New insights into the risk of breast cancer in childhood cancer survivors treated with chest radiation:

A report from the Childhood Cancer Survivor Study and the Women’s Environmental Cancer and Radiation Epidemiology Study

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Breast cancer occurs in excess following radiotherapy given to young girls treated for cancer.

Observed breast cancer risk beginning 8 years after exposure.

Estimates of breast cancer risk:
- SIRs range from 13.3 to 55.5
- AERs range from 18.6 to 79.0 per 10,000 person years
- Cumulative incidence estimates by age 40-45 years range from 13% to 20%

### Chest Radiation Fields for Specific Cancers

<table>
<thead>
<tr>
<th>Field</th>
<th>Dose, Gy</th>
<th>Primary Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantle</td>
<td>25-56 Gy</td>
<td>HL</td>
</tr>
<tr>
<td>Mediastinal/IFRT</td>
<td>15-40 Gy</td>
<td>HL, NHL, NB</td>
</tr>
<tr>
<td>Whole Lung</td>
<td>10-17 Gy</td>
<td>Wilms, STS, bone</td>
</tr>
<tr>
<td>Total body</td>
<td>10-15 Gy</td>
<td>ALL, AML, other</td>
</tr>
</tbody>
</table>

*IFRT = Involved field radiation therapy

- **Dose:** mantle > mediastinal/IFRT > whole lung, total body
- **Volume:** total body > whole lung > mantle > mediastinal/IFRT
Surveillance Recommendations

Children’s Oncology Group

• Mammogram and breast MRI annually
• Starting at age 25 or 8 years after radiation therapy
• Women treated with ≥ 20 Gy
Purpose

• Estimate breast cancer risk in childhood cancer survivors treated with chest radiation

• Contrast risk of breast cancer among childhood cancer survivors to that of a known high risk population
  – Carriers of a $BRCA1$ or $BRCA2$ mutation

• Evaluate subpopulations of childhood cancer survivors
Childhood Cancer Survivor Study

- NIH-supported U24 CA 55727 (PI: Robison)
- 26 institution North American cohort study of long term survivors of childhood cancer
- Participants diagnosed with cancer before age 21 during 1970-1986
- Survived at least 5 years after diagnosis
- 1286 females treated with chest radiation
Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study

• NIH-supported U01 CA83178, R01 CA097397, R01 CA129639 (PI: Bernstein)

• Population-based nested case-control study
  – 5 population-based registries in the US and Denmark

• Participants were women who:
  – Were diagnosed with primary breast cancer 1985-2000
  – Survived at least 1 year after diagnosis

• For our analysis:
  – Probands are WECARE Study participants with unilateral breast cancer
    • 1397 probands
    • BRCA1 and BRCA2 status ascertained
  – Analyze female first-degree relatives of probands
    • N = 4570
    • With breast cancer, N = 324
      – Median age at diagnosis = 55 years, range (26-90)
  – Analysis from Begg CB, et al., JAMA 2008;299(2):194-201
• Childhood cancer survivors
  – Cumulative incidence estimated non-parametrically
  – Competing risk of death
Methods

- **Childhood cancer survivors**
  - Cumulative incidence estimated non-parametrically
  - Competing risk of death
  - Standardized incidence ratios (SIRs) estimated using age-, sex-, and calendar-year-specific incidence rates from the general US population
Methods

• **Childhood cancer survivors**
  – Cumulative incidence estimated non-parametrically
  – Competing risk of death
  – Standardized incidence ratios (SIRs) estimated using age-, sex-, and calendar-year-specific incidence rates from the general US population

• **BRCA1** and **BRCA2** mutation carriers
  – Cumulative incidence estimated using kin-cohort method
Methods

• **Childhood cancer survivors**
  – Cumulative incidence estimated non-parametrically
  – Competing risk of death
  – Standardized incidence ratios (SIRs) estimated using age-, sex-, and calendar-year-specific incidence rates from the general US population

• **BRCA1 and BRCA2 mutation carriers**
  – Cumulative incidence estimated using kin-cohort method

• **US population**
  – From Surveillance, Epidemiology, and End Results (SEER) Program
  – Population incidence estimated using age-specific rates
  – Weighted to account for the calendar year in which members of the CCSS cohort were at risk
Childhood Cancer Survivor Study

