Childhood Cancer Survivors: Who is at Highest Risk and Essentials of a Survivorship Program

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Principal Investigator, Childhood Cancer Survivor Study

Department of Epidemiology and Cancer Control
Natural History of Cardiotoxicity: Differing Paradigms

- Cancer
- CHF
- CAD

Increasing risk

Quality Years Lost

Problem for Research
- Rare disease
- Long latency period
Goals

• View from 30,000 feet
  • What large cohort data tells us about risk for cardiotoxicity among survivors of childhood cancer
  • Core principles of cardiotoxicity

• The well-appearing survivor…surveillance/screening

• Modifiable cardiovascular risk factors

• Essentials of a survivorship program (in one slide!)

• The Good News
The View from 30,000 feet:
What large cohort data tells us about risk for cardiotoxicity
Survivorship Statistics

- >83% of children with a malignancy will achieve five-year survival
- In 2013, estimated 420,000 survivors of childhood cancer in the U.S.
- By 2020, estimated 500,000 survivors
- 1 in 750 in US is a childhood cancer survivor
Cause-specific Mortality Among Aging Survivors

Standardized Mortality Ratio

SMN = 15.2
Cardiac = 7.0

Coronary Artery Disease
CTCAE Grades 3-5  Childhood Cancer Survivor Study (CCSS)

At 45 Years
- 9.0%
- 1.0%
- 0.3%

Clinical Heart Failure
CTCAE Grades 3-5

At 45 Years
- RT + anthracycline: 11.8%
- Anthracycline alone: 6.8%
- RT alone: 5.0%
- No RT or anthracycline: 0.3%

Cumulative Incidence (%) vs. Age (years)

P < .001

• St. Jude Lifetime Cohort (SJLIFE)
  – 1,743 adult survivors
    • Median age 32 (18-60)
  – Cardiomyopathy at 50 years of age
    • 10% previously diagnosed
    • 21% true prevalence of cardiomyopathy
Risk for CHF after Anthracyclines is **DOSE DEPENDENT**

**Fig 1.** Dose-response relationship between cumulative anthracycline exposure and risk of cardiomyopathy. Patients with no exposure to anthracyclines served as the referent group. Magnitude of risk is expressed as odds ratio, which was obtained using conditional logistic regression adjusting for age at diagnosis, sex, and chest radiation.


There is NO safe dose of anthracycline!
### RT Dose and Cardiac Risk by Age

#### Any Cardiac Disease

<table>
<thead>
<tr>
<th>Mean Cardiac RT Dose (Gy)</th>
<th>Adjusted Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.1</td>
</tr>
<tr>
<td>0.1-9.9</td>
<td>0.5</td>
</tr>
<tr>
<td>10-19.9</td>
<td>1.0</td>
</tr>
<tr>
<td>20-29.9</td>
<td>2.0</td>
</tr>
<tr>
<td>30+</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Mean Cardiac RT Dose (Gy)</th>
<th>Adjusted Rate Ratio</th>
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<tbody>
<tr>
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</tr>
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<td>10-19.9</td>
<td>1.0</td>
</tr>
<tr>
<td>20-29.9</td>
<td>2.0</td>
</tr>
<tr>
<td>30+</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Age 0 – 4:**

- **RR = 2.2**
- p = 0.04

**Age 4 – 13:**

- **RR = 2.1**
- p = 0.03

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Bates et al, ASCO 2017 oral presentation
There is likely NO safe dose of chest-directed RT!
Risk for CHF **INCREASES** as Survivors Age


Survival Following Onset of CHF is **VERY BAD**

Proportion of Patients Surviving

- Peripartum cardiomyopathy
- Idiopathic cardiomyopathy
- Cardiomyopathy due to doxorubicin therapy
- Cardiomyopathy due to ischemic heart disease
- Cardiomyopathy due to infiltrative myocardial disease

The Well Appearing Survivor

Surveillance/Screening
Case #2

July 1984:

**History:** 12 yo female with ~6 wks R knee pain, edema, difficulty ambulating after trauma

**Diagnostic Imaging:** large mass distal R femur; chest neg, bone scan only uptake in femur

**Biopsy of R femur:** Osteosarcoma

**Treatment:** PG8107 protocol – completed 8/1985
- Right AKA
- Chemotherapy: anthracycline 380mg/m²
  - HD MTX, bleomycin, cisplatin, dactinomycin, cyclophosphamide (5700mg/m²)
Case #2

January 2009  S JLIFE Evaluation (Age 37)
• GERD – on PPI
• Iron deficiency anemia – iron injections
• Chronic Hepatits C – not requiring treatment to date
• Hypertension, dyslipidemia

Cardiac Evaluation
• Echocardiogram  ?
Evidence-Based Guidelines for Childhood Cancer Survivors: A Hybrid Model
Screening Recommendations for Cardiac Function: COG Guidelines

• Periodic evaluation
  - Detailed history yearly
  - EKG for evaluation of QT interval at baseline
  - 2D ECHO or MUGA for evaluation of systolic function at baseline, then periodically based on:
    • Age at treatment
    • History of chest radiation
    • Cumulative anthracycline dose
Screening Recommendations for Cardiac Function: COG Guidelines

