# Chronic Disease Working Group* 2012

Williamsburg

June, 2012

* Includes Neurology and Reproductive WGs

# Chronic Disease Working Group

## Core Members

- Chuck Sklar (Chair)
  - Lisa Diller
  - Eric Chow
  - Dan Green
  - Kevin Oeffinger
  - Roger Packer

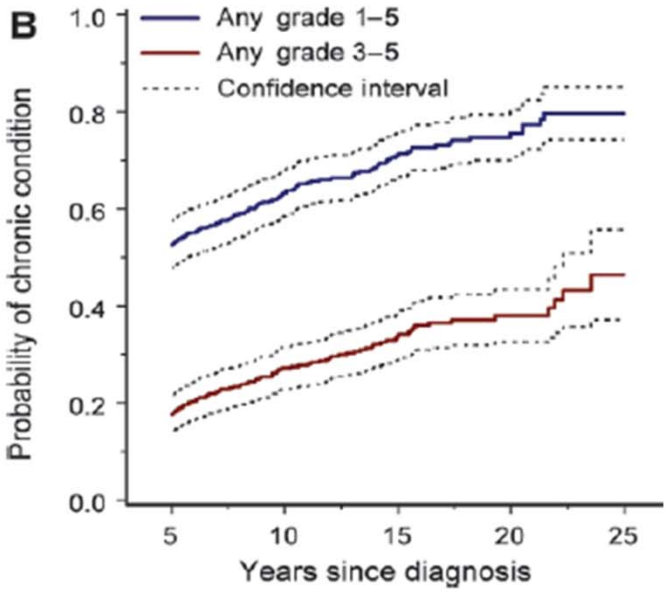
# Chronic Disease Working Group 2012
## Publications 2010-2012 (17)

- *Ocular late effects,* **Whelan (Pediatr Blood Cancer)**
- *Fertility of male survivors,* **Green *(JCO)***
- *CVRF in adult survivors,* **Meacham (Cancer Epi Biomarker Prev)**
- *Late neurological sequelae in leukemia survivors*, **Goldsby (JCO)**
- *Outcomes in survivors of osteosarcoma,* **Nagarajan et al (Cancer)**
- *Outcomes in Ewing's*, **Ginsberg (JNCI)**
- *Stillbirth and neonatal death in relation to RT*, **Signorello et al (Lancet)**
- *Long-term survivors of CNS malignancies*, **Armstrong (Eur J Neurol)**
- *Long-term health related outcomes HSCT vs standard*, **Armenian (Blood)**

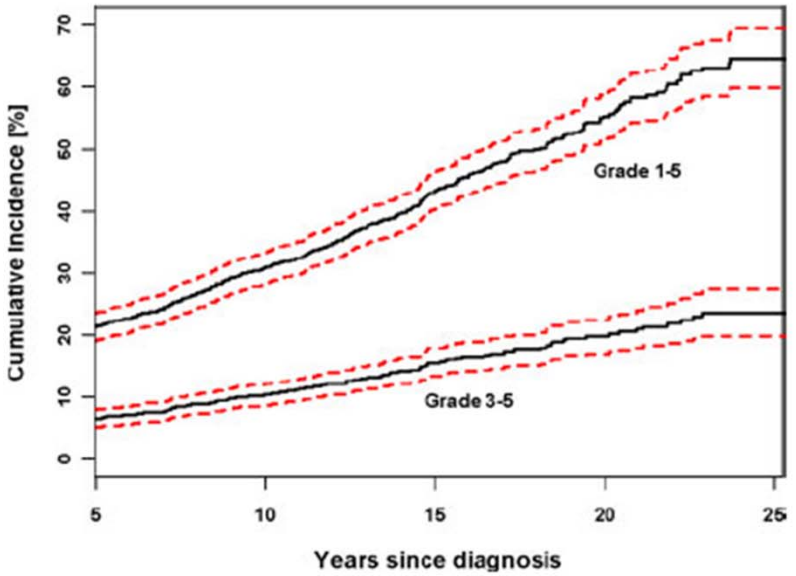
# Chronic Disease Working Group 2012
## Publications 2010-2012 (17)

- *Gastrointestinal complications,* **Goldsby (Gastroenterology)**
- *Decreased fertility among females after 22 to 27 Gy CRT*, **Green (Fertility Sterility)**
- *Auditory complications*, **Whelan (Pediatr Blood Cancer)**
- *Twenty-five year follow-up Wilms*, **Termuhlen (Pediatr Blood Cancer)**
- *Congenital anomalies in offspring*, **Signorello (JCO)**
- *Risk factors for obesity*, **Green (JCO)**
- *Fracture risk*, **Wilson (Cancer)**
- *Radiation and risk of growth/endocrine problems in leukemia*, **Chow (Pediatr Blood Cancer)**

# Chronic medical conditions




**Ewing's**




**Wilms**

# Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study

*Lisa B Signorello, John J Mulvihill, Daniel M Green, Heather M Munro, Marilyn Stovall, Rita E Weathers, Ann C Mertens, John A Whitton, Leslie L Robison, John D Boice Jr*

*Lancet* 2010;376:624

# Stillbirth and neonatal death

| | Treatment before menarche | | Treatment after menarche | |
|---|---|---|---|---|
| | Risk of stillbirth or neonatal death | Relative risk*† (95% CI) | Risk of stillbirth or neonatal death | Relative risk*‡ (95% CI) |
| No radiation | 5/494 (1%) | Reference | 13/447 (3%) | Reference |
| 0·01–0·99 Gy | 11/636 (2%) | 1·3 (0·5–3·9) | 7/599 (1%) | 0·3 (0·1–1·0) |
| 1·00–2·49 Gy | 3/69 (4%) | 4·7 (1·2–19·0) | 2/70 (3%) | 1·2 (0·2–6·4) |
| ≥2·50 Gy | 11/82 (13%) | 12·3 (4·2–36·0) | 1/85 (1%) | 0·2 (0·0–1·4) |

Data are n/N (%), unless otherwise indicated. Data are for the offspring of only 1481 (89%) of 1657 female survivors for whom timing of treatment in relation to menarche could be established. For the 160 women in whom age at menarche was missing and needed to be estimated, we assumed they were treated before menarche if they were treated at age 9 years or younger, and after menarche if they were treated at age 18 years or older. *Adjusted for calendar year of birth and maternal age. †p value for trend was 0·006. ‡p value for trend was 0·32.

