Screening for Radiation-Associated Late Effects Among Survivors of Childhood Cancer

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Memphis, TN
Outline

• Background
• Childhood Cancer Survivor Study (CCSS)
• Mortality, Second Malignancies and Other Chronic Conditions
• Children’s Oncology Group Long Term Follow-up Guidelines
• St. Jude Lifetime Cohort Study (SJLIFE)
• Yield from Risk Based Screening
Survivorship Statistics

- Five year survival > 80%
- In 2009, estimated 363,100 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)
### Childhood Cancer Survivor Study (U24 CA55727)

- Funded in 1994
- Retrospective Cohort, diagnosed 1970-1986
- 26 Contributing Centers
- 5-Year Survival
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Detailed Treatment Data, Wide Range of Outcomes
- 200+ Publications since 2001

<table>
<thead>
<tr>
<th>Eligible</th>
<th>Lost (n=3017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20,720</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Contacted</th>
<th>Refusal (n=3189)</th>
</tr>
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<tbody>
<tr>
<td>17,703</td>
<td></td>
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<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>14,372</td>
</tr>
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<table>
<thead>
<tr>
<th>Stored DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>5796</td>
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</table>

### Cohort Expansion:
1987-1999
n=20,729
<table>
<thead>
<tr>
<th>St. Jude Children’s Research Hospital</th>
<th>Children’s Hospital of Philadelphia</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Minnesota</td>
<td>U.T. - M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Children’s Hospital of Pittsburgh</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Children’s Hospitals of Minnesota</td>
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<td>Dana-Farber Cancer Institute</td>
<td>St. Louis Children’s Hospital</td>
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<tr>
<td>Children’s National Medical Center</td>
<td>Children’s Hospital of Los Angeles</td>
</tr>
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<td>Roswell Park Cancer Center</td>
<td>UCLA Medical Center/Miller Children’s</td>
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<tr>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>Riley Hospital for Children – Indiana Univ.</td>
</tr>
<tr>
<td>Texas Children’s Hospital</td>
<td>UAB/Children’s Hospital of Alabama</td>
</tr>
<tr>
<td>University of California, San Francisco</td>
<td>Children’s Medical Center of Dallas</td>
</tr>
<tr>
<td>Seattle Children’s Hospital</td>
<td>Fred Hutchinson Cancer Research Center</td>
</tr>
<tr>
<td>Toronto Hospital for Sick Children</td>
<td>Children’s Hospital of Orange County</td>
</tr>
<tr>
<td>Denver Children’s Hospital</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Nationwide Children’s Hospital, Columbus</td>
<td>Cook Children’s Medical Center</td>
</tr>
<tr>
<td>Emory University</td>
<td>University of Chicago</td>
</tr>
<tr>
<td></td>
<td>University of Michigan – Mott Children’s</td>
</tr>
</tbody>
</table>
Late Mortality Among 5+ Year Survivors - All-cause Mortality

Mertens, et al, JCO, 2000
Late Mortality Among 5+ Year Survivors - All-cause Mortality

Late Mortality Among 5+ Year Survivors - All-cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>SMR</th>
<th>95% CI</th>
</tr>
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<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>

Late Mortality Among 5+ Year Survivors - All-cause Mortality

Second Neoplasms Among 5+ Year Survivors of Childhood Cancer

N= 14,358 five-years survivors of leukemia, lymphoma, neuroblastoma, CNS, bone, soft-tissue and kidney cancer
Second Neoplasms Among 5+ Year Survivors of Childhood Cancer

Subsequent Neoplasm

Subsequent Malignant Neoplasm
### Second Malignancy Among Long-term Survivors of Childhood Cancer

<table>
<thead>
<tr>
<th>Cumulative Incidence (20 Yrs)</th>
<th>2.9</th>
<th>4.5</th>
<th>15.7</th>
<th>4.2</th>
<th>2.8</th>
<th>3.2</th>
<th>6.3</th>
<th>8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abs. Excess Risk</td>
<td>1.22</td>
<td>1.79</td>
<td>7.69</td>
<td>1.39</td>
<td>1.17</td>
<td>1.67</td>
<td>3.36</td>
<td>2.99</td>
</tr>
</tbody>
</table>

#### Standardized Incidence Ratio

- Leukemia
- CNS
- Hodgkin
- Non-Hodgkin
- Wilms
- NBL
- ST Sarcoma
- Bone

![Graph showing standardized incidence ratio for various types of malignancy among long-term survivors of childhood cancer](image-url)
Second Malignancy Among Long-term Survivors of Childhood Cancer

