Secondary Breast Cancer
A Paradigm for Survivorship Research

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Director, Duke Cancer Supportive Care and Survivorship Center
Second (subsequent) malignancies

- 1,685,210 new cases of cancer in the United States in 2016
- 20% of incident cases are a second or subsequent cancer (337,000 cases/yr)
- Etiologies:
  - Aging
  - Genetic factors
  - Lifestyle or unhealthy habits
  - Therapy-induced
  - Combination of any of the above
Radiation-Induced 2º Breast Cancer

- Historical perspective
- Estimating the magnitude of risk
- Identifying modifying factors
- Benefits and harms with different surveillance strategies
- Risk-reducing interventions
- Predicting (absolute) risk
- Future potential of precision-based care
Breast Cancer in Patients Irradiated for Hodgkin’s Disease: A Clinical and Pathologic Analysis of 45 Events in 37 Patients

By Joachim Yahalom, Jeanne A. Petrek, Paul W. Biddinger, Susan Kessler, D. David Dershaw, Beryl McCormick, Michael P. Osborne, David A. Kinne, and Paul Peter Rosen

Purpose: To characterize the clinical and pathologic features of patients who developed breast cancer (BC) after treatment for Hodgkin’s disease (HD). Recent epidemiologic studies have shown that women who are cured of HD have an increased risk of developing BC.

Patients and Methods: The clinical data, mammograms, and pathologic specimens of 37 women who developed 45 BCs (eight bilateral events), and had a prior history of treatment for HD were analyzed.

Results: The median age at diagnosis of HD was 27 years (range, 11 to 60). All patients received radiotherapy (RT) to the upper part of their body, and 10 also had chemotherapy for HD. The median interval from the treatment of HD to the diagnosis of BC was 15 years (range, 8 to 34). The median age at diagnosis of BC was 43 years (range, 27 to 75). 41% of patients were 39 years old or younger. Most mammograms (81%) showed abnormal findings of mass and/or microcalcifications. Of the eight patients (22%) with bilateral tumors, four were synchronous and four were metachronous. Involvement of the medial half of the breast occurred more frequently than in patients with primary BC (39% and 21%, respectively; P < .002). But, the histologic types, grades, presence of lymphocytic reaction, and lymphatic invasion were similar to those observed in 935 primary BC patients who were previously analyzed at our center. The 6-year actuarial relapse-free survival (RFS) for node-negative BC after HD was 85%. Node-positive patients had a significantly lower RFS of 53% (P = .002).

Conclusions: In comparison to patients with primary BC, patients who develop BC after HD are more likely to be younger, have bilateral disease, and have their tumors more frequently involve the medial half of the breast. Pathologic characteristics, nodal involvement, and prognosis are similar to those of primary BC. BC in women who were treated for HD is becoming an increasing problem, as more patients cured of HD reach a follow-up time of 10 to 15 years. Breast examination and mammography at an early age should be part of the follow-up program for women who are cured of HD.


Breast Cancer After Treatment of Hodgkin’s Disease

Steven L. Hancock, Margaret A. Tucker, Richard T. Hoppe*

Journal of the National Cancer Institute, Vol. 85, No. 1, January 6, 1993

Second Cancer After Hodgkin’s Disease—The Price of Success?

John D. Boice, Jr.*

Journal of the National Cancer Institute, Vol. 85, No. 1, January 6, 1993
32,591 HL patients in 16 population-based registries

<table>
<thead>
<tr>
<th>Age at HL</th>
<th>RR</th>
<th>AER</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 yrs</td>
<td>14.2</td>
<td>18.6</td>
</tr>
<tr>
<td>21-30</td>
<td>3.7</td>
<td>12.9</td>
</tr>
<tr>
<td>31-40</td>
<td>1.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>

• **Dose**: mantle > mediastinal/IFRT > whole lung, total body
• **Volume**: total body > whole lung > mantle > mediastinal
Participating Sites

Fred Hutchinson
Statistics and Data Center

Ohio State Univ.
Biopathology Center

Cincinnati Children's
Biorepository

Coordinating Center
St. Jude Children's Research Hospital

Original Contributing Clinical Centers

New Clinical Centers (Expansion Cohort)

Resource Centers

The Childhood Cancer Survivor Study
Breast cancer following chest radiation
Childhood Cancer Survivor Study