***Table 4:*** **Association between radiotherapy doses to uterus and ovaries and risk of stillbirth or neonatal death in offspring of survivors of childhood cancer**

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GASTROENTEROLOGY 2011;140:1464–1471

# Survivors of Childhood Cancer Have Increased Risk of Gastrointestinal Complications Later in Life

ROBERT GOLDSBY,[*] YAN CHEN,[‡] SHANNON RABER,[*] LINDA LI,[*] KAREN DIEFENBACH,[§] MARGARETT SHNORHAVORIAN,[‖] NINA KADAN-LOTTICK,[§] FAY KASTRINOS,[¶] YUTAKA YASUI,[‡] MARILYN STOVALL,[#] KEVIN OEFFINGER,[**] CHARLES SKLAR,[**] GREGORY T. ARMSTRONG,[‡‡] LESLIE L. ROBISON,[‡‡] and LISA DILLER[§§]

*[*]Pediatric Hematology/Oncology, UCSF Benioff Children's Hospital, San Francisco, California; [‡]Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada; [§]Pediatric Surgery, Yale University School of Medicine, New Haven, Connecticut; [‖]Urology, Seattle Children's Hospital, Seattle, Washington; [¶]Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, New York; [#]Radiation Physics, M.D. Anderson Cancer Center, Houston, Texas; [**]Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York; [‡‡]Epidemiology and Cancer Control, St Jude Children's Research Hospital, Memphis, Tennessee; and [§§]Pediatric Oncology, Dana-Farber Cancer Institute/Children's Hospital, Boston, Massachusetts*

# Gastrointestinal complications

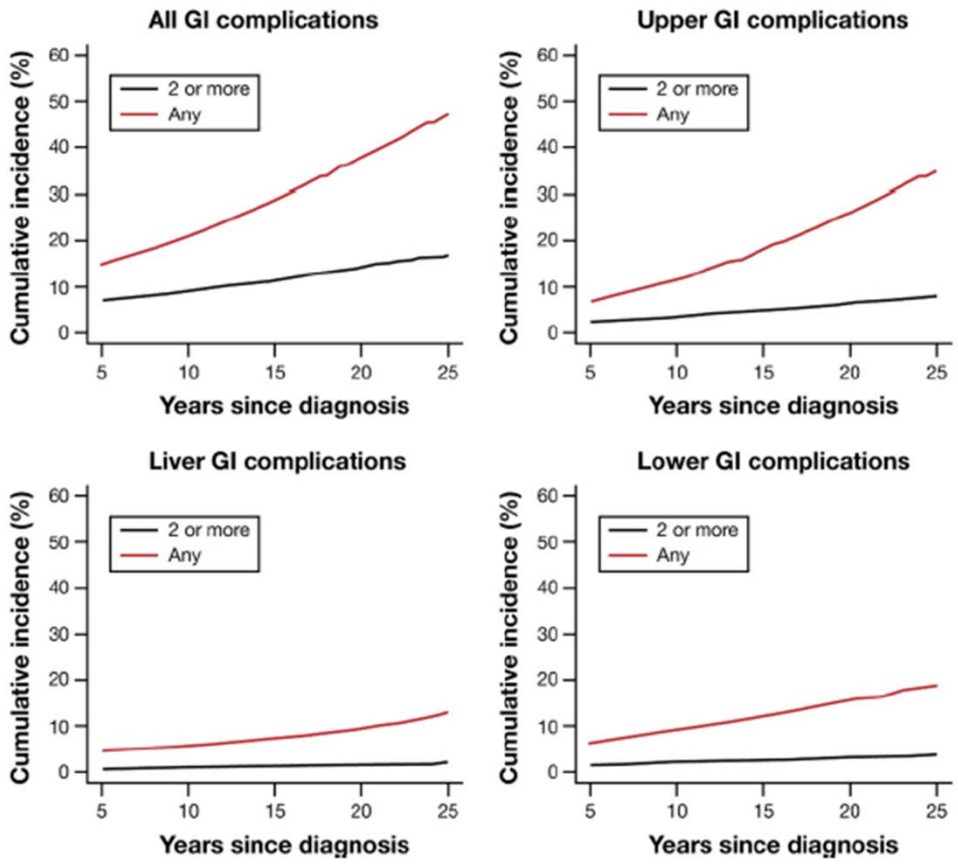


**Figure 1.** Cumulative incidence of GI conditions (any, *red*; 2 or more, *black*) among 5-year survivors.

# Gastrointestinal complications

**Table 4.** Multivariable Poisson Regression Analysis of Late-Onset GI outcomes

| | Upper GI complications | | Liver complications | | Lower GI complications | |
|---|---|---|---|---|---|---|
| | RR (95% CI) | *P* value | RR (95% CI) | *P* value | RR (95% CI) | *P* value |
| Age at diagnosis (*y*) | | | | | | |
| <3 (ref) | | | | | | |
| 3–9 | 1.3 (1.1–1.5) | <.001 | 2.2 (1.5–3.2) | <.001 | 1.2 (1.0–1.5) | .09 |
| 10+ | 1.5 (1.3–1.7) | <.001 | 2.6 (1.8–3.8) | <.001 | 1.3 (1.0–1.6) | .03 |
| Abdominal radiation | | | | | | |
| No (ref) | | | | | | |
| Yes | 1.3 (1.2–1.4) | <.001 | | | 1.3 (1.1–1.5) | .005 |
| Alkylating agents score | | | | | | |
| None (ref) (score = 0) | | | | | | |
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| Anthracycline ($mg/m^2$) | | | | | | |
| None (ref) | | | | | | |
| ≤100 | 1.1 (0.9–1.5) | .38 | 1.4 (0.7–2.6) | .30 | | |
| 101–200 | 1.3 (1.1–1.6) | .002 | 1.1 (0.6–1.8) | .80 | | |
| 201–300 | 1.1 (0.9–1.4) | .25 | 2.1 (1.5–3.0) | <.001 | | |
| >300 | 1.2 (1.1–1.4) | .007 | 1.3 (1.0–1.8) | .05 | | |
| Abdominal surgery | | | | | | |
| No (ref) | | | | | | |
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Pediatr Blood Cancer 2011;57:126–134

# Auditory Complications in Childhood Cancer Survivors: A Report From the Childhood Cancer Survivor Study

Kimberly Whelan, MD, MSPH,[1]* Kayla Stratton, MS,[2] Toana Kawashima, MS,[2] Wendy Leisenring, PhD,[2] Susan Hayashi,[3] John Waterbor, MD, PhD,[4] Julie Blatt, MD,[5] Charles A. Sklar, MD,[6] Roger Packer, MD,[7] Pauline Mitby, MPH,[8] Leslie L. Robison, PhD,[9] and Ann C. Mertens, PhD[10]

# Auditory complications

**TABLE III. Summary of Treatment Factors and Relative Risk of Late Auditory Conditions 5+ Years Post-Diagnosis**

| | Treatment factor relative risk[a] (95% CI) | |
|---|---|---|
| Auditory condition | Any platinum drug use versus none | Any radiation to posterior fossa or temporal lobe versus none |
| Problems hearing sounds | 2.1 (1.3–3.2)* | 1.7 (1.3–2.2)* |
| Tinnitus | 2.8 (1.9–4.2)* | 1.2 (0.9–1.6) |
| Hearing loss | 4.1 (2.5–6.7)* | 2.2 (1.4–3.5)* |
| Deafness | 1.7 (0.8–3.5) | 2.3 (1.2–4.2)* |

[a]Models for posterior fossa/temporal lobe radiation adjusted for any platinum drug use, gender, age at diagnosis, and VP shunt. Models for platinum drug adjusted for age at diagnosis, gender, VP shunt, and maximum radiation dose levels. *$P$-value <0.01.

