal cancer; however, the weight of evidence did not support the existence of sex differences.

(A 68) Many of the occupational cohorts are largely made up of men with the exception of those occupationally exposed in the medical field (e.g., radiologic technologists). This results in studies that restrict their analyses to men or do not allow for a robust evaluation of sex differences.

(A 69) Among several studies that reported ERR estimates in the occupationally exposed, no statistically significant sex differences were observed. Importantly, this included the higher ranked studies (e.g., Zablotska et al., 2014, Cardis et al., 2007). Studies on the Mayak workers suggest that women have a higher risk of lung cancer incidence and mortality (Stram et al., 2021; Labutina et al., 2013), however important dosimetry uncertainties for this cohort exist (especially for plutonium). The US Nuclear Power Plant Workers cohort estimate for lung cancer incidence (ERR/100 mGy), while larger in women, was not statistically significant (Boice et al., 2022).

(A 70) Overall, the identified studies on patients undergoing medical treatment (tinea capitis, diagnostic imaging/fluoroscopic interventions, thorotrast, and radiotherapy) suggest that women are more at risk compared to men for thyroid cancer (excess absolute risk, Shore et al., 1985), secondary cancers (relative risk, Wang et al., 2019), and solid cancer: (excluding brain) (incidence rate ratio and excess incidence rate, Mathews et al., 2013), but the weight of evidence does not support a significant sex difference.

(A 71) In line with the weight of evidence, pooled studies did not observe sex differences for thyroid cancer from childhood exposures (LSS+Medical: excess relative risk: Veiga et al., 2016, relative risk: Lubin et al., 2017), or for lung cancer (Occupational+Medical: excess relative risk: Boice et al., 2018).

A.3.2. Circulatory diseases

(A 72) According to the ICRP, cardiovascular disease, a tissue reaction, has a nominal threshold dose of 0.5 Gy, which is informed by epidemiological data, including that from the LSS (ICRP, 2012). Given that the LSS provides evidence for increased risk of cardiovascular disease at less than 5 Gy and with a mean dose of <0.5 Gy and that the form of the dose response <0.5 Gy is uncertain, the magnitude of risks of at low doses (<100 mGy) remain uncertain. To add to the uncertainty, there are many confounders that are associated with these diseases that are very common in the general population (Gillies et al., 2017).

(A 73) Risk of heart disease did not substantially vary by sex in the LSS cohort. Both a narrative and a systematic review on cardiovascular disease in the LSS cohort support this conclusion (Ozasa et al., 2017; Little et al., 2023).

(A 74) Important limitations and lack of consistency between the environmental exposure studies identified do not permit a firm conclusion regarding sex differences.

(A 75) The higher ranked evidence for occupational exposures indicates that women are at a higher risk of circulatory disease and ischemic heart disease mortality. While the sex difference was considered statistically significant, large uncertainties remain (female representation, large confidence intervals, low female cumulative dose, lack of high dose information) (Gillies et al., 2017, Cha et al., 2020).

(A 76) While several medical studies were included in Little et al.2023, our search identified only a few studies that analyzed both sexes. This can be explained partly by the fact that we did not include one sex-specific studies (e.g., women treated for breast cancer), or studies where patients received chemotherapy. Identified studies did not offer strong evidence for significant sex differences. There seems to be a suggestion that males are more at risk for carotid stenosis and ischemic attacks, however, important uncertainties remain (Yang et al., 2017, Chang et al., 2009).

A.3.3. Cataract

(A 77) According to the ICRP, cataracts are considered to be tissue reactions with a threshold of 0.5 Gy for low linear transfer radiation (ICRP, 2012). This threshold for acute exposure was determined by LSS studies on cataracts and cataract surgery (Nakashima et al., 2006, Neriishi et al., 2007), whereas the threshold for fractionated or protracted exposures was determined by a study on Chornobyl clean-up workers (Worgul et al., 2007, Hamada et al., 2020).

(A 78) While not numerous or consistent, there is evidence that exists for gender differences. Both the LSS and Mayak workers studies observed statistically significant higher cataract risk for females compared to males (Nakashima et al., 2006; Azizova et al., 2018). In the case of the Mayak workers, for all three types of cataracts (cortical, nuclear, posterior subcapsular), the ERRs/Sv were 2–4 times higher in females than in males ($p < 0.001$). No sex differences in the EAR were found however in the US Radiologic Technologist cohort (Little et al., 2020).

A.3.4. Cognitive effects

(A 79) The symptoms of radiation-related cognitive impairment include decreased verbal memory, spatial memory, attention, and novel problem-solving ability, and rarely dementia (Greene-Schloesser and Robbins, 2012). Only one identified study fits this narrow definition (Farjam et al., 2015). It demonstrated sex differences at very high doses, however, further studies are needed to draw more robust conclusions. This search excluded radiotherapy studies that evaluated neurocognitive functioning based on the fact that they included patients that had undergone chemotherapy (possible confounder).

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ACKNOWLEDGEMENTS

At its meeting in Stockholm, Sweden in October 2018, the Main Commission of ICRP approved the formation of a new Task Group 111, reporting to Committees 1 and 3, to undertake a review of the literature relating to the factors that govern individual radiation response in humans.

ICRP thanks all those involved in the development of this publication for their hard work and dedication over many years.

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The authors are very grateful for the contributions from D. Stram and M. Hauptmann to early discussions within the Task Group, from M. Utada for preparing some tables and from A. Denisova for excellent Technical Secretary support to the Task Group.

Finally, thank you very much to all organisations and individuals who took the time to provide comments on the draft of this publication during the consultation process.