

Genetic Predisposition to Radiation-related Cancer and Potential Implications for Risk Assessment

Alice Sigurdson, Ph.D.

Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics

ICRP Committee 1

ICRP Symposium on the International
System of Radiological Protection
Radiation Effects: Modulating Factors
and Risk Assessment

October 25, 2011

International Commission on Radiological Protection

Outline

- **Key questions (and some answers)**
- **Radiation “sensitive” groups**
- **Assumptions about the radiation dose-response**
 - **Possible influence of including radiation susceptible persons**
- **Recent findings from genome-wide association studies (GWAS) and GWAS of radiation-related cancers**
- **Other ways to identify those at increased risk**
 - **Aggregating adverse variants showing promise**
 - **New types of studies**

Q and A

- **Can genetic predisposition to radiation-related cancer be incorporated into risk assessment and radiation protection?**
 - **Answer:** Already is for observational studies in humans

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- Answer: Not really, but getting closer

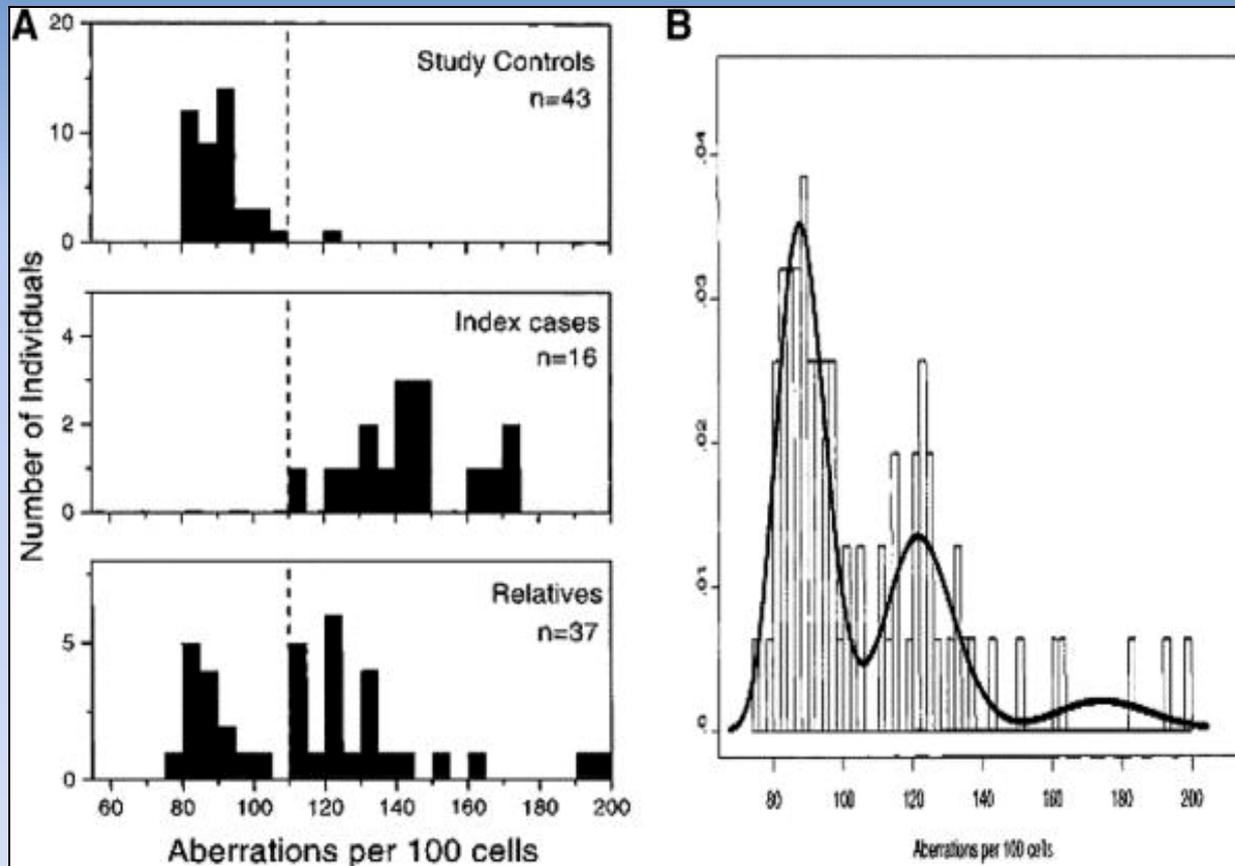
Q and A

- **Can information on genetic predisposition to radiation-related cancer be incorporated into risk assessment and radiation protection?**
 - Answer: Already is for observational studies in humans
- **Do radiosensitive subpopulations exist?**
 - Answer: Certainly they do
- **Do we know which tumors are radiation-related?**
 - Answer: Not really, but getting closer
- **Who's at risk for radiation-related cancers?**
 - Answer: We don't know [not yet without lots of work]

Radiation-sensitive groups (and less sensitive, too)

- Rare genetic syndromes
 - For eg. Defects in DNA double strand break repair
 - AT, NBS, Riddle, Ligase IV, XLF, DNA-PKcs deficiency
 - Many reviews on these DNA repair and other genes, radiation and increased cancer risk
- Relatives of AT and retinoblastoma patients
 - Clinically normal but show increased radiosensitivity by phenotypic assay
 - Review in Kato TA et al, 2009 Health Physics
- Relatives of breast cancer patients with G2 radiosensitivity
- Envision continuum of mild hyper- and hypo-sensitivity

Range of radiation-induced chromosome aberrations in lymphocytes in healthy controls, breast cancer cases testing “sensitive” and family members of “sensitive” cases



G2 chromosomal radiosensitivity (0.5 Gy) of peripheral blood lymphocytes (PBL) from breast cancer patients and first degree relatives. Panel A: Yields of radiation-induced chromosomal aberrations in lymphocytes exposed to 0.5 Gy x rays in the G2 phase of the cell cycle. Top: Healthy controls tested in parallel with samples from the families. The sensitive individual (to the right of the vertical dashed line) was tested twice and gave values of 120 aberrations/100 cells and 126 aberrations/100 cells, respectively. Middle: Patients with breast cancer, selected as being sensitive in the assay when tested before radiotherapy. Bottom: First-degree relatives of the patients with breast cancer who are shown in the middle panel. Panel B: Relative-density histogram of the distribution of the mean G2 chromosomal radiosensitivity values (aberrations per 100 cells) of the 78 family members in the study (excluding index cases). The line indicates the fitted density functions with three log-normal peaks of equal width. (Roberts SA et al. Am J Hum Genet, 1999).

VARIATIONS IN RADIOSENSITIVITY AMONG INDIVIDUALS: A POTENTIAL IMPACT ON RISK ASSESSMENT? Kato, Takamitsu; Wilson, Paul; Nagasawa, Hatsumi; Peng, Yuanlin; Weil, Michael; Little, John; Bedford, Joel Health Physics. 97(5):470-480, November 2009.

What is radiation “sensitive” in humans?