# Auditory complications

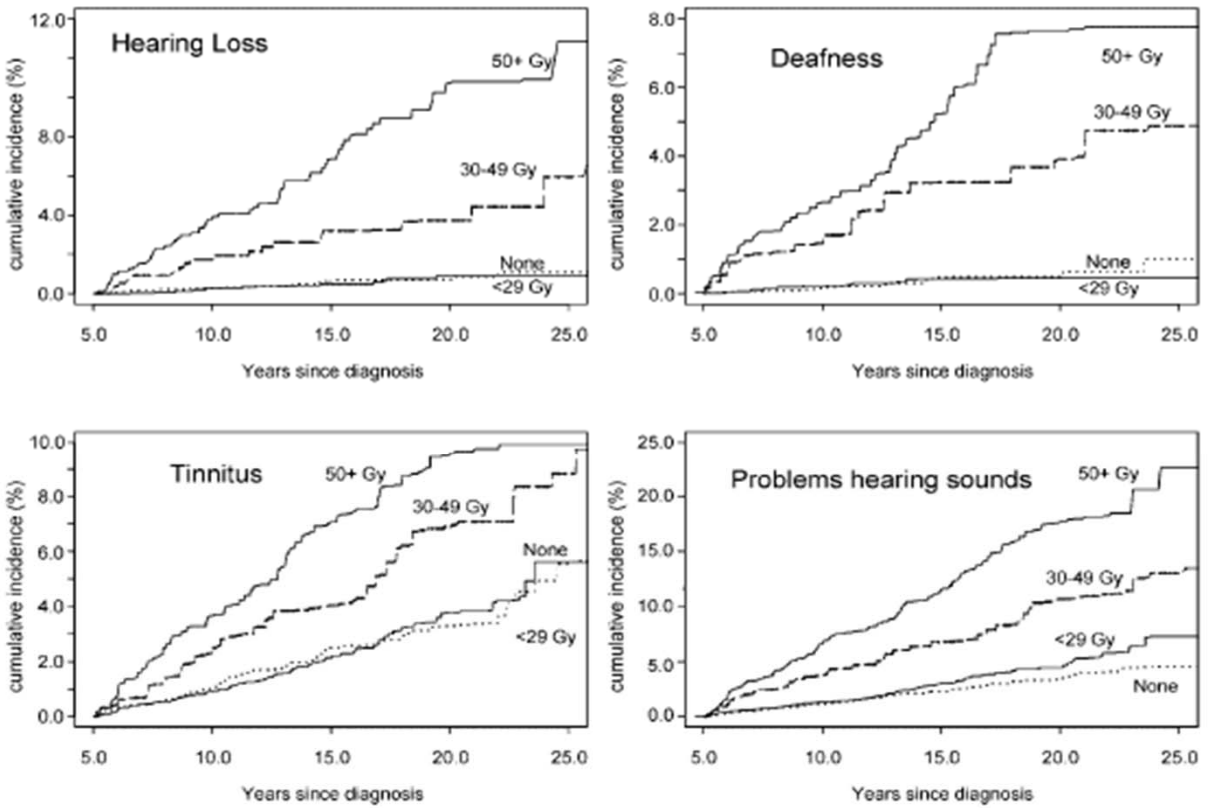
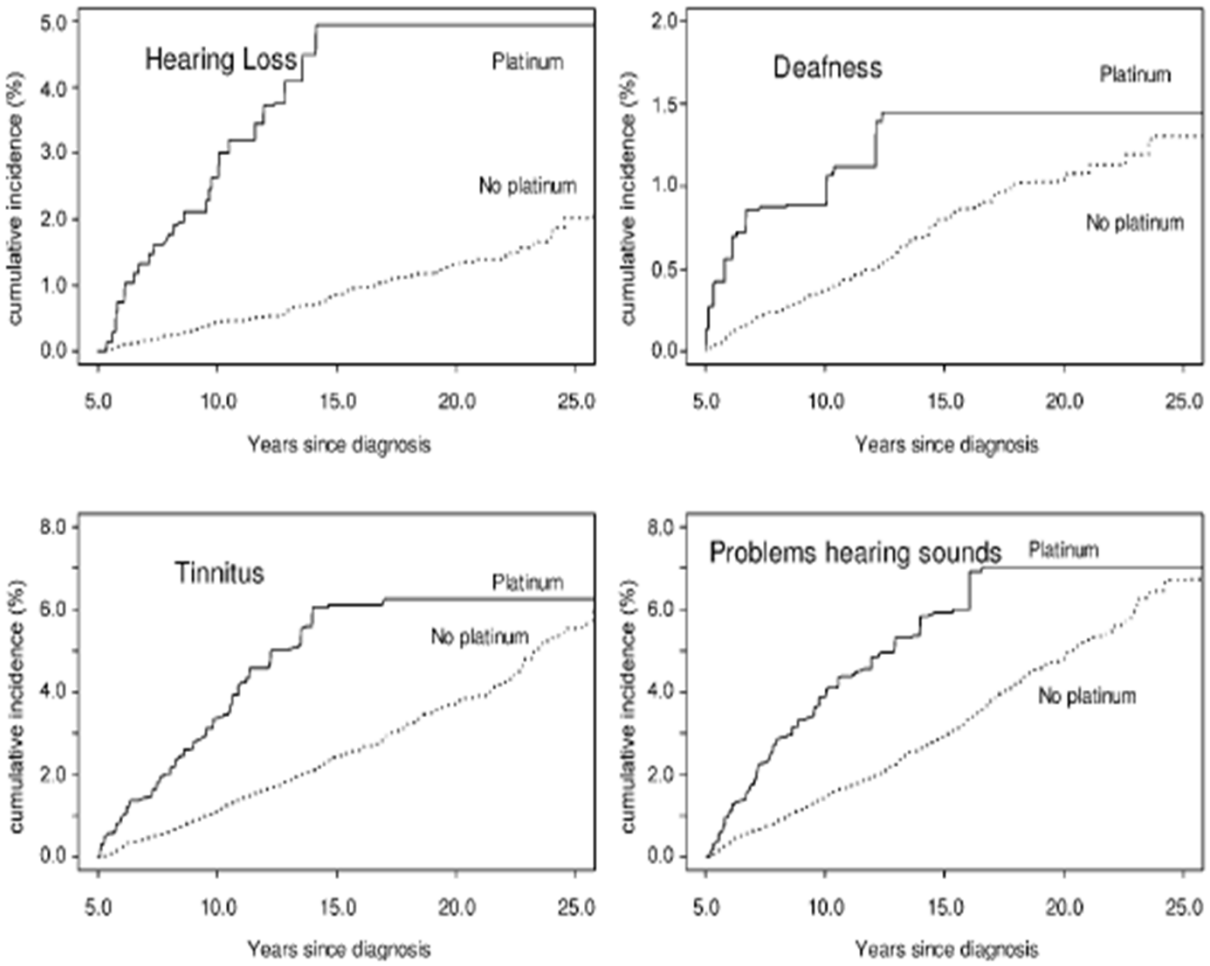