By age 50
BRCA-1 carrier 31%
Childhood cancer 30%
General population 4%

Breast cancer risk, dose and volume

Breast cancer by radiation field
Childhood Cancer Survivor Study

Standardized Incidence Ratios
Mantle 24.2 (20.7 - 28.3)
Whole lung 43.6 (27.1 - 70.2)
Mediastinal 13.0 (8.4 - 20.2)
Breast cancer risk decreases with concurrent radiation to the ovary

Childhood Cancer Survivor Study

Characteristics of Breast Cancer

- Median age is young
- Interval from radiation to breast cancer is often short (10-20 yrs)
- Upper outer quadrant (inner quadrant)
- Frequently bilateral
  - 26% bilateral: 12% synchronous, 14% asynchronous
  - 55% w/ bilateral mastectomy at time of 1st diagnosis
• 5-yr survival strongly associated with stage at diagnosis

• Limitations in therapy
  o Further radiation?
  o Anthracyclines (doxorubicin)

• Competing risks of morbidity and mortality
Mortality following breast cancer post RT

Childhood Cancer Survivor Study

Mortality following breast cancer post RT
Childhood Cancer Survivor Study

*SEER cohort matched 5:1 to CCSS by age at diagnosis, year of diagnosis and race/ethnicity
Mortality following breast cancer post RT
Childhood Cancer Survivor Study

*SEER cohort matched 5:1 to CCSS by age at diagnosis, year of diagnosis and race/ethnicity
Mortality following breast cancer post RT
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*SEER cohort matched 5:1 to CCSS by age at diagnosis, year of diagnosis and race/ethnicity

Unpublished data, 2018
SEER cohort matched 5:1 to CCSS by age at diagnosis, year of diagnosis and race/ethnicity

Unpublished data, 2018
1. Incidence and excess risk of breast cancer following chest radiation
2. Clinical characteristics and the outcomes following breast cancer
3. Harms and benefits associated with breast cancer surveillance
Annual mammogram and breast MRI
Starting at the age of 25 or 8 yrs after the RT
International Harmonization of Guidelines
Providers and women treated with chest radiation should be aware of breast cancer risk.

Breast cancer surveillance is recommended for women treated with > 20 Gy chest radiation.

Breast cancer surveillance is reasonable for women treated with 10-19 Gy chest radiation based on clinical judgment and considering additional risk factors.

Breast cancer surveillance may be reasonable for women treated with 1-9 Gy based on clinical judgment and considering additional risk factors.

Percent of women with a pattern of regular screening mammography following chest RT

Childhood Cancer Survivor Study

Breast MRI reported by < 3% of women

Oeffinger KC, et al. JAMA, 2009
EMPOWER Schema (R01CA134722)

CCSS At-Risk Women post RT
Ages 25-49 yrs
No history of breast cancer
No mammogram in past 2 yrs

Stepwise two-component intervention
- Mailed print information materials
- At 2 wks, telephone delivered brief motivational interview based on Transtheoretical Model (TTM)

Attention control
- Mailed information about heart health
- At 2 wks, telephone interview about general health

12-month measurements
1° outcome: completed screening mammogram (yes/no)
2° outcomes: modifying/mediating factors; screening breast MRI (yes/no) and barriers to completing an MRI; economic analysis (replicating costs of intervention, costs resulting from intervention)
Discuss getting screened for breast cancer with your health care provider.

Take this card to your doctor!

**MAMMOGRAM & BREAST MRI**

- Can detect breast cancer at an early stage.
- Early detection can increase survival rates from breast cancer.
- Should be a part of routine checkups!

**Your Screening Recommendations**
Because of your cancer therapy, the Children’s Oncology Group recommends that you have a yearly screening mammogram and breast MRI.

**When Screening Should Begin**
For you, screening should begin when you are 25 years of age or 8 years after completion of radiation therapy, whichever occurs last.

**Mammography & breast MRI**
 can detect breast cancer in women, including those that are premenopausal. Women treated for pediatric or young adult cancer with chest radiation have an elevated risk of breast cancer at a young age.

**Note to Physician**
Given the high risk status of your patient, many third party insurers as well as Medicaid/Medicare will provide coverage for mammography AND breast MRI.
Proportion of women completing screening with relative risk (strata adjusted)* and 95% CI

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>19.6%</td>
<td>39.8%</td>
<td>2.0 (1.2-3.5, p&lt;0.01)</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>15.0%</td>
<td>19.4%</td>
<td>1.3 (0.6-2.6, p=0.48)</td>
</tr>
</tbody>
</table>

*Adjusted for age at study and race/ethnicity

Oeffinger KC, et al. ASCO, 2016
Key Barriers

Percent of women who reported barrier to having imaging study as ‘quite a bit’ or ‘extremely’ important