<table>
<thead>
<tr>
<th>Age at Treatment</th>
<th>Radiation with Potential Impact to the Heart</th>
<th>Anthracycline Dose</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year old</td>
<td>Yes</td>
<td>Any</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt; 200 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 200 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>1-4 years old</td>
<td>Yes</td>
<td>Any</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;100 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100 to &lt;300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>≥5 years old</td>
<td>Yes</td>
<td>&lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>&lt;200 mg/m²</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 to &lt;300 mg/m²</td>
<td>Every 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥300 mg/m²</td>
<td>Every year</td>
</tr>
<tr>
<td>Any age with decrease in serial function</td>
<td></td>
<td></td>
<td>Every year</td>
</tr>
</tbody>
</table>

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 81], whichever was given first)

†See Section 81

Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, “Info Link (Dose Conversion)”]
NEW Screening Recommendations for Cardiac Function: 2018 COG Guidelines

<table>
<thead>
<tr>
<th>Anthracycline Dose*</th>
<th>Radiation Dose**</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&lt; 15 Gy or none</td>
<td>No screening</td>
</tr>
<tr>
<td></td>
<td>≥ 15 - &lt; 35 Gy</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td>≥ 35 Gy</td>
<td>Every 2 years</td>
</tr>
<tr>
<td>&lt; 250 mg/m²</td>
<td>&lt; 15 Gy or none</td>
<td>Every 5 years</td>
</tr>
<tr>
<td></td>
<td>≥ 15 Gy</td>
<td>Every 2 years</td>
</tr>
<tr>
<td>≥ 250 mg/m²</td>
<td>Any or none</td>
<td>Every 2 years</td>
</tr>
</tbody>
</table>

*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.

**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.
Prevalence of Echo Screening

![Graph showing the prevalence of various care and screening tests received, comparing community care (n = 7,276) and cancer center/long-term follow-up program (n = 1,246).](image)

**Care or Screening Test Received**
- General medical care
- General survivor-focused care
- Risk-based survivor-focused care
- Dental visit in past year
- Echo-cardiogram
- Mammogram

Nathan PC et al, JCO 2009
ECHOS: Randomized Intervention Trial

Standard of Care (n=206)

- LV Function Assessment Completed (n=46)
  - 22%
- No LV Assessment (n=160)
  - 78%

APN-counseling group > 2x more likely than Print media group to have screening (RR 2.31; 95% CI: 1.74-3.07).

Standard + APN Counsel (n=205)

- LV Assessment Completed (n=107)
  - 52%
- No LV Assessment (n=98)
  - 48%

Hudson MM et al, J Clin Oncol 2014
Late Onset Anthracycline Cardiomyopathy

Increased Cardiac injury

Exposure to anthracycline chemotherapy

5 year 10 year 15 year

Reduced EF

Progression to
1) Cardiac hospitalization
2) Cardiac Death

Asymptomatic Heart Failure Symptomatic Heart Failure

Normal
Late Onset Anthracycline Cardiomyopathy

- Increased Cardiac injury
- Exposure to anthracycline chemotherapy
- 5 year, 10 year, 15 year
- Normal

Increased Cardiac injury

Early Detection

Reduced EF

Asymptomatic Heart Failure
Symptomatic Heart Failure

Progression to
1) Cardiac hospitalization
2) Cardiac Death

Normal
Comprehensive Echocardiographic Detection of Treatment-related Cardiac Dysfunction

Armstrong GT, et al, JACC 2015
Comprehensive Echocardiographic Detection of Treatment-related Cardiac Dysfunction

- 1,820 adult survivors
  - Med. 31 yrs (range 18-65)
- Exposure
  - 1,050 anthracycline only
  - 306 chest RT only
  - 464 anthra + chest RT
- Results
  - 1/3 of survivors with normal EF had either abnormal longitudinal strain or diastolic dysfunction
  - 22% with chest RT had diastolic dysfunction
Exercise Intolerance

• 1769 potentially eligible survivors of childhood cancer
  – Refused SJLIFE (15%)
  – Active refusal (<1%)
  – Passive refusal (11%)
  – Medically ineligible for CARTOX (1%)

• 1260 participants
  – 1041 had a cardiopulmonary exercise test
  – 219 did not complete cardiopulmonary exercise testing/or test terminated
Reasons for no CPET results

- Cardiac: 45%
- Chronic health conditions: 17%
- Positive test: 15%
- Musculoskeletal: 11%
- Pulmonary: 15%
- Disability: 17%
- Cognitive: 2%

CEPT = Cardiopulmonary Exercise Test
# Cardiopulmonary Exercise Testing Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exposed Survivors (N=824)</th>
<th>Unexposed Survivors (N=436)</th>
<th>Community Controls (N=285)</th>
<th>Exposed vs. Controls</th>
<th>Unexposed vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>(p)</td>
<td>(p)</td>
</tr>
<tr>
<td><strong>VO₂ Peak (ml/kg/min)</strong></td>
<td>25.7 8.6</td>
<td>26.8 2.4</td>
<td>32.7 7.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VO₂ Peak (% predicted)</strong></td>
<td>78 22</td>
<td>82 21</td>
<td>98 20</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exercise Intolerance</strong></td>
<td><strong>(peak VO₂ uptake &lt;85% predicted)</strong></td>
<td>63.8%</td>
<td>55.7%</td>
<td>26.3%</td>
<td></td>
</tr>
</tbody>
</table>
## Risk of Exercise Intolerance (peak VO\textsubscript{2} uptake <85% predicted)
### Organ System Impairment and Lifestyle Factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Longitudinal Strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1.5 SD</td>
<td>1.76</td>
<td>1.19-1.62</td>
<td>0.005</td>
</tr>
<tr>
<td>&lt;1.5 SD</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEV1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>2.69</td>
<td>1.77-4.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥80%</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quadriceps Strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One SD decrease</td>
<td>1.55</td>
<td>1.30-1.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Modified Total Neuropathy Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.86</td>
<td>1.21-2.85</td>
<td>0.005</td>
</tr>
<tr>
<td>≥5</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for FEV1, quadriceps strength, modified total neuropathy score, physical activity, smoking, race/ethnicity and sex.
### Risk of Exercise Intolerance (peak V0₂ uptake <85% predicted)

