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Childhood Cancer Survivor Study

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Topics to Address

- Background
- Key accomplishments
- Data access policies
- Relationship of scientific research programs of COG and CCSS
- Incorporation of genomic studies into CCSS research program
- CCSS components

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Childhood Cancer Survivor Study (CCSS) Background

- **Retrospectively ascertained cohort of survivors of pediatric cancer diagnosed between1970-1986:**
  - Cohort initiated with first CCSS award in 1994
  - 14,370 long-term (five-year or more) survivors of childhood cancer diagnosed between 1970 and 1986
  - 3,737 sibling controls recruited for comparison purposes
- Data collected:
  - Clinical data on malignancy and treatment abstracted from medical records
  - Self-reported data on risk factors (e.g., family history), and health and psychosocial outcomes data collected via baseline and follow-up questionnaires
- Biospecimens; second cohort (1987-1999); intervention studies, public use dataset
- Independent evaluation confirmed value of CCSS as resource

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Scope of Published Research (n=151)

- 2 Alcohol/Diet
- 2 Cardiovascular
- 1 Chronic Health Conditions
- 1 Comp/Alternative Rx
- 1 Dental
- 8 Education/Employ/Insurance
- 5 Endocrine
- 11 General Survivorship
- 4 Genetics/Family History
- 10 Gonadal Function/Pregnancy
- 4 Growth Hormone
- 1 Health Status
- 9 Healthcare/Screening
- 1 Infection
- 1 Cancer History Knowledge
- 2 Mortality
- 4 Neurologic/Neurosensory
- 1 Osteonecrosis
- 12 Physical Function/QOL
- 10 Psychology
- 1 Pulmonary
- 1 Recurrence
- 17 Reviews
- 13 Second Neoplasms
- 1 Sleep/Fatigue
- 7 Smoking
- 2 Stroke
- 1 Sun Exposure
- 11 Survivorship Methods
- 6 Weight/Body Mass Index

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Growth Hormone Treatment and Risk of Second Malignancy

- No evidence that treating childhood cancer survivors with GH increased the risk of recurrence or death.
- Increased risk of developing a secondary solid tumor malignancy in childhood cancer survivors treated with GH compared with the risk seen in survivors not treated with GH.
  - Sklar, et al. J Clin Endocrinol Metab, 2002)
- Risk seems to decrease with increasing length of follow-up .
  - Ergun-Longmire, et al. J Clin Endocrinol Metab, 2006)

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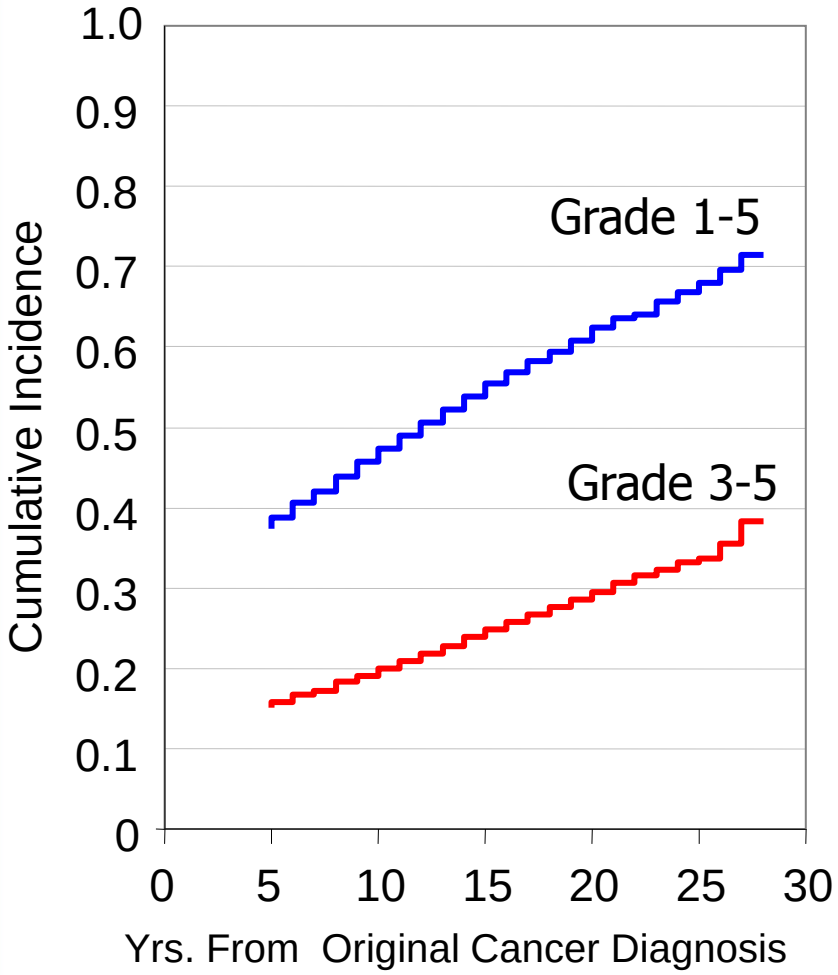
Cumulative Incidence of Chronic Health Conditions in 10,397 Childhood Cancer



