Long-term Effects of Radiation Exposure Among Adult Survivors of Childhood Cancer

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Survivorship Statistics*

- In 2005, estimated 328,600 childhood cancer survivors in the U.S.
- 1 in 900 is a survivor of childhood cancer
- 1 in 680 is a childhood cancer survivor (ages 20 to 50 years)

* Source: NCI Office of Cancer Survivorship, Mariotto et al, CEBP, 2009
## Childhood Cancer Survivors in US*

Jan. 2005 for cases diagnosed 0-19 years of age

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>328,652</td>
</tr>
<tr>
<td>ALL</td>
<td>49,271</td>
</tr>
<tr>
<td>AML</td>
<td>6,355</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>31,598</td>
</tr>
<tr>
<td>NHL</td>
<td>18,668</td>
</tr>
<tr>
<td>CNS</td>
<td>51,650</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>16,141</td>
</tr>
<tr>
<td>Renal</td>
<td>20,411</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>8,145</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>3,947</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>27,544</td>
</tr>
</tbody>
</table>

* Source: NCI Office of Cancer Survivorship, Mariotto et al, CEBP, 2009
## Selected Health-Related Outcomes of Childhood Cancer Survivors

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Neurocognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic</td>
<td>Ophthalmologic</td>
</tr>
<tr>
<td>Dental</td>
<td>Orthopedic</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Psychosocial</td>
</tr>
<tr>
<td>Educational</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Renal</td>
</tr>
<tr>
<td>Hearing</td>
<td>Reproduction</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Second Cancers</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Skeletal</td>
</tr>
</tbody>
</table>
Issues in Survivorship Research

Late Effect Risk

Host Factors
- Age
- Gender
- Race

Genetic
- BRCA, ATM, p53 polymorphisms

Tumor Factors
- Histology
- Site
- Biology
- Response

Health Behaviors
- Tobacco
- Diet
- Alcohol
- Exercise
- Sun

Premorbid conditions

Aging

Treatment Events

Treatment Factors
- Surgery
- Chemotherapy
- Radiation therapy

M. Hudson, Cancer, 2005
Assessment of Risk for Late Effects

GENETICS

SURGERY

CHEMOTHERAPY

RADIATION
Childhood Cancer Survivor Study (U24 CA 55727)

Participating Centers

Coordinating Center
Contributing Institutions
Resource Center
Childhood Cancer Survivor Study (U24 CA55727)

- Funded in 1994
- Retrospective Cohort, diagnosed 1970-1986
- 26 Contributing Centers
- 5-Year Survival (median age=23yrs, range 5-45)
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Detailed Treatment Data, Wide Range of Outcomes
- 100+ Publications since 2001

<table>
<thead>
<tr>
<th>Eligible</th>
<th>20,720</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost (n=3017)</td>
<td>17,703</td>
</tr>
<tr>
<td>Contacted Refusal (n=3189)</td>
<td>14,372</td>
</tr>
<tr>
<td>Participants</td>
<td>5796</td>
</tr>
<tr>
<td>Stored DNA</td>
<td>5796</td>
</tr>
<tr>
<td>Cohort Expansion: 1987-1999 n=20,729</td>
<td></td>
</tr>
</tbody>
</table>
Role of Radiation Exposure Among Selected Outcomes

- Knowledge of RT Exposure
- Health Status
- Late Mortality
- Second Neoplasms
- Obesity
- Pulmonary Function
- Thyroid Function
- Chronic Health Conditions
Adult Survivors’ Knowledge of the Cancer Diagnosis and Radiation Therapy Exposure

- Survivors generally knew the type of cancer they had.
- 89% accurately recalled whether they were treated with RT.
- 10% of those not exposed thought they were.
- >10% of Wilms, ALL, and Neuroblastoma did not know if they had been treated with RT.

Kadan-Lottick, et al, JAMA, 2002
## Health Status Among 5+ Year Survivors

<table>
<thead>
<tr>
<th>Health Domain</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>10.6%</td>
</tr>
<tr>
<td>Functional status</td>
<td>11.8%</td>
</tr>
<tr>
<td>Activity limitation</td>
<td>13.4%</td>
</tr>
<tr>
<td>Mental health</td>
<td>12.6%</td>
</tr>
<tr>
<td>Pain</td>
<td>10.2%</td>
</tr>
<tr>
<td>Anxiety/fears</td>
<td>13.2%</td>
</tr>
<tr>
<td><strong>Any health domain</strong></td>
<td><strong>41.3%</strong></td>
</tr>
</tbody>
</table>