#### Organ System Impairment and Lifestyle Factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate/Vigorous physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 min/wk</td>
<td>1.76</td>
<td>1.20-2.58</td>
<td>0.004</td>
</tr>
<tr>
<td>≥150 min/wk</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3.55</td>
<td>1.89-6.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for FEV1, quadriceps strength, modified total neuropathy score, physical activity, smoking, race/ethnicity and sex.
Conclusions

• Survivors (median age 36) have substantial rates of exercise intolerance
  – VO2max similar to general population in 7th-9th decade of life

• Exercise intolerance is attributable to multi-system disease and health behaviors
  – Cardiac, pulmonary, neuropathy, muscle weakness, physical activity, smoking (data not shown)

• Independent of other organ system dysfunction, GLS, not EF identifies survivors with exercise intolerance.
  – Early biomarkers are needed
  – Exercise intolerance in survivors previously undiagnosed with heart failure may be an intermediate marker for survivors at high risk for progression to heart failure, as it is in the general population
  – GLS provides an echo-based screening measure for identifying survivors with exercise intolerance
CCSS Cardiovascular Risk Calculator

This risk assessment tool predicts risk of heart failure, ischemic heart disease, and stroke by age 50 among survivors of childhood cancer. It uses information from the CCSS papers, "Individual prediction of heart failure among childhood cancer survivors" (Chow et al., ...) and "Prediction of ischemic heart disease and stroke among childhood cancer survivors" (Chow et al., ...), which created clinically useful models with readily available demographic and cancer treatment information. These models were designed specifically for patients who have recently completed cancer treatment (5 years from cancer diagnosis). These models have been validated in separate groups of childhood cancer survivors: Emma Children's Hospital and Academic Medical Center (Amsterdam, the Netherlands), the St. Jude Lifetime Cohort Study, and the National Wilms Tumor Study.

Depending on what level of treatment information is available, we created three different prediction models:

- Simple (if anthracycline, alkylator, platinum agent chemotherapy, and radiation exposures to the brain, neck, and chest are known, but not the doses)
- Standard (if anthracycline and chest radiation doses are known)
- Standard+heart (if anthracycline dose and heart-specific radiation dosimetry are known)

To determine one's risk of cardiovascular disease, please enter the information below (All fields are Required):

Gender?
- Male
- Female

Patient's age at diagnosis?
- < 5
- 5 - 9
- 10 - 14
- ≥ 15

Were any anthracyclines used?
- No
- Yes, cumulative dose known
- Yes, but cumulative dose unknown
- Unknown if anthracyclines used

Risk Calculator
ccss.stjude.org/cvcalc
Modifiable Cardiovascular Risk Factors

Longitudinal management of risk across the lifespan
Late Onset Anthracycline Cardiomyopathy

Increased Cardiac injury

Exposure to anthracycline chemotherapy

5 year 10 year 15 year

Normal

Progression to
1) Cardiac hospitalization
2) Cardiac Death

Asymptomatic Heart Failure Symptomatic Heart Failure

Additional effects of CVRFs

Early Detection

Reduced EF
Modifiable Risk Factors & Major Cardiac Events

Evaluate relative contribution to development of CHF

- Longitudinal evaluation
- 10,724 survivors, CCSS
- Is risk simply additive?

- Hypertension potentiates anthracycline-associated risk for CHF

- Multiple traditional CV risk factors increase risk

Chest RT and Multiple Risk Factors Including Hypertension

Coronary Artery Disease

- Multiple RFs alone: RR=7.9
- Chest RT alone: RR=5.0
- Chest RT + Multiple RFs: RR=39.8

p<0.001

Congestive Heart Failure

- Multiple RFs alone: RR=5.2
- Chest RT alone: RR=3.7
- Chest RT + Multiple RFs: RR=26.3

p=0.002

Blood Pressure Status in Adult Survivors of Childhood Cancer

Cumulative Prevalence of Hypertension by Attained Age in SJLIFE

Cumulative prevalence

Standardized Prevalence Ratio = 2.6 (1.7-4.7)

Expected based on age, sex, race/ethnicity and BMI-specific rates from NHANES

Gibson et al, Cancer Epidemiol Biomarkers Prev, 2017
Survivors have a higher prevalence of hypertension compared to the general population, even accounting for traditional risk factors
  – Need for interventions to prevent hypertension

Among hypertensive survivors who returned for a subsequent SJLIFE visit, 35% continued to have uncontrolled hypertension
  – Need for interventions to improve blood pressure management
**Randomized Intervention Trial**

**Study Aims:** Among survivors newly diagnosed with, or undertreated for CVRFs (hypertension, dyslipidemia, diabetes), randomized controlled intervention to **reduce under treatment of CVRFs**

**Intervention:** provision of lab results, survivorship care plan and remote counseling

**Data Collection:** 800 in-home assessments; 480 randomized to trial

**Principal Investigator:** Eric Chow, M.D. (Fred Hutchison Cancer Institute)

**Award:** *RO1 CA 204378*, $3.7 million
1. Determine how common underdiagnosis and undertreatment of hypertension, dyslipidemia, and diabetes are in CCSS participants at high risk of future heart disease.