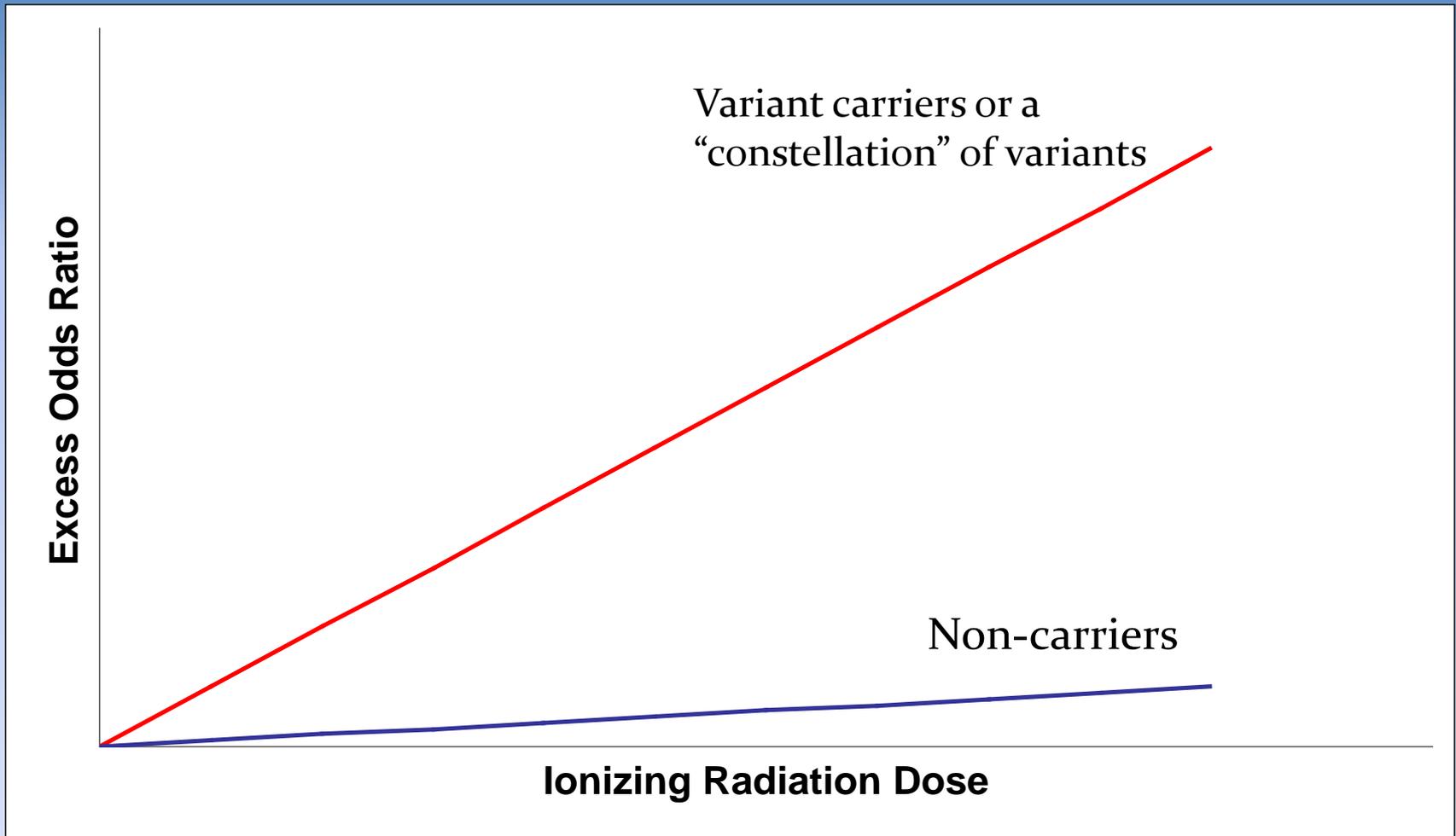
- Increase over “baseline” in a cancer risk biomarker assay
 - Number of chromosome aberrations or micronuclei
 - With or without a radiation “challenge”
- How common is radiation sensitivity (resistance)?
 - May depend on cut-off used
 - Mild hypersensitivity up to 30%?
- Does radiation sensitivity “predict” increased radiation-associated cancer risk?
 - G₂ bleomycin challenge assay and lung cancer
 - Some confirmation in prospective settings (about two-fold)
 - “Radiation sensitivity” may be non-specific (increased cancer risk in absence of radiation)
 - At present such tests lack good predictive abilities

What effect(s) would radiation-sensitive persons have on the dose response?

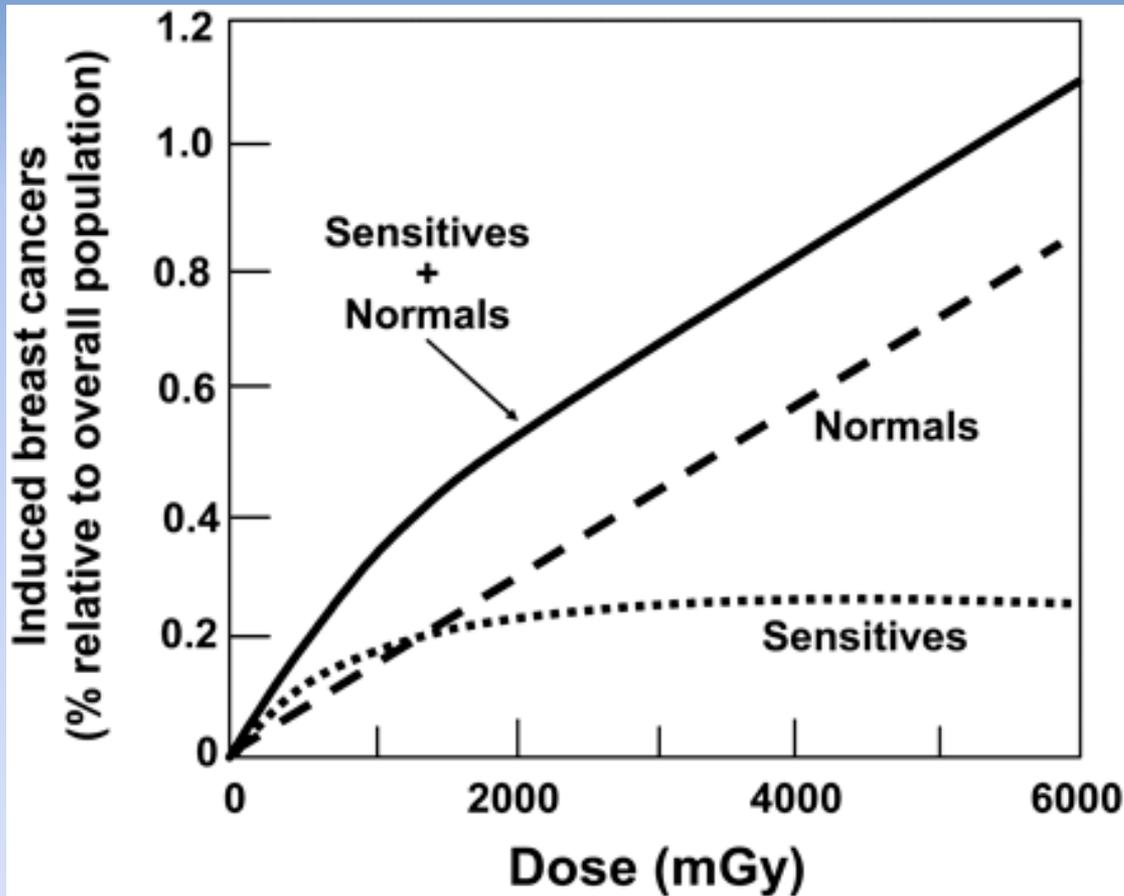
- Depends
 - What is the “real” cancer risk relationship at low doses?
 - How are other host factors (age, gender) implicated in risk?
 - Do low vs high or dose-rate effects differ by phenotype (sensitive, resistant, “normal”)?
 - Do we know which tumors are sporadic or radiation-related?
 - Radiation sensitivity varies by tumor type
 - Too simple to combine all solid or all liquid cancers
 - Need cancer-specific sensitivity
- How can sensitive persons be identified?

Graphic depictions of general effects of radiation sensitivity on the dose-response

Gene (SNP)-radiation interaction



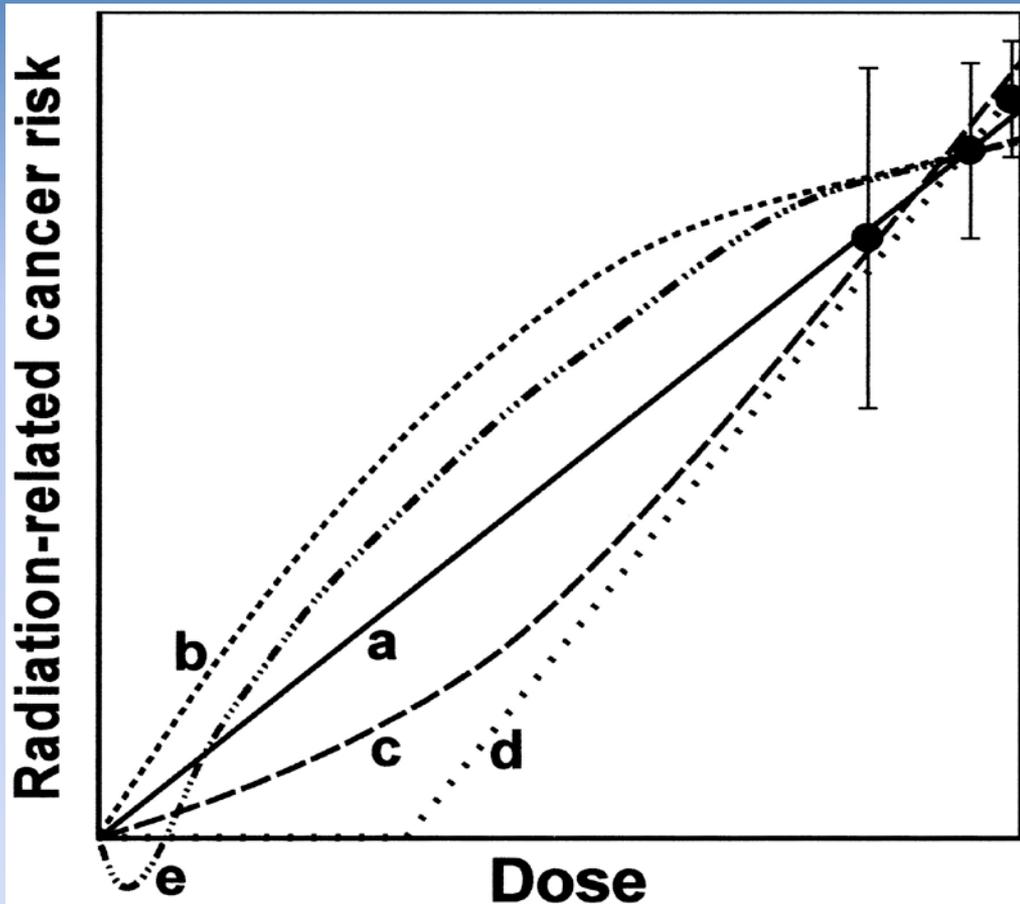
Radiation-sensitive sub-populations and breast cancer risk