Hudson et al, JAMA, 2004
<table>
<thead>
<tr>
<th>Health Domain</th>
<th>Survivors</th>
<th>RT-Exposed Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>10.6%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Functional status</td>
<td>11.8%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Activity limitation</td>
<td>13.4%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Mental health</td>
<td>12.6%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Pain</td>
<td>10.2%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Anxiety/fears</td>
<td>13.2%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Any health domain</td>
<td>41.3%</td>
<td>44.0%</td>
</tr>
</tbody>
</table>

*Hudson et al, JAMA, 2004*
<table>
<thead>
<tr>
<th>Health Domain</th>
<th>Head Brain</th>
<th>Chest Mantle</th>
<th>Brain Chest</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Functional status</td>
<td>2.1</td>
<td>1.1</td>
<td>3.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Activity limitation</td>
<td>1.3</td>
<td>1.3</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Mental health</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pain</td>
<td>1.5</td>
<td>1.4</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Anxiety/fears</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Any health domain</td>
<td>1.4</td>
<td>1.2</td>
<td>2.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Odds Ratio Adjusted for Age, Sex, Race, Surgery, and Chemotherapy

Hudson et al, JAMA, 2004
Late Mortality Among 5+ Year Survivors

All-cause Mortality

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN</td>
<td>15.2</td>
<td>13.9 – 16.6</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7.0</td>
<td>5.9 – 8.2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>8.8</td>
<td>6.8 – 11.2</td>
</tr>
</tbody>
</table>

RT-Associated Risk of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN</td>
<td>2.9</td>
<td>2.1 – 4.2</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3.3</td>
<td>2.0 – 5.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.4</td>
<td>0.7 – 2.9</td>
</tr>
<tr>
<td>Other causes</td>
<td>2.0</td>
<td>1.3 – 3.1</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, year of dx, follow-up, anthracycline dose, epidodophyllotoxin dose, Bleomycin dose

Second Neoplasms Occurring 5+ years (n=1039)
Including Nonmelanoma Skin Cancer

Original Diagnoses (n=14,131)
- Leukemia
- CNS
- Hodgkin Disease
- Non-Hodgkin lymphoma
- Wilms'
- Neuroblastoma
- Soft tissue sarcoma
- Bone
Second Neoplasms Occurring 5+ years (n=1039)

- SMN (excluding NMSC): 10%
- NMSC: 5%
- Cumulative incidence over years since diagnosis:

Years since diagnosis:
- 0%
- 5%
- 10%
- 15%
- 20%
- 25%
- 30%

Cumulative incidence:
- 0%
- 5%
- 10%
- 15%
Second Malignancies Occurring 5+ years (n=1039)
Including Nonmelanoma Skin Cancer

- Female: 30%
- Male: 20%
- Female, Nonmelanoma Skin Cancer: 25%
- Male, Nonmelanoma Skin Cancer: 15%
- Cumulative incidence over Years since diagnosis
Second Malignancies Occurring 5+ years (n=1039) Including Nonmelanoma Skin Cancer

- 30% for first cancer
- 25% for first cancer
- 15% for first cancer
- 10% for first cancer
- 0% for first cancer
- 0% for No RT

Cumulative incidence

Years since diagnosis

Received RT for first cancer

No RT
Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer

![Graph showing standardized incidence ratios for subsequent malignancies among long-term survivors of childhood cancer.](image)
Radiation-Associated Risk of Second Malignancies in Childhood Cancer Survivors

Neglia J, et al.  
*J Natl Cancer Inst, 98:1528-37, 2006*

Sigurdson A, et al.  

![Graph showing relative risk of second malignancies in relation to dose in Gy for Meningioma, Glioma, and Thyroid linear-exponential models.](image)
Cumulative Incidence of Breast Cancer in Adult Female 5+ Year Survivors of Childhood Cancer

Radiation-Associated Risk of Breast Cancer in Childhood Cancer Survivors

Inskip, et al, J Clin Oncol, in press
Radiation-Associated Risk of Breast Cancer in Childhood Cancer Survivors

Inskip, et al, J Clin Oncol, in press
• Obesity in childhood, adolescence, and young adulthood is an important predictor of Type 2 Diabetes, Hypertension, dyslipidemia, and ultimately CVD

• Risk of death from all causes, CVD, and cancer increases throughout the ranges of being overweight and obese
Risk of Obesity Among Adults Survivors of Childhood ALL Cranial RT >20 Gy (n=841)

- Obesity in childhood, adolescence, and young adulthood is an important predictor of Type 2 Diabetes, Hypertension, dyslipidemia, and ultimately CVD

- Risk of death from all causes, CVD, and cancer increases throughout the ranges of being overweight and obese

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>2.59</td>
<td>1.88 - 3.55</td>
</tr>
<tr>
<td>Males</td>
<td>1.86</td>
<td>1.33 - 2.57</td>
</tr>
</tbody>
</table>

