Genetics of Radiation-Related Cancer

Lindsay Morton, Ph.D.
Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
mortonli@mail.nih.gov

DCEG Radiation Epidemiology and Dosimetry Course 2019

Question #1: True or false?
We already know that individuals vary in their response to radiation exposure and risk for developing cancer.

A. True

B. False

Question #1: True or false?
We already know that individuals vary in their response to radiation exposure and risk for developing cancer.

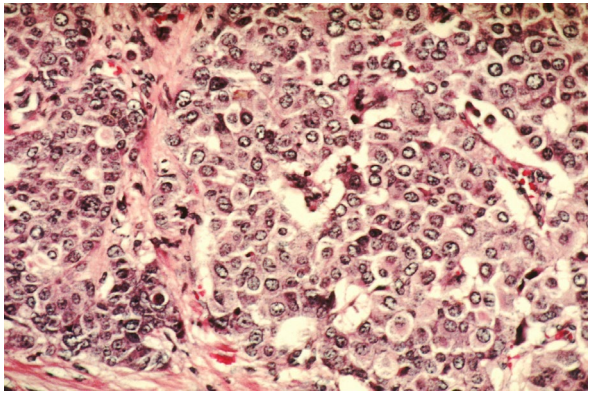
A. True

B. False

Learning Objectives

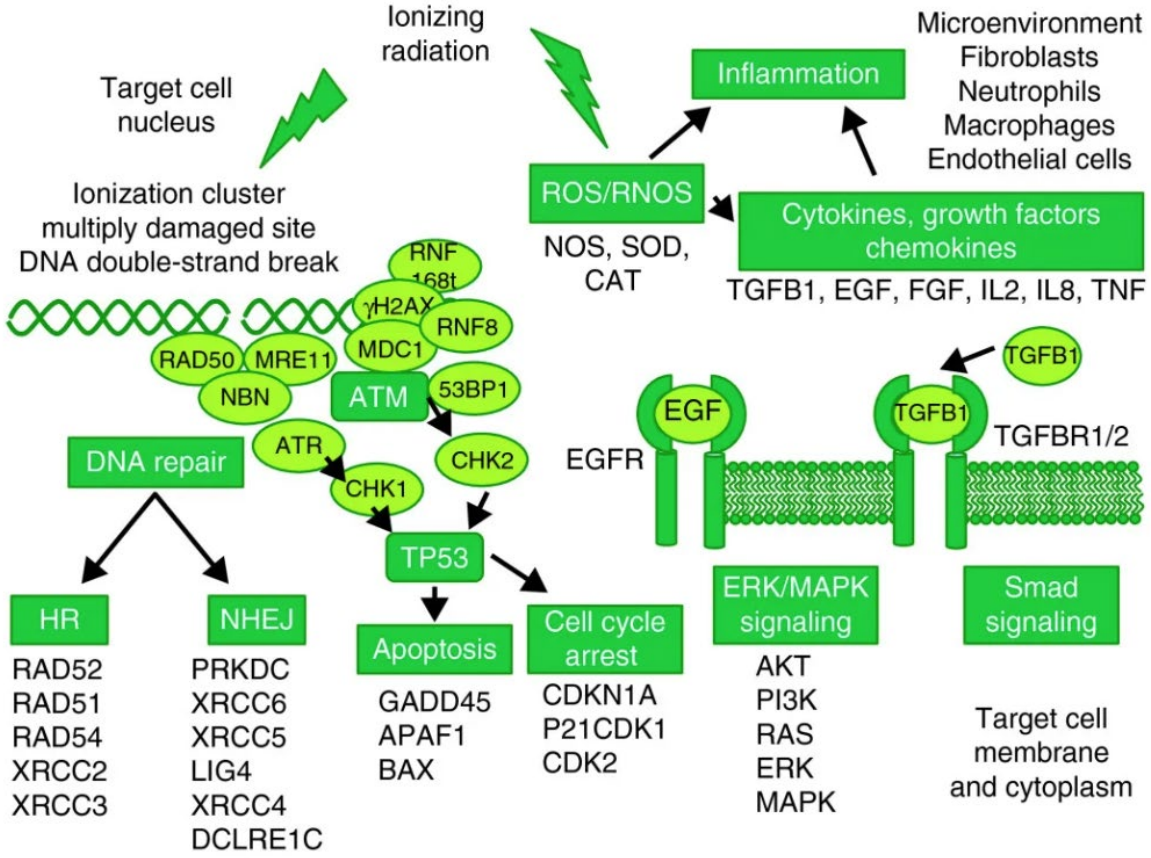
- Understand the general principles of genetic association studies conducted to date for radiation-related cancers
  - Candidate SNP/gene versus agnostic approaches
  - Specific populations and outcomes
  - Different statistical approaches to incorporate radiation exposures
- Understand the current key challenges and opportunities in the field

Ionizing radiation causes cancer



Invasive breast cancer cells. Fox C. National Cancer Institute

Cellular and tissue response to radiation exposure



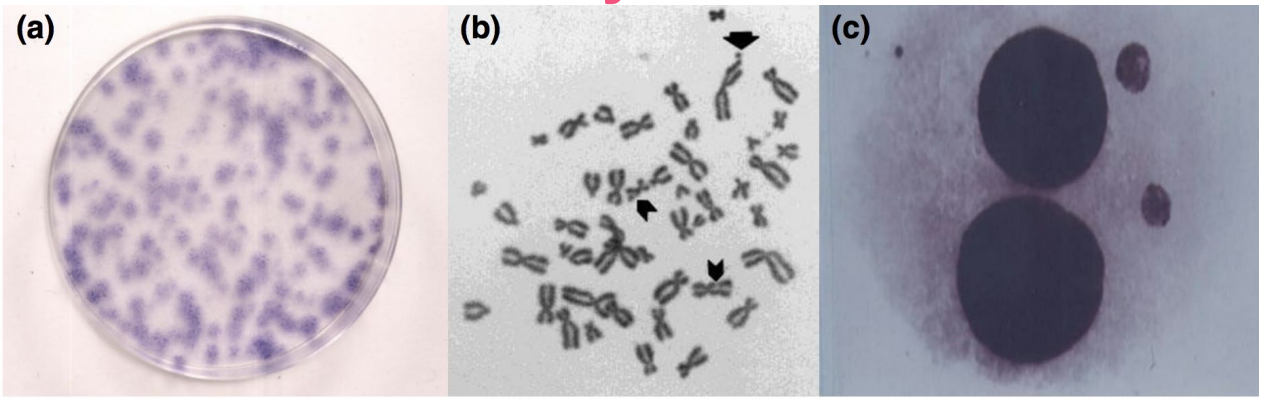
West and Barnett. *Genome Med* 2011.

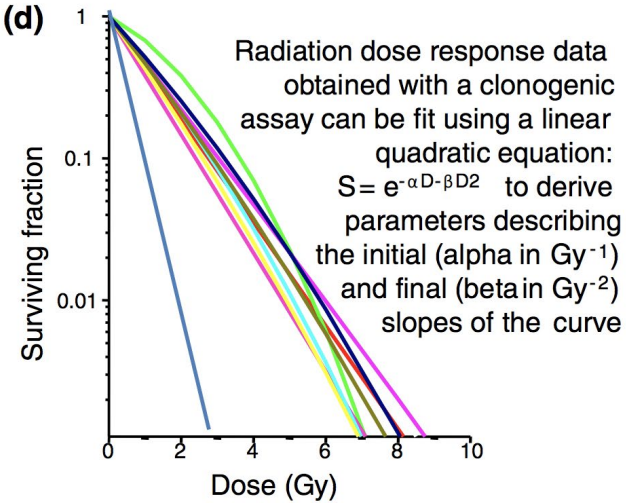
Variation in radiation sensitivity

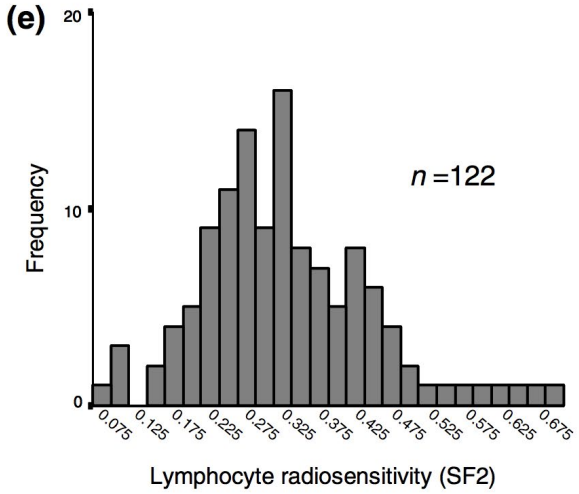
Cell

Tissue

Individual







West and Barnett. *Genome Med* 2011.

Genes involved in clinical radiation sensitivity syndromes

Syndrome	Gene(s)
Ataxia Telangiectasia	*ATM*
Ataxia Telangiectasia-like Disorder	*MRE11A*
Bloom Syndrome	*BLM*
Cornelia de Lange Syndrome*	*SMC1A, SMC3, NIPBL, HDAC8, RAD21*
DNA Ligase IV Deficiency	*LIG4†*
Fanconi Anemia	*FANCA, FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3*
Gorlin Syndrome*	*PTCH1, PTCH2, SUFU*
Li-Fraumeni Syndrome*	*TP53*
Neurofibromatosis Type 1*	*NF1*
Nijmegen Breakage Syndrome	*NBN†*
Nijmegen Breakage-Like Disorder	*RAD50*
Retinoblastoma*	*RB1*
RIDDLE Syndrome	*RNF168*
Radiosensitive SCID	*DCLRE1C, PRKDC, NHEJ1, LIG4†, NBN†*
X-linked Agammaglobulinemia	*BTK*
Xeroderma Pigmentosum	*XPC, ERCC2, POLH, DDB2, ERCC3, ERCC4, ERCC5, XPA, ERCC1*

* Autosomal dominant inheritance.

Additional reference sources

SAGE

ICRP
Annals of the ICRP

Evidence for variation in human radiosensitivity and its potential impact on radiological protection

S.D. Bouffler
Radiation Effects Department, Centre for Radiation, Chemical and Environmental Hazards, Public Health England, Chilton, Didcot, Oxfordshire, OX11 0RQ, UK; e-mail: simon.bouffler@phe.gov.uk

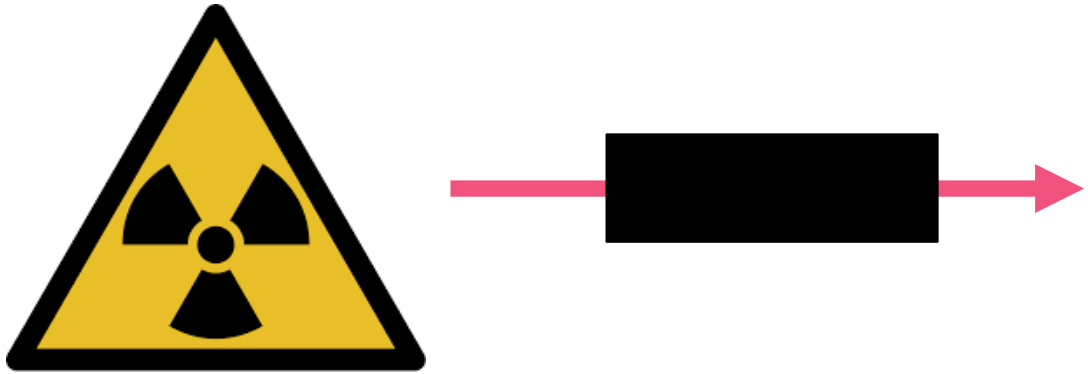
https://journals.sagepub.com/doi/full/10.1177/0146645315623158

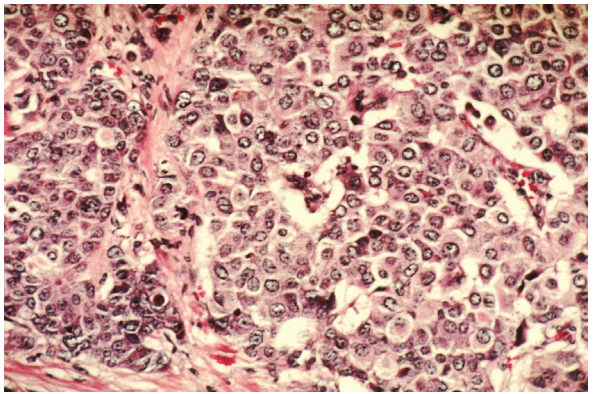
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/333058/RCE-21_v2_for_website.pdf