2. Among those underdiagnosed / undertreated, conduct an randomized trial to test the effect of a remotely delivered survivorship care plan & self-management intervention on rates of undertreatment after 1-year.
• **Population:** high (and moderate) cardiovascular risk CCSS participants (n~650)

• **Definition of primary abnormalities:**
  - *Average blood pressure* $\geq 130/80$ mmHg
  - *LDL* $\geq 160$ mg/dL
  - *Triglyceride* $\geq 150$ mg/dL ($\geq 200$ if not fasting)
  - *Glucose* $\geq 100$ mg/dL ($\geq 140$ if not fasting)
  - *HbA1c* $\geq 5.7\%$ ($\geq 7\%$ if known diabetic)
Essentials of a Survivorship Program

(In one slide)
Optimal Survivorship Care

Personalized/Risk-Based

• Surveillance for primary/subsequent neoplasms
• Screening and management of late effects
• Assessment and support of psychosocial functioning
• Education about cancer-related health risks
• Education of behaviors/conditions modifying risk
• Assistance with identifying and meeting medical and psychosocial challenges
So, can you give us some good news?

Historical reductions in therapeutic exposure and changes in risk patterns for cardiac outcomes
Temporal Changes in Anthracycline Exposure (mg/m²)

<table>
<thead>
<tr>
<th></th>
<th>Mean Cumulative Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>289 217 158</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>295 212 193</td>
</tr>
<tr>
<td>Wilms</td>
<td>267 244 179</td>
</tr>
</tbody>
</table>

- Red: 1970s
- Blue: 1980s
- Gray: 1990s
Cause-specific Mortality: Other Treatment-related Causes

15-Year Cumulative Mortality

1970s
3.1% (2.7 – 3.5)

1980s
2.4% (2.2 – 2.7)

1990s
1.9% (1.6 – 2.2)

Armstrong et al, NEJM 2016
## Treatment-related Cause Late Mortality: 15 Years from Diagnosis

<table>
<thead>
<tr>
<th>Era</th>
<th>Treatment-related Cause</th>
<th>Subsequent Neoplasms</th>
<th>Cardiac</th>
<th>Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-74</td>
<td>3.5%</td>
<td>1.8%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>1975-79</td>
<td>2.9%</td>
<td>1.5%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1980-84</td>
<td>2.7%</td>
<td>1.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>1985-89</td>
<td>2.2%</td>
<td>1.3%</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1990-94</td>
<td>2.1%</td>
<td>1.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

P-value: <0.001

Armstrong et al, NEJM 2016
Conclusions

• Survivors are at HIGH risk for poor cardiac outcomes at a relatively young age
  • No safe dose of Anthracyclines
  • No safe dose of chest RT
  • Risk increases with age and is always > the general population risk
  • Survival after clinical CHF is very poor

• Survivors need personalized, risk-based care
  • Principle of early detection, though no evidence (yet) for improved major outcomes
  • Reduced EF is a late finding in the natural history, early markers are needed
  • Personal risk calculator exists

• Traditional CVRFs increase risk in a near multiplicative fashion!!!
  • Importance of prevention, heart healthy lifestyle, and adequate treatment

• More recent survivors may have lower risk
• The Childhood Cancer Survivor Study is an NCI-funded resource 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:

  www.stjude.org/ccss
Among adult survivors of childhood cancer who were treated with anthracycline chemotherapy or chest-directed radiotherapy during childhood, how will the development of hypertension affect their risk for symptomatic heart failure as they age?

A) Minimal impact on risk as intense cardiotoxic treatment drives the risk for HF.

B) Additive increase in risk for heart failure (i.e. 1 + 1 = 2).

C) Near multiplicative increase in risk of HF (i.e. 1+1 = >2).  

D) The impact is not known.

Correct
Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade

Cumulative Incidence of Chronic Conditions: Grades 3-5

Armstrong GT, J Clin Oncol 2014
Multiple Chronic Medical Conditions: Grades 3-5

10% have three conditions by age 50

Armstrong GT, J Clin Oncol 2014
Subsequent Neoplasms Among 5+ Year Survivors of Childhood Cancer

N= 14,359 five-years survivors of leukemia, lymphoma, neuroblastoma, CNS, bone, soft-tissue and kidney cancer

- Cumulative incidence of second neoplasm at 30 years = 22%
- Cumulative incidence of second malignancy at 30 years = 11%
Late Mortality Among 5+ Year Survivors
All-cause Mortality

Survival function estimate

<table>
<thead>
<tr>
<th>Year</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.95</td>
<td>0.70</td>
</tr>
<tr>
<td>10</td>
<td>0.90</td>
<td>0.75</td>
</tr>
<tr>
<td>15</td>
<td>0.85</td>
<td>0.80</td>
</tr>
<tr>
<td>20</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td>25</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>30</td>
<td>0.70</td>
<td>1.00</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Years since diagnosis

