Prediction and Prevention of Morbidity across the Disease Trajectory

Lessons learned from our Children with Cancer

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Burden of Morbidity in Childhood Cancer Survivors

Severe/Life-threatening Chronic Health Conditions

Cumulative Incidence (%)

41% at 30y

Cumulative Cause-specific Mortality among 5-year Childhood Cancer Survivors

JAMA 304:172-179, 2010

[Graph showing cumulative mortality over years from childhood cancer diagnosis, highlighting recurrence and all causes except recurrence, with expected (background) mortality.]
Clearly-defined association between therapeutic exposures and specific chronic health conditions
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/sex

Identification of High Risk Groups

Modification of therapeutic exposures
Screening of “High Risk” Populations
Risk reduction in “High Risk” Populations

Chronic Health Conditions
Genetic Predisposition

Lifestyle Exposures

Viral Infections

Age/sex

Adverse Events

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Risk reduction in “High Risk” Populations
Therapeutic Exposure → "TRADITIONAL EPIDEMIOLOGY" → Adverse Outcome

Exposure → Internal dose → Biologically effective dose → Altered structure/function → Preclinical disease → Clinically Overt Outcome

"MOLECULAR EPIDEMIOLOGY" → Susceptibility
Case-control study of key adverse events after childhood cancer

COG ALTE03N1

Leukemia/ Lymphoma Society
National Cancer Institute (R01 CA139633)
National Cancer Institute (R35 CA220502)
The V Foundation
Eligibility - Cases
1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. Subsequent development of a key adverse event

Eligibility - Controls
1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. No evidence of key adverse events

Matching Criteria
- Primary cancer diagnosis
- Year of diagnosis (±5y)
- Race/ethnicity
- Time since primary cancer

Collect DNA from Cases and controls
Self-report of comorbidities

Summarize therapeutic exposures for cases and controls

Source documentation (Cases only)
- Osteonecrosis (diagnostic radiology)
- Subsequent neoplasms (pathology report)
- Congestive Heart Failure (echocardiogram report)
- Stroke (diagnostic radiology)
Cardiac Toxicity in Cancer Survivors

Cardiomyopathy → congestive heart failure

**Risk factors**
- Anthracycline chemotherapy

**Risk modifiers**
- Chest radiation
- Young age at exposure
- Female sex

~60% of children exposed to high-dose anthracyclines develop cardiotoxicity

*Circulation, 2013*

5-year survival rates of less than 50% after CHF diagnosis

*N Engl J Med, 2000*
Inter-individual variability in risk of anthracycline-related cardiomyopathy

Role for genetic susceptibility?
Pathogenesis of cardiomyopathy

Funding:
62771-11 LLS TRP
R35 CA220502
The V Foundation
Pathogenesis of cardiomyopathy

↑ Anthracycline

- Drug Transport/metabolism
  - NAD(P)H oxidase multi-enzyme complex
- NAD(P)H
- Dox-quinone
- Dox-semiquinone*
- O₂*/H₂O₂
- Dox-ol
- Aconitase/IRP1
- Loss of Fe Homeostasis

↑ ROS

Mitochondrial dysfunction

Myocyte apoptosis

Maladaptive LV Remodeling

Heart Failure

1. Candidate gene approach
2. Carefully-curated SNP arrays
3. Agnostic-genome wide association studies
4. Functional studies
**Genetic Associations**

**Candidate gene**
- CBR3:GG
- CBR3:GA/AA

*J Clin Oncol, 2012*

**Odds Ratios**
- CBR3:GG: 10.85
- CBR3:GA/AA:
  - 0.82
  - 2.16
  - 6.15
  - 6.37
  - 10.85

**Cardiovascular SNP array**
- HAS3 gene

*J Clin Oncol, 2014*

**Genome-wide SNP array**
- CBR3 gene
- CELF4 gene

*J Clin Oncol, 2016*

**Odds Ratios**
- AA: OR=39.1
- GA: OR=4.9
- GG: OR=0.6

**Anthraclycline Dose**
- 0
- 50
- 100
- 150
- 200
- 250
- 300
- 350
- 400
- 450
- 500
Pathogenesis of Cardiomyopathy

Drug Transport/metabolism
SLC28A3, ABCB1, ABCB4, ABCC1, MRP2, GSTM1 deletion

↑Anthracycline

NAD(P)H oxidase multi-enzyme complex

Dox-quinone

↑ROS

Dox-ol

Aconitase/IRP1

Loss of Fe Homeostasis

HFE2

ECM and Remodeling

HAS 3
HA

DECREASSED MYOCARDIAL CONTRACTILITY

RARG

CELF-mediated alternative splicing of TNNT2

>1 isoforms of TNNT2

Myocyte apoptosis

Maladaptive LV Remodeling

Decomposed myocardial contractility

Heart Failure
Genetic Predisposition

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Adverse Events
Risk prediction models for anthracycline-related cardiomyopathy

Prediction model was successfully replicated in CCSS
- Final Model performed significantly better than the Clinical Model, $P=0.02$. 

Final Model (AUC=0.88)
Clinical + Genetic Model (AUC=0.86)
Clinical Model (AUC=0.80)

P <0.0001
Identification of High Risk Groups

- Genetic Predisposition
- Lifestyle Exposures
- Viral Infections
- Age/sex

Risk reduction in “High Risk” Populations

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Adverse Events
Subsequent Neoplasms

Case-control study of key adverse events after childhood cancer

COG ALTE03N1

Leukemia/ Lymphoma Society
National Cancer Institute R01 CA139633
National Cancer Institute R35 CA220502
• Childhood cancer survivors are at a 10-fold increased risk for developing histologically distinct subsequent CNS tumors c/w general population

• High-grade gliomas and meningiomas are most common types of subsequent CNS tumors
  • significant morbidity and mortality
    • Five-year survival is <20% for gliomas
    • Meningiomas are often accompanied by significant morbidity
**Risk factors**

- Exposure to cranial radiation is the major risk factor.
- The risk is especially increased after exposure to radiation at a very young age.