**Fig. 1.** Cumulative incidence (%) of conditions based on maximum radiation to temporal lobe or posterior fossa.

*diatr Blood Cancer* DOI 10.1002/pbc

**RT DOSE (temporal lobe or posterior fossa)**

# Auditory complications



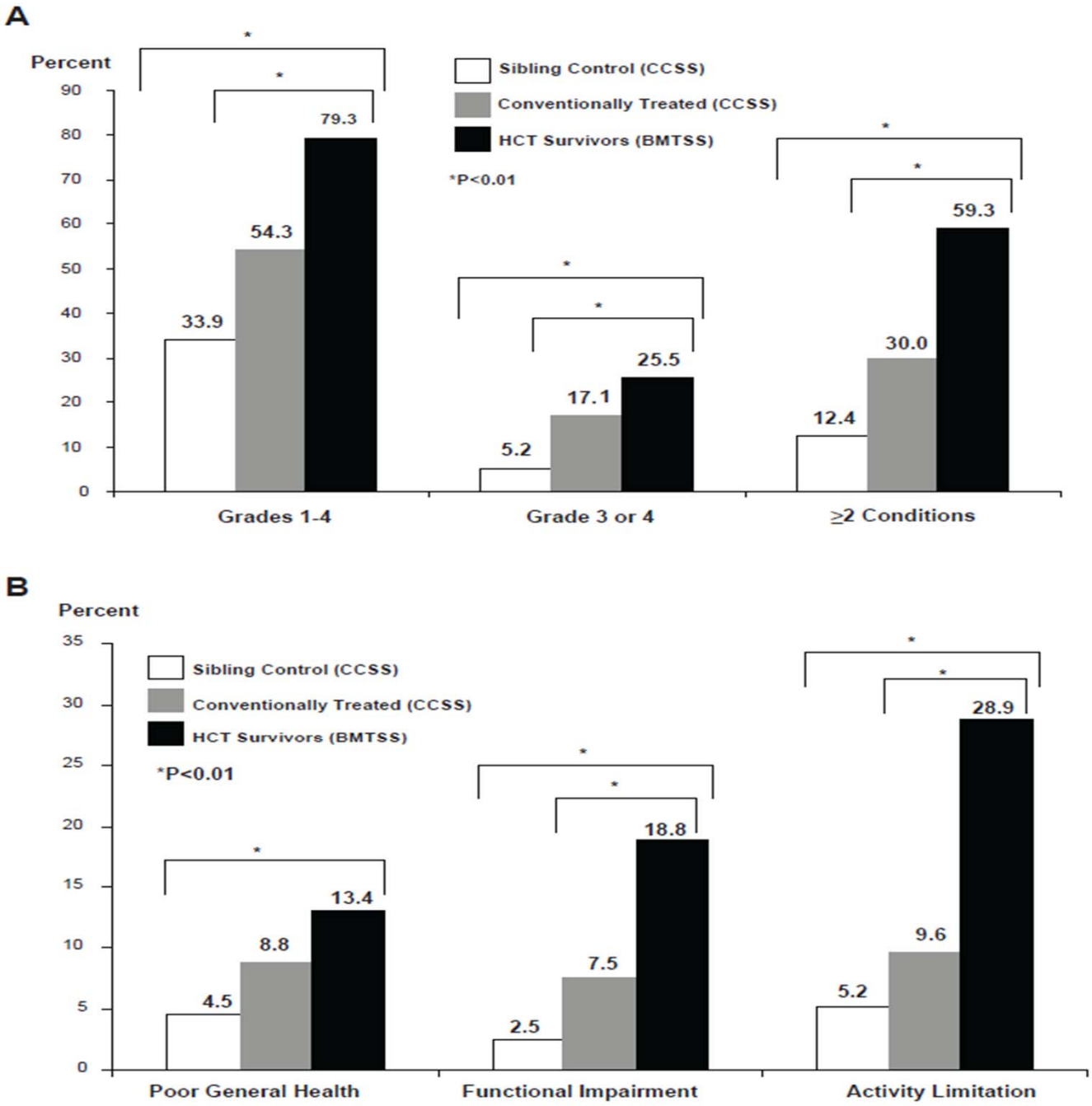

**PLATINUM Y/N**

blood

2011 118: 1413-1420
Prepublished online June 7, 2011;
doi:10.1182/blood-2011-01-331835

# Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS)

Saro H. Armenian, Can-Lan Sun, Toana Kawashima, Mukta Arora, Wendy Leisenring, Charles A. Sklar, K. Scott Baker, Liton Francisco, Jennifer Berano Teh, George Mills, F. Lennie Wong, Joseph Rosenthal, Lisa R. Diller, Melissa M. Hudson, Kevin C. Oeffinger, Stephen J. Forman, Leslie L. Robison and Smita Bhatia


A
Percent
Sibling Control (CCSS)
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*P<0.01
90
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70
60
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30
20
10
0
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30.0
59.3
*
Grades 1-4
Grade 3 or 4
≥2 Conditions
B
Percent
Sibling Control (CCSS)
Conventionally Treated (CCSS)
HCT Survivors (BMTSS)
*P<0.01
35
30
25
20
15
10
5
0
4.5
8.8
13.4
2.5
7.5
18.8
5.2
9.6
28.9
*
Poor General Health
Functional Impairment
Activity Limitation