US Female
US Male
Female
Male

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

Survival function estimate

Years since diagnosis

Survival estimate as a function of years since diagnosis for US Female and US Male patients. The graph shows the declining survival function estimates with time, highlighting the increased risk of mortality beyond the initial diagnosis period. The data is sourced from Mertens, et al., JCO, 2000.
Reduction in Late Mortality, but Not Adverse Health Status, by Treatment Era

Cumulative Late Effects Mortality (%)

Years since diagnosis

<table>
<thead>
<tr>
<th>Treatment Decade</th>
<th>15-Year Late Effects Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-79</td>
<td>3.1% (2.7-3.5)</td>
</tr>
<tr>
<td>1980-89</td>
<td>2.4% (2.2-2.7)</td>
</tr>
<tr>
<td>1990-99</td>
<td>1.9% (1.6-2.2)</td>
</tr>
</tbody>
</table>

(p < 0.001)

Cumulative Incidence of Grade 3-5 Chronic Conditions by Treatment Decade

<table>
<thead>
<tr>
<th>Treatment Decade</th>
<th>N</th>
<th>15-Yr Cumulative Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-79</td>
<td>6,223</td>
<td>12.7%</td>
<td>(11.8-13.6)</td>
</tr>
<tr>
<td>1980-89</td>
<td>9,420</td>
<td>10.1%</td>
<td>(9.4-10.7)</td>
</tr>
<tr>
<td>1990-99</td>
<td>7,958</td>
<td>8.9%</td>
<td>(8.3-9.5)</td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

Years Since Diagnosis

$p < 0.0001$
Cumulative Incidence of Grade 3-5 Chronic Conditions by Treatment Decade

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<th>N</th>
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<td>7,958</td>
<td>8.9%</td>
<td>(8.3-9.5)</td>
</tr>
</tbody>
</table>

HR per decade = 0.82 (0.78-0.87)
Decrease in Grade 3-5 Chronic Conditions by Decade

HR = hazard ratio per 10-year treatment interval, adjusted for sex, attained age and time since diagnosis
No Decrease in Grade 3-5 Chronic Conditions by Decade

15 Year Cumulative Incidence (%)

- **Acute Myeloid Leukemia** (n=866)
  - HR = 0.87
  - p = 0.38

- **Neuroblastoma** (n=1,838)
  - HR = 1.00
  - p = 0.97

- **Soft Tissue Sarcoma** (n=1,162)
  - HR = 0.96
  - p = 0.76

- **Osteosarcoma** (n=1,205)
  - HR = 0.96
  - p = 0.81

- **Medulloblastoma/PNET** (n=997)
  - HR = 1.14
  - p = 0.30
Reduced Risk for Subsequent Cancers in More Modern Eras

<table>
<thead>
<tr>
<th>Decade</th>
<th>Subsequent Neoplasms (%)</th>
<th>Subsequent Malignant Neoplasms (%)</th>
<th>Meningioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>2.9%</td>
<td>2.1%</td>
<td>-</td>
</tr>
<tr>
<td>1980s</td>
<td>2.4%</td>
<td>1.7%</td>
<td>-</td>
</tr>
<tr>
<td>1990s</td>
<td>1.5%</td>
<td>1.3%</td>
<td>-</td>
</tr>
</tbody>
</table>

Turcotte et al, JAMA 2017
Genetic Contribution to Risk for Late Effects
Cardiovascular complications are one of the more common and devastating late outcomes of childhood cancer therapy.

*CBR3* is involved in reduction of anthracyclines to cardiotoxic alcohol metabolites.

Survivors exposed to anthracycline chemotherapy who had the G/G genotype demonstrated a 10-fold increased risk of cardiomyopathy.

This finding was subsequently replicated in an independent sample of childhood cancer survivors from the Children’s Oncology Group (Blanco, JCO, 2012).
Survivors of childhood cancer, particularly survivors of Hodgkin lymphoma, are at increased risk for developing a treatment-related second cancer.

Most common second cancers are skin, breast, thyroid, CNS, and soft-tissue sarcoma.

Using a genome-wide approach, PRDM1 was found to be significantly associated with radiation-associated second cancers.

Homozygosity for the risk allele was associated with a 29% incidence of second cancer compared to only 3.5% in those without the risk allele.

Best et al. Nat Med 2011;17:941-3
Shorter telomere length has been associated with increased cancer incidence.

Intensive cancer chemotherapy and radiation has been observed to shorten telomeres.

A statistically significant inverse relationship was found between telomere content and occurrence of second malignant neoplasms among survivors of childhood cancer.

The association was most apparent for risk of secondary thyroid cancer.