Human Radiosensitivity

Report of the independent Advisory Group on Ionising Radiation

Ionizing radiation causes cancer

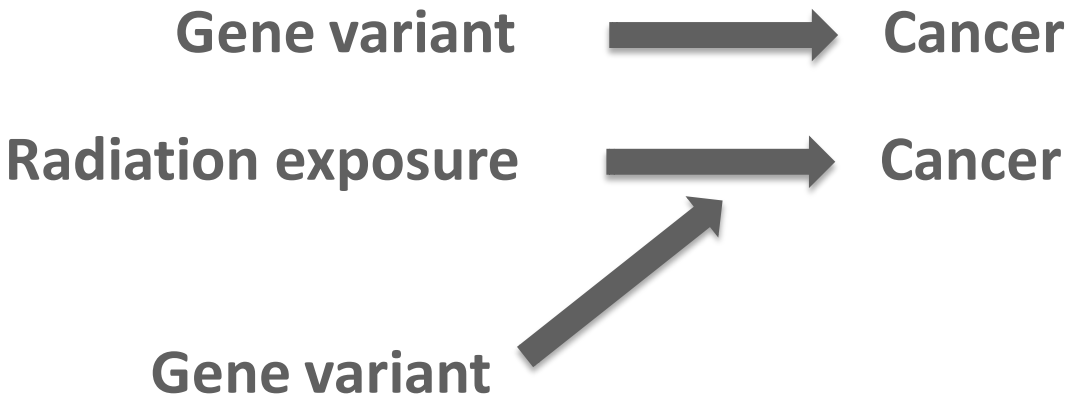




Invasive breast cancer cells. Fox C. National Cancer Institute

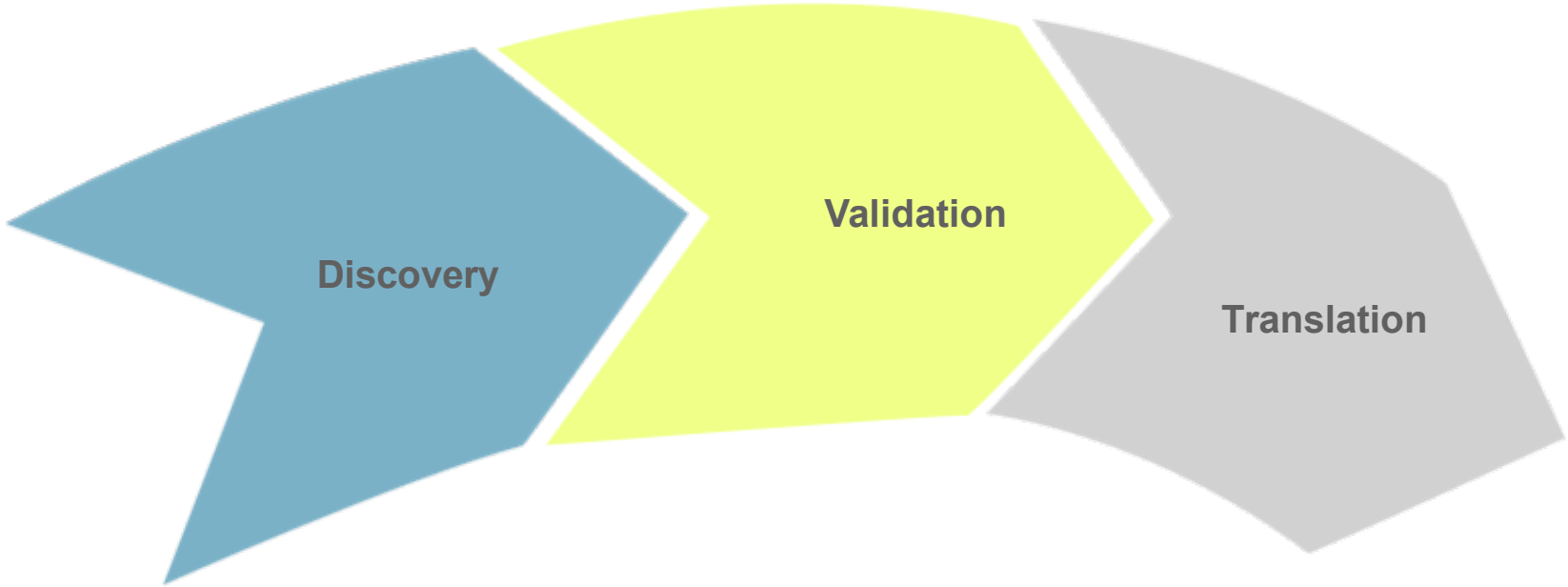
- Insight into radiation carcinogenesis
- Impact on (clinical) decision-making
  - Risk/benefit assessment of radiation exposure
  - Surveillance recommendations

Genetic susceptibility to radiation-related cancer



- Key challenges:
  - Few studies have necessary data (radiation exposure, long-term follow-up, DNA)
  - Complex interrelationships between radiation exposure, age, latency, and cancer type

Arc of genetics



Two Myths

- One technology can do it all
- Single studies tell the full story

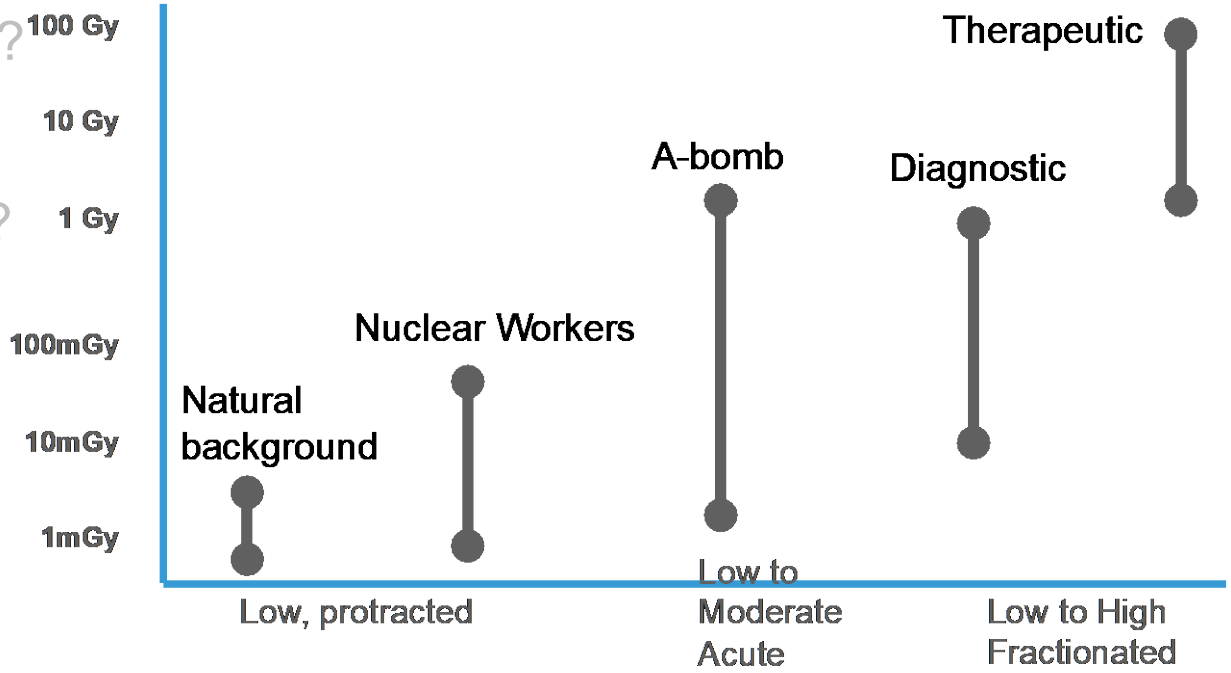
Courtesy of
SJ Chanock

Key questions

- Which radiation exposure?
- Which study population?
- Which outcome?
- Which genetic variants?

Key questions (2)

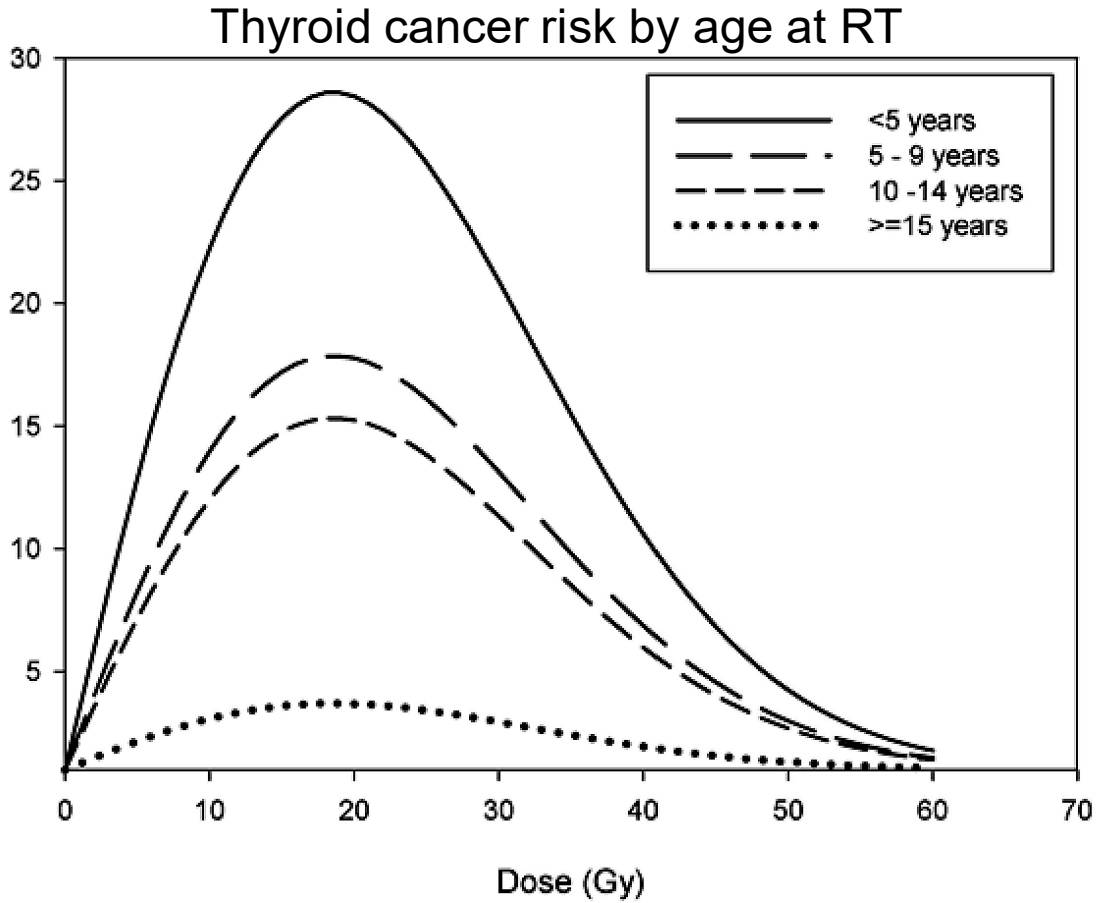
- **Which radiation exposure?**
- Which study population?
- Which outcome?
- Which genetic variants?



Courtesy S. Schonfeld, A. Berrington de Gonzalez

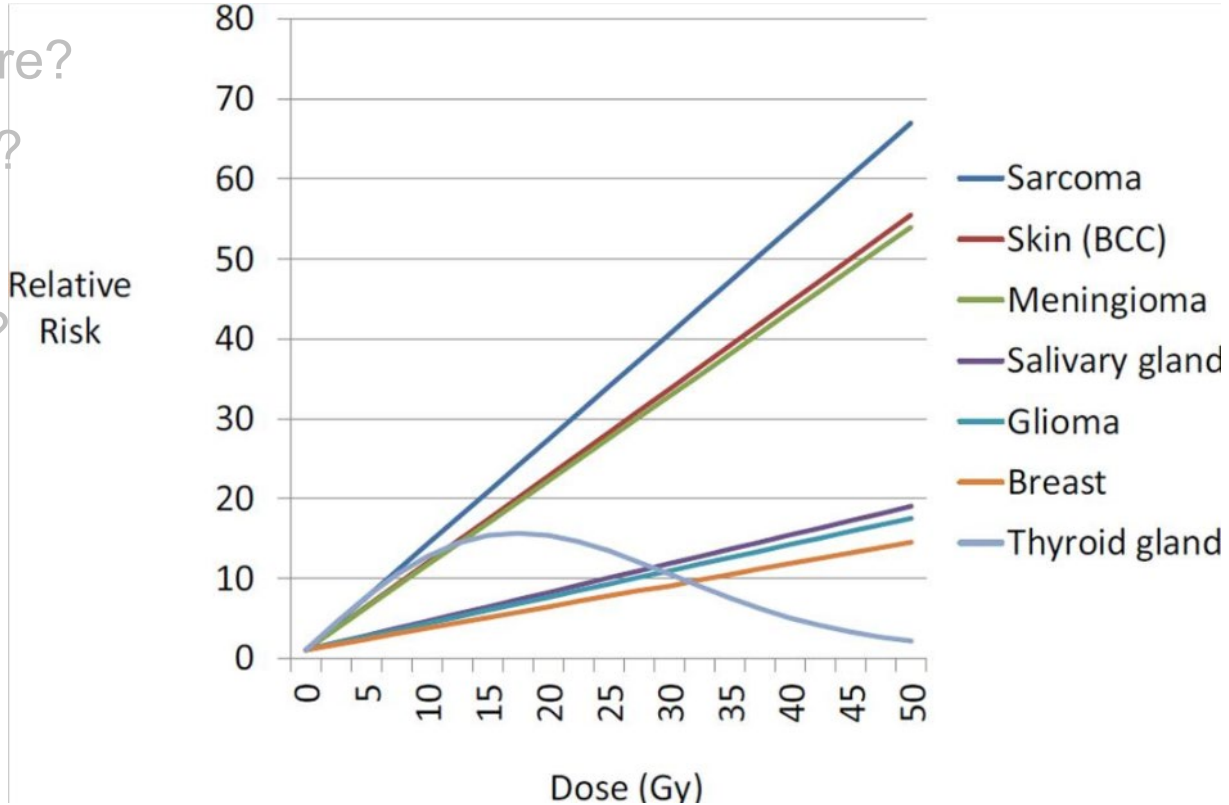
Key questions (3)

- Which radiation exposure?
- **Which study population?**
- Which outcome?
- Which genetic variants?