Schematic representation of the potential effect of a small (0.25%) population of women, who are extremely sensitive for radiation-induced breast cancer, compared with the general (normal) population. Schematized is the number of radiation-induced breast cancers as a percentage of the overall population. The dose-risk relations for both the normal and the sensitive populations are assumed to be linear. Because the number of radiation-induced breast cancers in the sensitive population would saturate as the dose increases (because all the exposed women would have developed breast cancer), the dose-response for the whole population would be downwardly curving.

From Brenner DJ et al, PNAS, 2003

Various possible relationships with radiation-related cancer risk and very low radiation doses

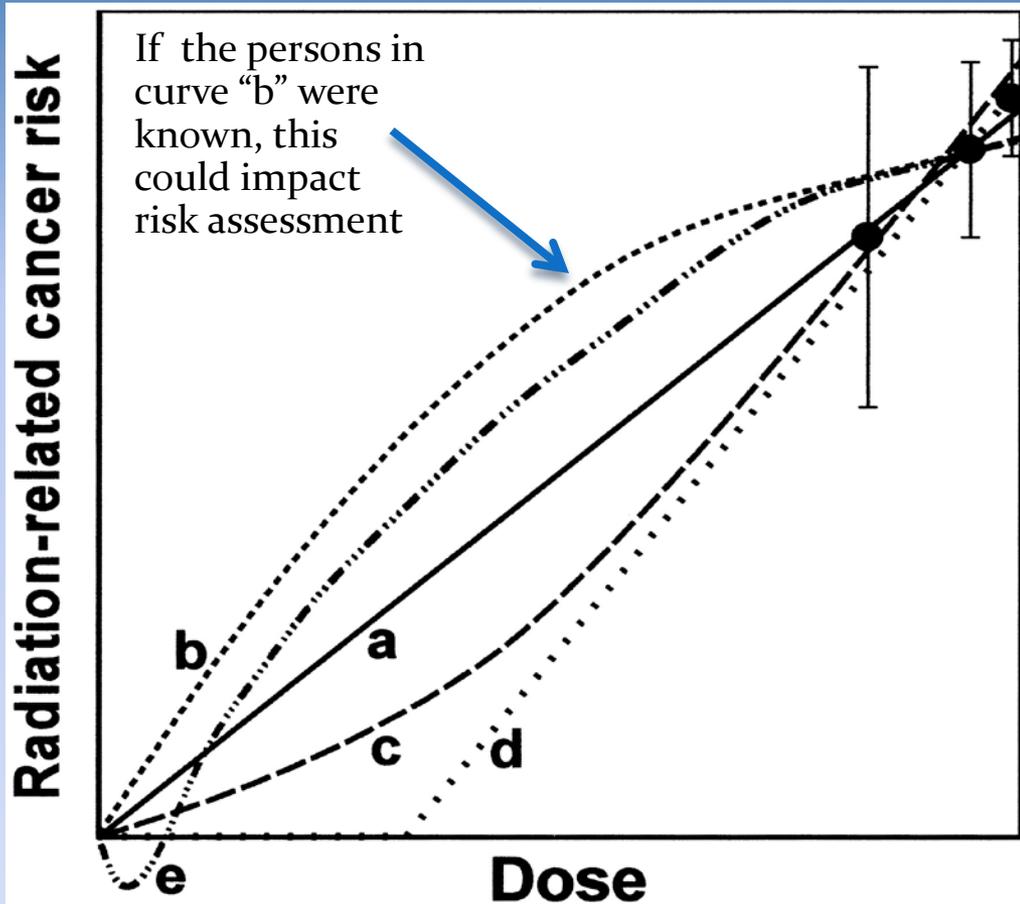


Schematic representation of different possible extrapolations of measured radiation risks down to very low doses, all of which could, in principle, be consistent with higher-dose epidemiological data.

- a) linear dose response
- b) downwardly curving:
radiation sensitive persons,
adaptive response,
bystander effects
- c) upwardly curving:
acute radiation and leukemia
or chromosome aberrations
- d) threshold
- e) hormesis

Brenner DJ et al. PNAS
2003;100:13761-13766

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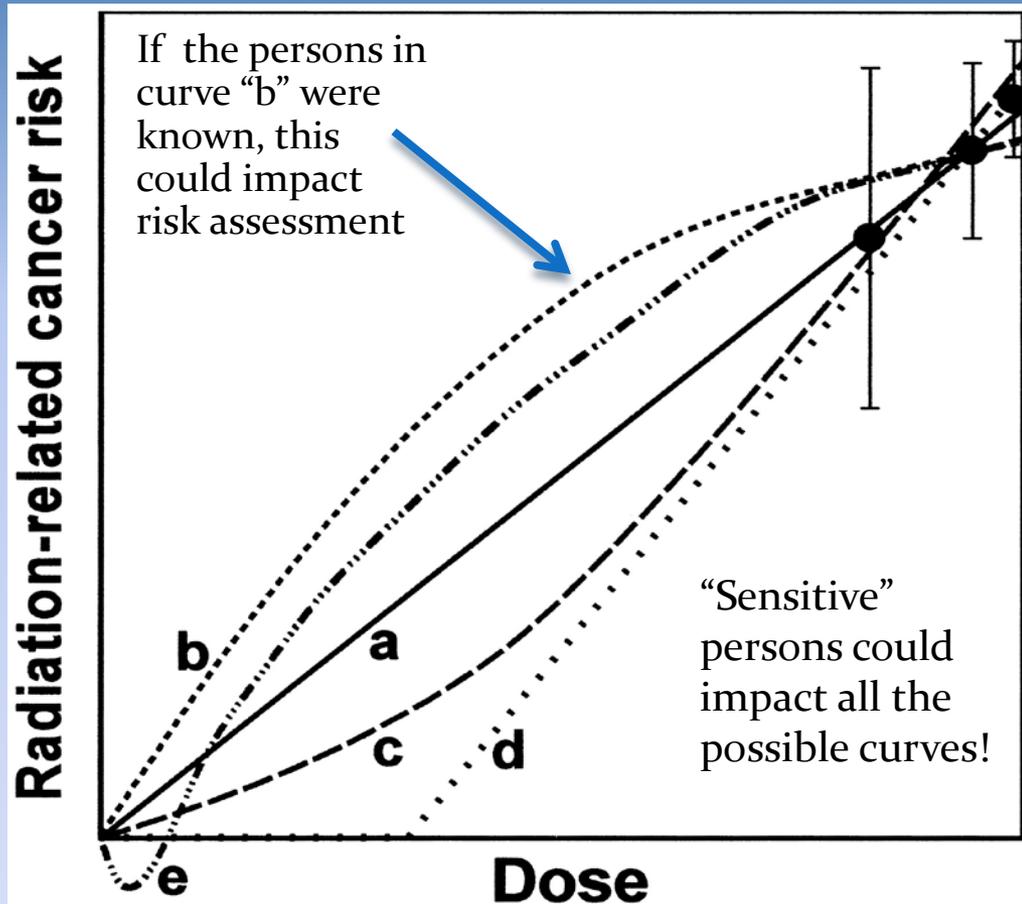