Childhood Cancer Diagnoses (N=1286)

- Hodgkin lymphoma: 53%
- Wilms tumor: 11%
- Neuroblastoma: 7%
- NHL: 8%
- CNS cancer: 1%
- Leukemia: 9%
- Soft tissue sarcoma: 5%
- Bone cancer: 6%

Childhood Cancer Survivor Study
Childhood Cancer Diagnoses (N=1286)
# Childhood Cancer Survivor Study: Women with Breast Cancer

- Median duration follow-up of 26 years, range (5-39)
- 176 women with breast cancer

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at childhood cancer diagnosis in years, median (range)</td>
<td>16</td>
<td>(3-20)</td>
</tr>
<tr>
<td>Childhood cancer diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>147</td>
<td>(84%)</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>(16%)</td>
</tr>
<tr>
<td>Age at breast cancer diagnosis in years, median (range)</td>
<td>38</td>
<td>(24-53)</td>
</tr>
<tr>
<td>Latency period in years, median (range)</td>
<td>23</td>
<td>(7-38)</td>
</tr>
<tr>
<td>Vital status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>124</td>
<td>(70%)</td>
</tr>
<tr>
<td>Deceased</td>
<td>52</td>
<td>(30%)</td>
</tr>
</tbody>
</table>
## Breast Cancer Risk

### Childhood Cancer Survivor Study

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest irradiated cohort</td>
<td>1286</td>
<td>176</td>
<td>8.7</td>
<td>20.8</td>
<td>(17.7, 23.5)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>682</td>
<td>147</td>
<td>6.7</td>
<td>21.9</td>
<td>(18.7, 25.8)</td>
</tr>
<tr>
<td>Other childhood cancer</td>
<td>604</td>
<td>29</td>
<td>2.0</td>
<td>14.6</td>
<td>(10.2, 21.0)</td>
</tr>
</tbody>
</table>
Childhood Cancer Survivor Study

Breast Cancer Risk

By age 40: 10%
By age 50: 24%
Breast Cancer Risk

Childhood Cancer Survivor Study and WECARE Study

By age 40

Hodgkin lymphoma (HL): 14%
Other: 7%

Breast Cancer Risk

Age, years

Cumulative Incidence

0 5 10 15 20 25 30 35 40 45 50 55 60

Hodgkin lymphoma (HL)
Other childhood cancer
Childhood Cancer Survivor Study and WECARE Study

Breast Cancer Risk

By age 50
HL: 30%

Hodgkin lymphoma (HL)
Other childhood cancer
Childhood Cancer Survivor Study and WECARE Study

Breast Cancer Risk

By age 50
Hodgkin lymphoma (HL): 30%
SEER: 4%

Hodgkin lymphoma (HL)  
Other childhood cancer
SEER Benchmark
Childhood Cancer Survivor Study and WECARE Study
Breast Cancer Risk

By age 50
HL: 30%
SEER: 4%
BRCA1: 31%

Hodgkin lymphoma (HL)
BRCA1 Carrier*
Other childhood cancer
SEER Benchmark

* Population-based estimate
Childhood Cancer Survivor Study and WECARE Study

Breast Cancer Risk

By age 50
- HL: 30%
- SEER: 4%
- BRCA1: 31%
- BRCA2: 10%

Hodgkin lymphoma (HL)
BRCA1 Carrier*
BRCA2 Carrier*
Other childhood cancer

* Population-based estimate
Childhood Cancer Survivor Study: Risk of Breast Cancer

By Radiation Dose from Treatment Summary

<table>
<thead>
<tr>
<th>Radiation dose</th>
<th>N</th>
<th>Breast cancer</th>
<th></th>
<th></th>
<th>SIR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19 Gy</td>
<td>194</td>
<td>12</td>
<td>0.5</td>
<td>22.7</td>
<td>(12.9, 40.0)</td>
<td></td>
</tr>
<tr>
<td>20+ Gy</td>
<td>944</td>
<td>161</td>
<td>7.7</td>
<td>21.0</td>
<td>(18.0, 24.5)</td>
<td></td>
</tr>
</tbody>
</table>