Key questions (4)

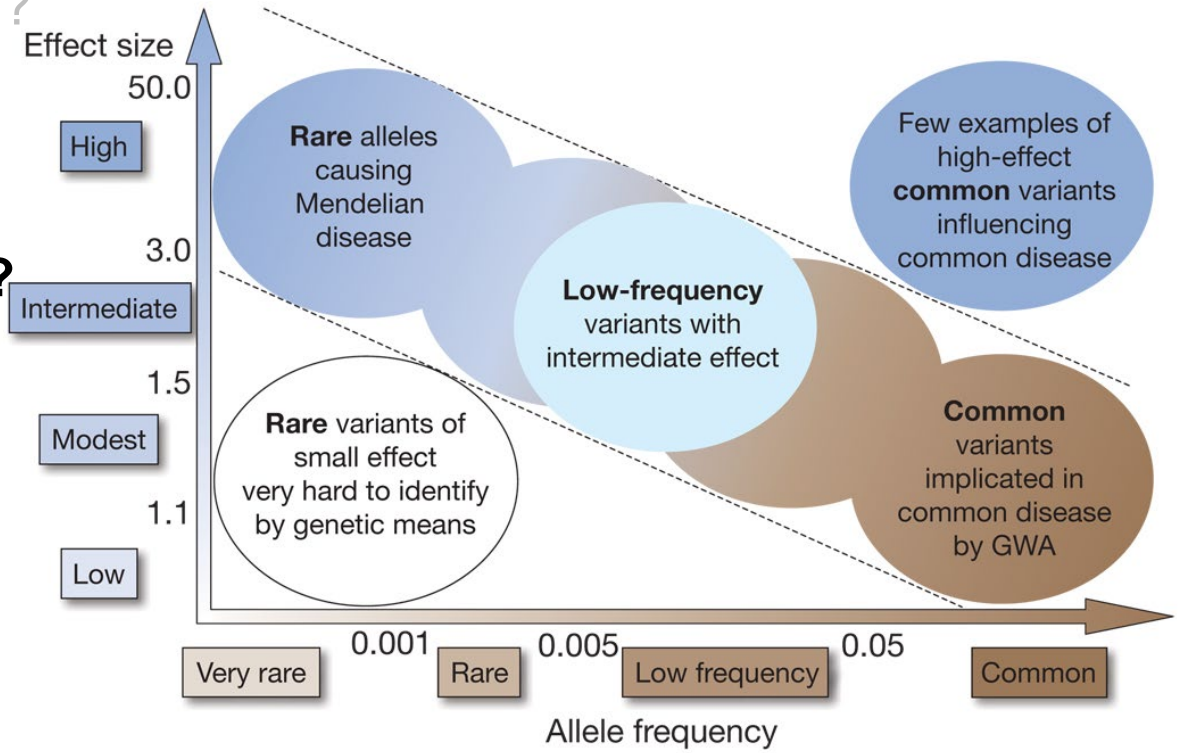
- Which radiation exposure?
- Which study population?
- **Which outcome?**
- Which genetic variants?



Inskip et al. *Int J Radiat Oncol Biol Phys* 2016

Key questions (5)

- Which radiation exposure?
- Which study population?
- Which outcome?
- **Which genetic variants?**



Manolio et al. *Nature* 2009

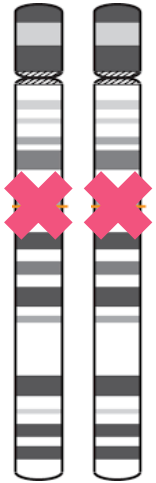
Genes involved in clinical radiation sensitivity syndromes

Syndrome	Gene(s)
Ataxia Telangiectasia	***ATM* (WECARE Study)**
Ataxia Telangiectasia-like Disorder	*MRE11A*
Bloom Syndrome	*BLM*
Cornelia de Lange Syndrome*	*SMC1A, SMC3, NIPBL, HDAC8, RAD21*
DNA Ligase IV Deficiency	*LIG4†*
Fanconi Anemia	*FANCA, FANCB, FANCC, **BRCA2**, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, **BRCA1**, UBE2T, XRCC2, MAD2L2, RFWD3*
Gorlin Syndrome*	*PTCH1, PTCH2, SUFU*
Li-Fraumeni Syndrome*	***TP53* (LiFE Consortium)**
Neurofibromatosis Type 1*	***NF1* (Bhatia S et al. *J Clin Oncol* In press)**
Nijmegen Breakage Syndrome	*NBN†*
Nijmegen Breakage-Like Disorder	*RAD50*
Retinoblastoma*	***RB1* (IRiSC Consortium)**
RIDDLE Syndrome	*RNF168*
Radiosensitive SCID	*DCLRE1C, PRKDC, NHEJ1, LIG4†, NBN†*
X-linked Agammaglobulinemia	*BTK*
Xeroderma Pigmentosum	*XPC, ERCC2, POLH, DDB2, ERCC3, ERCC4, ERCC5, XPA, ERCC1*

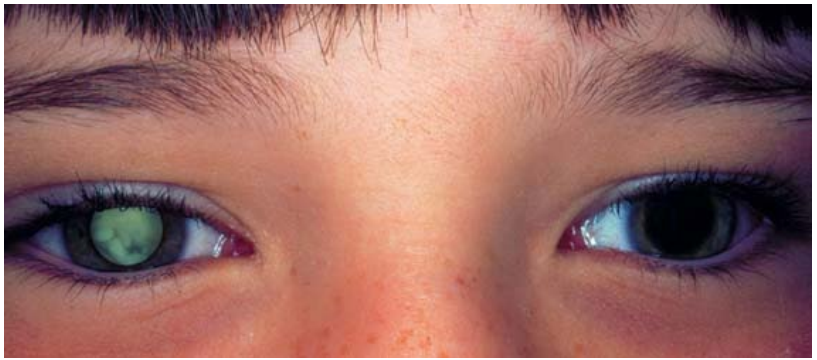
* Autosomal dominant inheritance.

Retinoblastoma

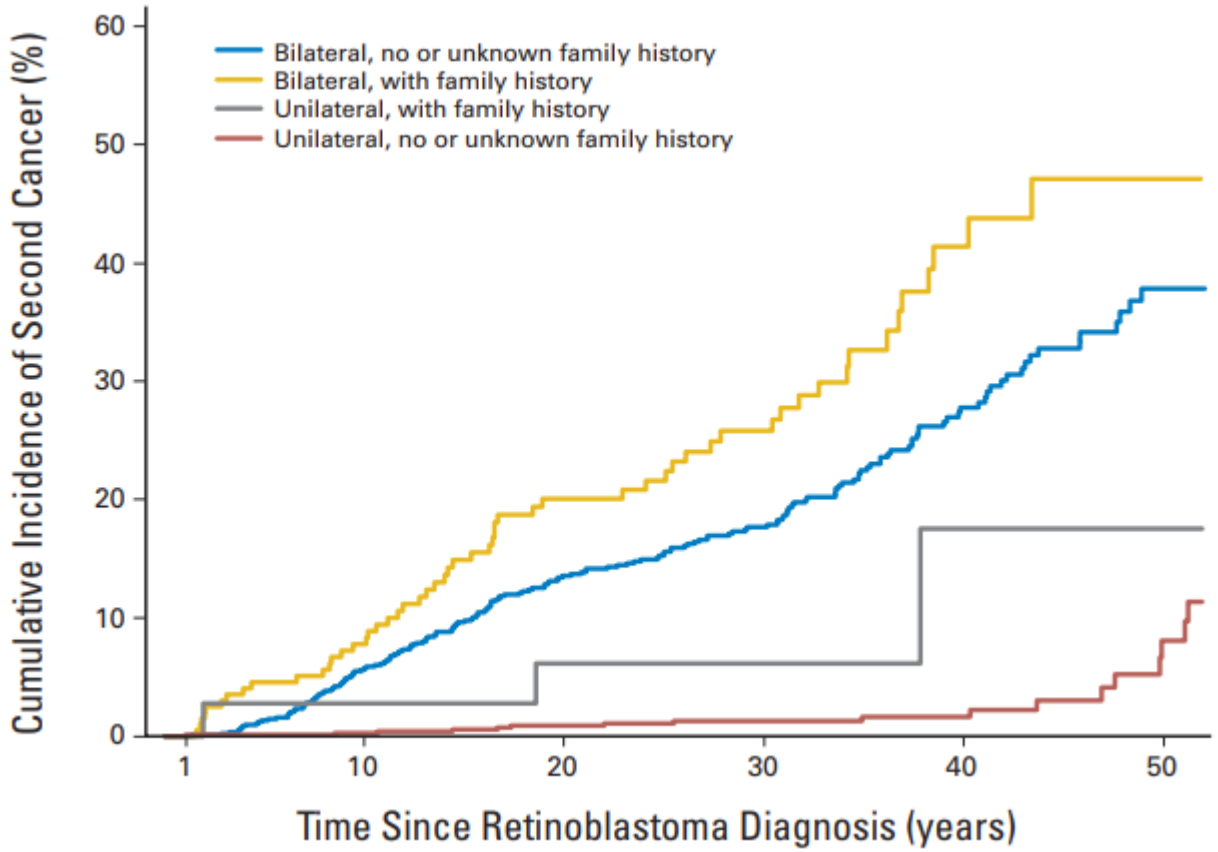
- Rare childhood retinal tumor
  - Hereditary retinoblastoma
  - Non-hereditary retinoblastoma



