Challenges in studying risk factors for childhood cancer

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Children’s Oncology Group
Overview

• Childhood cancer: major types, incidence, trends

• Risk factors including low dose radiation

• Children’s Oncology Group: Childhood Cancer Research Network

• Challenges to consider
Estimated 13,500 children under the age of 19 years are diagnosed with cancer in each year.

- **Leukemia (ALL, AML)**: 28%
- **Hodgkin disease**: 8%
- **Non-Hodgkin lymphoma**: 7%
- **Central nervous system**: 16%
- **Soft tissue**: 7%
- **Wilms’ tumor**: 4%
- **Bone**: 5%
- **Neuroblastoma**: 5%
- **Germ cell tumor**: 7%
- **Retinoblastoma**: 2%
- **Thyroid**: 3%
- **Melanoma**: 3%
- **Other**: 5%

* Source, SEER 2006
**Childhood Cancer Incidence Rates by Sex: SEER 1973-2003**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Incidence Rate/ Million</th>
<th>M:F Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>160.3</td>
<td>143.7</td>
</tr>
<tr>
<td>Leukemias</td>
<td>41.2</td>
<td>33.5</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>13.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>13.8</td>
<td>6.3</td>
</tr>
<tr>
<td>CNS</td>
<td>29.2</td>
<td>24.5</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>8.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Wilms’ Tumor</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Ewing Sarcoma</td>
<td>3.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>5.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Germ Cell Tumor</td>
<td>11.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>1.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>3.7</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Figure 29.2

Childhood Cancer: SEER Incidence Rates 2003-2007 by ICCC Group (includes Group III benign brain (2004-2007) and myelodysplastic syndromes) and Race/Ethnicity Both Sexes, Under 20 Years of Age

Rate per 1,000,000

- I - Leukemia
- II - Lymphoma
- III - Brain/CNS
- Other

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Rate per 1,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>50.4</td>
</tr>
<tr>
<td>Black</td>
<td>22.3</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>37.5</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>43.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>54.8</td>
</tr>
</tbody>
</table>
What’s been increasing/ decreasing recently?

Annual Percent Change 1992-2004

Cancer Type

Source: Linabery & Ross, Cancer 2008; 112:416-32, *p <0.05
Risk factors - genetics

Hereditary cancer syndromes (gene involved)

- Retinoblastoma (RB1)
- Wilms’ tumor (WT1, others)
- Li-Fraumeni syndrome (p53)
- Gorlin syndrome (Ptch)
- Multiple endocrine neoplasia (RET)
Risk factors- genetic syndromes

Genetic syndromes at high risk

- Down syndrome (leukemia)
- Neurofibromatosis (leukemia, brain tumors)
- Beckwith-Wiedemann syndrome (Wilms’ tumor)
Overall, it is estimated that less than 10% of childhood cancers are due to a familial or genetic syndrome component.
Other Risk Factors?

• High birth weight (ALL)

• Low birth weight (hepatoblastoma)

• Maternal vitamin supplementation? (brain tumors, neuroblastoma, ALL)

• Pesticides/solvents? (AML/ALL)

• Early life infections? (ALL)

• Assisted reproductive technology? (embryonal tumors)
Ionizing Radiation

- Prenatal x-rays
- Atomic bomb survivors
- Chernobyl
- Occupational exposure (nuclear power plant (NPP) workers, radiologic technologists)
- Geographical proximity to NPP
How do we (typically) study childhood cancer?

• Assemble a large enough series of cases and controls

• Through interview/survey, compare experiences in cases compared to controls
Children’s Oncology Group (COG)

• North American cooperative clinical trials group

• Depending on diagnosis, treat upwards of 80% of children with cancer in the US
Ecological analysis comparing observed registrations in the CCG/POG at the zip code/county level to expected numbers calculated from regional SEER rates and population-level data