Radiation dose: N is the number of individuals treated. Breast cancer: SIR is the standardized incidence ratio, with (95% CI) indicating the 95% confidence interval.
Childhood Cancer Survivor Study: Risk of Breast Cancer
By Radiation Field

• Other = mediastinal/IFRT and hemithorax fields
Childhood Cancer Survivor Study: Risk of Breast Cancer

By Radiation Field

<table>
<thead>
<tr>
<th>Field</th>
<th>N</th>
<th>Radiation dose, Gy</th>
<th>Breast cancer</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>Mantle</td>
<td>594</td>
<td>39.6</td>
<td>7.5-54.5</td>
<td>138</td>
</tr>
<tr>
<td>Whole lung</td>
<td>124</td>
<td>14.2</td>
<td>2.0-20.0</td>
<td>15</td>
</tr>
<tr>
<td>Other*</td>
<td>283</td>
<td>30.0</td>
<td>3.0-65.0</td>
<td>18</td>
</tr>
</tbody>
</table>

*Other = mediastinal/IFRT and hemithorax fields
Childhood Cancer Survivor Study: Risk of Breast Cancer

Other Exposures to Chest Radiation

- Other chest fields

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>N</th>
<th>Radiation dose, Gy</th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body irradiation</td>
<td>110</td>
<td>12.0</td>
<td>2</td>
</tr>
<tr>
<td>High abdominal radiation only</td>
<td>74</td>
<td>20.0</td>
<td>1</td>
</tr>
<tr>
<td>Posterior spinal / paravertebral / posterior chest</td>
<td>58</td>
<td>30.6</td>
<td>1</td>
</tr>
</tbody>
</table>

- Multiple fields
  - 37% treated with 2 or more fields
  - No evidence of associated increased risk of breast cancer
Conclusions

- Women treated for Hodgkin’s lymphoma with mantle radiation
  → Risk of breast cancer comparable to carriers of a \textit{BRCA1} mutation

- Survivors of other childhood cancer treated with chest radiation
  → Risk of breast cancer comparable to carriers of a \textit{BRCA2} mutation

- Whole lung radiation associated with a higher risk of breast cancer than previously recognized
  → May warrant screening
The Childhood Cancer Survivor Study is an NCI-funded resource (U24 CA55727) to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.

Investigators interested in potential uses of this resource are encouraged to visit: http://ccss.stjude.org
Childhood Cancer Survivor Study: Risk of Breast Cancer

Mantle Field Radiation

Cumulative Incidence

Age, years

< 30 Gy
30-40 Gy
40 Gy

Childhood Cancer Survivor Study: Risk of Breast Cancer

Mantle Field Radiation
• 37% of participants treated with more than 1 field of radiation
  – Range 1-6 fields
  – Average 1.4 fields of radiation per patient

• 79 women with BC

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<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>463</td>
<td>79</td>
</tr>
<tr>
<td><strong>Second field</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High abdominal</td>
<td>372 (80%)</td>
<td>69 (87%)</td>
</tr>
<tr>
<td>Mediastinal/IFRT, hemithorax</td>
<td>64 (14%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td><strong>Primary diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>335 (72%)</td>
<td>73 (92%)</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>70 (15%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>58 (13%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>
# Childhood Cancer Survivor Study: Risk of Breast Cancer

## Additional Radiation with High Abdominal Field

<table>
<thead>
<tr>
<th>Field</th>
<th>N</th>
<th>Breast cancers</th>
<th>SIR (95% CI)</th>
<th>AER/10,000 pyrs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td></td>
</tr>
<tr>
<td>Chest only</td>
<td>556</td>
<td>93</td>
<td>4.3</td>
<td>21.5 (17.5, 26.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79.3 (62.4, 96.2)</td>
</tr>
<tr>
<td>Chest + abdominal</td>
<td>358</td>
<td>69</td>
<td>3.1</td>
<td>22.9 (18.1, 29.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93.6 (70.5, 116.6)</td>
</tr>
</tbody>
</table>

*Excluding posterior spinal, TBI, and abdominal fields, and including only those people treated with 1 field.