- 96% survival at 10 years in the United States

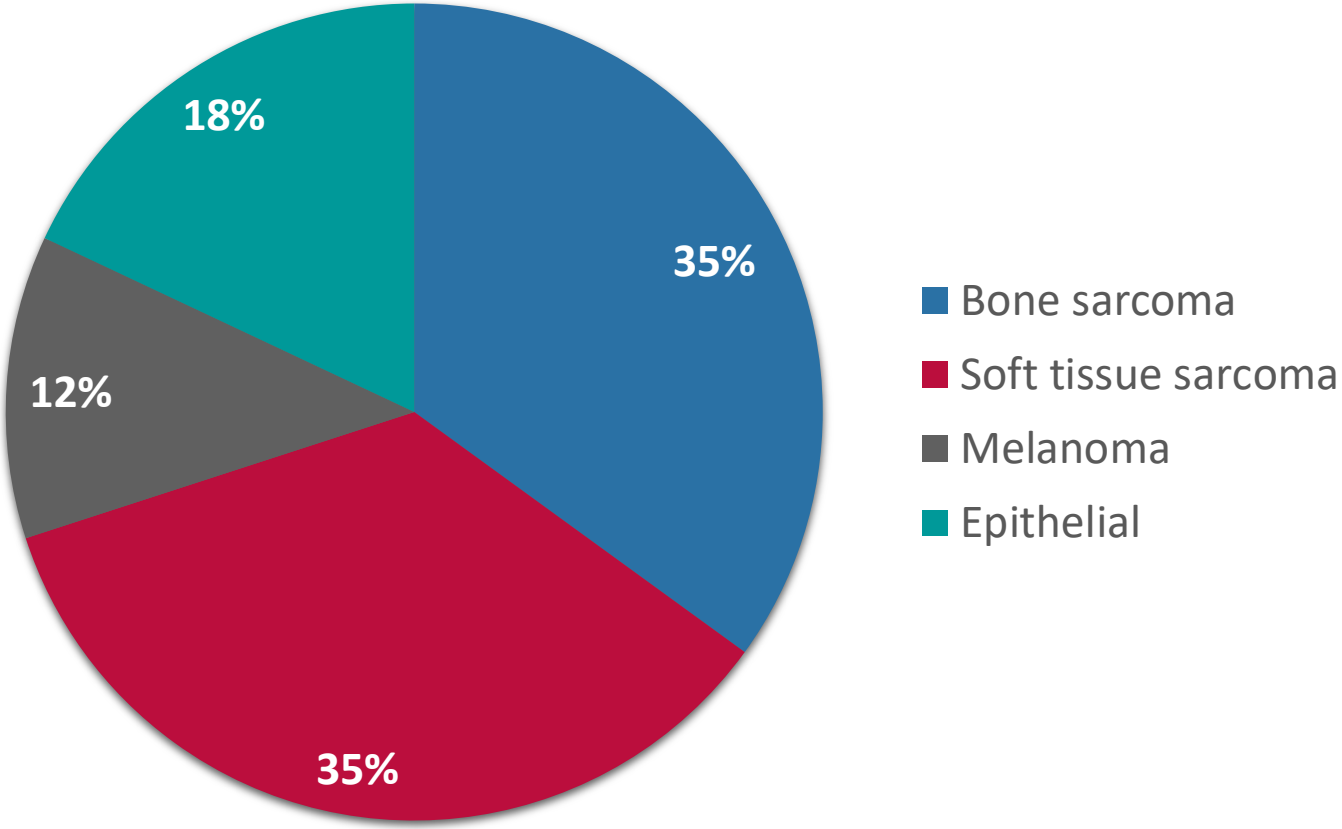


Cumulative second cancer incidence in RB survivors

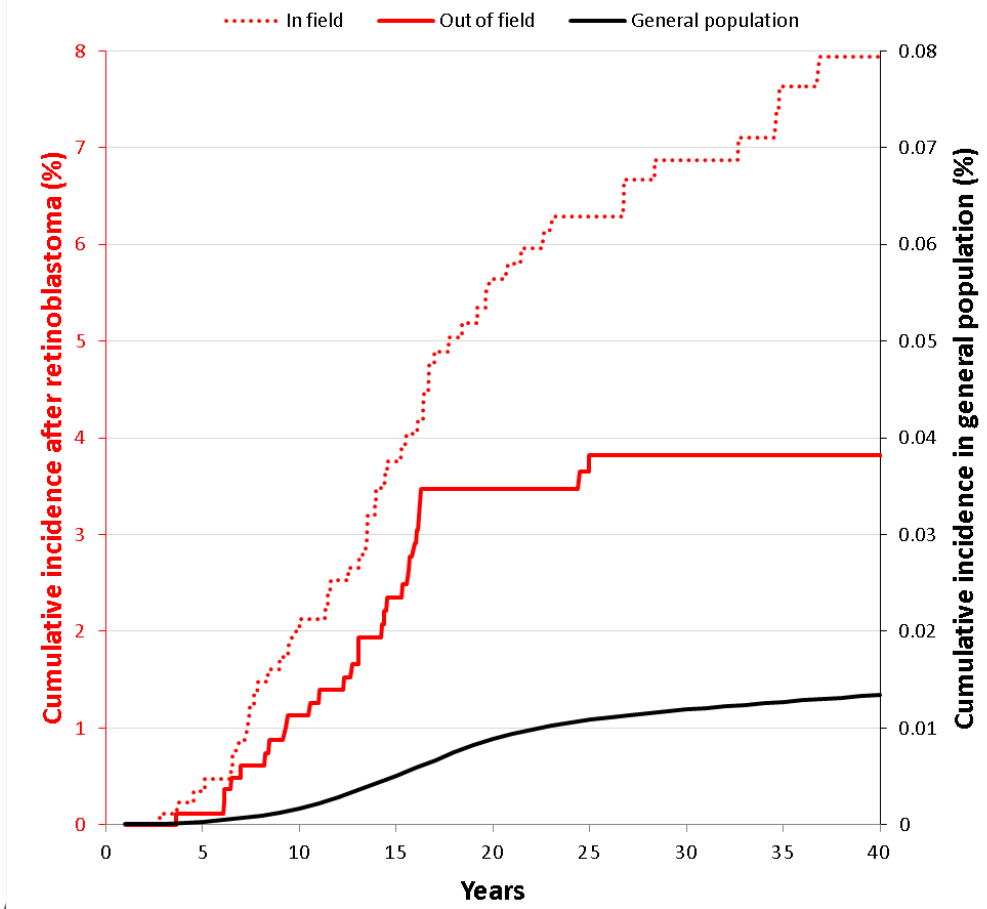


Kleinerman RA et al. *J Clin Oncol* 2012

Most common second cancers after hereditary RB



Bone sarcoma risk after hereditary RB

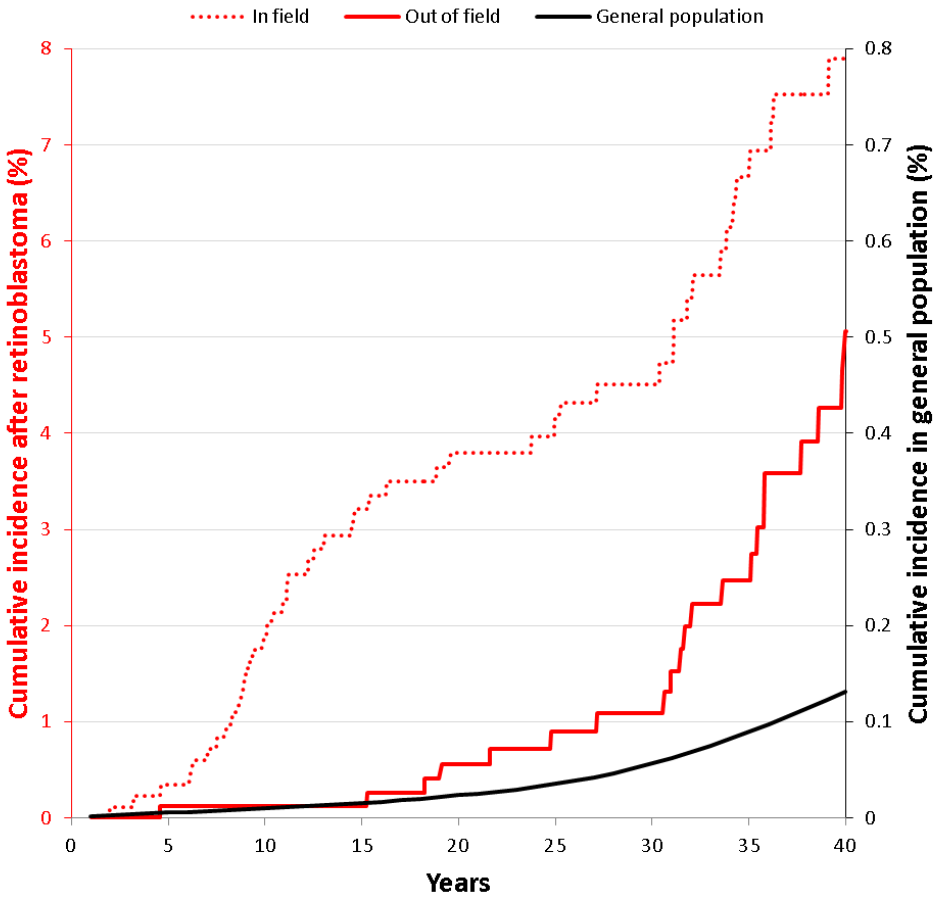


In field:
Radiation + genetics
SIR = 2213

Out of field:
Genetics only
SIR = 169

Kleinerman RA et al. *J Clin Oncol* in press

Soft tissue sarcoma risk after hereditary RB



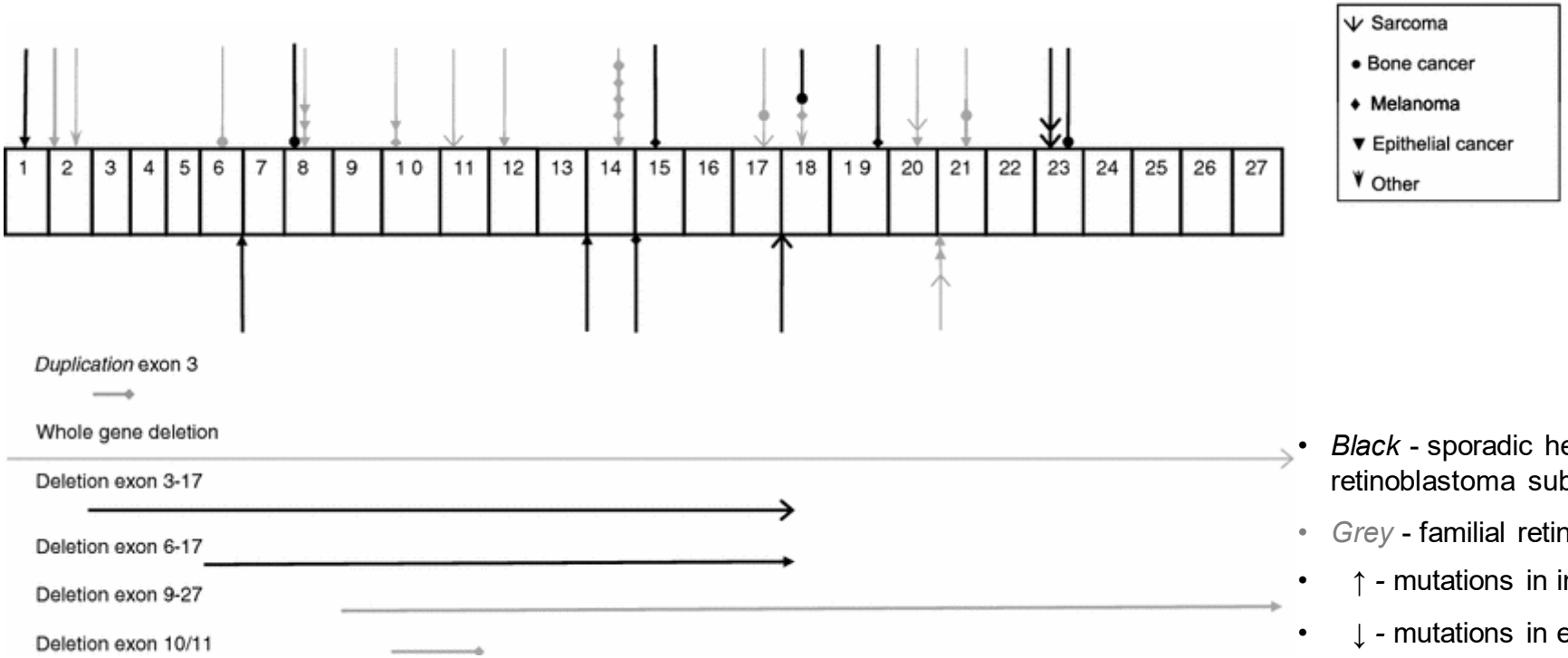
In field:
Radiation + genetics
SIR = 542

Out of field:
Genetics only
SIR = 46

Kleinerman RA et al. *J Clin Oncol* In press

RB1 mutations and subsequent neoplasm risk

- 199 hereditary Rb survivors, 44 developed subsequent neoplasm



- *Black* - sporadic hereditary retinoblastoma subjects
- *Grey* - familial retinoblastoma
- ↑ - mutations in introns
- ↓ - mutations in exons
- → - large rearrangements

Dommering CJ et al. *Fam Cancer* 2012

International collaboration: RB survivorship

- Broad group of interdisciplinary investigators
- Led by Dutch group
- Primary aims:
  - Evaluate treatment-related subsequent neoplasm risk
  - Evaluate genetic susceptibility to subsequent neoplasms
  - Contribute to survivorship guidelines

IRISC | INTERNATIONAL RETINOBLASTOMA AND SECOND CANCERS

Genes involved in clinical radiation sensitivity syndromes

Syndrome	Gene(s)
Ataxia Telangiectasia	***ATM* (WECARE Study)**
Ataxia Telangiectasia-like Disorder	*MRE11A*
Bloom Syndrome	*BLM*
Cornelia de Lange Syndrome*	*SMC1A, SMC3, NIPBL, HDAC8, RAD21*
DNA Ligase IV Deficiency	*LIG4†*
Fanconi Anemia	*FANCA, FANCB, FANCC, **BRCA2**, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, **BRCA1**, UBE2T, XRCC2, MAD2L2, RFWD3*
Gorlin Syndrome*	*PTCH1, PTCH2, SUFU*
Li-Fraumeni Syndrome*	***TP53* (LiFE Consortium)**
Neurofibromatosis Type 1*	***NF1* (Bhatia S et al. *J Clin Oncol* In press)**
Nijmegen Breakage Syndrome	*NBN†*
Nijmegen Breakage-Like Disorder	*RAD50*
Retinoblastoma*	***RB1* (IRiSC Consortium)**
RIDDLE Syndrome	*RNF168*
Radiosensitive SCID	*DCLRE1C, PRKDC, NHEJ1, LIG4†, NBN†*
X-linked Agammaglobulinemia	*BTK*
Xeroderma Pigmentosum	*XPC, ERCC2, POLH, DDB2, ERCC3, ERCC4, ERCC5, XPA, ERCC1*

* Autosomal dominant inheritance.