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Observed/Expected</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1.01</td>
<td>0.99-1.03</td>
</tr>
<tr>
<td>5-9</td>
<td>0.93</td>
<td>0.90-0.95</td>
</tr>
<tr>
<td>10-14</td>
<td>0.84</td>
<td>0.82-0.87</td>
</tr>
<tr>
<td>15-19</td>
<td>0.21</td>
<td>0.20-0.21</td>
</tr>
</tbody>
</table>
Direct analysis comparing pediatric cancer data from 11 SEER registries to registrations within CCG/POG from 1992-1997

**TABLE 4**
Rates of Registration by Cooperative Groups of Children Diagnosed with Cancer by Tumor Type, 1992–1997, All SEER Regions

<table>
<thead>
<tr>
<th>ICCG diagnostic group</th>
<th>Ages Birth–14 yrs&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ages 15–19 yrs</th>
<th>Ages Birth–19 yrs&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Leukemia</td>
<td>84.7 (1985/2341)</td>
<td>44.2 (168/380)</td>
<td>72.9 (2153/2721)</td>
</tr>
<tr>
<td>II Lymphomas and reticuloendothelial neoplasms</td>
<td>69.9 (498/683)</td>
<td>26.7 (188/705)</td>
<td>57.4 (686/1388)</td>
</tr>
<tr>
<td>III CNS and miscellaneous intracranial and intraspinal neoplasms</td>
<td>61.0 (906/1487)</td>
<td>25.2 (75/298)</td>
<td>50.5 (975/1785)</td>
</tr>
<tr>
<td>IV Sympathetic nervous system tumors</td>
<td>69.1 (429/549)</td>
<td>33.3 (5/15)</td>
<td>58.5 (434/764)</td>
</tr>
<tr>
<td>V Retinoblastoma</td>
<td>30.2 (95/232)</td>
<td>0.0 (0/1)</td>
<td>21.2 (95/233)</td>
</tr>
<tr>
<td>VI Renal tumors</td>
<td>80.1 (352/442)</td>
<td>23.5 (4/17)</td>
<td>63.6 (356/441)</td>
</tr>
<tr>
<td>VII Hepatic tumors</td>
<td>81.9 (79/95)</td>
<td>40.0 (6/15)</td>
<td>69.7 (85/110)</td>
</tr>
<tr>
<td>VIII Malignant bone tumors</td>
<td>64.6 (214/327)</td>
<td>50.2 (121/241)</td>
<td>66.5 (335/529)</td>
</tr>
<tr>
<td>IX Soft tissue sarcomas</td>
<td>67.4 (315/477)</td>
<td>30.0 (64/213)</td>
<td>56.5 (379/690)</td>
</tr>
<tr>
<td>X Germ cell trophoblastic and other gonadal neoplasms</td>
<td>47.3 (134/289)</td>
<td>10.9 (52/476)</td>
<td>36.8 (136/765)</td>
</tr>
<tr>
<td>XI Carcinomas and other malignant epithelial neoplasms</td>
<td>26.3 (60/232)</td>
<td>6.3 (37/585)</td>
<td>26.4 (978/37)</td>
</tr>
<tr>
<td>XII Other and unspecified malignant neoplasms</td>
<td>46.4 (12/24)</td>
<td>13.6 (3/22)</td>
<td>37.0 (15/48)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>71.1 (5073/7140)</td>
<td>24.4 (723/2968)</td>
<td>57.5 (5796/10108)</td>
</tr>
</tbody>
</table>

SEER: Surveillance, Epidemiology, and End Results; ICCG: International Classification of Childhood Cancer<sup>a</sup>; CNS: Central nervous system.

<sup>a</sup> Registration rates were standardized to the age distribution of children diagnosed with cancer in all SEER regions from 1992 through 1997.
# Table 1. Children’s Cancer Group/COG etiology of childhood cancer studies