- Mean age of 26.6 years (18-48 years)
- By 30 years post cancer: 73% survivors with at least one chronic health condition;
- 42% with a Grade 3-5 (severe, life-threatening, death);
- 39% had ≥2 chronic health conditions
- Survivors – 8.2 times more likely to have a severe or life threatening condition compared to siblings

Oeffinger et al, N Engl J Med, 2006

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Breast Cancer after Childhood Cancer

- Series of CCSS publications have clarified association between chest radiation therapy and risk of subsequent breast cancer;
- Among 6068 women who survived childhood cancer, 95 developed breast cancer at median age of 35 yrs;
  - Childhood sarcoma, chest irradiation, +FH of breast cancer and personal history of thyroid disease increased the risk.
  - Exposure to pelvic radiation protective
  - Kenney, et al. Ann Int Med 2004
- CCSS first group to document breast screening practices in female pediatric cancer survivors who were treated with chest radiation.
  - 63.5% of women aged 25 to 39 and 23.5% aged 40 to 50 years, had not had mammography screening for breast cancer within 2 years.
  - Oeffinger, et al. JAMA 2009

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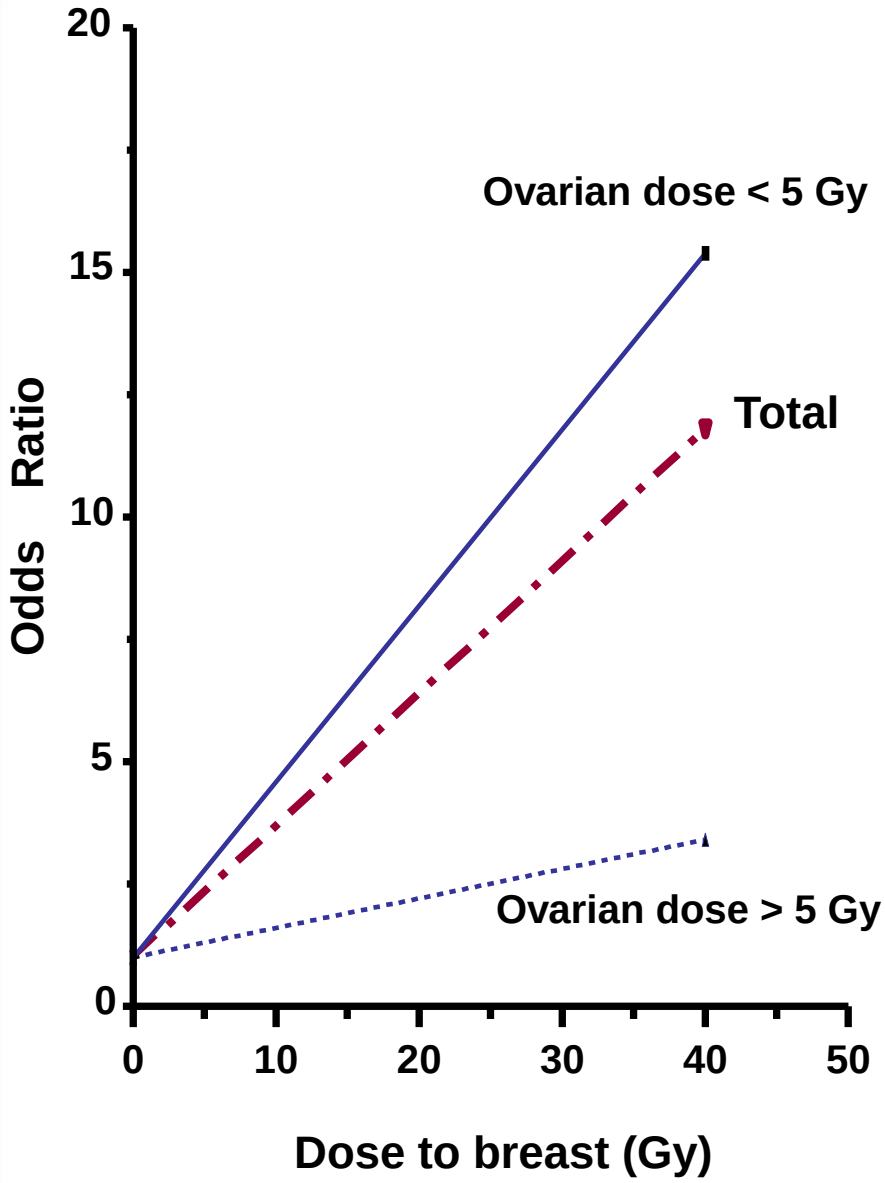
Dose-Risk Relationship for Tissue-Specific Radiation Exposure and Breast Cancer