Diagnostic x-rays → breast cancer risk among BRCA1/2 mutation carriers

- Conflicting results in the literature
- GENE-RAD-RISK study: Retrospective cohort of 1122 female *BRCA1/2* mutation carriers pooled from three nationwide studies (France, UK, Netherlands)

Dose (Gy) before age 30 years	RR (95%CI)
0	Reference
>0-<0.002	1.63 (0.96-2.77)
0.002-0.0065	1.78 (0.88-3.58)
0.0066-0.0173	1.75 (0.72-4.25)
≥0.0174	3.84 (1.67-8.79)

Pijpe et al. *BMJ* 2012

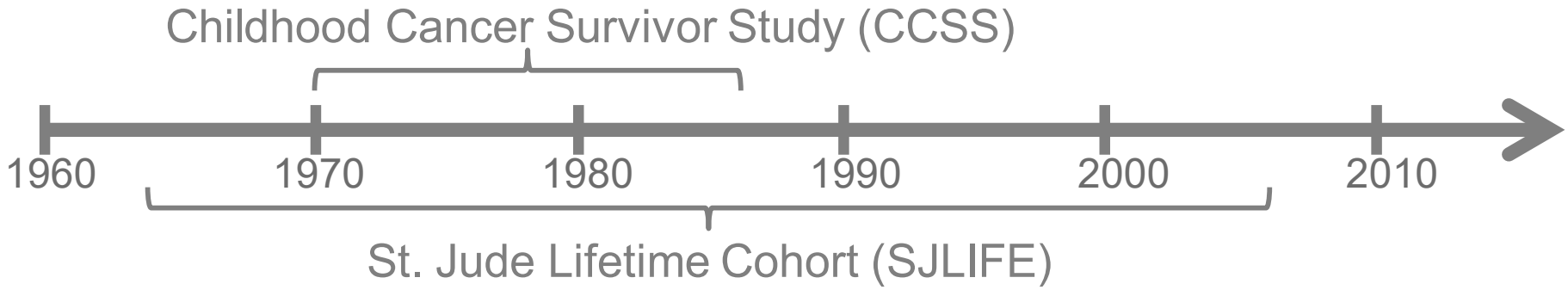
Contralateral breast cancer risk

- WECARE study: matched case/control (708 cases, 1397 controls)

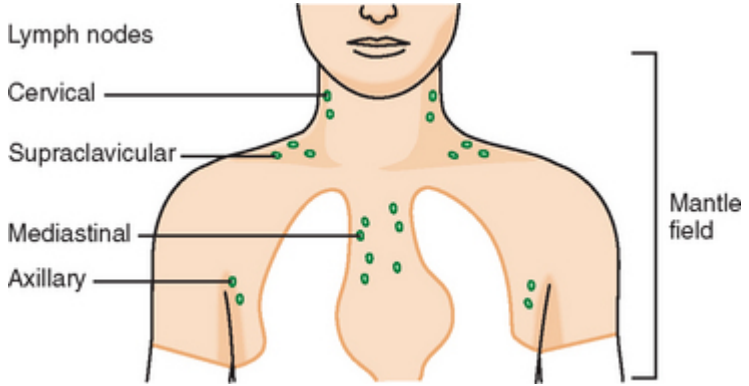
Gene	Mutation status	Risk estimate (95%CI)
ATM		ERR/Gy
	Non-carrier	0.0 (<9-0.3)
	Tolerated missense	0.8 (-0.1-3.6)
	Deleterious	2.6 (0.0-10.6)
BRCA1/2		OR ≥1 vs. <1 Gy
	Non-carrier	1.2 (1.0-1.6)
	Carrier	1.0 (0.4-2.8)

Bernstein et al. *J Natl Cancer Inst* 2010, *Eur J Cancer* 2013

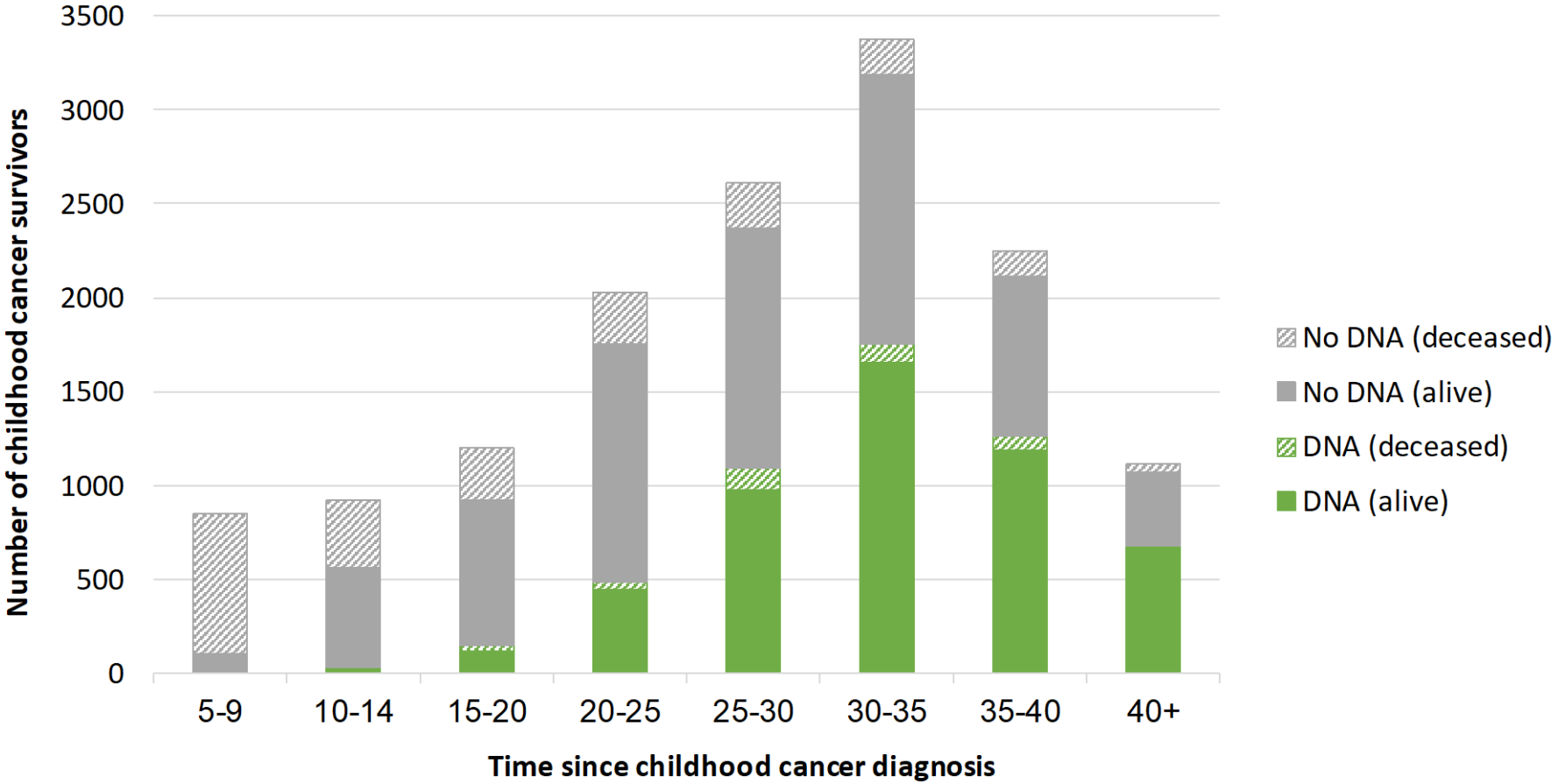
Genomics in childhood cancer cohorts



- Long-term, systematic follow-up for new malignancies
- Germline DNA
- Detailed treatment data

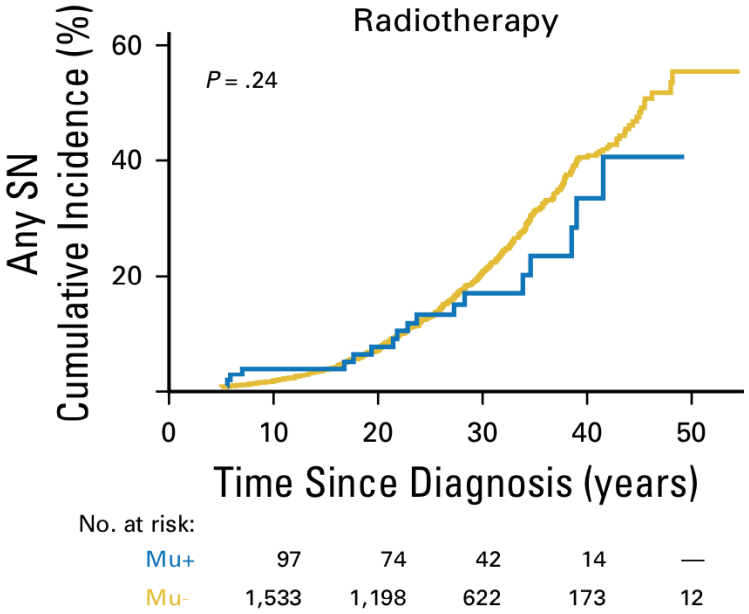


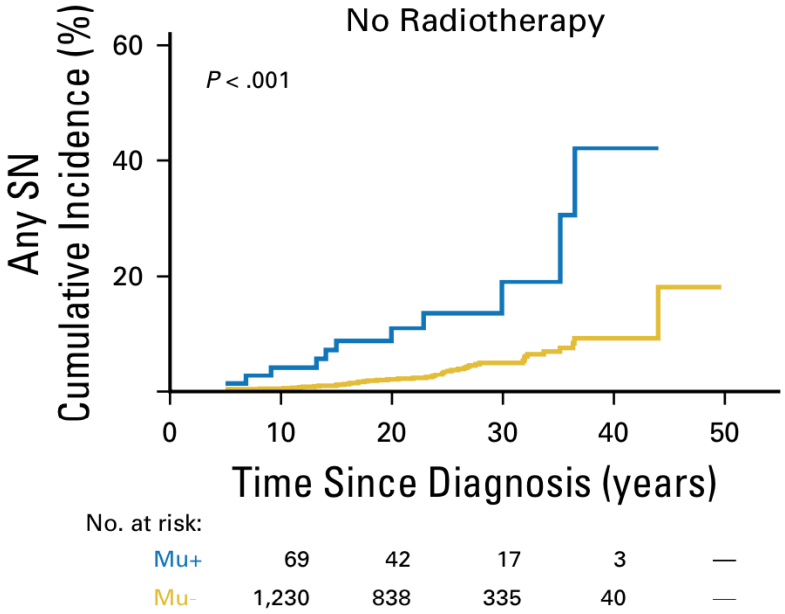
Survival and DNA participation bias in a cohort study



Known cancer predisposition gene mutations → subsequent neoplasm risk

- St. Jude Lifetime Cohort study: 3006 long-term survivors with whole genome sequencing data; 439 developed 1+ subsequent neoplasm

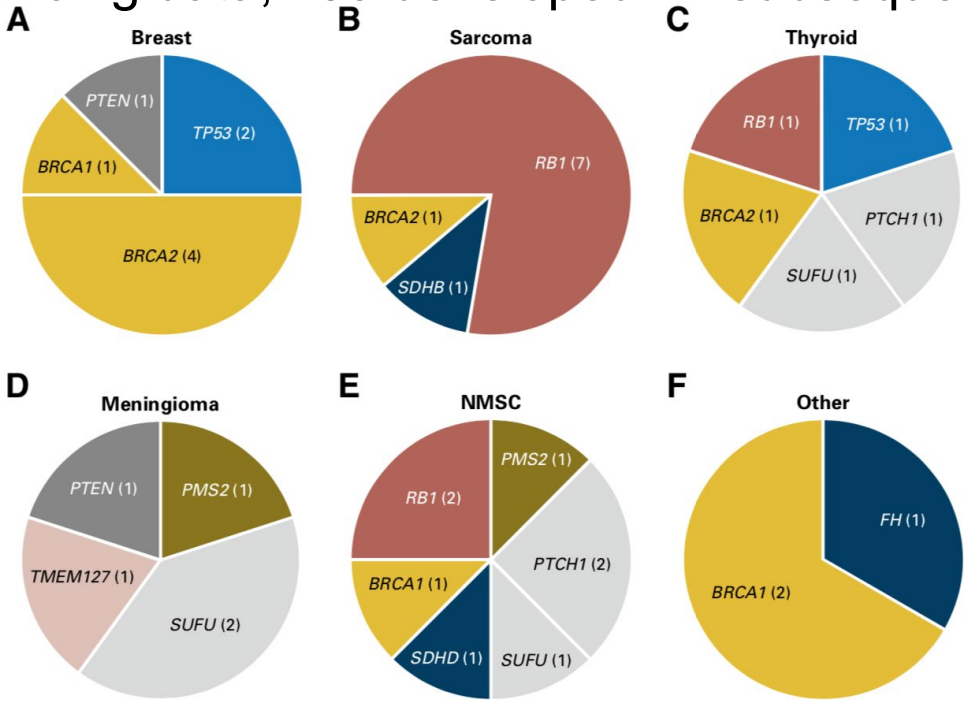




Wang Z et al. *J Clin Oncol* 2018

Known cancer predisposition gene mutations → subsequent neoplasm risk

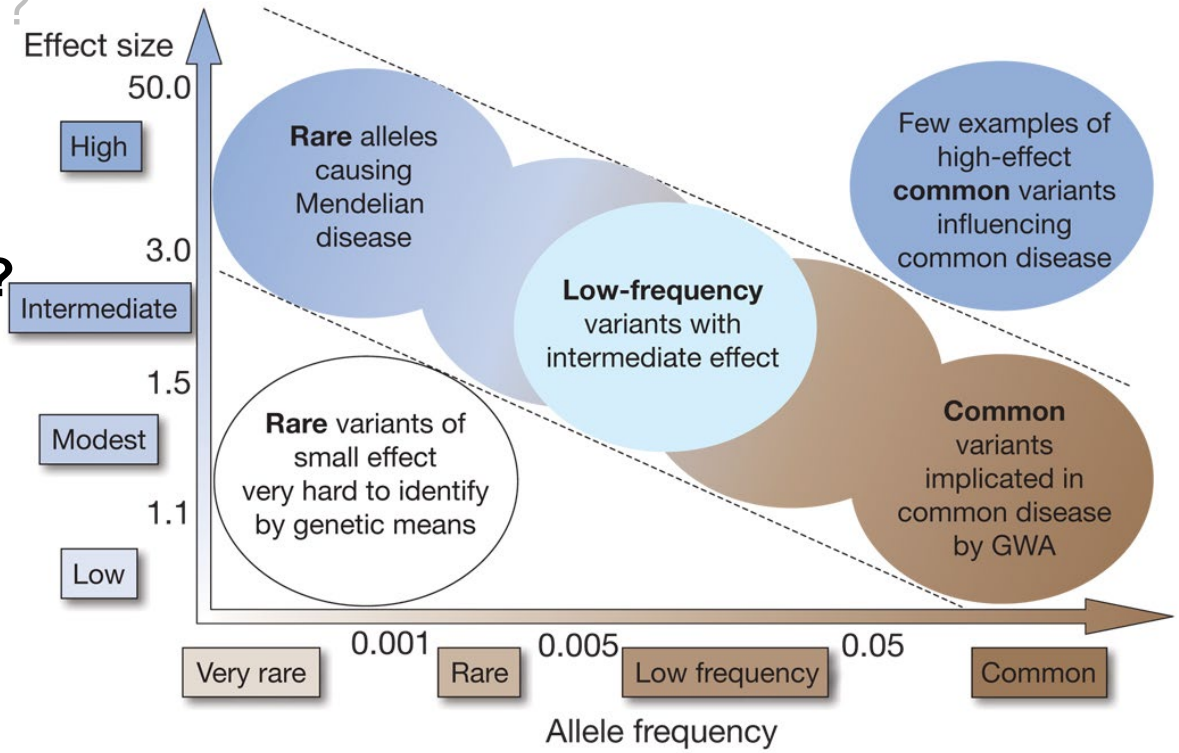
- St. Jude Lifetime Cohort study: 3006 long-term survivors with whole genome sequencing data; 439 developed 1+ subsequent neoplasm