The risk for subsequent CNS tumors demonstrates a linear relation with radiation dose.
The risk for subsequent CNS tumors demonstrates a linear relation with radiation dose.

Risk factors

- Exposure to cranial radiation is the major risk factor.
- The risk is especially increased after exposure to radiation at a very young age.
Cranial radiation dose and subsequent CNS tumors - inter-individual variability in risk

Role for Genetic Susceptibility?

Candidate gene approach
• Examined genetic variants associated with de novo brain tumors
### Replication of Candidate SNPs – Results

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<th>SNP</th>
<th>Chromosome</th>
<th>MAF_ca</th>
<th>MAF_co</th>
<th>Gene</th>
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<td>rs15869</td>
<td>Chr13</td>
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<td>TP53</td>
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<td>0.29</td>
<td>0.24</td>
<td>ERCC1</td>
<td>DNA repair</td>
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</table>
Proposed Pathogenesis of Subsequent CNS tumors

Efficient DNA repair → Mutational burden

Radiation therapy → Aberrant DNA repair → Specific genetic lesions → Clonal expansion → Subsequent CNS Tumor

Mutational burden
Genetic Predisposition

Lifestyle Exposures

Viral Infections

Age/sex

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Adverse Events
Risk prediction models for subsequent CNS tumors

- **Base Model**
  - AUC = 0.59

- **Genetic Model**
  - AUC = 0.71

- **Clinical Model**
  - AUC = 0.73

- **Final Model**
  - AUC = 0.81

Replication case-control set:
- \( AUC_{CL} = 73\% \)
- \( AUC_{F} = 89\% \)

Risk variants:
- rs15869 [BRCA2]
- rs8079544 [TP53]
- rs498872 [PHLB1]
- rs1673041 [POLD1]
- rs25489 [XRCC1]
- rs11615 [ERCC1]
- rs828699 [XRCC5]

\( P = 0.002 \)
Therapeutic Exposures

- Genetic Predisposition
- Lifestyle Exposures
- Viral Infections
- Age/sex

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Adverse Events
Radiation-induced Breast Cancer

Radiation increases the risk of breast cancer.

Breast Cancer Risk by Radiation Dose

*J Clin Oncol, 2009*

Increased risk similar to BRCA mutation

*NEJM, 1996*

19% at 45 years of age
Radiation-induced Breast Cancer

Endogenous estrogen modifies breast cancer risk.

The only FDA-approved chemopreventive option in both pre- and post-menopausal women is tamoxifen.

Estrogen-blocking intervention is expected to prevent radiation-induced breast cancer in survivors.

*J Clin Oncol*, 2009
Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction

Survivors of childhood or AYA cancer treated with chest radiation

- Female, ≥25 yr old
- ≥12 Gy at age ≤40 y
- NED for 2+ y
- Has at risk tissue

Randomize

Tamoxifen 5 mg x 2y

Placebo x 2y

Endpoints

1° MBD
2°Histologic
2°Circulating Markers

Funding:
R01 CA140245

Mammogram

RPFNA/ Blood/ Urine

Mammogram

Blood/ Urine

Mammogram

RPFNA/ Blood/ Urine
Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction

Graphs showing mammographic density and IGF1 levels over years for Placebo and LDTam groups.
Genetic Predisposition
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Modification of Therapeutic Exposures

• Elimination of cranial radiation therapy for children with standard/low risk acute lymphoblastic leukemia
  • Reduction in risk of secondary brain tumors and cognitive impairment

• Reduction in dose of radiation and field of chest radiation
  • Reduction in risk of secondary breast cancer, pulmonary toxicity, coronary artery disease

• Reduction in anthracycline dose
  • Reduction in risk of cardiomyopathy

• Reduction of dose and type of alkylators
  • Reduction in risk of secondary leukemia
Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer

A. Death from Any Cause

- 15-Yr cumulative mortality:
  - 1970s: 10.7% (10.1–11.4)
  - 1980s: 7.9% (7.4–8.3)
  - 1990s: 5.8% (5.4–6.3)

- P < 0.001

B. Death from Health-Related Cause

- 15-Yr cumulative mortality:
  - 1970s: 3.1% (2.7–3.5)
  - 1980s: 2.4% (2.2–2.7)
  - 1990s: 1.9% (1.6–2.2)

- P < 0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>1970s</th>
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<td>8,182</td>
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<td>1980s</td>
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<td>13,105</td>
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<td>1990s</td>
<td>11,436</td>
<td>11,411</td>
<td>3,924</td>
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</tr>
</tbody>
</table>

Estimated number of cancer survivors in the US (1975 to 2016)

Projected to exceed 26 million by 2040

Cancer Survivors (in millions)

- 3 million in 1975
- 17.0 million in 2017
- Childhood cancer survivors: 0.5 million
The burden of morbidity in adults is substantial and needs to be addressed urgently.
Not yet...

...But we are solidly on the right path
Acknowledgements

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U10 CA098543
R35 CA220502

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fighting blood cancers

Scholar Award for Clinical Research 2191-02
Translational Research Program 6093-08
Translational Research Program 6563-19
Patients and their families