- Haven't had problems
- Doctor didn't order it
- Cost
- Put it off

Percent

0 10 20 30 40

Mammogram
MRI

Put it off
Cost
Doctor didn't order it
Haven't had problems
Key Barriers

Percent of women who reported barrier to having imaging study as ‘quite a bit’ or ‘extremely’ important

- Haven't had problems
- Doctor didn't order it

87% of women in the Intervention Group who did not have a breast MRI reported that their primary physician did NOT recommend the test.
Post-Study Pilot

• Cost was one of the primary barriers to MRI
• Partnered with Right Action for Women / Christina Applegate Foundation and Diagnostic Works to offer free breast MRIs for EMPOWER participants
• Required a copy of last year’s tax return
Conclusions

• Intervention with mailed print materials and brief motivational telephone interview:
  – Near doubling of mammogram rate ($1^\circ$ outcome)
  – Minimal effect on breast MRI rate ($2^\circ$ outcome)

• Intervention might be more efficacious for younger women

• Key barriers to completing a breast MRI in the intervention group:
  – doctor didn’t order it
  – put it off
  – cost
EMPOWER-II

- Boosting **breast MRI** screening rates
  - Use of 2-way smartphone technology for patient activation
  - Primary care physician practice activation

<table>
<thead>
<tr>
<th>291 women in CCSS</th>
<th>C</th>
<th>PA</th>
<th>PA+PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>X</td>
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<td></td>
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<tr>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **C** EMPOWER-I materials
- **PA** Patient activation
- **PA+PCP** Patient activation plus primary care activation

**Intervention**
- targeted print materials
- text messages, video vignettes, CCSSapp / SCP
- mail/fax information and screening recommendation

R01CA134722-06
Start date: April 1, 2018
Predicting Risk
Chaya Moskowitz, PhD
R01CA136783
Potential Risk Factors

<table>
<thead>
<tr>
<th>Treatment-related factors</th>
<th>Gail model predictors</th>
<th>Other potential risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RT dose/volume, chest</td>
<td>• Age</td>
<td>• Age at menopause</td>
</tr>
<tr>
<td>• RT dose fractionation</td>
<td>• Age at menarche</td>
<td>• Years of intact ovarian function after radiation</td>
</tr>
<tr>
<td>• RT, pelvis or abdomen</td>
<td>• Age at first live-birth</td>
<td>• Oral contraceptive/ HRT</td>
</tr>
<tr>
<td>• Alkylating agent</td>
<td>• # of first degree relatives with breast ca</td>
<td>• BMI at breast cancer diagnosis</td>
</tr>
<tr>
<td>• Age at exposure</td>
<td>• # previous breast bx</td>
<td></td>
</tr>
<tr>
<td>• Interval from primary cancer diagnosis</td>
<td>• Biopsy with atypical hyperplasia</td>
<td></td>
</tr>
<tr>
<td>• Primary cancer diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aim 1: Build Breast Cancer Risk Prediction Model

Original CCSS Cohort (N=1677; DX 1970-1986)
- Treatment-related and other factors (complete)
- Traditional risk factors (N=765)

Aim 2: External Model Validation

Dutch LATER Cohort (N=600; DX 1970-1999)
- Treatment-related and other factors (complete)
- Traditional risk factors (N=250)

Expanded CCSS Cohort (N=1225; DX 1987-1999)
- Treatment-related and other factors (in process)
- Traditional risk factors (in process)

Aim 3: Develop Breast Cancer Risk Calculator

Research Team
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Lois Travis, MD, ScD
Michael Kattan, PhD
Robert Smith, PhD
Breast Cancer Risk Prediction Model

Timing of chest radiation relative to menarche
- No menarche
- 3+ yrs before menarche
- 1-3 yrs before menarche
- +/- 1 yr of menarche
- 1-2 yrs after menarche
- 2-3 yrs after menarche
- 3+ yrs after menarche

Any chest radiation within 1 year of menarche
- No
- Yes

Years of ovarian function after chest radiation
- Less than 10
- 10+
Estrogen Replacement Post Radiation

### Table 3. Risk of breast cancer among women \((n = 259)\) who experienced menopause by oestrogen + progestin hormone therapy \((E + P)\)

<table>
<thead>
<tr>
<th></th>
<th>All breast cancers</th>
<th>ER + breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of breast cancers</td>
<td>HR</td>
</tr>
<tr>
<td>Total women</td>
<td>All (n = 38)</td>
<td></td>
</tr>
<tr>
<td>E + P</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; ER = oestrogen receptor; HR = hazard ratio; Ref = reference. Analysis uses age as the time scale split into 1-year intervals and is adjusted for chest radiation field and delivered dose, age at primary childhood cancer diagnosis, exposure to anthracyclines, and age at menopause. The HR quantifies the risk of breast cancer after menopause or age 20 years, whichever comes later.