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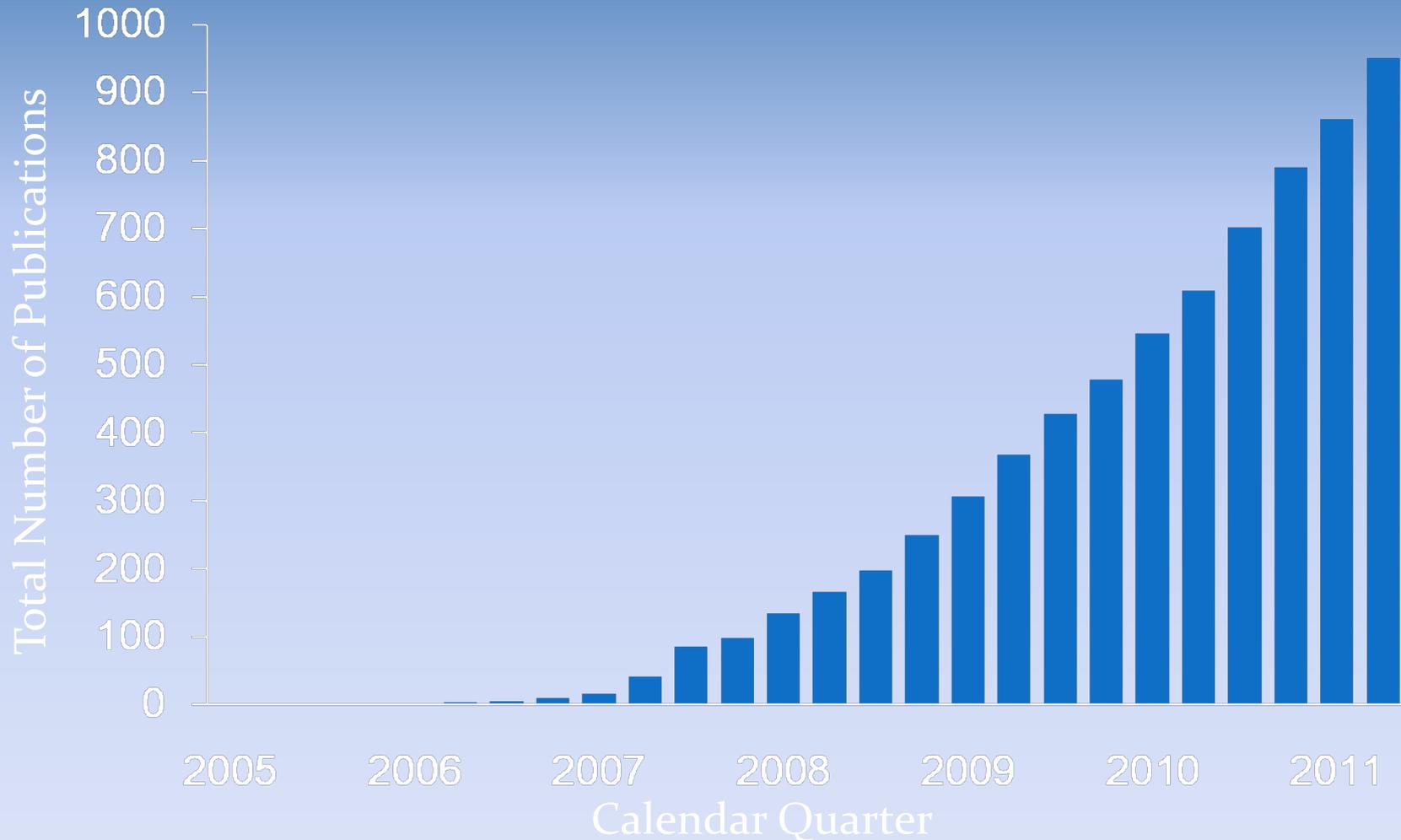
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What about cancer susceptibility from genome-wide association studies?