**RO1 CA 194473, Gramatges PI: Shortened Telomere length, defects in telomere maintenance associated with thyroid SMN**

* Risk per unit change to single-copy gene ratio, adjusted for sex, race, family history, smoking status, age at primary cancer

GWAS Resource for Genomic Investigation

• GWAS resource for genetic investigation (n=5,739)
  
  – Identify genetic variants that modify the effect of RT and chemotherapy on risk of subsequent neoplasms, and of risk independent of treatment exposure
  
  – Collaboration with Division of Cancer Epidemiology and Genetics (Morton, PI)
  
  – **Request for Proposals (RFP)**: unparalleled resource for investigation of other chronic health conditions

**www.stjude.org/ccss**
GWAS identifies susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer

Lindsay M. Morton, PhD
Radiation Epidemiology Branch
Division of Cancer Epidemiology & Genetics

In Press, JNCI
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, $\geq$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 1q41</th>
<th>Radiation exposure to the breast $\geq 10$ Gy</th>
<th>$&lt;10$ Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk = 1.92 $P = 7.09 \times 10^{-9}$</td>
<td>Relative risk = 1.04 $P = 0.81$</td>
</tr>
<tr>
<td>Chromosome 11q23</td>
<td>Relative risk = 2.59 $P = 5.84 \times 10^{-8}$</td>
<td>Relative risk = 1.19 $P = 0.79$</td>
</tr>
</tbody>
</table>
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
CCSS GWAS Request for Proposals

• To investigate the role of genetic susceptibility in the development of non-malignant, treatment-related outcomes

www.stjude.org/ccss

• Proposals due June, October and February 1st
  • To date: 6 applications, 5 approved

• Separate approval process for replication

- Sequencing: 5,591 complete (2% failure rate)
- Final quality control complete
- 5,451 in final analytic build
- Plan for RFP similar to GWAS RFP
• Collection and DNA extraction on 4,646 CCSS participants
  • 3,962 (85%) oragene
  • 137 (3%) blood
  • 547 (12%) both

• SJCRH has committed to whole genome sequencing (30x) and whole exome sequencing (100x coverage)
Expansion Biospecimens

• Collaboration with St. Jude lifetime cohort (N=3000) to create the largest data set of children with cancer to date

• Data will be publicly available via the European Genomics Archive (EGA) and the St. Jude Cloud
Direct Assessment:

New CCSS Support facility: CCSS mHealth Technology Center at UCSF (Jeff Olgin, PI)

- Primary engagement: App-based interaction with CCSS, Eureka Platform
- Establish a “connected” sub-cohort of 12,000, sensor-based outcomes
- Resource for mHealth/technology-based intervention studies
- Mechanism for real-time PRO reporting
Eureka Platform for CCSS Research

- mHealth based studies
- Chronic pain
  - sensor-based respiration
- Autonomic function
  - Heart rate variability
- Tremendous potential for PROs in real time!
Model for Late Effect Research and Future of Survivorship Research

CANCER SURVIVORS

Cancer Diagnosis and Treatment

“Primary” Prevention

Implementation

“Secondary” Prevention

Clinical Trials of Efficacy

Evidence-based Clinical Care Guidelines

High-risk Groups

Development of Intervention Strategies

Health-related and QOL Outcomes

### Population by Primary Cancer Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort</th>
<th>% of Overall Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13,032</td>
<td>53.5</td>
</tr>
<tr>
<td>Female</td>
<td>11,336</td>
<td>46.5</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>20,012</td>
<td>82.1</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1,536</td>
<td>6.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,806</td>
<td>7.4</td>
</tr>
<tr>
<td>Other</td>
<td>1,014</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Current Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 yrs</td>
<td>503</td>
<td>2.6</td>
</tr>
<tr>
<td>20-29 yrs</td>
<td>3751</td>
<td>22.6</td>
</tr>
<tr>
<td>30-39 yrs</td>
<td>7974</td>
<td>36.7</td>
</tr>
<tr>
<td>40-49 yrs</td>
<td>6347</td>
<td>25.7</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>3066</td>
<td>12.4</td>
</tr>
</tbody>
</table>
## Attrition and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>N (% ) of Participants Original Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased at Baseline</td>
<td>1,177 (8.2%)</td>
</tr>
<tr>
<td>Deceased after Baseline</td>
<td>866 (6.2%)</td>
</tr>
<tr>
<td>Refused Further Follow-up</td>
<td>1,680 (11.7%)</td>
</tr>
</tbody>
</table>

### Follow-up Survey Participation

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-Up 2000</td>
<td>81%</td>
</tr>
<tr>
<td>Follow-Up 2003</td>
<td>78%</td>
</tr>
<tr>
<td>Follow-Up 2005</td>
<td>78%</td>
</tr>
<tr>
<td>Follow-Up 2007</td>
<td>82%</td>
</tr>
</tbody>
</table>
**Cause of Death** | **Year of Diagnosis*** | **95% CI**
--- | --- | ---
Other Health-related Causes: | 0.86 | 0.82 - 0.89
Subsequent Neoplasm | 0.83 | 0.78 - 0.88
Cardiac | 0.77 | 0.68 - 0.86
Pulmonary | 0.77 | 0.66 - 0.89

*Adjusted for age at diagnosis, sex, diagnosis and follow-up time
Childhood Cancer Survivor Study  (U24 CA 55727)
Participating Centers

St. Jude Children’s Research Hospital
University of Minnesota
Children’s Hospital of Pittsburgh
Stanford University
Dana-Farber Cancer Institute
Children’s National Medical Center
Roswell Park Cancer Center
Memorial Sloan-Kettering Cancer Center
Texas Children’s Hospital
University of California San Francisco
Seattle Children’s Hospital
Toronto Hospital for Sick Children
Denver Children’s Hospital
Nationwide Children’s Hospital
Emory University
Cook Children’s Medical Center