### Table 4. Risk of breast cancer by menopausal status and oestrogen + progestin hormone therapy \((E + P)\)

<table>
<thead>
<tr>
<th></th>
<th>No. of breast cancers</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstruating, no E + P</td>
<td>52</td>
<td>Ref</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Menstruating, E + P</td>
<td>33</td>
<td>0.90</td>
<td>(0.57, 1.42)</td>
<td>0.653</td>
</tr>
<tr>
<td>Postmenopausal, no postmenopausal E + P</td>
<td>2</td>
<td>0.30</td>
<td>(0.07, 1.26)</td>
<td>0.101</td>
</tr>
<tr>
<td>Age at menopause &lt;20 years</td>
<td>7</td>
<td>0.61</td>
<td>(0.27, 1.37)</td>
<td>0.233</td>
</tr>
<tr>
<td>Age at menopause 20–39 years</td>
<td>8</td>
<td>0.56</td>
<td>(0.23, 1.39)</td>
<td>0.214</td>
</tr>
<tr>
<td>Age at menopause 40 + years</td>
<td>8</td>
<td>0.66</td>
<td>(0.31, 1.42)</td>
<td>0.287</td>
</tr>
<tr>
<td>Postmenopausal, postmenopausal E + P</td>
<td>11</td>
<td>0.47</td>
<td>(0.23, 0.94)</td>
<td>0.033</td>
</tr>
<tr>
<td>Age at menopause &lt;20 years</td>
<td>8</td>
<td>0.66</td>
<td>(0.31, 1.42)</td>
<td>0.287</td>
</tr>
<tr>
<td>Age at menopause 20–39 years</td>
<td>3</td>
<td>0.84</td>
<td>(0.25, 2.85)</td>
<td>0.778</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference. Analysis uses age as the time scale split into 1-year intervals and is adjusted for chest radiation field and delivered dose, age at primary childhood cancer diagnosis, and exposure to anthracyclines.
Breast Cancer Risk Prediction Model

![Graphs showing AUC over age]

Age, years

AUC
Precision-Based Approach

• Gene-Radiation interaction
• Micro (cellular) vs macro (stromal) environment
Gene-Radiation Interaction

Identified two variants at chromosome 6q21 associated with radiation-induced SMN in Hodgkin lymphoma survivors


Identified a genetic profile for breast cancer following Hodgkin lymphoma

# Genome-Wide Association Study to Identify Susceptibility Loci That Modify Radiation-Related Risk for Breast Cancer After Childhood Cancer

**Characteristics of breast cancer cases (N=207)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>First primary childhood cancer</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>65%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>26%</td>
</tr>
<tr>
<td>Radiation exposure to the breast, ≥10 gray</td>
<td>63%</td>
</tr>
<tr>
<td>Median age at breast cancer diagnosis</td>
<td>39 years</td>
</tr>
</tbody>
</table>
## Top SNP associations

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Radiation exposure to the breast</th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q41</td>
<td>≥10 Gy</td>
<td>1.92</td>
<td>7.09 x 10^{-9}</td>
</tr>
<tr>
<td>11q23</td>
<td>&lt;10 Gy</td>
<td>1.04</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Genome-Wide Association Study to Identify Susceptibility Loci That Modify Radiation-Related Risk for Breast Cancer After Childhood Cancer

What are these SNPs?

- Chromosome 1 marker: *PROX1* (prospero homeobox 1)
  - Involved in embryonic development, cellular proliferation, and migration
  - Alterations present in breast tumor cells

- Chromosome 11 marker: *TAGLN* (transgelin)
  - Involved in cellular migration
  - Overexpressed in breast tumor cells

• 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
Using a large clinical repository of CT images to evaluate longitudinal breast density changes.
And changes within and outside of the radiation field
Precision-Based Approach

- Gene-Radiation interaction
- Micro (cellular) vs macro (stromal) environment
- cfDNA in survivors at high risk of SMNs
  - Stratify screening
  - Prevention / interception
Questions for Discussion

• How do we quantify harm?
• Can absolute risk be used to counsel regarding screening?
• Prevention?
• What can be generalized to other populations at high risk of a secondary breast cancer?
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Nassim Anderson, MA
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