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

Variation in radiation sensitivity

(a) Cell
(b) Tissue
(c) Individual

(d) Radiation dose response data obtained with a clonogenic assay can be fit using a linear quadratic equation:

\[ S = e^{-\alpha D - \beta D^2} \]

to derive parameters describing the initial (alpha in Gy\(^{-1}\)) and final (beta in Gy\(^{-2}\)) slopes of the curve.

(e) Lymphocyte radiosensitivity (SF2) with histogram of frequency distribution, \( n = 122 \).
### Genes involved in clinical radiation sensitivity syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia Telangiectasia</td>
<td>ATM</td>
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* Autosomal dominant inheritance.
Additional reference sources

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

Human Radiosensitivity
Report of the independent Advisory Group on Ionising Radiation
Ionizing radiation causes cancer

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

Invasive breast cancer cells. Fox C. National Cancer Institute
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
Key questions

- Which radiation exposure?
- Which study population?
- Which outcome?
- Which genetic variants?
Key questions (2)

- Which radiation exposure?
- Which study population?
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Key questions (3)

- Which radiation exposure?
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Key questions (5)

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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

Most common second cancers after hereditary RB

- Bone sarcoma: 35%
- Soft tissue sarcoma: 18%
- Melanoma: 12%
- Epithelial: 35%
Bone sarcoma risk after hereditary RB

In field:
Radiation + genetics
SIR = 2213

Out of field:
Genetics only
SIR = 169
Soft tissue sarcoma risk after hereditary RB

In field:
Radiation + genetics
SIR = 542

Out of field:
Genetics only
SIR = 46
**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
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* 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)

<table>
<thead>
<tr>
<th>Dose (Gy) before age 30 years</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;0-&lt;0.002</td>
<td>1.63 (0.96-2.77)</td>
</tr>
<tr>
<td>0.002-0.0065</td>
<td>1.78 (0.88-3.58)</td>
</tr>
<tr>
<td>0.0066-0.0173</td>
<td>1.75 (0.72-4.25)</td>
</tr>
<tr>
<td>≥0.0174</td>
<td>3.84 (1.67-8.79)</td>
</tr>
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</table>
## Contralateral breast cancer risk

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

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<th>Gene</th>
<th>Mutation status</th>
<th>Risk estimate (95%CI)</th>
</tr>
</thead>
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<tr>
<td>ATM</td>
<td></td>
<td>ERR/Gy</td>
</tr>
<tr>
<td></td>
<td>Non-carrier</td>
<td>0.0 (&lt;9-0.3)</td>
</tr>
<tr>
<td></td>
<td>Tolerated missense</td>
<td>0.8 (-0.1-3.6)</td>
</tr>
<tr>
<td></td>
<td>Deleterious</td>
<td>2.6 (0.0-10.6)</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td></td>
<td>OR ≥1 vs. &lt;1 Gy</td>
</tr>
<tr>
<td></td>
<td>Non-carrier</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td></td>
<td>Carrier</td>
<td>1.0 (0.4-2.8)</td>
</tr>
</tbody>
</table>
Genomics in childhood cancer cohorts

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

Childhood Cancer Survivor Study (CCSS)

St. Jude Lifetime Cohort (SJLIFE)
Survival and DNA participation bias in a cohort study

![Bar chart showing the number of childhood cancer survivors by time since diagnosis and DNA participation status.](chart_image)
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

![Graphs showing cumulative incidence of subsequent neoplasms with and without radiotherapy.](image)

- Radiotherapy
  - Cumulative Incidence (%)
  - Time Since Diagnosis (years)
  - No. at risk:
    - Mu+ 97 74 42 14 —
    - Mu- 1,533 1,198 622 173 12
  - $P = .24$

- No Radiotherapy
  - Cumulative Incidence (%)
  - Time Since Diagnosis (years)
  - No. at risk:
    - Mu+ 69 42 17 3 —
    - Mu- 1,230 838 335 40 —
  - $P < .001$
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
Key questions

- Which radiation exposure?
- Which study population?
- Which outcome?
- Which genetic variants?
Cumulative breast cancer risk

Hodgkin lymphoma chest RT
BRCA1 carrier
Other childhood cancer chest RT
BRCA2 carrier
SEER benchmark