Wang Z et al. *J Clin Oncol* 2018

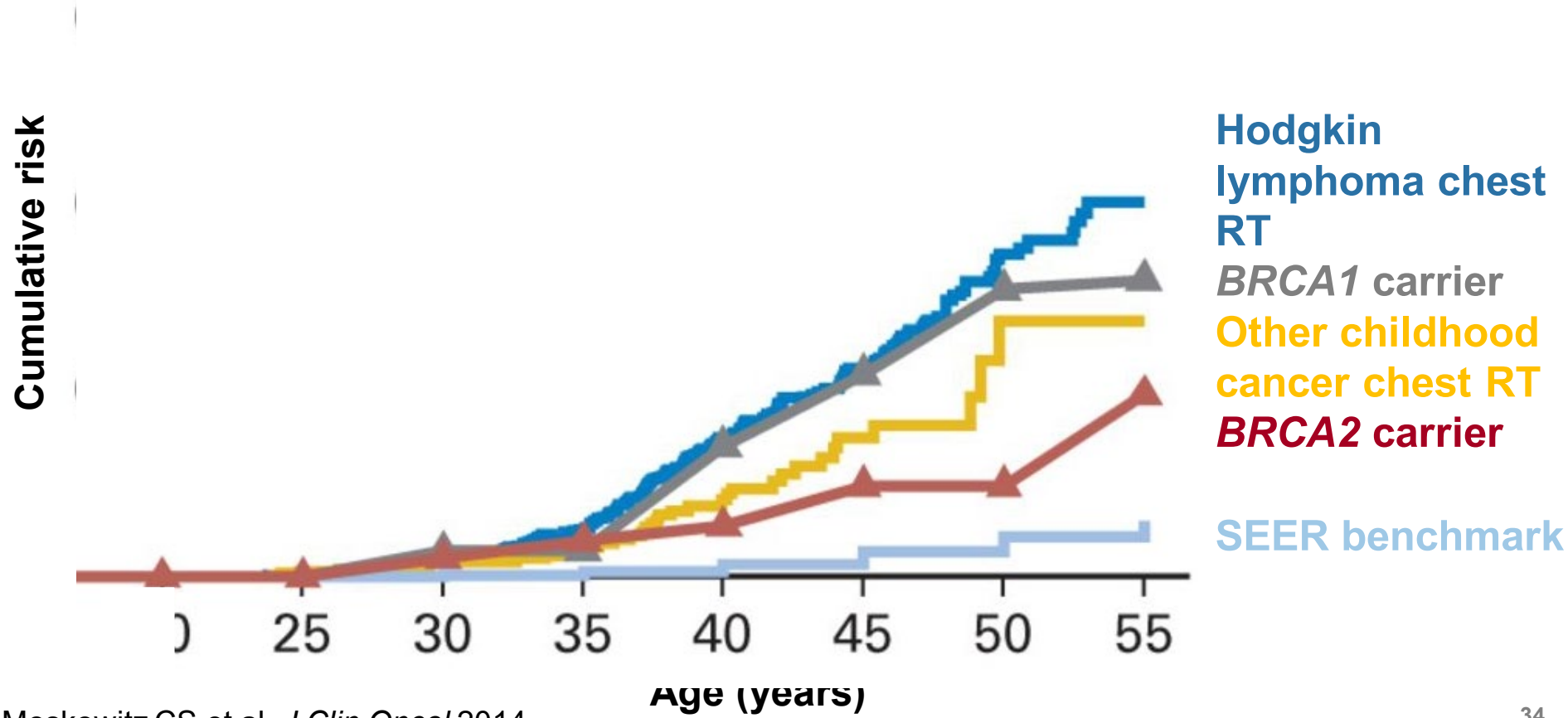
Key questions

- Which radiation exposure?
- Which study population?
- Which outcome?
- **Which genetic variants?**



Manolio et al. *Nature* 2009

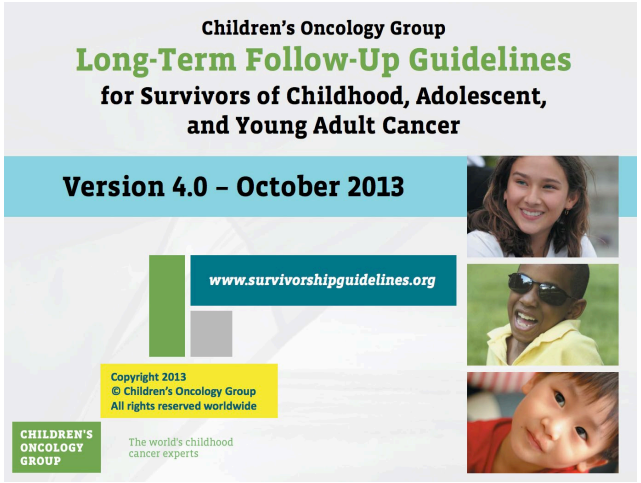
Cumulative breast cancer risk



Moskowitz CS et al. *J Clin Oncol* 2014

Breast cancer: current screening recommendations

- Annual mammography with adjunct MRI for those with ≥20 Gy chest irradiation beginning 8 years after treatment or at age 25 years, whichever occurs last



http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf

Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Renée L Mulder, Leontien C M Kremer, Melissa M Hudson, Smita Bhatia, Wendy Landier, Gill Levitt, Louis S Constine, W Hamish Wallace, Flora E van Leeuwen, Cécile M Ronckers, Tara O Henderson, Mary Dwyer, Roderick Skinner, Kevin C Oeffinger

Lancet Oncol 2013

Study population

	Pooled	CCSS	SJLIFE
Female survivors of European descent with genotype data	**N=3426**	N=2739	N=687
→ Developed breast cancer	**N=207**	N=178	N=29
→ Did not develop any 2nd cancers	**N=2774**	N=2200	N=574
Genotyping + imputation	**16,958,466 SNPs & InDels**	Illumina 5M+Exome	Affymetrix 6.0

Morton LM*, Sampson JN*, Armstrong GT*, et al. *J Natl Cancer Inst* 2017

Population characteristics

Characteristics	Breast cancer (N=207)	No 2nd cancer (N=2774)
First primary type		
Hodgkin lymphoma	65%	9%
Leukemia	10%	35%
Other	26%	56%
≥10 Gy radiation exposure to breast	63%	18%
Median age at childhood cancer	15.6 years	6.1 years
Median attained age	39.2 years	32.9 years

Morton LM*, Sampson JN*, Armstrong GT*, et al. *J Natl Cancer Inst* 2017

Multi-stage analysis approach

1. Mantel Haenszel test statistic (exact conditional distribution) comparing:

Minor allele	Breast SN	No SN
0	N	N
1	N	N

Stratified by study/DNA input

2. For SNPs with $P_{MH}<1 \times 10^{-6}$:
   - Cox regression, age as time scale
   - Gene x radiation (multiplicative model)
   - Sensitivity analyses (first primary, age, survival, etc.)
   - Technical validation of top SNPs

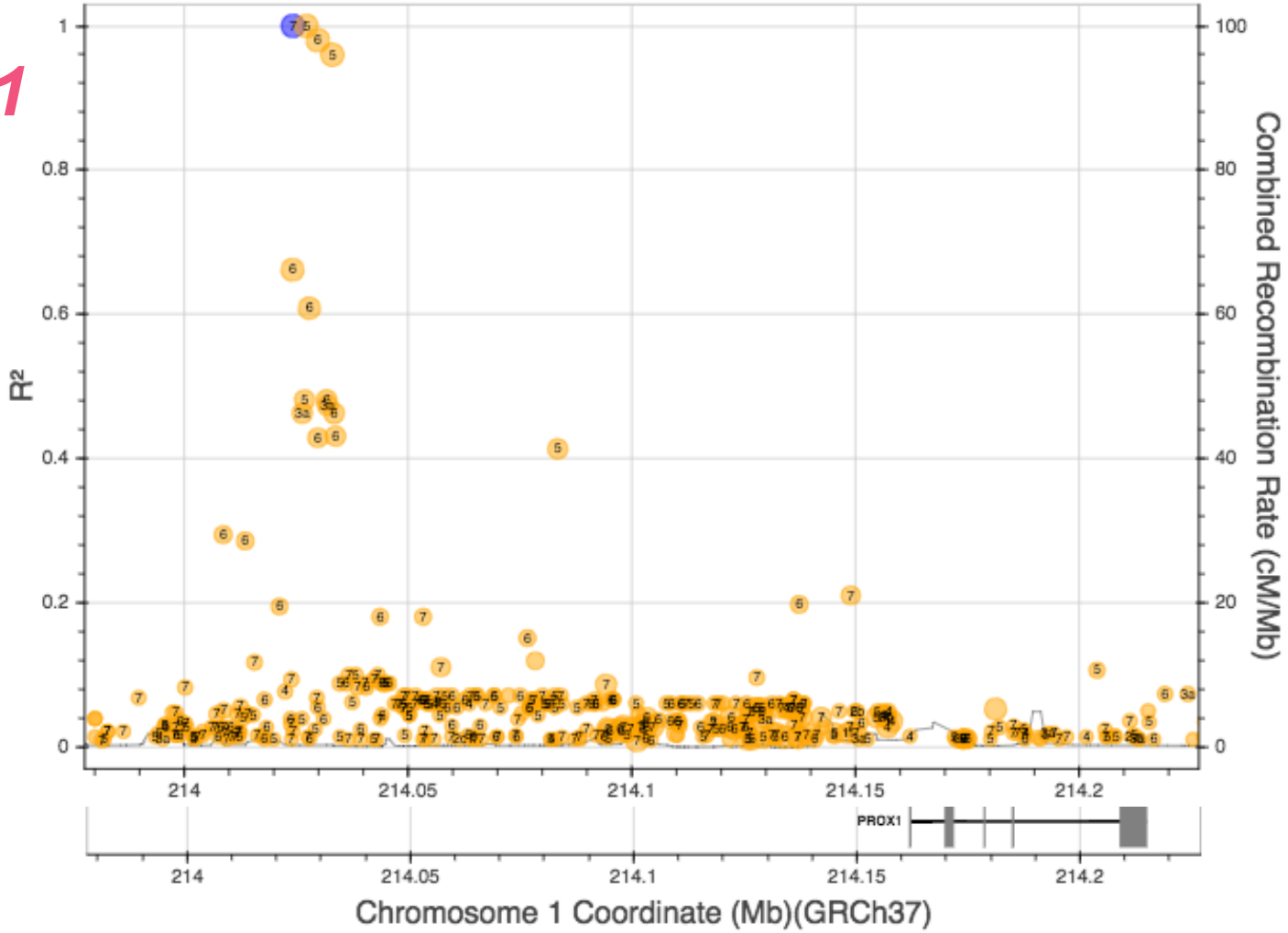
Evaluate consistency in CCSS and SJLIFE results

Top association: 1q41, rs4342822

	Radiation exposure to the breast ≥10 Gy	Radiation exposure to the breast <10 Gy
Cases / Controls	131 / 493	69 / 2144
Risk allele frequency, cases / controls	0.66 / 0.46	0.52 / 0.51
P_{MH}	7.09×10^{-9}	0.81
Multivariate Cox model, HR(95% CI)	1.92 (1.29-2.44)	1.04 (0.75-1.45)
P_{Cox}	7.00×10^{-9}	0.81
Gene x radiation interaction *P* value	0.006	