- 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 ≥ 5 Gy ovarian RT
- Age at RT exposure not a risk factor for breast cancer

Inskip et al, J Clin Oncol, 2009

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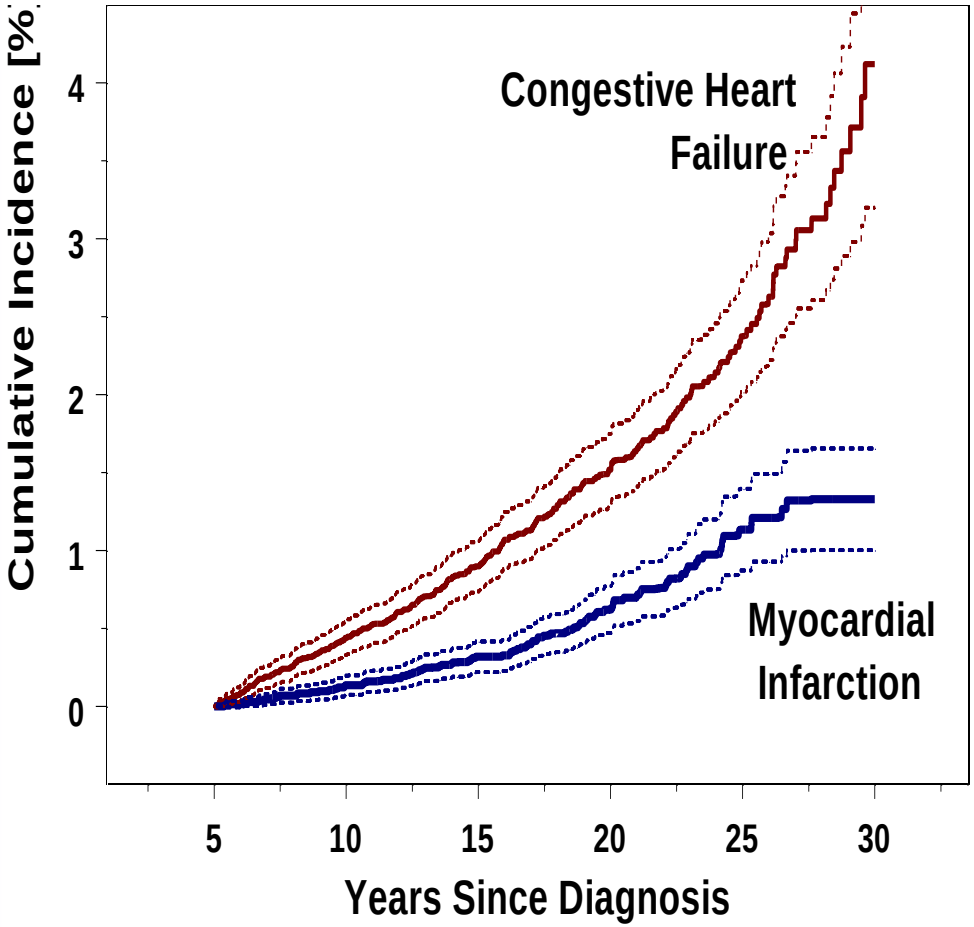
Cardiac Outcomes Among Long-Term Survivors of Childhood Cancer



- Compared to siblings, survivors had a 5.9-fold increased risk of congestive heart failure, 5-fold risk of myocardial infarction, and 4.8-fold risk of valvular disease.
- Risk of cardiac event was significantly associated with anthracycline exposure >250 mg/m2 and >15 Gy cardiac radiation.
- Risk is apparent at lower exposures to anthracyclines and radiation therapy than previously recognized.