.....and there have been a fair number

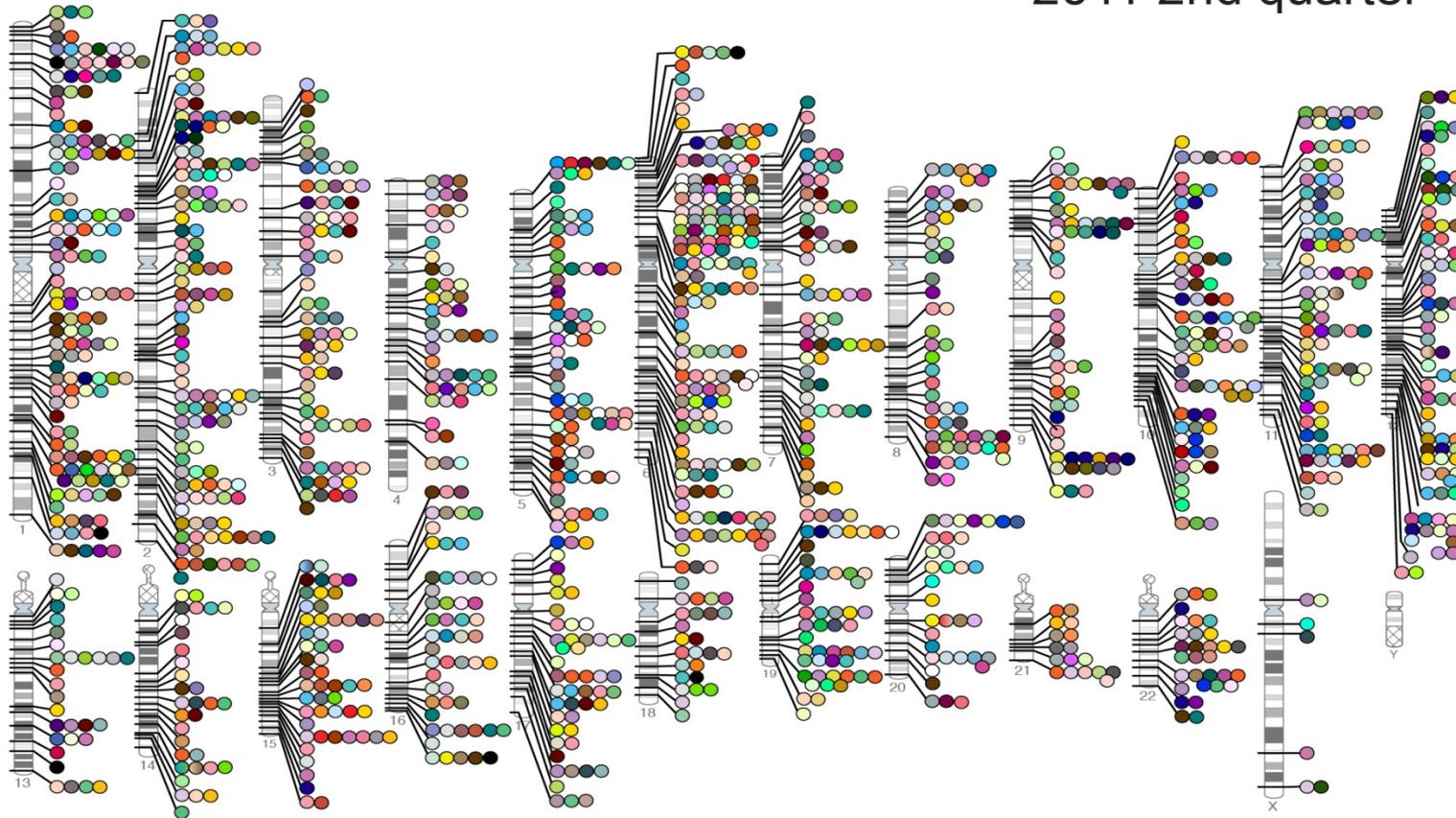
Published GWA Reports, 2005 – 6/2011



Information from GWA studies

NHGRI manually curated Catalog of Published Genome-Wide Association Studies

2011 2nd quarter



Published
Genome-Wide
Associations
through 06/2011,
1,449 published
GWA at $p \leq 5 \times 10^{-8}$
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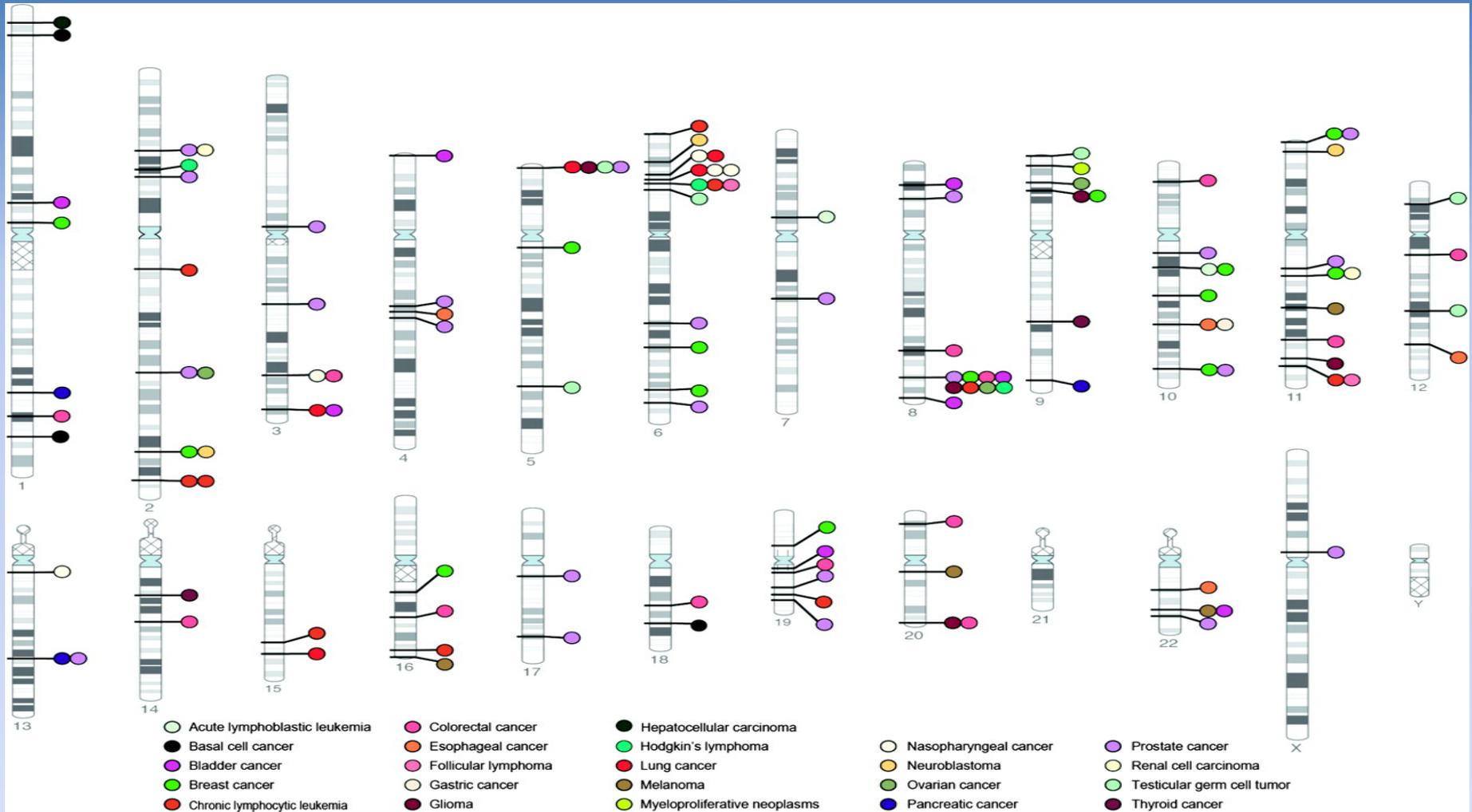
Information from GWA studies

NHGRI manually curated Catalog of Published Genome-Wide Association Studies

- Abdominal aortic aneurysm
- Acute lymphoblastic leukemia
- Adhesion molecules
- Adiponectin levels
- Age-related macular degeneration
- AIDS progression
- Alcohol dependence
- Alopecia areata
- Alzheimer disease
- Amyloid A levels
- Amyotrophic lateral sclerosis
- Angiotensin-converting enzyme activity
- Ankylosing spondylitis
- Arterial stiffness
- Asparagus anosmia
- Asthma
- Atherosclerosis in HIV
- Atrial fibrillation
- Attention deficit hyperactivity disorder
- Autism
- Basal cell cancer
- Behcet's disease
- Bipolar disorder
- Biliary atresia
- Bilirubin
- Bitter taste response
- Birth weight
- Bladder cancer
- Bleomycin sensitivity
- Blond or brown hair
- Blood pressure
- Blue or green eyes
- BMI, waist circumference
- Bone density
- Breast cancer
- C-reactive protein
- Calcium levels
- Cardiac structure/function
- Cardiovascular risk factors
- Carnitine levels
- Carotenoid/tocopherol levels
- Celiac disease
- Celiac disease and rheumatoid arthritis
- Cerebral atrophy measures
- Chronic lymphocytic leukemia
- Chronic myeloid leukemia
- Cleft lip/palate
- Coffee consumption
- Cognitive function
- Conduct disorder
- Colorectal cancer
- Corneal thickness
- Coronary disease
- Creutzfeldt-Jakob disease
- Crohn's disease
- Crohn's disease and celiac disease
- Cutaneous nevi
- Cystic fibrosis severity
- Dermatitis
- DHEA-s levels
- Diabetic retinopathy
- Dilated cardiomyopathy
- Drug-induced liver injury
- Drug-induced liver injury (amoxicillin-clavulanate)
- Endometrial cancer
- Endometriosis
- Eosinophil count
- Eosinophilic esophagitis
- Erectile dysfunction and prostate cancer treatment
- Erythrocyte parameters
- Esophageal cancer
- Essential tremor
- Exfoliation glaucoma
- Eye color traits
- F cell distribution
- Fibrinogen levels
- Folate pathway vitamins
- Follicular lymphoma
- Fuch's corneal dystrophy
- Freckles and burning
- Gallstones
- Gastric cancer
- Glioma
- Glycemic traits
- Hair color
- Hair morphology
- Handedness in dyslexia
- HDL cholesterol
- Heart failure
- Heart rate
- Height
- Hemostasis parameters
- Hepatic steatosis
- Hepatitis
- Hepatocellular carcinoma
- Hirschsprung's disease
- HIV-1 control
- Hodgkin's lymphoma
- Homocysteine levels
- Hypospadias
- Idiopathic pulmonary fibrosis
- IFN-related cytopeni
- IgA levels
- IgE levels
- Inflammatory bowel disease
- Insulin-like growth factors
- Intracranial aneurysm
- Iris color
- Iron status markers
- Ischemic stroke
- Juvenile idiopathic arthritis
- Keloid
- Kidney stones
- LDL cholesterol
- Leprosy
- Leptin receptor levels
- Liver enzymes
- Longevity
- LP (a) levels
- LpPLA(2) activity and mass
- Lung cancer
- Magnesium levels
- Major mood disorders
- Malaria
- Male pattern baldness
- Mammographic density
- Matrix metalloproteinase levels
- MCP-1
- Melanoma
- Menarche & menopause
- Meningococcal disease
- Metabolic syndrome
- Migraine
- Moyamoya disease
- Multiple sclerosis
- Myeloproliferative neoplasms
- Myopia (pathological)
- N-glycan levels
- Narcolepsy
- Nasopharyngeal cancer
- Natriuretic peptide levels
- Neuroblastoma
- Nicotine dependence
- Obesity
- Open angle glaucoma
- Open personality
- Optic disc parameters
- Osteoarthritis
- Osteoporosis
- Otosclerosis
- Other metabolic traits
- Ovarian cancer
- Pancreatic cancer
- Pain
- Paget's disease
- Panic disorder
- Parkinson's disease
- Periodontitis
- Peripheral arterial disease
- Personality dimensions
- Phosphatidylcholine levels
- Phosphorus levels
- Photic sneeze
- Phytosterol levels
- Platelet count
- Polycystic ovary syndrome
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- PR interval
- Progranulin levels
- Progressive supranuclear palsy
- Prostate cancer
- Protein levels
- PSA levels
- Psoriasis
- Psoriatic arthritis
- Pulmonary funct. COPD
- QRS interval
- QT interval
- Quantitative traits
- Recombination rate
- Red vs. non-red hair
- Refractive error
- Renal cell carcinoma
- Renal function
- Response to antidepressants
- Response to antipsychotic therapy
- Response to carbamazepine
- Response to clopidogrel therapy
- Response to hepatitis C treat
- Response to interferon beta therapy
- Response to metaformin
- Response to statin therapy
- Restless legs syndrome
- Retinal vascular caliber
- Rheumatoid arthritis
- Ribavirin-induced anemia
- Schizophrenia
- Serum metabolites
- Skin pigmentation
- Smoking behavior
- Speech perception
- Sphingolipid levels
- Statin-induced myopathy
- Stroke
- Sudden cardiac arrest
- Suicide attempts
- Systemic lupus erythematosus
- Systemic sclerosis
- T-tau levels
- Tau AB1-42 levels
- Telomere length
- Testicular germ cell tumor
- Thyroid cancer
- Thyroid volume
- Tooth development
- Total cholesterol
- Triglycerides
- Tuberculosis
- Type 1 diabetes
- Type 2 diabetes
- Ulcerative colitis
- Urate
- Urinary albumin excretion
- Urinary metabolites
- Uterine fibroids
- Venous thromboembolism
- Ventricular conduction
- Vertical cup-disc ratio
- Vitamin B12 levels
- Vitamin D insufficiency
- Vitiligo
- Warfarin dose
- Weight
- White cell count
- White matter hyperintensity
- YKL-40 levels