* Genotyping status: CCSS=imputed (0.996), SJLIFE=genotyped

PROX1

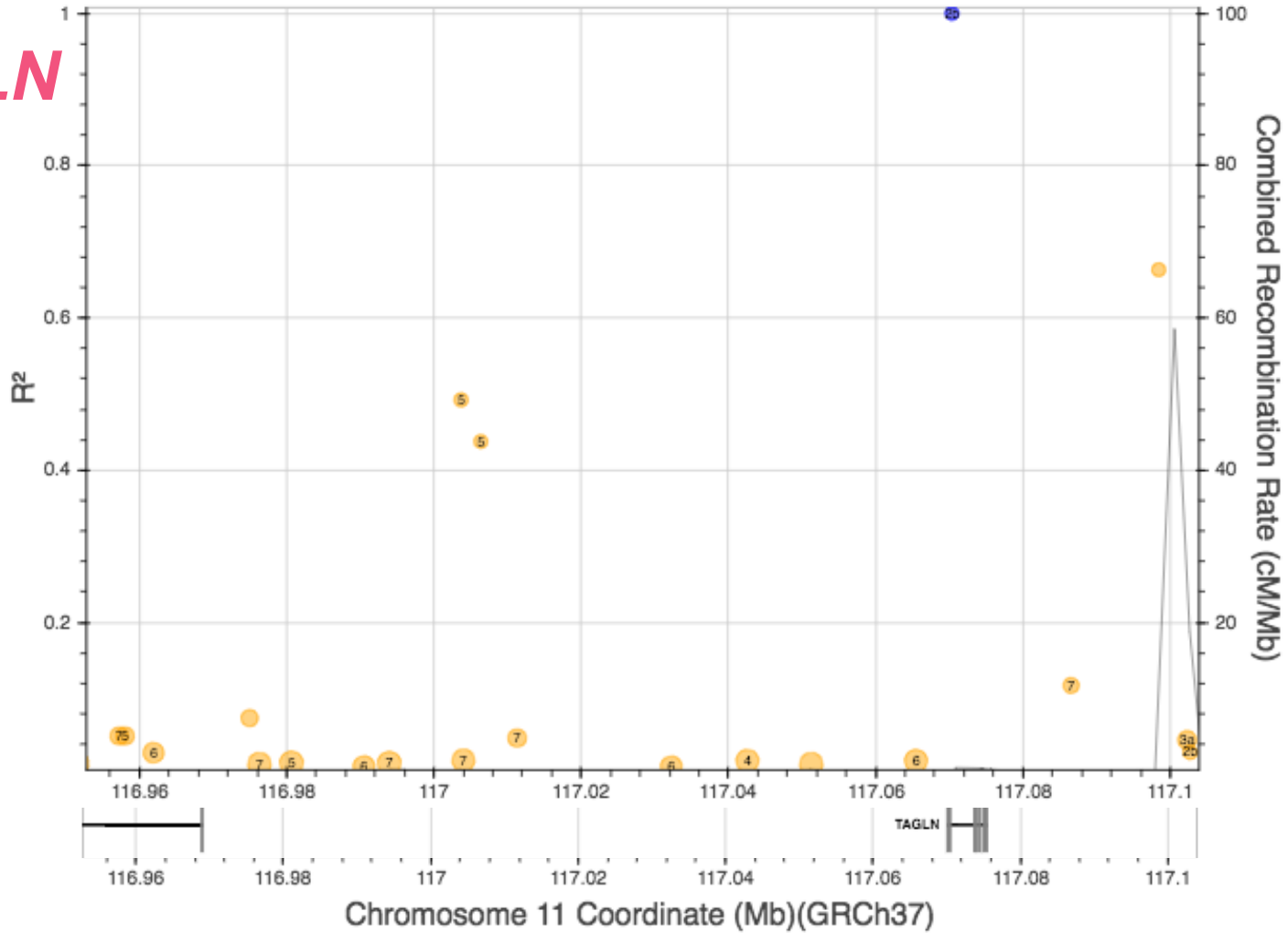

R²
Combined Recombination Rate (cM/Mb)
PROX1
214
214.05
214.1
214.15
214.2
Chromosome 1 Coordinate (Mb)(GRCh37)

Suggestive association: 11q23, rs74949440

	Radiation exposure to the breast ≥10 Gy	Radiation exposure to the breast <10 Gy
Cases / Controls	131 / 493	69 / 2144
Risk allele frequency, cases / controls	0.09 / 0.02	0.03 / 0.03
P_{MH}	5.84×10^{-8}	0.79
Multivariate Cox model, HR(95% CI)	2.59 (1.62-4.16)	1.19 (0.41-3.45)
P_{Cox}	8.40×10^{-8}	0.75
Gene x radiation interaction *P* value	0.06	

* Genotyping status: CCSS=imputed (0.906), SJLIFE=imputed (0.674)

TAGLN


R²
Combined Recombination Rate (cM/Mb)
1
0.8
0.6
0.4
0.2
100
80
60
40
20
116.96
116.98
117
117.02
117.04
117.06
117.08
117.1
TAGLN
Chromosome 11 Coordinate (Mb)(GRCh37)

Susceptibility to breast cancer after childhood cancer

- Hypothesis:

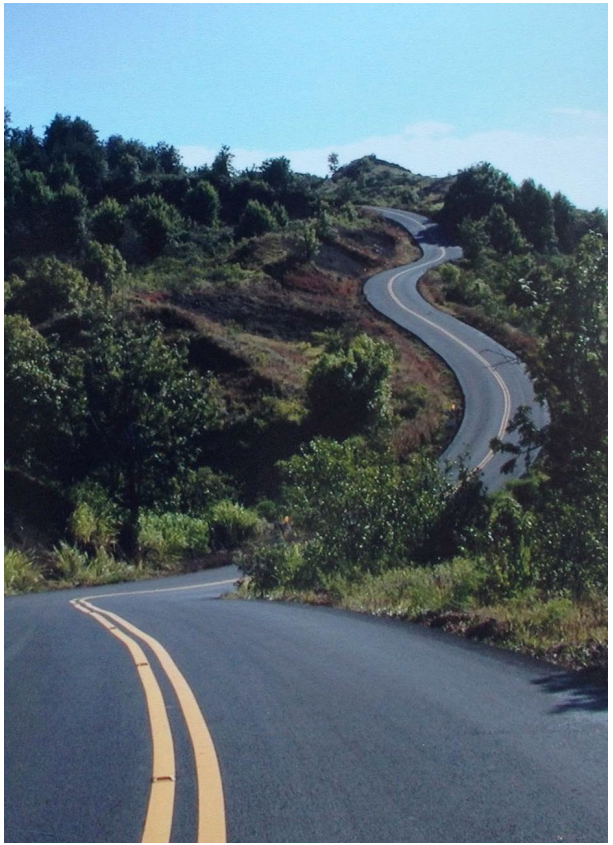
  germline variants → pro-proliferative, pro-invasive phenotype that supports the growth of malignant cells following transformation by ionizing radiation

- Conclusion:

  evidence that germline genetics outside high-risk syndromes could modify the effect of radiation exposure on breast cancer risk after childhood cancer

The road ahead

- Future potential
  - Screening recommendations
  - Front-line therapy decisions
- Discovery study → requires replication before clinical translation
  - Radiation exposure
  - Age at treatment
  - Breast cancer subtype
  - Functional studies



Napali coast, Kauai

CCSS GWAS – data resource

- Data deposited to dbGaP

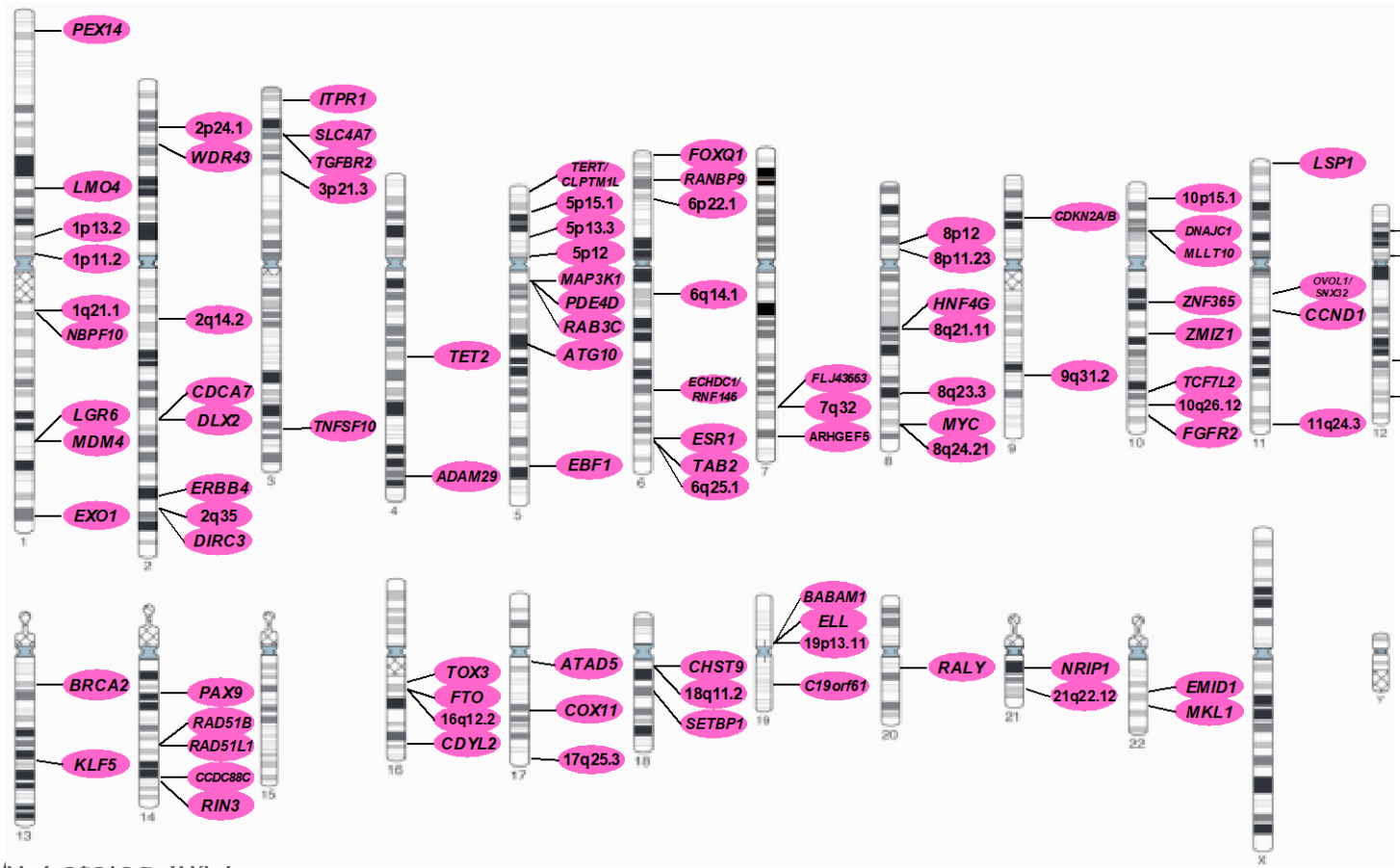
(database of genotypes and phenotypes)

- CCSS Request for Proposals

  (Genetics Working Group)
- Separate framework for proposals to replicate

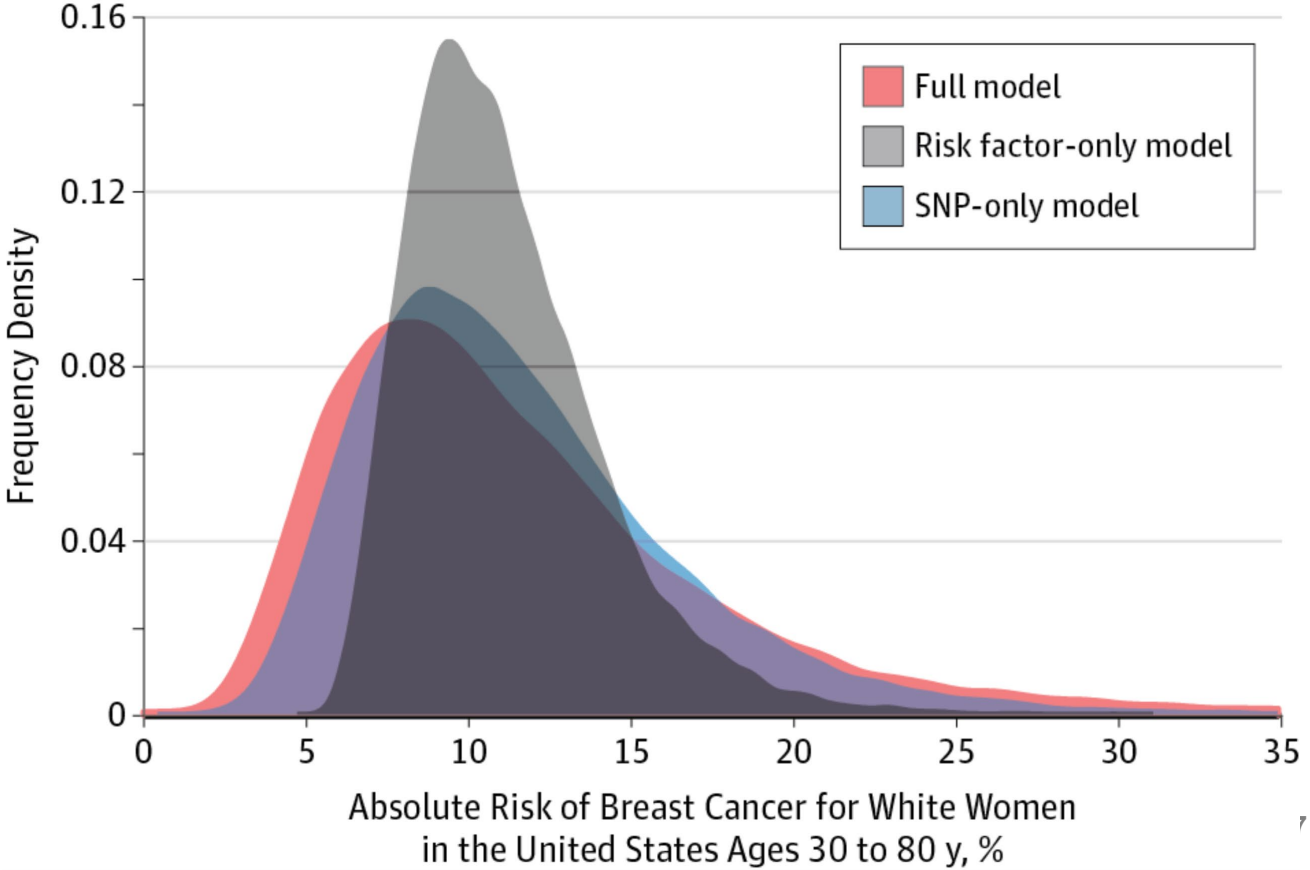
https://ccss.stjude.org/

Breast cancer in the general population



Breast cancer in the general population: polygenic risk score

- Each individual variant has small effect but combination of variants substantially improves risk stratification