Standardized Incidence Ratio

Subsequent Malignancy

- Total: 751
- Breast: 218
- Bone: 38
- Thyroid: 107
- ST Sarcoma: 81
- CNS: 60
- Leukemia: 29
- Melanoma: 36
- Lymphoma: 28
- Other: 154

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, 2009
Second Malignancy Among Long-term Survivors of Childhood Cancer

![Graph showing standardized incidence ratio for second malignancy among long-term survivors of childhood cancer.](image-url)
Cumulative Incidence of Thyroid Cancer Among Long-term Survivors of Childhood Cancer
Radiation-Associated Risk of Subsequent Thyroid Malignancy in Childhood Cancer Survivors

Cumulative Incidence

Dose in Gy

Thyroid - Linear
Exponential

Sigurdson et al., Lancet, 2005
Second Malignancy Among Long-term Survivors of Childhood Cancer

Subsequent Malignancy

- Total: 751
- Breast: 218
- Bone: 38
- Thyroid: 107
- ST Sarcoma: 81
- CNS: 60
- Leukemia: 29
- Melanoma: 36
- Lymphoma: 28
- Other: 154

Standardized Incidence Ratio
Second Neoplasms of the CNS Among 5+ Year Survivors of Childhood Cancer
Risk of Radiation-Associated Central Nervous System Second Neoplasm

Neglia et al, JNCI, 2006
Risk of Radiation-Associated Central Nervous System Second Neoplasm

Neglia et al, JNCI, 2006
Non-Melanoma Skin Cancer Among 5+ Year Survivors of Childhood Cancer
Non-Melanoma Skin Cancer Among 5+ Year Survivors of Childhood Cancer

Perkins, et al., J Clin Oncol, 2005
Mean age of 26.6 years (18-48 years)

By 30 years post cancer:

- 73% survivors with at least one chronic health condition
- 42% with a Grade 3-5 (severe, life-threatening, death)
- 39% had ≥2 chronic health conditions

Survivors – 8.2 times more likely to have a severe or life threatening condition compared to siblings
## Adjusted Relative Risk* of Physical Health Conditions in Survivors Compared with Siblings

<table>
<thead>
<tr>
<th>Cancer Therapy</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
<th>&gt; 2 Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chemo/RT</td>
<td>1.5</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Any radiation</td>
<td>3.4</td>
<td>7.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Brain RT</td>
<td>3.1</td>
<td>7.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Chest RT</td>
<td>2.5</td>
<td>10.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Abd RT</td>
<td>2.4</td>
<td>8.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Pelvic RT</td>
<td>2.6</td>
<td>10.5</td>
<td>6.8</td>
</tr>
</tbody>
</table>

All risk estimates p<0.001

* Adjusted for age, sex, and race

Cardiac Outcomes

Cumulative Incidence [%]

Years Since Diagnosis

Congestive Heart Failure

Myocardial Infarction
Pericardial Disease by Cardiac RT Dose

Cumulative Incidence vs Years Since Diagnosis

- 35+ Gy
- 15-34 Gy
- 5-14 Gy
- No RT
- 1-4 Gy

Mulrooney et al. BMJ 2009
Valvular Disease by Cardiac RT Dose

Cumulative Incidence

Years Since Diagnosis

- 35+ Gy
- 15-34 Gy
- 5-14 Gy
- 1-4 Gy

1-4 Gy

Mulrooney et al. BMJ 2009
Myocardial Infarction by Cardiac RT Dose

Cumulative Incidence

Years Since Diagnosis

0.0  5.0  10.0  15.0  20.0  25.0  30.0

0.0  3.0  6.0  9.0  12.0  15.0

No RT  1-4 Gy  5-14 Gy  15-34 Gy  35+ Gy

Mulrooney et al. BMJ 2009
Cumulative Incidence
Years Since Diagnosis

No RT
1 - 4 Gy
5 - 14 Gy
15 - 34 Gy
35+ Gy

Congestive Heart Failure by Cardiac RT Dose

Mulrooney et al. BMJ 2009
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
Among 1791 five year survivors of Hodgkin Disease, 34% were diagnosed with at least one thyroid abnormality.