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Title</th>
<th>Cases (n)</th>
<th>Chairperson</th>
<th>Source of funds</th>
</tr>
</thead>
<tbody>
<tr>
<td>E01</td>
<td>Case-control study of osteogenic sarcoma</td>
<td>200</td>
<td>T. Pendergrass</td>
<td>Local</td>
</tr>
<tr>
<td>E02</td>
<td>Case-control study of hepatoblastoma</td>
<td>75</td>
<td>J. Buckley</td>
<td>Local</td>
</tr>
<tr>
<td>E03</td>
<td>Case-control study of Ewing’s sarcoma</td>
<td>170</td>
<td>L. Robison</td>
<td>NIH</td>
</tr>
<tr>
<td>E04</td>
<td>Self-administered questionnaire</td>
<td>3,500</td>
<td>J. Buckley</td>
<td>Local</td>
</tr>
<tr>
<td>E05</td>
<td>Case-control study of acute nonlymphoblastic leukemia</td>
<td>204</td>
<td>L. Robison</td>
<td>NIH</td>
</tr>
<tr>
<td>E06</td>
<td>Case-control study of Wilms’ tumor*</td>
<td>240</td>
<td>A. Olshan</td>
<td>March of Dimes</td>
</tr>
<tr>
<td>E07</td>
<td>Case-control study of retinoblastoma</td>
<td>270</td>
<td>A. Meadows</td>
<td>NIH</td>
</tr>
<tr>
<td>E08</td>
<td>Case-control study of non-Hodgkin’s lymphoma</td>
<td>249</td>
<td>J. Buckley</td>
<td>NIH</td>
</tr>
<tr>
<td>E09</td>
<td>Case-control study of infant leukemia</td>
<td>302</td>
<td>L. Robison</td>
<td>NIH</td>
</tr>
<tr>
<td>E10</td>
<td>Case-control study of rhabdomyosarcoma*</td>
<td>300</td>
<td>S. Grufferman</td>
<td>NIH</td>
</tr>
<tr>
<td>E11</td>
<td>Twin concordance study</td>
<td>850</td>
<td>J. Buckley</td>
<td>American Chemical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Society</td>
</tr>
<tr>
<td>E12</td>
<td>Case-control study of primitive neural ectodermal tumor and astrocytoma</td>
<td>321</td>
<td>G. Bunin</td>
<td>NIH</td>
</tr>
<tr>
<td>E13</td>
<td>Case-control study of Hodgkin’s disease*</td>
<td>300</td>
<td>S. Grufferman</td>
<td>NIH</td>
</tr>
<tr>
<td>E14</td>
<td>Case-control study of acute nonlymphoblastic leukemia</td>
<td>525</td>
<td>M. Steinbuch</td>
<td>NIH</td>
</tr>
<tr>
<td>E15</td>
<td>Case-control study of childhood acute lymphoblastic leukemia</td>
<td>1,915</td>
<td>L. Robison</td>
<td>NIH</td>
</tr>
<tr>
<td>E16</td>
<td>Parental occupation and childhood cancer</td>
<td>3,500</td>
<td>G. Bunin</td>
<td>March of Dimes</td>
</tr>
<tr>
<td>E18</td>
<td>Case-control study of neuroblastoma*</td>
<td>640</td>
<td>A. Olshan</td>
<td>NIH</td>
</tr>
<tr>
<td>E21</td>
<td>Case-control study of primitive neural ectodermal tumor</td>
<td>700</td>
<td>G. Bunin</td>
<td>NIH</td>
</tr>
<tr>
<td>AE22</td>
<td>Case-control study of germ cell tumors</td>
<td>600</td>
<td>X. Shu</td>
<td>NIH</td>
</tr>
<tr>
<td>B955</td>
<td>Environmental exposures and Ras mutations in childhood leukemia</td>
<td>2,440</td>
<td>J. Perentesis</td>
<td>NIH</td>
</tr>
<tr>
<td>B956</td>
<td>Glutathione S-transferase genotype in childhood leukemia</td>
<td>2,440</td>
<td>S. Davies</td>
<td>NIH</td>
</tr>
<tr>
<td>AE23</td>
<td>Case-control study of Down syndrome-leukemia and Down syndrome</td>
<td>160</td>
<td>J. Ross</td>
<td>NIH</td>
</tr>
<tr>
<td>AE24</td>
<td>Case-control study of infant leukemia</td>
<td>480</td>
<td>J. Ross</td>
<td>NIH</td>
</tr>
<tr>
<td>A0026</td>
<td>Case-control study of Wilms' tumor</td>
<td>600</td>
<td>A. Olshan</td>
<td>NIH</td>
</tr>
<tr>
<td>AADM01P1</td>
<td>Pilot for the Childhood Cancer Research Network</td>
<td>1,400</td>
<td>J. Ross</td>
<td>NIH</td>
</tr>
<tr>
<td>AE27</td>
<td>Case-control study of hepatoblastoma</td>
<td>600</td>
<td>L. Spector</td>
<td>Pending, NIH</td>
</tr>
</tbody>
</table>