U.T. - M.D. Anderson Cancer Center
Mayo Clinic
Children’s Hospitals of Minnesota
Children’s Hospital of Philadelphia
St. Louis Children’s Hospital
Children’s Hospital of Los Angeles
UCLA Medical Center/Miller Children’s
Children’s Hospital of Orange County
Riley Hospital for Children – Indiana Univ.
UAB/Children’s Hospital of Alabama
University of Michigan – Mott Children’s
Children’s Medical Center of Dallas
Fred Hutchinson Cancer Research Center
Northwestern University
University of Chicago
Psychological Outcomes & Health-related Quality of Life

- Compared 7,147 survivors vs. siblings

**Psychological distress** (BSI-18)
  - Global distress greater among survivors (mean 49.17 vs. 46.64) than siblings, yet scores for both were below population norms

**HRQOL** (SF-36)
  - Survivors scored worse than siblings on overall physical (51.3 vs. 54.9, p<0.001) but not emotional scales, effect sizes were small

**Life-satisfaction** (Cantril Ladder of Life)
  - Most survivors reported present and future predicted life satisfaction

**Risk factors**: female, unmarried, low educational attainment, low income, having a major medical condition, treatment with cranial radiation

- **Conclusion**: Compared with population norms, survivors and siblings report positive psychological health, good HRQOL and life satisfaction

Zeltzer LK et al, Cancer Epidemiol Biomarkers Prev, 2008
Neurocognitive Function in Survivors of Non-CNS Cancers

5,937 adult survivors

- CCSS Neurocog. Questionnaire (CCSS-NCQ)
- Self-reported function
- Impairment for survivors = <10th percentile of siblings across four domains

Conclusions:
- Significant impairment compared to siblings
- Impairment associated with increasing dose of cranial RT

Kadan-Lottick NS et al, JNCI 2010
Affordable Care Act:
Perceptions and Understanding

- Ancillary Study, Elyse Park (Harvard): 698 survivors, 210 siblings
- ACA became law 2010, survey 2011-2012, enrollment 2014
- 89% of survivors with insurance, 92% of siblings
- Familiarity with the ACA:

Park et al, J Clin Oncol 2015
### 2014 CCSS Publications* (n=34)
Published + In Press

<table>
<thead>
<tr>
<th>Impact Factor &gt;10</th>
<th>Impact Factor &lt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Intern Med</td>
<td>Health Psychol (2)</td>
</tr>
<tr>
<td>Lancet Oncology</td>
<td>Biometrics</td>
</tr>
<tr>
<td>J Clin Oncol (8)</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>JNCI</td>
<td>Cancer (3)</td>
</tr>
<tr>
<td>Nat Commun</td>
<td>CEBP</td>
</tr>
<tr>
<td></td>
<td>Clin Cancer Res</td>
</tr>
<tr>
<td></td>
<td>Psychooncology</td>
</tr>
<tr>
<td></td>
<td>J Cancer Surv (2)</td>
</tr>
<tr>
<td></td>
<td>Pediatr Blood Cancer (5)</td>
</tr>
<tr>
<td></td>
<td>Arch Phys Med Rehab</td>
</tr>
<tr>
<td></td>
<td>Am J Obstet Gynecol</td>
</tr>
<tr>
<td></td>
<td>Neuropsychology</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact Factor 5-10</td>
<td></td>
</tr>
<tr>
<td>J Clin Endocrinol Metab</td>
<td></td>
</tr>
<tr>
<td>Neuropyscology</td>
<td></td>
</tr>
</tbody>
</table>

*as of December
 Survivors of childhood acute lymphoblastic leukemia, treated with radiation to the brain, are more likely to be obese as adults (Females 2.6-times, Males 1.9-times)

- Females treated at a young age are at highest risk (3.8-fold).

- Among female survivors, homozygosity for the Arg allele of the leptin receptor polymorphism demonstrated a statistically significant gene-radiation interaction (6.1-fold increased risk of being overweight or obese).
Communication with Participants

- Survey completion
  - Paper (snail mail)
  - Telephone interview
  - Web-based completion (Datstat)

- Mobile/tablet-based communication
  - Smart phone? 81%
  - Access the internet? PC (93%); Smartphone (74%); Tablet (48%)
  - Willing to receive study-related text messages? 61%
  - Participate in electronic health monitoring studies? Very likely (50%); Possibly (33%), Unlikely (17%)
Vision for Mobile-based Communication

1. Push
   - Newsletters and Health-related information/updates (i.e. a resource)
   - Reminders to complete surveys
   - Invite to participate in additional studies

2. Pull
   - Updates on key health outcomes (second cancers, heart disease)
   - Complete full surveys (tablet)

3. Monitor and Intervene

   A Completely Connected Survivor Cohort
Key Concerns

1. Security
2. Will it be used? (culture change)
3. Flexibility
4. Cost
Potential for Collaboration

- Co-recruitment of CCSS participants into Health eHeart
  - Provide data on participant interest in a “technology-based” study
  - Create a sub cohort for subsequent cardiac monitoring-based interventions

- Health eHeart as a new Support Facility for CCSS for all mHealth monitoring and intervention-based research
Significant and Lasting Influence on the Field for the next Five Years

- Exploitation of expanded cohort data (1986-99)

15,247 Eligible
10,102 Participants
9,806 Complete Medical Record Abstraction

296 Partial abstractions
5,154 Non-participants

24,466 Participants Overall Cohort
Dose-Risk Relationship for Tissue-Specific Radiation Exposure and Breast Cancer