Mulrooney et al, Br Med J, 2009

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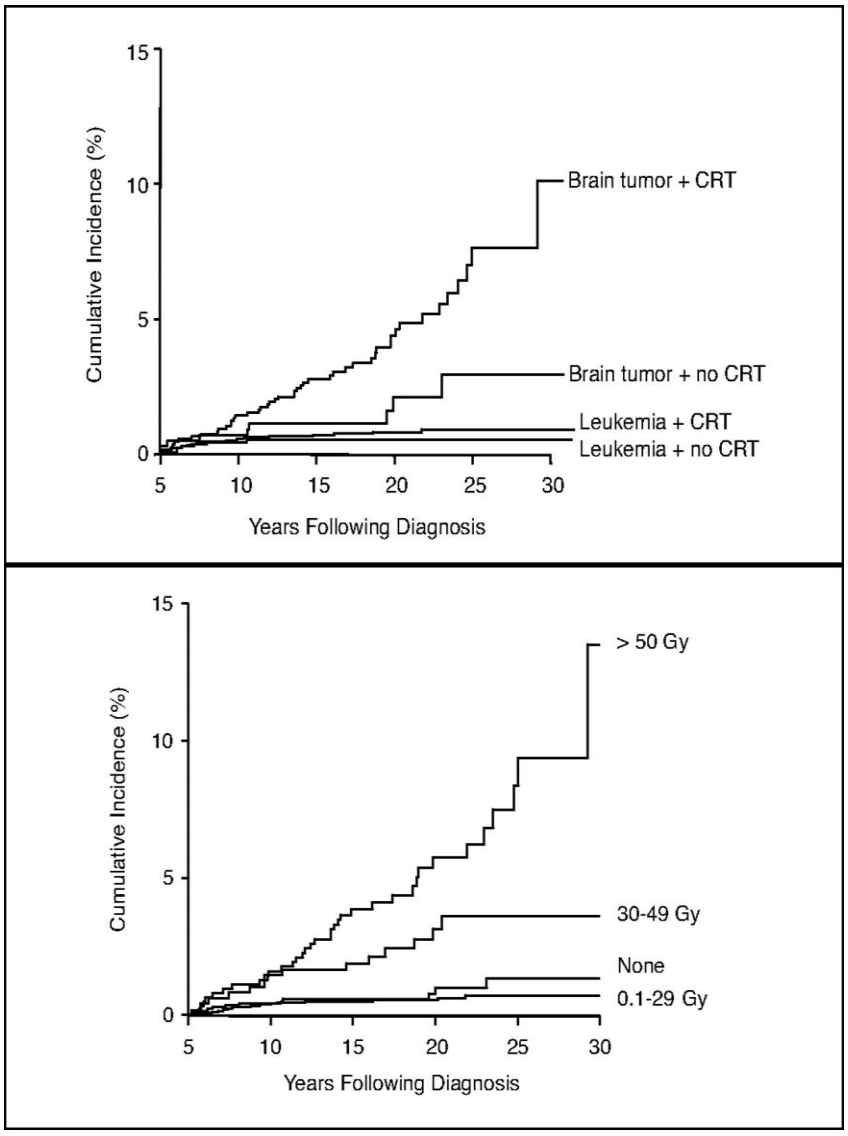
Risk of Stroke in Childhood Cancer Survivors

- First study to examine risk of late-occurring stroke in long term childhood survivors of leukemia (57.9/100,000 person years; RR 6.4).
- Largest study to examine the risk of stroke in childhood brain tumor survivor.(267.6/100,000 person years; RR 29.0).
- Increased risk of late-occurring stroke was associated with CRT doses greater than 30 Gy and highest risk ≥ 50 Gy.
- Justifies continued attempts to reduce radiation to these 2 groups.