# BMT vs conventional

**Table 4. Relative risk of chronic health conditions and adverse health status among HSCT survivors (BMTSS), as compared with conventionally treated cancer survivors (CCSS)**

| | Grades 1-5 (95% CI) | Grade 3-5 (95% CI) | ≥ 2 conditions (95% CI) | Poor general health (95% CI) | Functional impairment (95% CI) | Activity limitation (95% CI) |
|---|---|---|---|---|---|---|
| Conventionally treated (CCSS) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| BMTSS | 1.5 (1.1-2.2) | 3.9 (2.4-6.4) | 2.6 (1.7-3.8) | 2.8 (1.8-6.8) | 3.5 (1.8-6.8) | 5.8 (3.2-10.5) |
| *P* | < .01 | < .01 | < .01 | < .01 | < .01 | < .01 |
| **Donor source, BMTSS*** | | | | | | |
| Autologous | 1.3 (1.0-1.8) | 3.0 (1.6-5.6) | 1.8 (1.1-2.8) | 3.3 (1.2-9.6) | 2.7 (0.8-9.1) | 3.1 (1.2-8.2) |
| Allogeneic, related | 1.6 (1.4-1.9) | 4.1 (2.7-6.3) | 2.8 (2.1-3.7) | 2.7 (1.3-5.6) | 3.7 (1.9-7.0) | 6.9 (3.7-12.8) |
| Allogeneic, unrelated | 1.7 (1.2-2.4) | 6.8 (3.1-14.9) | 3.4 (2.1-5.6) | 1.7 (0.2-20.2) | 4.1 (0.7-24.6) | 9.5 (3.5-25.5) |
| *P* value (trend) | < .01 | < .01 | < .01 | .05 | < .01 | < .01 |

Model adjusted for: age at the time of the study, sex, race or ethnicity, health insurance, treatment era, time from diagnosis, underlying diagnosis, radiation (brain, chest), and chemotherapy (anthracycline, alkylating agent, platinum agent, epidophyllotoxin).

BMTSS indicates Bone Marrow Transplant Survivor Study; CCSS, Childhood Cancer Survivor Study; and CI, confidence interval.

*Referent group: conventionally treated cancer survivors (CCSS).

# BMT vs conventional

**Table 4. Relative risk of chronic health conditions and adverse health status among HSCT survivors (BMTSS), as compared with conventionally treated cancer survivors (CCSS)**

| | Grades 1-5 (95% CI) | Grade 3-5 (95% CI) | ≥ 2 conditions (95% CI) | Poor general health (95% CI) | Functional impairment (95% CI) | Activity limitation (95% CI) |
|---|---|---|---|---|---|---|
| Conventionally treated (CCSS) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| BMTSS | 1.5 (1.1-2.2) | 3.9 (2.4-6.4) | 2.6 (1.7-3.8) | 2.8 (1.8-6.8) | 3.5 (1.8-6.8) | 5.8 (3.2-10.5) |
| *P* | < .01 | < .01 | < .01 | < .01 | < .01 | < .01 |
| **Donor source, BMTSS*** | | | | | | |
| Autologous | 1.3 (1.0-1.8) | 3.0 (1.6-5.6) | 1.8 (1.1-2.8) | 3.3 (1.2-9.6) | 2.7 (0.8-9.1) | 3.1 (1.2-8.2) |
| Allogeneic, related | 1.6 (1.4-1.9) | 4.1 (2.7-6.3) | 2.8 (2.1-3.7) | 2.7 (1.3-5.6) | 3.7 (1.9-7.0) | 6.9 (3.7-12.8) |
| Allogeneic, unrelated | 1.7 (1.2-2.4) | 6.8 (3.1-14.9) | 3.4 (2.1-5.6) | 1.7 (0.2-20.2) | 4.1 (0.7-24.6) | 9.5 (3.5-25.5) |
| *P* value (trend) | < .01 | < .01 | < .01 | .05 | < .01 | < .01 |

Model adjusted for: age at the time of the study, sex, race or ethnicity, health insurance, treatment era, time from diagnosis, underlying diagnosis, radiation (brain, chest), and chemotherapy (anthracycline, alkylating agent, platinum agent, epidophyllotoxin).

BMTSS indicates Bone Marrow Transplant Survivor Study; CCSS, Childhood Cancer Survivor Study; and CI, confidence interval.

*Referent group: conventionally treated cancer survivors (CCSS).

# BMT vs conventional

**Table 4. Relative risk of chronic health conditions and adverse health status among HSCT survivors (BMTSS), as compared with conventionally treated cancer survivors (CCSS)**

| | Grades 1-5 (95% CI) | Grade 3-5 (95% CI) | ≥ 2 conditions (95% CI) | Poor general health (95% CI) | Functional impairment (95% CI) | Activity limitation (95% CI) |
|---|---|---|---|---|---|---|
| Conventionally treated (CCSS) | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| BMTSS | 1.5 (1.1-2.2) | 3.9 (2.4-6.4) | 2.6 (1.7-3.8) | 2.8 (1.8-6.8) | 3.5 (1.8-6.8) | 5.8 (3.2-10.5) |
| *P* | < .01 | < .01 | < .01 | < .01 | < .01 | < .01 |
| **Donor source, BMTSS*** | | | | | | |
| Autologous | 1.3 (1.0-1.8) | 3.0 (1.6-5.6) | 1.8 (1.1-2.8) | 3.3 (1.2-9.6) | 2.7 (0.8-9.1) | 3.1 (1.2-8.2) |
| Allogeneic, related | 1.6 (1.4-1.9) | 4.1 (2.7-6.3) | 2.8 (2.1-3.7) | 2.7 (1.3-5.6) | 3.7 (1.9-7.0) | 6.9 (3.7-12.8) |
| Allogeneic, unrelated | 1.7 (1.2-2.4) | 6.8 (3.1-14.9) | 3.4 (2.1-5.6) | 1.7 (0.2-20.2) | 4.1 (0.7-24.6) | 9.5 (3.5-25.5) |
| *P* value (trend) | < .01 | < .01 | < .01 | .05 | < .01 | < .01 |

Model adjusted for: age at the time of the study, sex, race or ethnicity, health insurance, treatment era, time from diagnosis, underlying diagnosis, radiation (brain, chest), and chemotherapy (anthracycline, alkylating agent, platinum agent, epidophyllotoxin).

BMTSS indicates Bone Marrow Transplant Survivor Study; CCSS, Childhood Cancer Survivor Study; and CI, confidence interval.

*Referent group: conventionally treated cancer survivors (CCSS).

# BMT vs conventional

**Table 5. Prevalence and relative risk of common chronic health conditions among HSCT survivors (BMTSS), as compared with conventionally treated cancer survivors (CCSS) and sibling controls (CCSS)**

| | Relative risk grade 3-5 conditions | | | Relative risk grade 3-4 conditions | |
|---|---|---|---|---|---|
| | BMTSS (N = 145), % | Conventionally treated, CCSS (N = 7207), % | RR (95% CI)* | Sibling control, CCSS (N = 4020), % | RR (95% CI)† |
| Second malignant neoplasm‡ | 6.9 | 3.1 | 8.6 (2.9-25.3) | 0.6 | 14.5 (7.1-29.8) |
| Endocrine | 29.7 | 4.9 | 7.7 (4.2-14.3) | 1.3 | 29.6 (21.0-41.8) |
| Musculoskeletal | 2.1 | 0.5 | 7.4 (2.4-23.1) | 0.05 | 76.5 (11.0-531.3) |
| Gastrointestinal | 2.8 | 2.0 | 4.8 (1.0-21.7) | 0.4 | 10.4 (3.5-31.1) |
| Neurosensory impairment | 9.0 | 3.9 | 3.8 (1.4-10.3) | 1.4 | 6.6 (3.6-12.1) |
| Genitourinary | 1.4 | 0.3 | 2.9 (1.1-7.8) | 0.05 | 26.4 (3.5-196.2) |
| Cardiovascular | 4.8 | 3.2 | 0.5 (0.1-2.5) | 0.5 | 12.7 (5.4-30.0) |