*Collaborative study with the Pediatric Oncology Group.

†COG study (others were Children’s Cancer Group studies unless otherwise noted).
COG Organizational Structure

COG Institution

- Institution/ PI
- Faculty/ Staff members

- Group Chair
- Scientific Council
- Statistical/ Administrative Office

Committees:
- Epidemiology Committee
- Disease Committees
- Biology Committee
- Other Disciplines
COG Administrative Process

Scientific Council

Concept ─ Full App

Epi Committee
Disease Committee

Grant Funding

Protocol

3-5 months

1-2 months

Study Begins

3-5 months
IRB FOR DUMMIES

A Reference for the Rest of Us!

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by the EU IRB
Nathan Corbitt
Walter Chung
Emily Langan
Wendy Steinberg, &
Dave Unander

Eastern University
(daniel.eastern.edu)

University of Minnesota
Driven to Discover™
How was it working??


N=73
COG Epidemiology Research Program
(Ross JA, Olshan AF. Cancer Epi Biom Prev 2004; 13:1552-54)

- Formation of a national pediatric cancer research registry
- Gene-environment interactions
- Methodological issues (control selection, exposure assessment)
- Education
A proposal for the establishment of a North American research registry for childhood cancer
Why a *nearly* population-based research registry?

Facilitate enrollment on COG epidemiology, survivorship, and cancer control protocols

Potentially provide a means to address cancer clustering

Potential for linkage with other databases
CCRN History

NCI / EPA / CDC / ATSDR / DOE / COG (1998)
CCRN Concept development (1999)
External advisory committee (2000)
NAACCR Meeting (2000)
Supplemental funding received (2000)
External advisory committee meeting (2000)
ATSDR Workshop (2000)
Planning meeting with Registry Reps (2000)
Supplemental funding for pilot (2000)
COG Meeting Phoenix (2000)
COG Meeting Chicago (2001)
Pilot Activated (May 2001)
NAACCR Meeting (2001)
CCRN / COG Meeting (2001)
COG Meeting San Antonio (2001)
COG Pilot Enrollments (2002-2007)
CCRN / COG Meeting Arcadia (2002)
NCI Meeting (2002)
COG / CCRN Meetings (2003-2005)
NCCF Funding for Groupwide Implementation (2005)
Workshop on CCRN usage (2005)
CDC Funding for Groupwide Implementation (2006)
Development of complete protocol (2006)
Informatics / Registration Updates (2006)
Protocol to PCIRB (2006-2007)
COG would form the basis of the CCRN

Could eventually include record linkage with existing cancer registries

Simplify the IRB/REB review process
“Consent Protocol”
(COG-AADM01P1)

May 2001 – Jan 2007 Piloted at 23 C.O.G. institutions

• Obtain consent near diagnosis to provide personal identifiers* at registration

• Obtain consent for possible future contact for non-therapeutic studies
<table>
<thead>
<tr>
<th><strong>CCRN Personal Identifiers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child’s name (first, middle, last)</strong></td>
</tr>
<tr>
<td><strong>Date of birth</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td><strong>Race and ethnicity using the North American Association for Central Cancer Registries data standards</strong></td>
</tr>
<tr>
<td><strong>Zip/postal code</strong></td>
</tr>
<tr>
<td><strong>Patients SSN/SIN (requested, not required)</strong></td>
</tr>
<tr>
<td><strong>Diagnosis information (including date of diagnosis) using ICD-0 version 3</strong></td>
</tr>
<tr>
<td><strong>Name (first, middle, last) of one parent/guardian</strong></td>
</tr>
<tr>
<td><strong>Report of death</strong></td>
</tr>
</tbody>
</table>