Bowers, et al. JCO 2006

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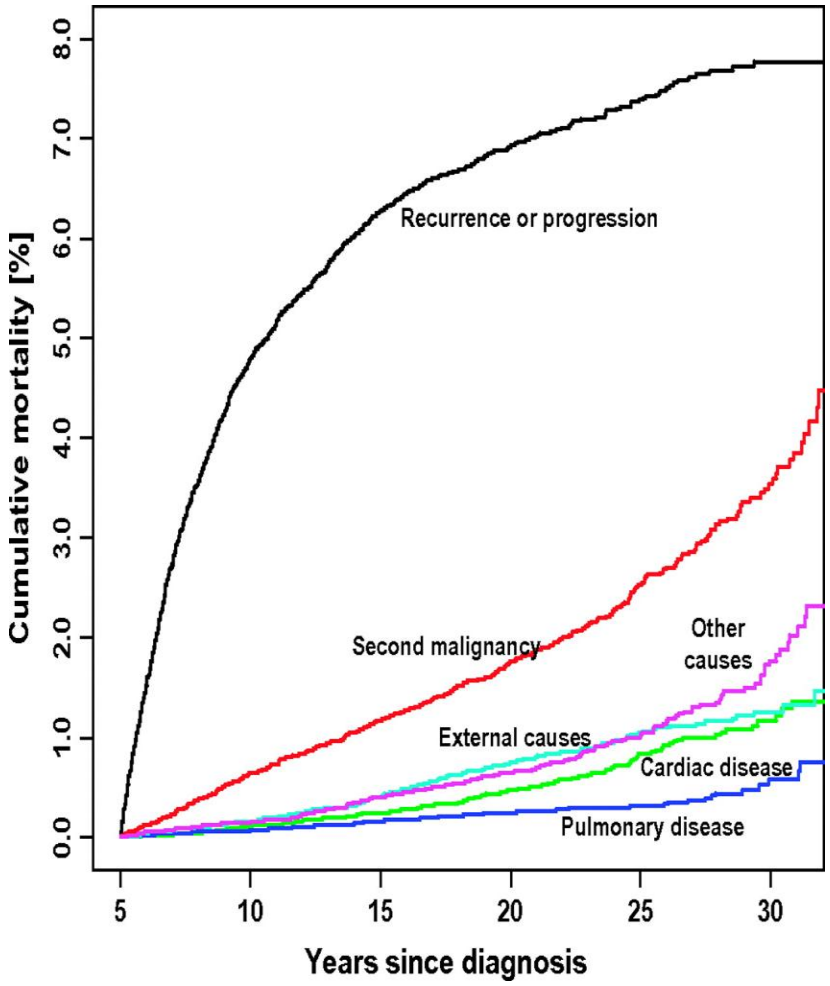
Cause-Specific Late Mortality Among Five-Year Survivors of Childhood Cancer



Cumulative mortality due to recurrence of cancer, second malignancy, cardiac disease, pulmonary disease, external causes, and all other causes.

- First to document the magnitude of excess in cause-specific late mortality.
- Increasing and excess rate of late mortality secondary to cardiac and pulmonary causes at 15-30 years after diagnosis.

Mertens, et al. JCO 2001 and Mertens, et al. JNCI 2008.

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Original Discoveries vs Verification

- Large size of CCSS cohort allows more precise estimation of frequency of both new and previously suspected late effects
- At least 50% or more report new original findings regarding late effects
- Contributed to knowledge base for design of intervention trials and risk-based clinical screening guidelines

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Data Access Policies

- CCSS provides public access data tables on the CCSS website.
- Option to request project-specific analytic datasets
- 100 analytic datasets provided to investigators
- Analyses conducted by independent investigators are reviewed and approved by CCSS statisticians.
- CCSS is open to investigating options for maximizing the use of CCSS data.

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The Relationship Between the Children's Oncology Group (COG) and CCSS (1)

- Survivors in CCSS are not restricted to those enrolled on COG trials.
  - Not all children between 1-15 years old are treated on COG protocols and hence these survivors would be missed;
- Increased heterogeneity of treatment regimens/exposures by including patients treated on local protocols such as St. Jude, Dana-Farber, MSKCC, Stanford, etc.
- CCSS directly abstracts treatment (e.g., chemotherapy doses and radiation doses/fields) from medical records.
  - COG classifies patients according to protocol specified treatment (inferred exposure vs actual exposure)

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The Relationship Between the Children's Oncology Group (COG) and CCSS (2)

- COG focuses on therapeutic research in which patients are followed closely for 5-10 years
  - Local institution based research centered around children's hospitals.
- CCSS focuses on survivor research involving research subjects who are generally 10 or more years from diagnosis
  - Local institutions typically do not maintain a relationship with these survivors into adulthood
  - Long-term follow-up infrastructure needed for tracking survivors and maintaining contact.
- Given distinctive research missions/methods, separate structures for COG & CCSS seem appropriate

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Should CCSS Be Driven to Develop Scientific Components to their Followup Studies?

- CCSS is funded through a U24 research resource grant award mechanism.
- CCSS involved in multiple projects in which scientific components are being explored.
- For projects using biological specimens, each project must meet scientific priority criteria to justify use of the limited biological material.
- Utilization of the CCSS resource driven by research community.