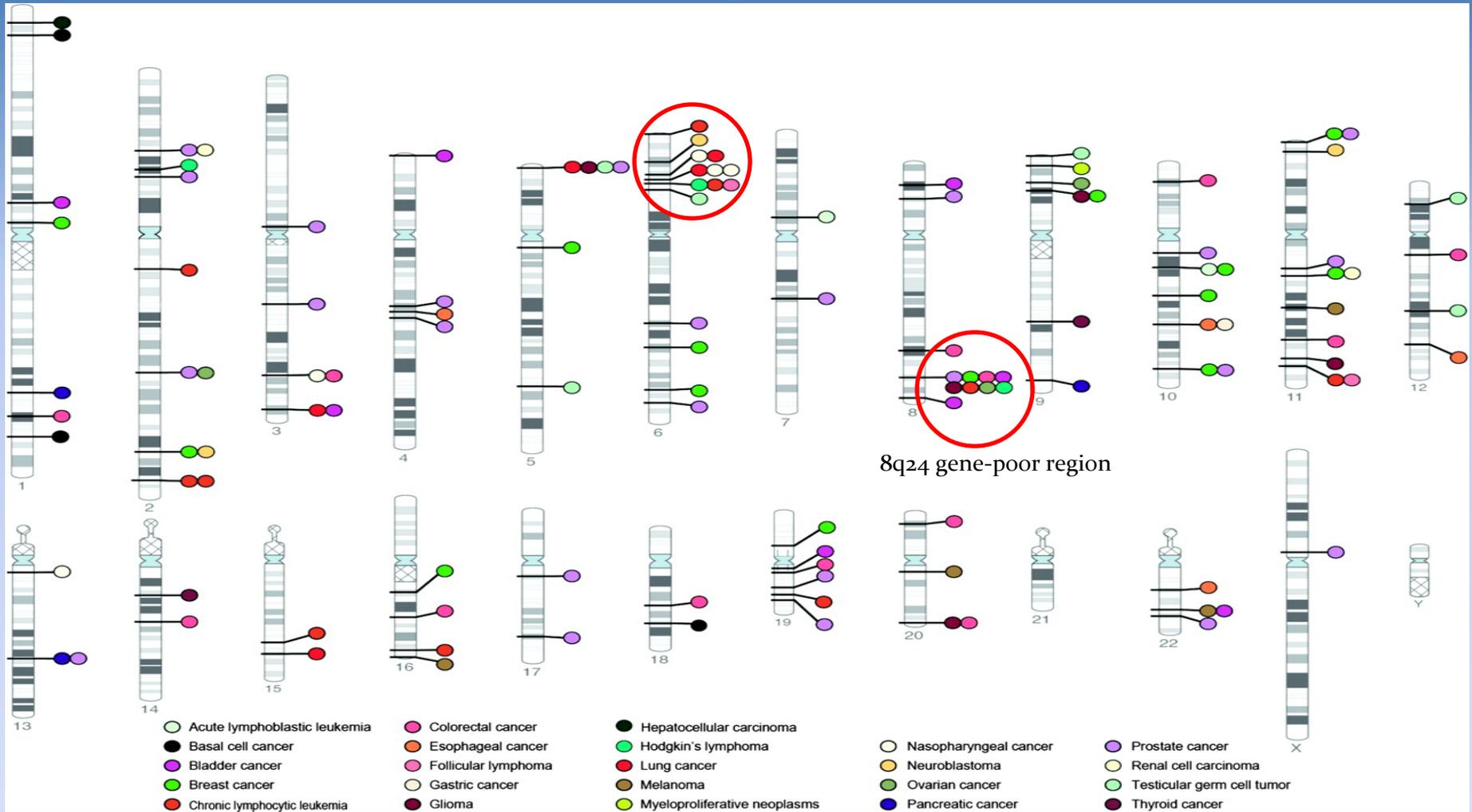
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Cancer-associated genetic variants identified through GWA studies.



Genetic variants were identified from the NHGRI Genome-wide Association Study catalog (www.genome.gov/gwastudies) and include all cancer associations at $P < 5 \times 10^{-8}$ through 2010.

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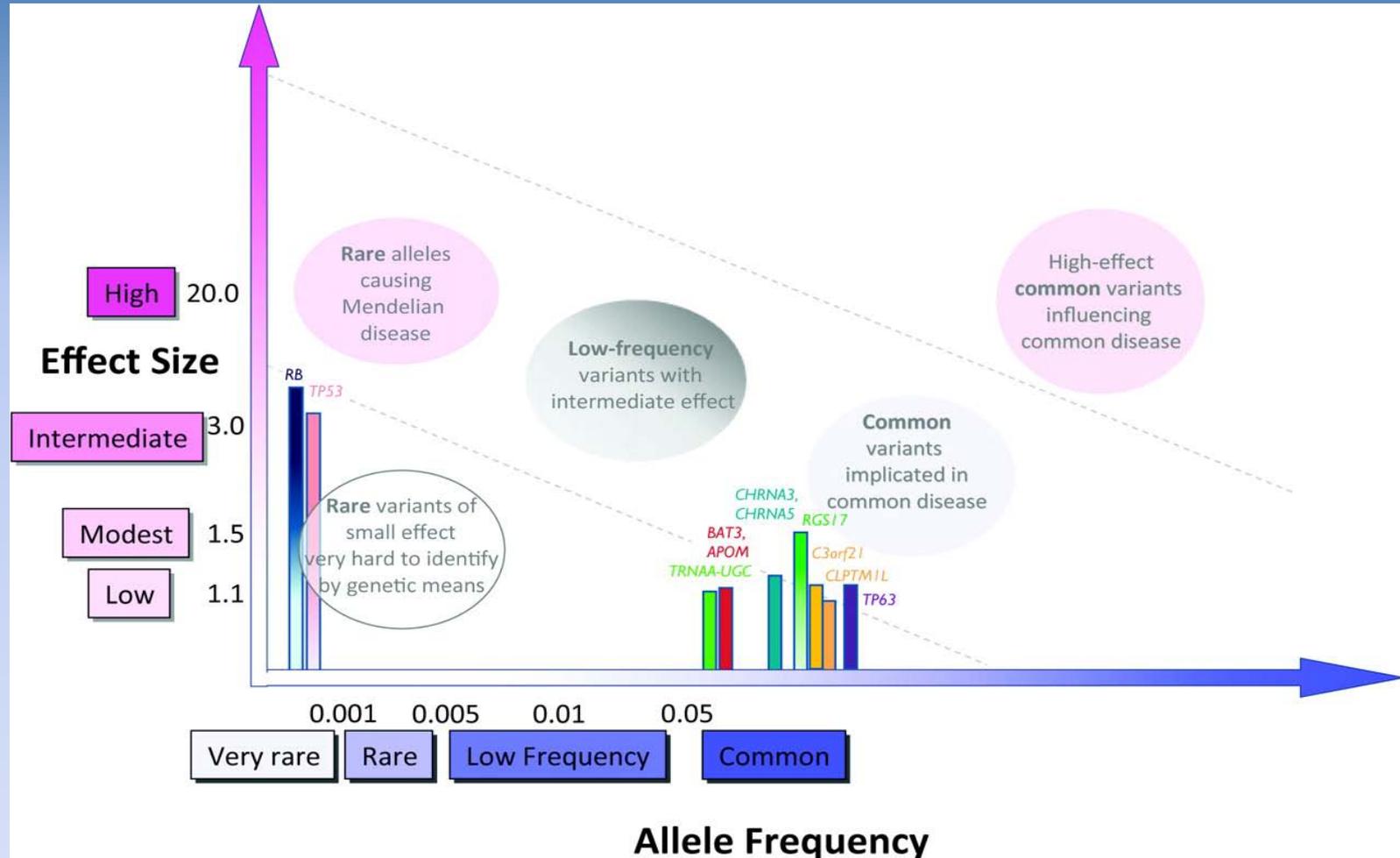


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Different “constellations” of genes associated with specific cancers