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


Lancet Oncol 2013
## Study population

<table>
<thead>
<tr>
<th>Study population</th>
<th>Pooled</th>
<th>CCSS</th>
<th>SJLIFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female survivors of European descent with genotype data</td>
<td>N=3426</td>
<td>N=2739</td>
<td>N=687</td>
</tr>
<tr>
<td>→ Developed breast cancer</td>
<td>N=207</td>
<td>N=178</td>
<td>N=29</td>
</tr>
<tr>
<td>→ Did not develop any 2\textsuperscript{nd} cancers</td>
<td>N=2774</td>
<td>N=2200</td>
<td>N=574</td>
</tr>
<tr>
<td>Genotyping + imputation</td>
<td>16,958,466  SNPs &amp; InDels</td>
<td>Illumina 5M+Exome</td>
<td>Affymetrix 6.0</td>
</tr>
</tbody>
</table>
## Population characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Breast cancer (N=207)</th>
<th>No 2\textsuperscript{nd} cancer (N=2774)</th>
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<tbody>
<tr>
<td>First primary type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>65%</td>
<td>9%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td>Other</td>
<td>26%</td>
<td>56%</td>
</tr>
<tr>
<td>≥10 Gy radiation exposure to breast</td>
<td>63%</td>
<td>18%</td>
</tr>
<tr>
<td>Median age at childhood cancer</td>
<td>15.6 years</td>
<td>6.1 years</td>
</tr>
<tr>
<td>Median attained age</td>
<td>39.2 years</td>
<td>32.9 years</td>
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Multi-stage analysis approach

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

<table>
<thead>
<tr>
<th>Minor allele</th>
<th>Breast SN</th>
<th>No SN</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
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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

<table>
<thead>
<tr>
<th></th>
<th>Radiation exposure to the breast</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥10 Gy</td>
<td>&lt;10 Gy</td>
</tr>
<tr>
<td>Cases / Controls</td>
<td>131 / 493</td>
<td>69 / 2144</td>
</tr>
<tr>
<td>Risk allele frequency, cases / controls</td>
<td>0.66 / 0.46</td>
<td>0.52 / 0.51</td>
</tr>
<tr>
<td>$P_{MH}$</td>
<td>$7.09 \times 10^{-9}$</td>
<td>0.81</td>
</tr>
<tr>
<td>Multivariate Cox model, HR(95% CI)</td>
<td>1.92 (1.29-2.44)</td>
<td>1.04 (0.75-1.45)</td>
</tr>
<tr>
<td>$P_{Cox}$</td>
<td>$7.00 \times 10^{-9}$</td>
<td>0.81</td>
</tr>
<tr>
<td>Gene x radiation interaction $P$ value</td>
<td></td>
<td>0.006</td>
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* Genotyping status: CCSS=imputed (0.996), SJLIFE=genotyped
PROX1
## Suggestive association: 11q23, rs74949440

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<th>Cases / Controls</th>
<th>Risk allele frequency, cases / controls</th>
<th>$P_{\text{MH}}$</th>
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<td>$8.40 \times 10^{-8}$</td>
<td>0.06</td>
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<tr>
<td>$&lt; 10$ Gy</td>
<td>69 / 2144</td>
<td>0.03 / 0.03</td>
<td>0.79</td>
<td>1.19 (0.41-3.45)</td>
<td>0.75</td>
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* Genotyping status: CCSS=imputed (0.906), SJLIFE=imputed (0.674)
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
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
Breast cancer risk after Hodgkin lymphoma

1st step: Case-only study
- Test 194,106 SNPs for statistical interaction with RT among:
  - RT for HL
  - BC
  - 327 BC after HL cases
  - BC
  - 4671 1st primary BC 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:
  - RT for HL
  - BC
  - 327 BC after HL cases
  - RT for HL
  - No BC
  - 491 HL controls

* Mavaddat et al JNCI 2015

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

327 cases of breast cancer after HL vs. 491 HL cases (no breast cancer)
Breast cancer risk after Hodgkin lymphoma

\[ P \text{ for trend} = 9.1 \times 10^{-5} \]
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
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
(Recent) History of germline cancer genetics studies

**Common variants**
- Candidate SNPs (1-20 SNPs)
- Candidate gene (20-200)
- Candidate pathway (50-10,000)
- Genome-wide (150,000-4,000,000+)

1990

**Rare variants**
- Single genes
- Gene panels
- Whole exome
- Whole genome

2000

2010