# BMT vs conventional

**Table 5. Prevalence and relative risk of common chronic health conditions among HSCT survivors (BMTSS), as compared with conventionally treated cancer survivors (CCSS) and sibling controls (CCSS)**

| | Relative risk grade 3-5 conditions | | | Relative risk grade 3-4 conditions | |
|---|---|---|---|---|---|
| | BMTSS (N = 145), % | Conventionally treated, CCSS (N = 7207), % | RR (95% CI)* | Sibling control, CCSS (N = 4020), % | RR (95% CI)† |
| Second malignant neoplasm‡ | 6.9 | 3.1 | 8.6 (2.9-25.3) | 0.6 | 14.5 (7.1-29.8) |
| Endocrine | 29.7 | 4.9 | 7.7 (4.2-14.3) | 1.3 | 29.6 (21.0-41.8) |
| Musculoskeletal | 2.1 | 0.5 | 7.4 (2.4-23.1) | 0.05 | 76.5 (11.0-531.3) |
| Gastrointestinal | 2.8 | 2.0 | 4.8 (1.0-21.7) | 0.4 | 10.4 (3.5-31.1) |
| Neurosensory impairment | 9.0 | 3.9 | 3.8 (1.4-10.3) | 1.4 | 6.6 (3.6-12.1) |
| Genitourinary | 1.4 | 0.3 | 2.9 (1.1-7.8) | 0.05 | 26.4 (3.5-196.2) |
| Cardiovascular | 4.8 | 3.2 | 0.5 (0.1-2.5) | 0.5 | 12.7 (5.4-30.0) |

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ORIGINAL REPORT

# Congenital Anomalies in the Children of Cancer Survivors: A Report From the Childhood Cancer Survivor Study

*Lisa B. Signorello, John J. Mulvihill, Daniel M. Green, Heather M. Munro, Marilyn Stovall, Rita E. Weathers, Ann C. Mertens, John A. Whitton, Leslie L. Robison, and John D. Boice Jr*

# Congenital anomalies

**Table 3.** Distribution of Congenital Anomalies Among 4,699 Offspring of 1,627 Female and 1,128 Male Cancer Survivors, Stratified by the Parent's Exposure to Radiotherapy

| | Offspring of Female Survivors | | | | Offspring of Male Survivors | | | |
|---|---|---|---|---|---|---|---|---|
| | Mother Irradiated (n = 1,753) | | Mother Not Irradiated (n = 1,021) | | Father Irradiated (n = 1,218) | | Father Not Irradiated (n = 707) | |
| Congenital Anomaly | No. | % | No. | % | No. | % | No. | % |
| Congenital malformations, total* | 50 | 2.9 | 27 | 2.6 | 16 | 1.3 | 14 | 2.0 |
| Nervous system | 3 | 0.2 | 3 | 0.3 | 1 | 0.1 | 2 | 0.3 |
| Eye, ear, face, and neck | 7 | 0.4 | 7 | 0.7 | 1 | 0.1 | 1 | 0.1 |
| Heart and blood vessels | 13 | 0.7 | 6 | 0.6 | 3 | 0.2 | 2 | 0.3 |
| Respiratory organs | | | | | | 0 | 0 | 0 |
| Lip and palate | | | | | | 0.2 | 3 | 0.4 |
| Digestive system | | | | | | 0 | 2 | 0.3 |
| Genitalia | | | | | | 0.2 | 0 | 0 |
| Urinary organs | | | | | | 0 | 1 | 0.1 |
| Extremities | | | | | | 0.2 | 0 | 0 |
| Musculoskeletal system | | | | | | 0.2 | 0 | 0 |
| Skin, hair, nails | | | | | | 0.2 | 2 | 0.3 |
| Endocrine disorder | | | | | | 0 | 1 | 0.1 |
| Multiple simple malformations† | | | | | | 0.1 | 0 | 0 |
| Single-gene defects, total | | | | | | 0.2 | 0 | 0 |
| Polydactyly/syndactyly/hypodactyly | | | | | | 0.2 | 0 | 0 |
| Neurofibromatosis | | | | | | 0 | 0 | 0 |
| Tourette syndrome | | | | | | 0 | 0 | 0 |
| Goldenhar syndrome | | | | | | 0 | 0 | 0 |
| Wolfe-Parkinson-White syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Achondroplasia | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Deafness | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Congenital megacolon | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cytogenetic abnormalities, total | 0 | 0 | 4 | 0.4 | 3 | 0.2 | 1 | 0.1 |
| Down syndrome (trisomy 21) | 0 | 0 | 3 | 0.3 | 1 | 0.1 | 0 | 0 |
| Shone syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Angelman syndrome | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |
| 13q deletion syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 |
| Edwards syndrome (trisomy 18) | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |

**Prevalence 2.7%**

NOTE. One offspring with reported mental retardation, although included in the analyses of total anomalies, is not included in Table 3, because the lack of detail on the child's condition prevented definitive classification in one of the three categories.

*Total reflects the total number of offspring with malformations (n = 107), although the individual malformations sum to 116 because nine children had multiple malformations.

†Nine children had multiple malformations, and these children were counted only once each in the regression analyses.

# Congenital anomalies

**Table 3.** Distribution of Congenital Anomalies Among 4,699 Offspring of 1,627 Female and 1,128 Male Cancer Survivors, Stratified by the Parent's Exposure to Radiotherapy