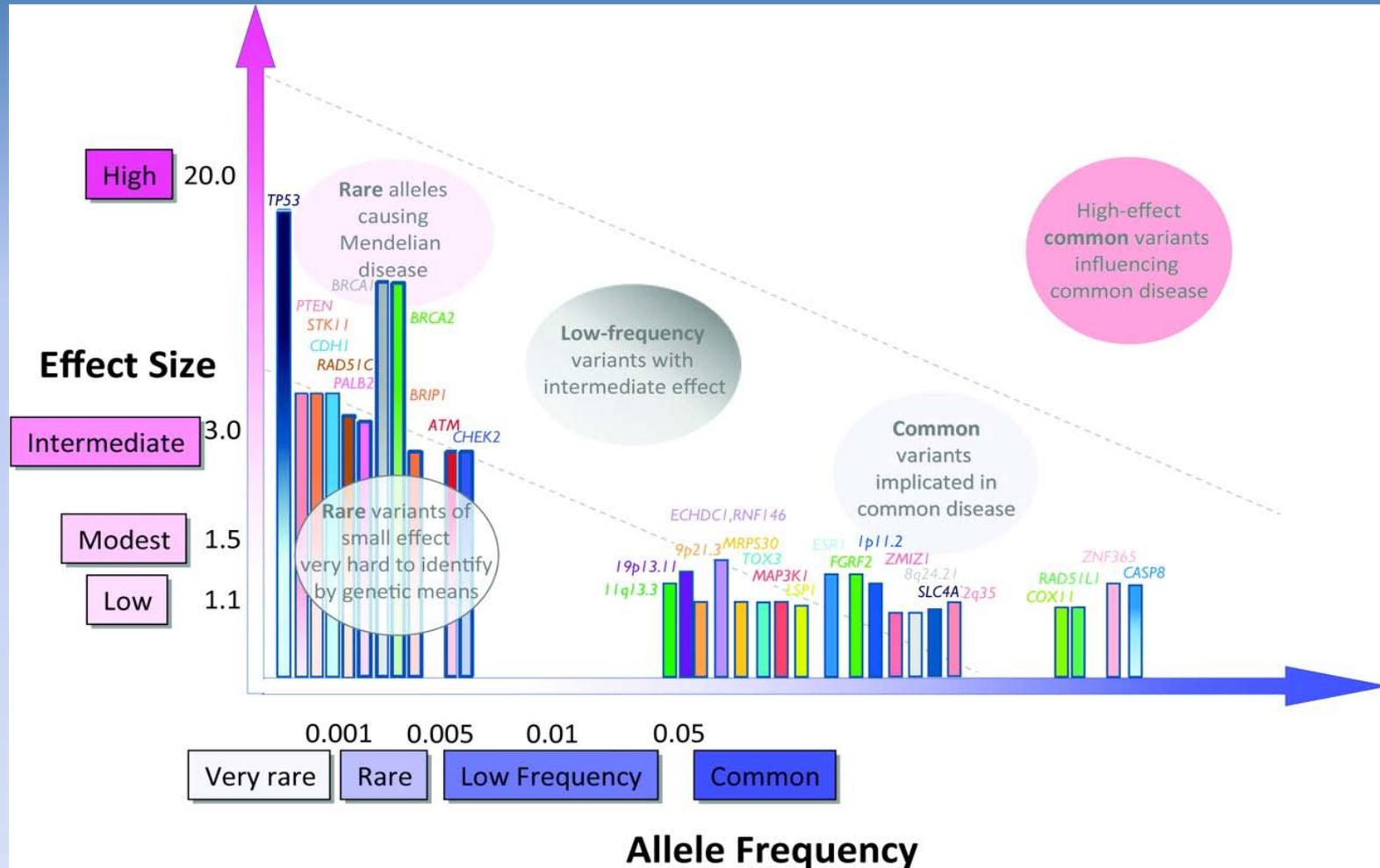
- **Examples of Lung and Breast cancer**

Allele frequency and effect sizes for genetic variants associated with lung cancer.



Associations identified through GWA or GWA follow-up studies are shown with solid colored bars; all others are shaded from dark (top) to light (bottom)

Allele frequency and effect sizes for genetic variants associated with breast cancer.



Associations identified through GWA or GWA follow-up studies are shown with solid colored bars; all others are shaded from dark (top) to light (bottom)

What about radiation-related cancers?

- Similar “constellations” just different genes/SNPs for radiation-related cancers?
- Or, one region/gene/SNP affects risk of multiple radiogenic cancers?
- Some of both
 - GWAS examples
 - Gene/SNP combinations to predict risk
 - Hierarchical modeling, counting functional SNPs, pathway-specific combinations

GWAS of therapy-induced second cancers after Hodgkin's lymphoma

- All HL survivors treated with radiation as children
 - Followed to second malignant neoplasm (SMN)
 - Or 27 years on average for controls
- Discovery set
 - 100 SMN cases and 89 SMN free controls
- Replication set
 - 62 SMN cases and 71 SMN free controls
- Implicated two SNPs in *PRDM1* after correction
 - Corroborated by several functional studies
- *PRDM1* (aka *BLIMP1*) involved in proliferation, differentiation, apoptosis and negatively regulates *MYC*

Best T et al, Nature Med, August 2011

Thyroid cancer GWAS

Common variants on 9q22.33 [*FOXE1*] and 14q13.3 predispose to thyroid cancer in European populations Gudmundsson J, April 2009 Nature Genetics

The *FOXE1* locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. Takahashi M et al, Hum Mol Genet 2010 (12):2516-23.

- Only *FOXE1* common to both studies
 - Important in sporadic & radiation-related thyroid cancer
- Familial risk for thyroid cancer around 4-6-fold
 - Likely more variants to be discovered in future
 - Assess interaction with radiation dose

Better prospects to identify radiation-induced tumors?

- **Gene expression signatures to distinguish sporadic from radiotherapy-induced tumors**
 - **Thyroid Cancer and Sarcomas**
 - Transcriptome profiles using 322 genes and 135 genes, respectively
 - Signature prospectively confirmed in new blinded tumor set
 - Methods described in detail (PLoS One)
- **Idea bears watching, especially if successful at low radiation doses**

-
- **Gene expression signature discriminates sporadic from post-radiotherapy-induced thyroid tumors.** Ory C, et al. *Endocr Relat Cancer* 2011 Jan 19;18(1):193-206.
 - **A transcriptome signature distinguished sporadic from postradiotherapy radiation-induced sarcomas.** Hadi-Manou NS et al. *Carcinogenesis* 2011 Jun;32(6):929-34. Epub 2011 Apr 5.
 - **Strategy to find molecular signatures in a small series of rare cancers: validation for radiation-induced breast and thyroid tumors.** Ugolin N et al, *PLoS One*; Epub 2011 Aug 11.

Multiple variants with adverse effects and selected pathways

- **Improves power over individual risk alleles with small effects**
 - Johnson N et al. Counting potentially functional variants in BRCA1, BRCA2 and ATM predicts breast susceptibility . Hum Molecular Genet 2007
- **Stronger risk signal with a collective set of variants classified with adverse risk**
 - Capanu M et al. Assessment of rare BRCA1 and BRCA2 variants of unknown significance using Hierarchical modeling. Genet Epidemiol 2011
- **Haplotype in RAD50 (4.9% prevalence) showed significant interaction with radiation but no main effect with breast cancer risk in the WECARE (Women's Environmental, Cancer, and Radiation Epidemiology) Study**
 - Variants in downstream pathways of ATM preferentially included in the selection of genes
 - Brooks JD et al. Variants in activators and downstream targets of ATM, radiation exposure, and contralateral breast cancer risk in the WECARE study

What's happening and on the horizon?

- GWAS Platforms with 1 M, 2.5 M, or 5 M SNPs
 - SNPs with $MAF > 1\% < 5\%$
- Exome Sequencing (exons only 1% of the genome)
- Increase sample sizes through consortia
- Shared and *in silico* control groups (n=10,000 or more)
- Pursue the “Variome”
 - Copy number variation, insertions/deletions
 - EWAS: Epigenome-wide association studies
 - Variation in DNA methylation
- Pool rarer variants with deleterious function
 - Regaining favor

What's needed to use genetic predisposition for risk assessment?