- Linear dose-response for secondary breast cancer
- 11-fold increased risk at 40 Gy (compared to no RT)
- Risk of breast cancer markedly reduced for women with $\geq$ 5 Gy ovarian RT
- Age at RT exposure not a risk factor for breast cancer

Inskip et al, J Clin Oncol, 2009
Cumulative Incidence

By age 40: 12%
By age 50: 30%

Childhood Cancer Survivor Study
Breast Cancer Risk

Moskowitz et al, J Clin Oncol, 2014
Childhood Cancer Survivor Study and WECARE Study
Breast Cancer Risk

By age 40
Hodgkin lymphoma (HL): 15%
Other: 8%

Moskowitz et al, J Clin Oncol, 2014
Childhood Cancer Survivor Study and WECARE Study

Breast Cancer Risk

By age 50
HL: 35%

Hodgkin lymphoma (HL)

Other childhood cancer

Moskowitz et al, J Clin Oncol, 2014
Breast Cancer Risk

Childhood Cancer Survivor Study and WECARE Study

By age 50

Hodgkin lymphoma (HL)

Other childhood cancer

SEER Benchmark

By age 50

HL: 35%

SEER: 4%

Moskowitz et al, J Clin Oncol, 2014
Childhood Cancer Survivor Study and WECARE Study

Breast Cancer Risk

By age 50
- Hodgkin lymphoma (HL): 35%
- SEER: 4%
- BRCA1: 31%

BRCA1 Carrier*

Other childhood cancer

SEER Benchmark

* Population-based estimate

Moskowitz et al, J Clin Oncol, 2014
Breast Cancer Risk Without a History of Chest RT Exposure

- 47 women
- Mean age at breast cancer 38 yrs
- SIR 4.0 (95% CI 3.0-5.3)
- Highest risk after sarcoma, leukemia

4.5% by age 45
Subsequent Neoplasms beyond age 40

No Radiotherapy

Radiotherapy

Race/Ethnicity Differences in Outcomes

- Evaluated late mortality, subsequent neoplasms and chronic health conditions among:
  - Hispanic (n=750)
  - Non-Hispanic Black (n=694)
  - Non-Hispanic Whites (n=12,397)

- NHB and Hispanic had ↓ SES and ↑ obesity and hypertension

- NHB ↑ risk for late mortality
  - Abrogated after adjustment for SES (RR=1.0)

- No differences in SNs

- NHB at ↑ risk for cardiac conditions
  - Attenuated after adjusting for CV risk factors

- Therapeutic exposures did not impact racial/ethnic differences in outcomes

Bhatia et al, J Clin Oncol, 2016
Significant and Lasting Influence on the Field

- Exploitation of expanded cohort data (1970-99)
  - Identify how risk stratification of therapy has changed patterns of late effects
    - **Low risk patients**: reduced therapeutic expose, fewer late effects?
      - ALL with no cranial RT, reduced chest RT and anthracyclines for HL
    - **High risk patients**: intensified therapy, changing pattern of late effects?
      - High risk neuroblastoma, multi-modal therapy for CNS tumors
• GWAS resource for genetic investigation (n=5,959)
  • Collaboration with Division of Cancer Epidemiology and Genetics
  • Identify genetic variants that modify the effect of RT and chemotherapy on risk of subsequent neoplasms, and of risk independent of treatment exposure

• Request For Proposals (RFP):
  • unparalleled resource for investigation of associations between genetic variants and risk of other chronic health conditions
  • To be issued Summer 2016
  • GWAS data available on dbGaP
  • Full annotation with exposure and outcome data pending completion and approval through the application process
• Ongoing resource for intervention studies

• Addition of direct assessment of survivors to historical survey-based outcomes
  • Use of mobile health technology
    • Sensor-based direct outcome measures including: blood pressure, activity, EKG, diet etc.
Background:
Compared with the general population, adult survivors under 35 who had radiation have nearly 40 times greater risk for NMSC, while survivors ages 35-44 have 26 times the risk. Melanoma rates are 2 times greater.

Goal:
Improve rates of thorough skin self-examination and receipt of provider full-body skin cancer examination measured at 12 and 18 months.
Randomized Intervention Trial

**Arm 1:**
Web-based and print materials (including 12 text messages) on early detection

**Arm 2:**
Web-based and print materials (including 12 text messages) on early detection + physician education

**Arm 3:**
Web-based and print materials on early detection (including 12 text messages) + physician education + teledermatology
Potential for Direct Assessment through Mobile Health Technology

91% of smartphone owners keep their smartphones within **3 feet**, **24 hours** a day.
Decrease in Grade 3-5 Chronic Conditions by Decade

HR = hazard ratio per 10-year treatment interval, adjusted for sex, attained age and time since diagnosis

- Endocrine: HR = 0.61, p < 0.0001
- Second Malignant Neoplasms: HR = 0.82, p = 0.001
- Neurological: HR = 0.79, p = 0.003
- Gastrointestinal: HR = 0.73, p = 0.001

CCSS
No Decrease in Grade 3-5 Chronic Conditions by Decade

HR = hazard ratio per 10-year treatment interval, adjusted for sex, attained age and time since diagnosis
Aim: To test a 2-armed intervention to increase screening for left ventricular (LV) dysfunction in childhood cancer survivors at risk

Hypothesis: Survivors randomized to standard care + Advanced Practice Nurse phone counseling will have greater proportion completing CV screening.

R01NR011322  Hudson PI

Hudson MM et al, J Clin Oncol 2014