**If agree to future contact:**

- Up to 2 parents/guardian names/addresses & telephone numbers
- Patient’s address if different than above
- Language spoken in the home
- Email address
“Consent Protocol” (COG-AADM01P1)

May 2001 – Jan 2007 Piloted at 23 C.O.G. institutions

• Obtain consent near diagnosis to provide personal identifiers* at registration

• Obtain consent for possible future contact for non-therapeutic studies

Future studies would then be overseen by the IRB/REB at the institution(s) of the investigator(s) conducting the study.
All institutions obtained IRB approval by 2002

2242 parents/patients approached

2145 (96%) agreed to both consent levels

70 (~3%) agreed to name only

27 (~1%) refused both
CCRN: Group Wide Opening

Dec 2007

- Mandatory to open for all COG institutions for membership
- $100.00 credit per parent/patient approached
- Reminder to parents at 3 months
- Consent patients at age of majority

April 2011

- ~ 200 Institutions with IRB/REB approval
- ~ 20,500 cases enrolled

Consent patients at age of majority

University of Minnesota
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Caveats

• Comparisons to COG registrations (clinical trials, non-therapeutic/non-CCRN studies)
  – Difficulty in determining denominator (language barriers, institutional variations, etc)

• Overall denominator amongst various diagnostic subgroups
Some challenges

• Heterogeneity in the presence of very small sample size

• Timing of exposure and implications for causation

• Additional factors to consider
Epidemiology of Childhood Leukemia

- Leukemia
  - ALL
  - AML

Morphology
Cytogenetics
Molecular Biology
Immunophenotype

Down syndrome

Infants

MLL gene

GWAS
Epigenetics
microRNA

1960
1970
1980
1990
2000
2010

Fetal origins
# Fetal Origins: Newborn Dried Blood Spots

<table>
<thead>
<tr>
<th>MDL Lab No.</th>
<th>REPEAT (Y)</th>
<th>TEST (N)</th>
<th>Birth Weight (Grams)</th>
<th>Sex (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby's Last Name</td>
<td>First Name</td>
<td>Birth Date (Yr, Mo, Day)</td>
<td>Date Specimen Collected (Mo, Day, Yr)</td>
<td>Birth time 24 hr clock</td>
</tr>
<tr>
<td>Baby's Hospital I.D. Number</td>
<td>Mother's Medical Record No</td>
<td>Blood Collection Time 24 hr clock</td>
<td>Collect time 24 hr clock</td>
<td></td>
</tr>
<tr>
<td>Newborn Last Name</td>
<td>First</td>
<td>Mother's Age</td>
<td>Mother's Race</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td>Zip</td>
<td>Baby Transfused (Y/N)</td>
<td>Date</td>
<td></td>
</tr>
</tbody>
</table>

- **PKU/other newborn metabolic disorders**

- **Translocations at birth**
“Backtracking” leukemia

Source: Greaves, 2002
"Backtracking" *MLL* rearrangements in infant leukemias

<table>
<thead>
<tr>
<th># Guthrie cards positive/# tested</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/3</td>
<td>Gale et al, 1997</td>
</tr>
<tr>
<td>2/2</td>
<td>Yagi et al, 2000</td>
</tr>
<tr>
<td>1/5</td>
<td>Maia et al, 2004</td>
</tr>
<tr>
<td><strong>TOTAL: 6/10</strong></td>
<td></td>
</tr>
</tbody>
</table>
Timing of Events

Pre-conception

Conception

In utero

Post-natal

Exposure

Mom/ Dad

Genetic susceptibility

Mom/ (Fetus)

Genetic susceptibility

(Dad)

Child

Genetic susceptibility

(Mom/Dad)

Establishment of imprints/methylation
Additional factors to consider...

• Population mixing?

• Rural versus urban areas

• Under-represented populations/counts?

• Exposure measurement: workers versus those in proximity to plants

• Direct interviews versus record linkages