Hypothyroidism was most common with a RR 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
Changes in Mean Body Mass Index and CRT

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>25.9 yrs.</td>
<td>33.7 yrs.</td>
<td>26.2 yrs.</td>
<td>34.0 yrs.</td>
</tr>
<tr>
<td>Mean from Dx</td>
<td>19.0 yrs.</td>
<td>26.8 yrs.</td>
<td>19.0 yrs.</td>
<td>26.9 yrs.</td>
</tr>
</tbody>
</table>

Mean BMI
Baseline
Follow-up

Siblings
Survivors

706 ALL survivors treated with 20+ Gy Cranial RT

Garmey et al., J Clin Oncol, 2008
Risk of BMI >25 in 294 Female Childhood ALL Survivors

Leptin Receptor Polymorphism Q223R

- Arg/Arg
  \[ \text{OR}_{(\text{adj})} = 2.5 \]
  \( (95\% \text{ CI} = 1.3 - 4.8) \)
  \( P = 0.004 \)

- Arg/Arg \times CRT
  \[ \text{OR} = 6.1 \]
  \( (95\% \text{ CI} = 2.1 - 22.0) \)
  \( P_{(\text{inter})} = 0.04 \)

Ross et al, J Clin Oncol, 2004
St. Jude for **LIFE**

• **Objective:**
  – To establish a lifetime cohort of childhood cancer survivors
  – To facilitate longitudinal evaluation of health outcomes in aging adults surviving pediatric cancer

• **Eligibility:**
  – Diagnosis of cancer treated at St. Jude
  – At least 18 years of age
  – At least 10 years from diagnosis
**Pre-visit**
- Medical Records: treatment and medical events
- Questionnaires: Self-report of socio-demographics, health status, and medical events

**Clinical Assessment**
- Risk-based Screening per COG Guidelines
- Human Performance Lab
- Collection of biological specimens
- Externally funded ancillary research studies
- Priority pilot studies

**Post-visit**
- Follow-up and validation of outcomes
- Use of bio-repository for biomarkers, genome wide and candidate gene studies

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**St. Jude LIFE Database**
Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers

- Exposure-based potential late effects and screening recommendations
  - Any cancer experience
  - Transfusions
  - Chemotherapy
  - Radiation
  - Hematopoietic cell transplant
- Appropriate for asymptomatic survivor ≥ 2 years after completion of therapy
- Screening performed by primary care

www.survivorshipguidelines.org
Yield From Risk Based Screening

Breast Cancer

Years since diagnosis

Total

Before SJ Visit

Number at risk

Before SJLIFE 133 (1) 132 (2) 89 (8) 34 (3) 3 (0) 0
Total 133 (1) 132 (7) 89 (12) 34 (7) 3 (1) 0
Yield From Risk Based Screening

Cardiomyopathy

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Number at risk Before SJLIFE</th>
<th>Number at risk Before SJ Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1214 (1)</td>
<td>1214</td>
</tr>
<tr>
<td>10</td>
<td>1213 (7)</td>
<td>1213</td>
</tr>
<tr>
<td>20</td>
<td>1198 (5)</td>
<td>1198</td>
</tr>
<tr>
<td>30</td>
<td>747 (10)</td>
<td>747</td>
</tr>
<tr>
<td>40</td>
<td>268 (19)</td>
<td>268</td>
</tr>
<tr>
<td>50</td>
<td>33 (7)</td>
<td>33</td>
</tr>
<tr>
<td>60</td>
<td>1 (2)</td>
<td>1</td>
</tr>
</tbody>
</table>

Total

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Number at risk Total</th>
<th>Number at risk Before SJ Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1214 (1)</td>
<td>1214</td>
</tr>
<tr>
<td>10</td>
<td>1213 (7)</td>
<td>1213</td>
</tr>
<tr>
<td>20</td>
<td>1198 (5)</td>
<td>1198</td>
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<tr>
<td>30</td>
<td>747 (10)</td>
<td>747</td>
</tr>
<tr>
<td>40</td>
<td>268 (18)</td>
<td>268</td>
</tr>
<tr>
<td>50</td>
<td>33 (7)</td>
<td>33</td>
</tr>
<tr>
<td>60</td>
<td>1 (2)</td>
<td>1</td>
</tr>
</tbody>
</table>

Total
Yield From Risk Based Screening

Heart Valve Disorder

Number at risk

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Before SJLIFE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>501 (1)</td>
<td>500 (2)</td>
</tr>
<tr>
<td>10 - 20</td>
<td>498 (59)</td>
<td>368 (154)</td>
</tr>
<tr>
<td>20 - 30</td>
<td>368 (104)</td>
<td>171 (95)</td>
</tr>
<tr>
<td>30 - 40</td>
<td>171 (7)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>40 - 50</td>
<td>29 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>50 - 60</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Before SJ Visit