- Understand predictive abilities of
 - Sensitivity assays
 - Genetic and Epigenetic information
 - Likely cancer site-specific
 - Other contributing factors
- Understand different biologic mechanisms at low or high doses
- Identify the radiogenic tumors
 - Especially with low doses

- Enormous amount of work

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ICRP
SYMPOSIUM
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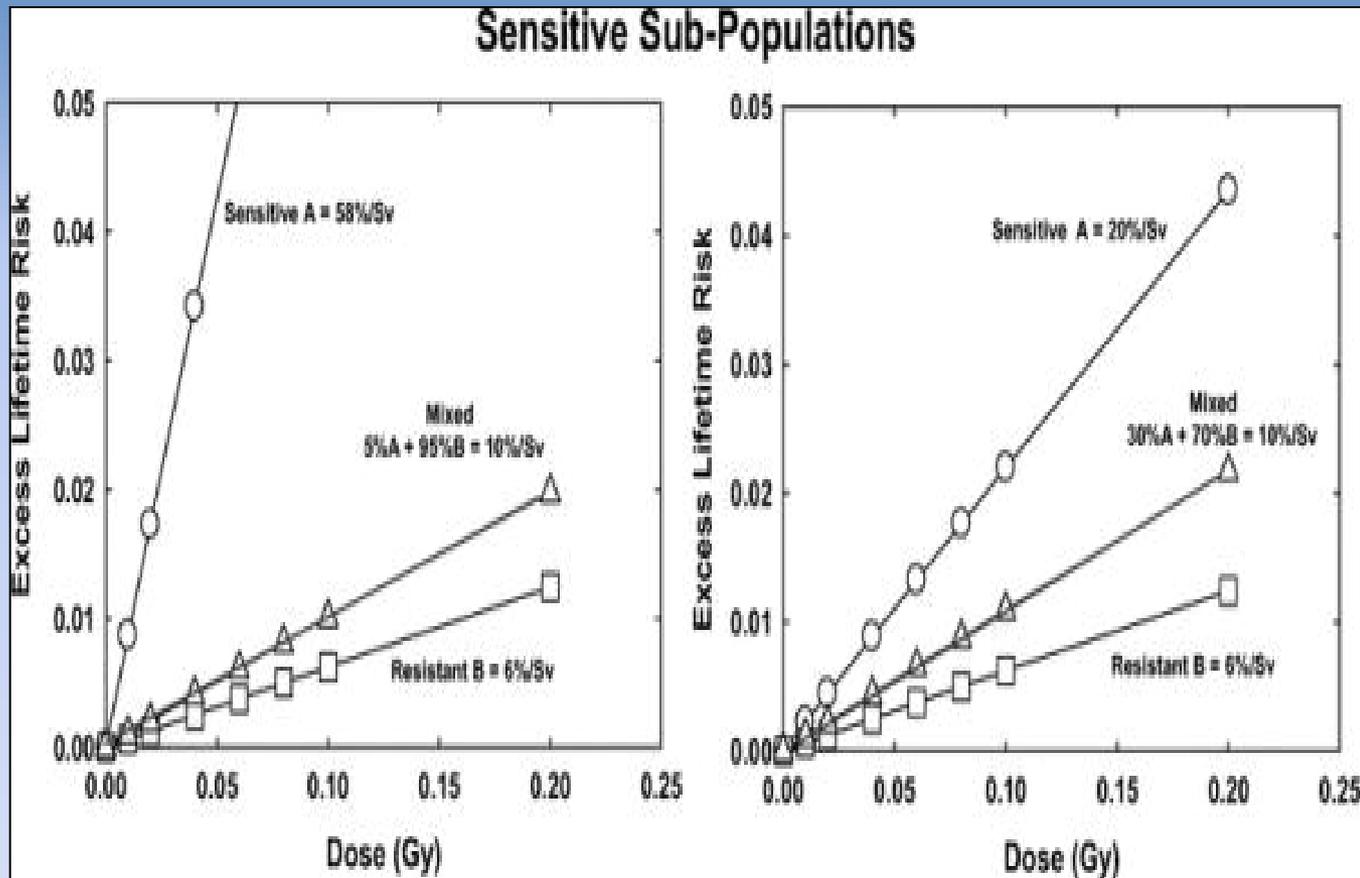
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Impact of variation in radiosensitivity prevalence and magnitude: 5% who are 6-fold more sensitive and 30% 2-fold more sensitive compared to general lifetime excess risk in A-bomb survivors

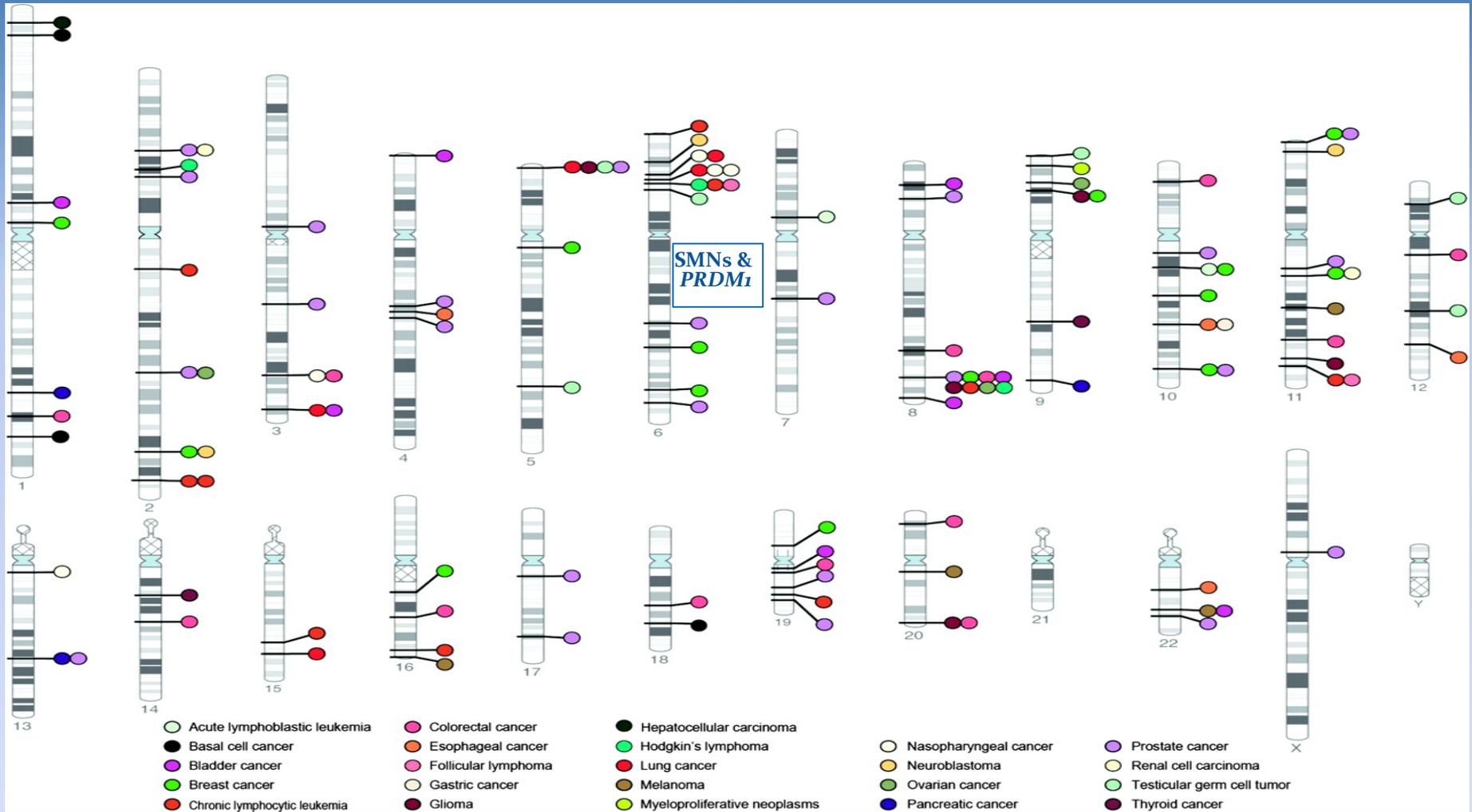
Sensitive Sub-Populations



The dose response for excess lifetime risk (incidence) for all cancers represented by the open triangles could result from populations consisting of two (or more) subpopulations where the proportions of each differed along with the radiosensitivities of the subpopulations. In this example, a subpopulation consisting of 30% of the total where the radiosensitivity for this effect is twice the average (right panel) could produce the same overall effect as a situation where only 5% of the population was about six-fold more sensitive than average (left panel). The curves followed the expression $Y(A+B) = f_A(1 - e^{-D/D_{sens}}) + f_B(1 - e^{-D/D_{resist}})$, where $Y(A+B)$ is the total lifetime excess risk, f_A and f_B are the fractions of sensitive or resistant individuals, respectively, D is the radiation dose (Gy), and D_{sens} and D_{resist} are dose parameters describing the radiosensitivities of these populations.

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**Variants Near *FOXE1* are Associated with
Hypothyroidism and Other Thyroid Conditions:
Using Electronic Medical Records for Genome- and
Phenome-wide Studies.**

Denny JC et al, Am J Hum Genet. 2011 Oct
7;89(4):529-42.