* Age and Race Adjusted Compared to Sibling Cohort

Oeffinger et al, J Clin Oncol, 2003
Females: Cranial RT > 20 Gy

<table>
<thead>
<tr>
<th>Age at Dx</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>3.81</td>
<td>2.34 - 5.99</td>
</tr>
<tr>
<td>5-9</td>
<td>2.30</td>
<td>1.39 - 3.59</td>
</tr>
<tr>
<td>10-14</td>
<td>2.16</td>
<td>1.11 - 3.61</td>
</tr>
<tr>
<td>15-21</td>
<td>0.88</td>
<td>0.00 - 2.63</td>
</tr>
</tbody>
</table>

* Age and Race Adjusted

Oeffinger et al, J Clin Oncol, 2003
Mean Body Mass Index Among 706 Long-term Survivors of Childhood ALL with >20 Gy Cranial RT

Female (n=359) | Male (n=347)
--- | ---
Baseline | Follow-up | Baseline | Follow-up
Mean Age | 26.2 yrs. | 26.9 yrs. | 27.6 yrs. | 28.1 yrs.
Mean from Dx | 19.0 yrs. | 19.0 yrs. | 21.8 yrs. | 22.2 yrs.

p=0.39 \( \text{p}<0.02 \)

Garmey et al., J Clin Oncol, 2008
Five year survivors were 3.5-times more likely to be diagnosed with lung fibrosis, 5-times more likely to experience recurrent pneumonia, and 3-times more likely to require supplemental oxygen.

Survivors treated with lung irradiation were 4.3-times more likely to have lung fibrosis.

*Mertens et al., Cancer, 2002*
Thyroid Dysfunction Among Survivors of Hodgkin’s Disease

• Among 1791 five year survivors of Hodgkin Disease, 34% were diagnosed with at least one thyroid abnormality.

• Hypothyroidism was the most common abnormality with a relative risk of 17.1 (p<0.001).

• Increasing dose of radiation to the thyroid, older age at diagnosis of Hodgkin disease, and female sex were all independently predictive of hypothyroidism.

Sklar et al., J Clin Endocrinol Metab, 2000
Chronic Health Conditions Among 5+ Year Survivors of Childhood Cancer

- 10,397 survivors, diagnosed 1970-1986
- 3,034 siblings

Grading of conditions: CTCAE v3.0

Common Terminology Criteria for Adverse Events

- Grade 1  Mild
- Grade 2  Moderate
- Grade 3  Severe
- Grade 4  Life-threatening or disabling
- Grade 5  Death

Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade

Relative Risk* of Chronic Health Conditions in Survivors Compared with Siblings

Survivors N= 10,397
Siblings N= 3,034

* Adjusted for age, sex, and race

Relative Risk* of Chronic Health Conditions in Survivors Compared with Siblings

* Adjusted for age, sex, and race

OTHER OUTCOMES ASSOCIATED WITH RADIATION EXPOSURE

- Neurocognitive
- Fertility/Gonadal
- Cardiac/Stroke/Vascular
- Growth
- Dental
- Vision
- Auditory
- Metabolic Syndrome
- Quality of Life
Childhood Cancer Survivor Study (U24 CA55727)

- CCSS is an NCI-funded Resource
- Available to Researchers
- Analysis and Publication of Existing Data
- Use of Biological Samples
- Investigator Initiated Research - Grants
- Interventional Research
- www.stjude.org/ccss
The Childhood Cancer Survivor Study (CCSS) was created to take advantage of 1) the opportunity to gain new knowledge about the long-term effects of cancer and therapy, knowledge that can be used to help design treatment protocols and intervention strategies that will increase survival and minimize harmful health effects, and 2) the obligation to educate survivors about the potential impacts of cancer diagnosis and treatment on their health, and to provide follow-up care, for example, by creating and implementing programs for the prevention and early detection of late effects.

The CCSS is a component of the Long-Term Follow-Up Study. A collaborative, multi-institutional study funded by the National Cancer Institute, the CCSS is composed of individuals who survived five or more years after treatment for cancer, leukemia, tumor, or similar illness diagnosed during childhood or adolescence.

The CCSS, which includes all participants in the Long-Term Follow-Up Study with a confirmed diagnosis of cancer, is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed between 1970 and 1986. It also includes approximately 4,000 siblings of survivors who serve as the comparison group for the study.

The CCSS cohort has been assembled through the efforts of 27 participating centers in the United States and Canada. It is coordinated through St. Jude Children’s Research Hospital in Memphis, Tennessee. Other core facilities include the Statistical Center, located at the Fred Hutchinson Cancer Research Center (Seattle); the Biopathology Center (Columbus); and the Radiation Physics Center at MD Anderson Cancer Center (Houston). Initiated in 1993, the study is funded by a grant from the National Cancer Institute.
www.stjude.org/ccss