Total
Yield From Risk Based Screening

Pituitary Dysfunction

Age in years

Number at risk
Before SJLIFE
Total

0.0 0.2 0.4 0.6 0.8 1.0

Before SJ Visit
Total
Yield From Risk Based Screening

Abnormal Pulmonary Function

Years since diagnosis

Number at risk
Before SJLIFE
Total

<table>
<thead>
<tr>
<th>Years since diagnosis</th>
<th>Before SJLIFE</th>
<th>Total</th>
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<tbody>
<tr>
<td>0</td>
<td>417 (78)</td>
<td>417 (78)</td>
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<tr>
<td>10</td>
<td>339 (34)</td>
<td>339 (60)</td>
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<tr>
<td>20</td>
<td>236 (4)</td>
<td>236 (66)</td>
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<tr>
<td>30</td>
<td>103 (4)</td>
<td>103 (63)</td>
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<tr>
<td>40</td>
<td>8 (1)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Neurocognitive Outcomes
ALL Survivors 20+ Years from Treatment
St. Jude LIFE Assessment

Pre-visit

Medical Records: treatment and medical events
Questionnaires: Self-report of socio-demographics, health status, and medical events

Clinical Assessment

Risk-based Screening per COG Guidelines
Human Performance Lab
Collection of biological specimens
Externally funded ancillary research studies
Priority pilot studies

Post-visit

Follow-up and validation of outcomes
Use of bio-repository for biomarkers, genome wide and candidate gene studies

SJLIFE Database
## Adult Survivors of Childhood Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female</td>
<td>33</td>
<td>53.2%</td>
</tr>
<tr>
<td>Ethnicity: Caucasian</td>
<td>55</td>
<td>88.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Age (years)</td>
<td>42.2 (4.8)</td>
<td>34.4-55.4</td>
</tr>
<tr>
<td>Survivors’ Education (years)</td>
<td>14.4 (2.5)</td>
<td>9-20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis (years)</td>
<td>15.1 (3.3)</td>
<td>5.9-19.0</td>
</tr>
<tr>
<td>Time Since Diagnosis (years)</td>
<td>27.1 (5.7)</td>
<td>18.3-39.6</td>
</tr>
<tr>
<td>Mantle Radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 Gy</td>
<td>20.6 (1.7)</td>
<td>19.2-26.3</td>
</tr>
<tr>
<td>≥ 30 Gy</td>
<td>36.7 (2.0)</td>
<td>34.1-45.0</td>
</tr>
</tbody>
</table>
# Adult Survivors of Childhood HL Outcomes by RT Dose

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt; 30 Gy</th>
<th>≥ 30 Gy</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>% Abn</td>
<td>% Abn</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular Functions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>21.7%</td>
<td>26.3%</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic Function (E/E’)</td>
<td>21.7%</td>
<td>60.5%</td>
<td>0.003</td>
</tr>
<tr>
<td>Aortic Valve Regurgitation</td>
<td>8.7%</td>
<td>31.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>Mitral Valve Regurgitation</td>
<td>13.0%</td>
<td>55.3%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pulmonary Functions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced Vital Capacity</td>
<td>8.3%</td>
<td>13.2%</td>
<td>0.003</td>
</tr>
<tr>
<td>Forced Expiratory Volume</td>
<td>8.3%</td>
<td>18.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>Total Lung Capacity</td>
<td>4.2%</td>
<td>5.3%</td>
<td>0.12</td>
</tr>
<tr>
<td>Diffusing Capacity (D_LCO)</td>
<td>12.5%</td>
<td>10.5%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Brain Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>34.8%</td>
<td>64.5%</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemosiderin Deposits</td>
<td>26.1%</td>
<td>45.2%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Krull et al, J Clin Oncol 2012
Adult Survivors of Childhood HL Multifocal Leukoencephalopathy
Adult Survivors of Childhood HL
Hemosiderin Deposits
Adult Survivors of Childhood HL Pulmonary Function and Neurocognitive Outcomes

Krull et al, J Clin Oncol 2012
Adult Survivors of Childhood HL Cardiac Function and Neurocognitive Outcomes

Krull et al, J Clin Oncol 2012
Adult Survivors of Childhood HL
Proposed Model

- Impaired Cardiac Function
- Thoracic Radiation
- Impaired Pulmonary Function
- Cerebrovascular Pathology
- Multifocal Leukoencephalopathy
- Hemosiderin Deposits
- Neurocognitive Impairment
- Cerebral Cortex Thinning
- Functional Limitation

Krull et al, J Clin Oncol 2012
Cancer Survivorship Research: Impact on Prevention

- Cancer Diagnosis and Treatment
- CANCER SURVIVORS
  - Health-related and QOL Outcomes
  - Evidence-based Clinical Care Guidelines
  - Development of Intervention Strategies
  - High-risk Groups
- “Secondary” Prevention
- Implementation-Dissemination
- Clinical Trials of Efficacy
- “Primary” Prevention