| | Offspring of Female Survivors | | | | Offspring of Male Survivors | | | |
|---|---|---|---|---|---|---|---|---|
| | Mother Irradiated (n = 1,753) | | Mother Not Irradiated (n = 1,021) | | Father Irradiated (n = 1,218) | | Father Not Irradiated (n = 707) | |
| Congenital Anomaly | No. | % | No. | % | No. | % | No. | % |
| Congenital malformations, total* | 50 | 2.9 | 27 | 2.6 | 16 | 1.3 | 14 | 2.0 |
| Nervous system | 2 | 0.2 | 2 | 0.2 | 1 | 0.1 | 2 | 0.3 |
| Eye, ear, face, and neck | 7 | 0.4 | 7 | 0.7 | 1 | 0.1 | 1 | 0.1 |
| Heart and blood vessels | 13 | 0.7 | 6 | 0.6 | 3 | 0.2 | 2 | 0.3 |
| Respiratory organs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lip and palate | 4 | 0.2 | 1 | 0.1 | 2 | 0.2 | 3 | 0.4 |
| Digestive system | 3 | 0.2 | 1 | 0.1 | 0 | 0 | 2 | 0.3 |
| Genitalia | 4 | 0.2 | 3 | 0.3 | 2 | 0.2 | 0 | 0 |
| Urinary organs | 2 | 0.1 | 0 | 0 | 0 | 0 | 1 | 0.1 |
| Extremities | 1 | 0.1 | 3 | 0.3 | 2 | 0.2 | 0 | 0 |
| Musculoskeletal system | 9 | 0.5 | 2 | 0.2 | 3 | 0.2 | 0 | 0 |
| Skin, hair, nails | 9 | 0.5 | 4 | 0.4 | 3 | 0.2 | 2 | 0.3 |
| Endocrine disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 |
| Multiple simple malformations† | 5 | 0.3 | 3 | 0.3 | 1 | 0.1 | 0 | 0 |
| Single-gene defects, total | 5 | 0.3 | 6 | 0.6 | 2 | 0.2 | 0 | 0 |
| Polydactyly/syndactyly/hypodactyly | 3 | 0.2 | 1 | 0.1 | 2 | 0.2 | 0 | 0 |
| Neurofibromatosis | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Tourette syndrome | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Goldenhar syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Wolfe-Parkinson-White syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Achondroplasia | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Deafness | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Congenital megacolon | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cytogenetic abnormalities, total | 0 | 0 | 4 | 0.4 | 3 | 0.2 | 1 | 0.1 |
| Down syndrome (trisomy 21) | 0 | 0 | 3 | 0.3 | 1 | 0.1 | 0 | 0 |
| Shone syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Angelman syndrome | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |
| 13q deletion syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 |
| Edwards syndrome (trisomy 18) | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |

NOTE. One offspring with reported mental retardation, although included in the analyses of total anomalies, is not included in Table 3, because the lack of detail on the child's condition prevented definitive classification in one of the three categories.

*Total reflects the total number of offspring with malformations (n = 107), although the individual malformations sum to 116 because nine children had multiple malformations.

†Nine children had multiple malformations, and these children were counted only once each in the regression analyses.

# Congenital anomalies

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| | Offspring of Female Survivors | | | | Offspring of Male Survivors | | | |
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| Congenital Anomaly | No. | % | No. | % | No. | % | No. | % |
| Congenital malformations, total* | 50 | 2.9 | 27 | 2.6 | 16 | 1.3 | 14 | 2.0 |
| Nervous system | 3 | 0.2 | 3 | 0.3 | 1 | 0.1 | 2 | 0.3 |
| Eye, ear, face, and neck | 7 | 0.4 | 7 | 0.7 | 1 | 0.1 | 1 | 0.1 |
| Heart and blood vessels | 13 | 0.7 | 6 | 0.6 | 3 | 0.2 | 2 | 0.3 |
| Respiratory organs | | | | | | 0 | 0 | 0 |
| Lip and palate | | | | | | 0.2 | 3 | 0.4 |
| Digestive system | | | | | | 0 | 2 | 0.3 |
| Genitalia | | | | | | 0.2 | 0 | 0 |
| Urinary organs | | | | | | 0 | 1 | 0.1 |
| Extremities | | | | | | 0.2 | 0 | 0 |
| Musculoskeletal system | | | | | | 0.2 | 0 | 0 |
| Skin, hair, nails | | | | | | 0.2 | 2 | 0.3 |
| Endocrine disorder | | | | | | 0 | 1 | 0.1 |
| Multiple simple malformations† | | | | | | 0.1 | 0 | 0 |
| Single-gene defects, total | | | | | | 0.2 | 0 | 0 |
| Polydactyly/syndactyly/hypodactyly | | | | | | 0.2 | 0 | 0 |
| Neurofibromatosis | | | | | | 0 | 0 | 0 |
| Tourette syndrome | | | | | | 0 | 0 | 0 |
| Goldenhar syndrome | | | | | | 0 | 0 | 0 |
| Wolfe-Parkinson-White syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Achondroplasia | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Deafness | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Congenital megacolon | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cytogenetic abnormalities, total | 0 | 0 | 4 | 0.4 | 3 | 0.2 | 1 | 0.1 |
| Down syndrome (trisomy 21) | 0 | 0 | 3 | 0.3 | 1 | 0.1 | 0 | 0 |
| Shone syndrome | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| Angelman syndrome | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |
| 13q deletion syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.1 |
| Edwards syndrome (trisomy 18) | 0 | 0 | 0 | 0 | 1 | 0.1 | 0 | 0 |

**Risk Not Related to Gonadal RT or AA Exposure**

NOTE. One offspring with reported mental retardation, although included in the analyses of total anomalies, is not included in Table 3, because the lack of detail on the child's condition prevented definitive classification in one of the three categories.

*Total reflects the total number of offspring with malformations (n = 107), although the individual malformations sum to 116 because nine children had multiple malformations.

†Nine children had multiple malformations, and these children were counted only once each in the regression analyses.

# Fractures Among Long-Term Survivors of Childhood Cancer

## A Report From the Childhood Cancer Survivor Study

Carmen L. Wilson, PhD[1]; Kimberley Dilley, MD, MPH[2]; Kirsten K. Ness, PhD, PT[1]; Wendy L. Leisenring, ScD[3]; Charles A. Sklar, MD[4]; Sue C. Kaste, DO[5]; Marilyn Stovall, PhD[6]; Daniel M. Green, MD[1]; Gregory T. Armstrong, MD, MSCE[1]; Leslie L. Robison, PhD[1]; and Nina S. Kadan-Lottick, MD[7]

*Cancer* 2012

# Fracture risk

**Table 2.** The Absolute Number of Fractures Among Survivors and Siblings by Site

| | Survivors | | Siblings | | |
|---|---|---|---|---|---|
| Site | No | % | No | % | $P^a$ |
| Other lower body | 1371 | 30.1 | 447 | 29.7 | |
| Unclassified[c] | 73 | 1.6 | 12 | 0.8 | |
| Total | 4564 | | 1565 | | |

[a] Chi-square statistic.

**Prevalence**
**35% (survivors) vs 39% (sibs)**

# Fracture risk

**Table 2.** The Absolute Number of Fractures Among Survivors and Siblings by Site

| | Survivors | | Siblings | | |
|---|---|---|---|---|---|
| Site | No. | % | No. | % | $P^a$ |
| Skull | 243 | 5.3 | 95 | 6.3 | .031 |
| Spine | 89 | 2 | 45 | 3 | |
| Rib | 123 | 2.7 | 35 | 2.3 | |
| Upper body[b] | 2504 | 54.9 | 897 | 55.6 | |
| Humerus | 150 | 3.3 | 48 | 3.2 | |
| Radius/ulna | 105 | 2.3 | 39 | 2.6 | |
| Other upper body | 1906 | 49.3 | 810 | 49.8 | |
| Lower body[c] | 1532 | 33.6 | 481 | 32 | |
| Femur/pelvis | 161 | 3.5 | 34 | 2.3 | |
| Other lower body | 1371 | 30.1 | 447 | 29.7 | |
| Unclassified[c] | 73 | 1.6 | 12 | 0.8 | |
| Total | 4564 | | 1565 | | |

[a] Chi-square statistic.