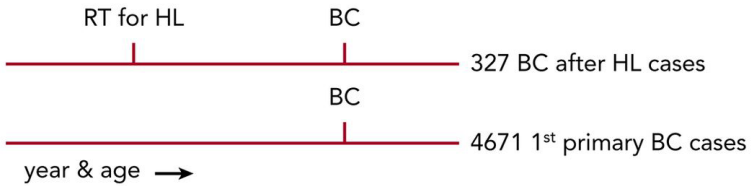


Maas et al. *JAMA Oncol* 2016

Breast cancer risk after Hodgkin lymphoma

1st step: Case-only study

– Test 194,106 SNPs for statistical interaction with RT among:



327 cases of breast cancer after HL vs. 4671 primary breast cancer cases

– Obtain IOR (Interaction Odds Ratio) per SNP

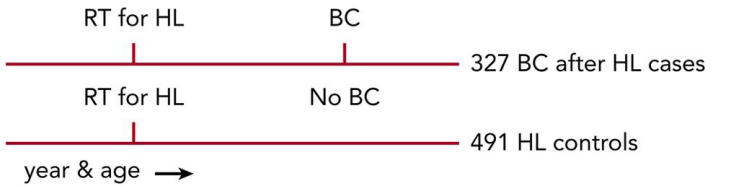
– Select most significant SNPs for validation in 2nd step

2nd step: Case-Control study

– Calculate Polygenic Risk Score (risk-weighted sum) of:

- SNPs significantly interacting with RT (RT-interaction-PRS)
- 77 SNPs associated with BC in general population* (BC-PRS)

– Test association of both PRSs with BC after HL among:

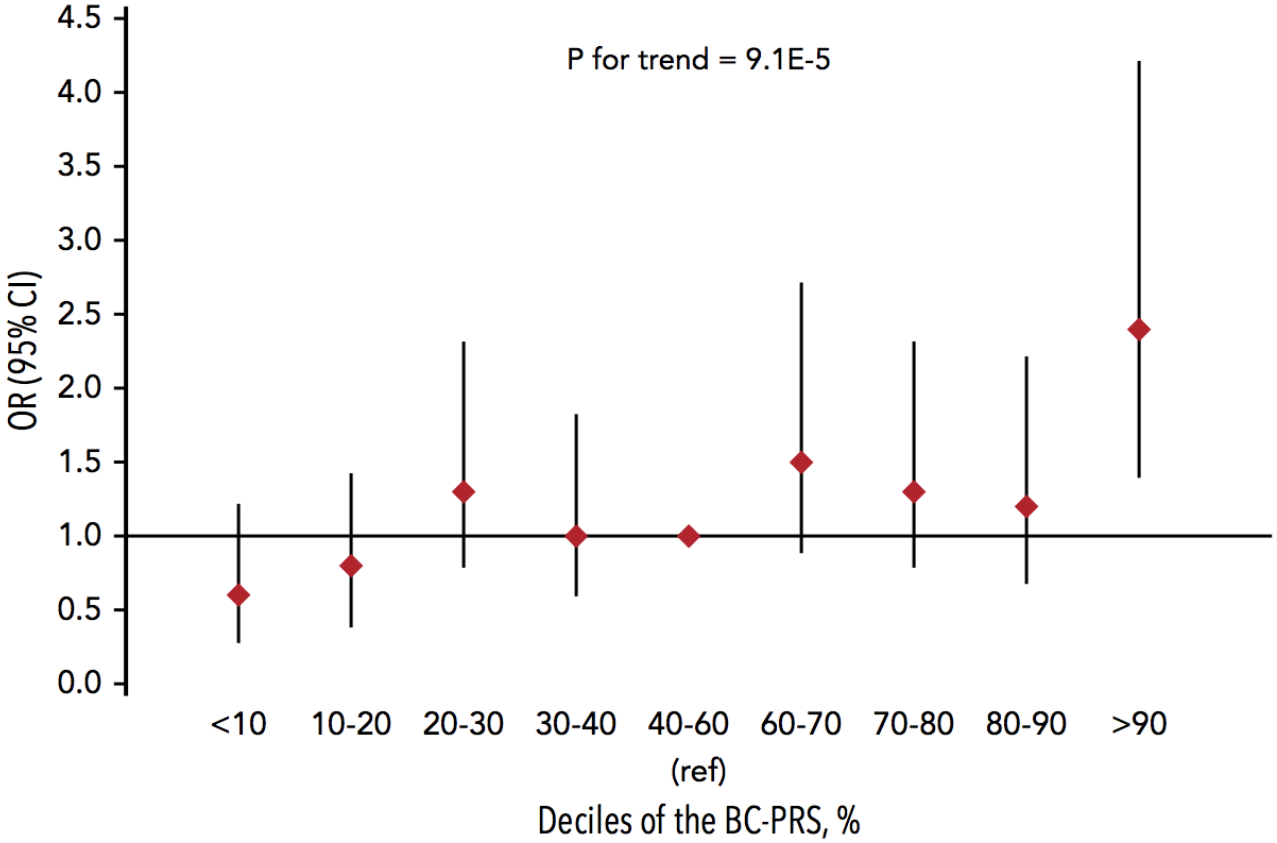


327 cases of breast cancer after HL vs. 491 HL cases (no breast cancer)

* Mavaddat et al JNCI 2015

Opstal-van Winden AWJ et al. *Blood* 2019

Breast cancer risk after Hodgkin lymphoma

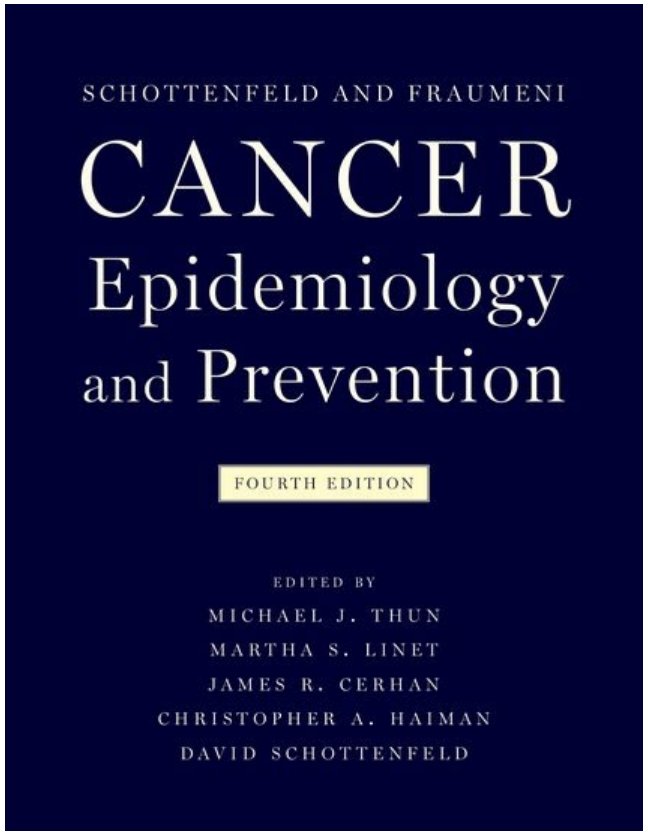


Opstal-van Winden AWJ et al. *Blood* 2019

Learning Objectives

- Understand the general principles of genetic association studies conducted to date for radiation-related cancers
  - Candidate SNP/gene versus agnostic approaches
  - Specific populations and outcomes
  - Different statistical approaches to incorporate radiation exposures
- Understand the current key challenges and opportunities in the field

Additional reference sources



Chapter 5: Genetic Epidemiology of Cancer

KL Penney, K Michailidou, DA Carere, C Zhang, B Pierce, S Lindstrom, P Kraft

Chapter 13: Ionizing Radiation

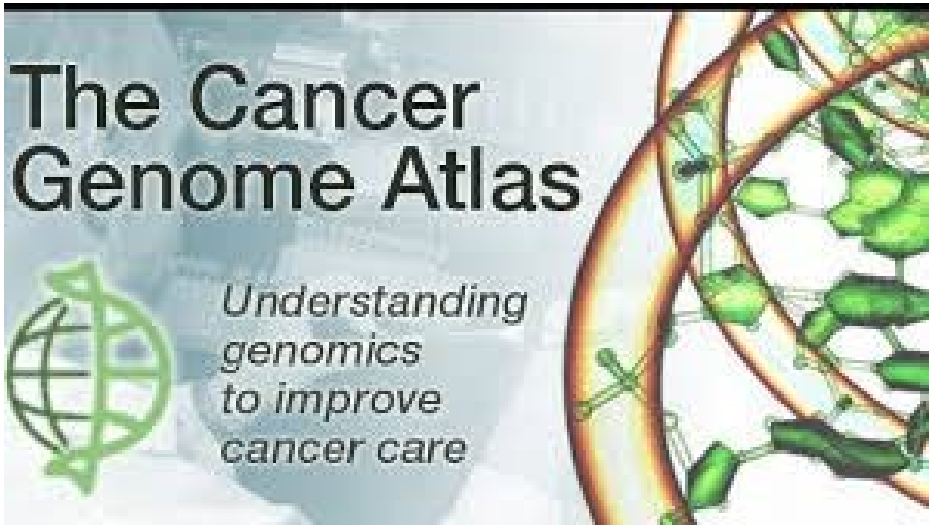
A Berrington de González, A Bouville, P Rajaraman, M Schubauer-Berigan

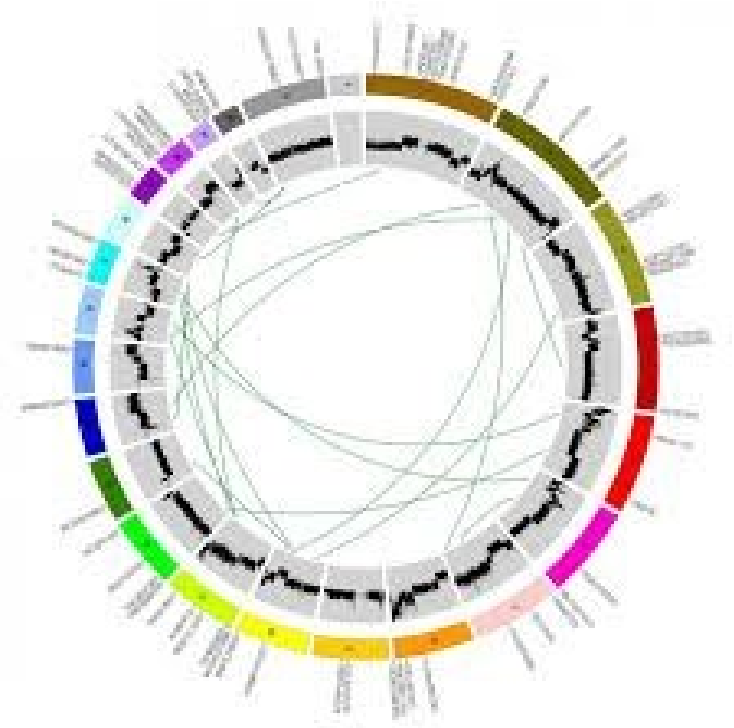
Chapter 60: Multiple Primary Cancers

LM Morton, SA Savage, S Bhatia

A final comment: somatic changes in tumors

- Can we use cancer genomics to profile tumors and identify a "signature" of radiation exposure?





…stay tuned!

Question #2: True or false?
Candidate SNP or gene approaches are the best way to discover important genetic variants associated with radiation-related cancer because we already know which genes to study.

A. True

B. False

Question #2: True or false?
Candidate SNP or gene approaches are the best way to discover important genetic variants associated with radiation-related cancer because we already know which genes to study.

A. True

B. False

Question #3: Which scenario has the most statistical power for identifying genetic variants associated with radiation-related cancer?

A. Smaller study population, moderate or high relative risks

B. Larger study population, small relative risks

C. Larger study population, moderate or high relative risks

D. Smaller study population, small relative risks

Question #3: Which scenario has the most statistical power for identifying genetic variants associated with radiation-related cancer?

A. Smaller study population, moderate or high relative risks

B. Larger study population, small relative risks

C. Larger study population, moderate or high relative risks

D. Smaller study population, small relative risks

U.S. Department of Health & Human Services

National Institutes of Health | National Cancer Institute

dceg.cancer.gov/

1-800-4-CANCER

Produced September 2019

(Recent) History of germline cancer genetics studies