[b] Includes fractures of the humerus, radius, ulna, scapula, clavicle, carpals, metacarpals, and phalanges of the hand.

[c] Includes fractures of the pelvis, femur, tibia, fibula, patella, tarsals, metatarsals. and phalanges of the foot.

[d] Insufficient information was provided by the study participant to determine the site of the fracture.

# Fracture risk

**Table 2.** The Absolute Number of Fractures Among Survivors and Siblings by Site

| | Survivors | | Siblings | | |
|---|---|---|---|---|---|
| Site | No | % | No | % | $P^a$ |
| Other lower body | 1371 | 30.1 | 447 | 29.7 | |
| Unclassified[c] | 73 | 1.6 | 12 | 0.8 | |
| Total | 4564 | | 1565 | | |

[a] Chi-square statistic.

**Risk Factors ♂:**

**Smoking hx**

**White race**

# Fracture Risk

**Table 2.** The Absolute Number of Fractures Among Survivors and Siblings by Site

| | Survivors | | Siblings | | |
|---|---|---|---|---|---|
| Site | No | % | No | % | $P^a$ |
| Other lower body | 1371 | 30.1 | 447 | 29.7 | |
| Unclassified[c] | 73 | 1.6 | 12 | 0.8 | |
| Total | 4564 | | 1565 | | |

[a] Chi-square statistic.

**Risk Factors ♀:**

**Increasing age**
**White race**
**MTX exposure**
**Balance problems**

## Chronic Disease Working Group 2012

Manuscripts submitted/under review (2)

- Male infertility, **K Wasilewski-Masker**
- Stroke risk, **S Mueller**

## Chronic Disease Working Group 2012

Manuscripts in prep (3)

- Infectious complications, **J Perkins**
- Psychosexual functioning females, **J Ford**
- Cyclophosphamide equivalent dose score, **D Green**

# Chronic Disease Working Group 2012

## Approved AOI/ Concepts Active:

| Date Received | Title | Author/ Institution | Secondary Working Group(s) | Date Investigator Notified | AOI Outcome | Concept to Publication Committee |
|---|---|---|---|---|---|---|
| 05.02.08 | Genitourinary Complications in Survivors of Childhood Cancer | Shnorhavorian/ FHRC | | 06.10.08 | Approved | Approved |
| 06.06.08 | Solid Organ Transplantation in 5-year Survivors of Childhood Cancer. | Termuhlen / Nationwide Children's Hospital | | 07.11.08 | Approved | Approved |
| 06.12.08 | A Comparison of Mortality and Morbidity in Hodgkin's Survivors of Contemporary Therapy | Castilenno / Wake Forest University | SMN<br>Chronic Disease | 07.11.08 | Approved | Pending |
| 03.11.09 | Creation of a Risk Score Algorithm to Predict Individual Risk of Future Serious Cardiovascular Disease | Chow/FHRC | Cancer Control | 04.03.09 | Approved | Approved |
| 06.11.09 | Outcome of Pregnancies Exposed to Cancer Therapy | Mulvihill/U. of Oklahoma | Genetics | 07.10.09 | Approved | Approved |
| 09.08.09 | Pulmonary complications in Long-term Survivors of Childhood CNS Tumors with Craniospinal Irradiation | Tein/SJCRH | Psychology | 10.06.09 | Approved | Approved |
| 01.29.10 | Longitudinal Assessment of Chronic Health Conditions | Armstrong/SJCRH | | 02.12.10 | Approved | Approved |
| 02.26.10 | Health and Functional Status of Long Term Adult Medulloblastoma Survivors | King/Wash. U. | Psychology<br>SMN<br>Chronic Disease | 03.31.10 | Approved | Pending |
| 03.04.10 | Health Status of Older Adult Survivors of Childhood Cancer | Kenney/DFCI | Psychology<br>Epi/Biostats | 03.31.10 | Approved | Pending |
| 05.12.10 | Evaluation of Long-term Outcomes in Ewing Sarcoma Survivors | Marina/Stanford | SMN | 6.17.10 | Approved | Approved |
| 06.10.10 | Neurologic and Neurosensory Deficits in Long-term Survivors of Childhood Brain Tumors: Occurrence of New Deficits and Effects of Aging in Occurrence as Assessed in 2007 Survey | Wells/Children's National | SMN<br>Psychology | 6.25.10 | Approved | Approved |

# Chronic Disease Working Group 2012

## Approved AOI/ Concepts Active:

| Date Received | Title | Author/ Institution | Secondary Working Group(s) | Date Investigator Notified | AOI Outcome | Concept to Publication Committee |
|---|---|---|---|---|---|---|
| 06.24.10 | Premature Menopause in Survivors of Childhood Cancer | Levine/Columbia | | 07.06.10 | Approved | Approved |
| 11.05.10 | Infertility and Use of Fertility Treatments | Barton/Brigham & Women's | | 11.23.10 | Approved | Approved |
| 02.18.11 | BMI and Diabetes Mellitus in Survivors of ALL | Tonorezos/MSKCC | Cancer Control | 03.16.11 | Approved | Pending |
| 04.22.11 | Changes in BMI Among Adult Survivors of Childhood CNS Tumors | Chang/MD Anderson | Psychology | 05.03.11 | Approved | Pending |
| 05.23.11 | Longitudinal Analysis of Outcomes for Acute Lymphoblastic Leukemia Survivors | Dilley/Northwestern | Cancer Control | 05.30.11 | On Hold | Pending |
| 05.06.12 | Chronic Medical Conditions Among Long-term Survivors of Pediatric Non-Hodgkin Lymphoma | Bluhm/Washington Hospital | Epi/Biostats | 05.15.12 | | |

# Chronic Disease Working Group 2010
## Ancillary studies

- **Active**
  - **Testicular and sexual dysfunction in male survivors**, Meacham (LAF)
    - Data collection complete, analysis underway

# Chronic Disease Working Group 2012

## Future Directions

**Home/work visits**

- **Blood sampling**
- **Clinical/anthropomorphic measures**
- **Brief questionnaire**

- **Pilot/feasibility study**
  - **Fasting blood for glucose, lipids, insulin**
  - **Measure height, weight, BP waist circumference**
  - **Random sample of 200 survivors in cohort**
    - » **Select from among those with and without previously reported CVRF**

**Longitudinal outcomes using 2007 dataset**

**Expanded cohort specific exposures (eg, ifosfamide, cisplatin)**

**Risk model**