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Ancillary Projects Using Biological Samples Within CCSS

INVESTIGATOR	PROJECT
Yang	Genomic alterations in radiation-related breast cancer
DuBois	SNPs in EWS breakpoint region in Ewing sarcoma
Gramatges	Telomere length and risk of second malignancy
Ross	Obesity-related genes in childhood ALL
Onel	GWAS in secondary cancer
Kamdar	GWAS in obesity in ALL survivors
Stambrook	Susceptibility alleles in a DNA damage response pathway
Davies	Radiation sensitivity in children with basal cell carcinoma
Swerdlow	Genetic investigation of secondary breast cancer in Hodgkins
Mertens	GST and XRCC1 in RT-related SMN in Hodgkins
Blanco	CBR3 and NQ01 and anthracycline-related congestive heart failure
Davies	MDM2 and secondary malignancy
Brackett	SNPs in antioxidant enzyme systems and neurocognitive effects

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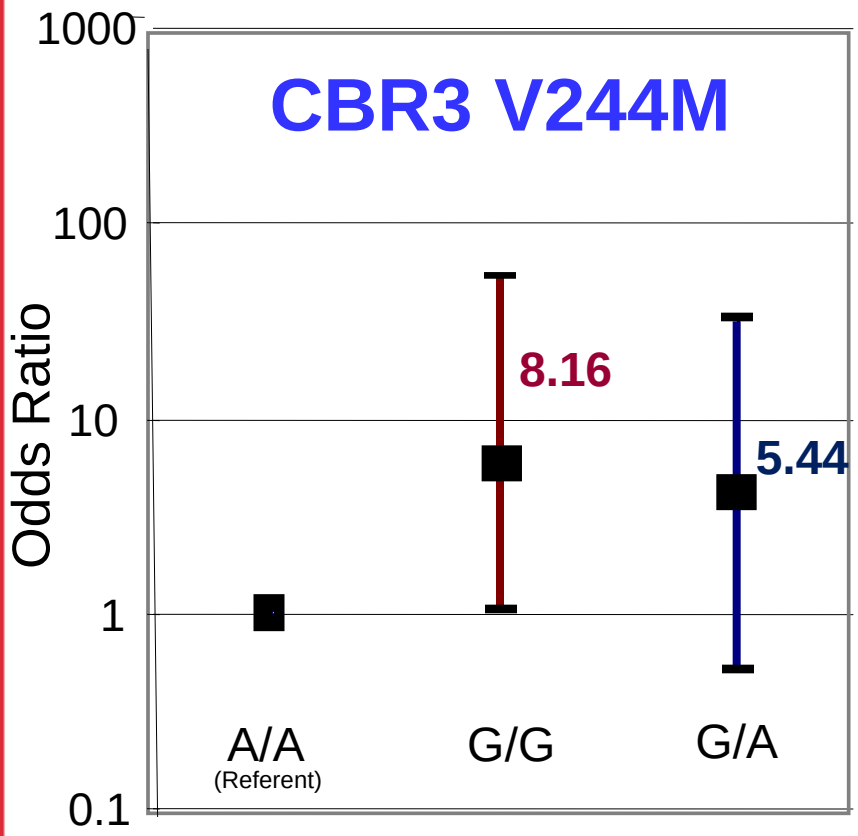
Relative Odds of Anthracycline-related CHF by Polymorphisms in Secondary Alcohol Formation



Adjusted for heart in beam, gender, smoking status, and recurrence status

- Pilot study of candidate genes involved in pharmacodynamics of anthracyclines
- 8-fold increased risk of congestive heart failure associated with G/G genotype in carbonyl reductase 3 gene (CBR3)
- Association of CBR3 V244M and risk of CHF validated in large series from Children's Oncology Group (Blanco, ASCO, 2010)

Blanco et al, Cancer, 2008

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Which Components of CCSS Could be Identified and Designated for Open Competition for Funding?

Activity	Approximate Cost per Year*
Statistical Center (data management and analysis): Seattle	$680,000
Molecular Genetics Bank: Cincinnati	$190,000
Biopath: Columbus (including creating of tissue microarrays)	$89,000
Radiation Physics Center: Houston	$450,000

*Estimates based upon previous application.

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Which Components of CCSS Could be Identified and Designated for Open Competition for Funding?

- CCSS has established a highly effective interactive infrastructure and research organization.
- Changes in the existing structure would disrupt the continuity of this highly successful project.
- Major deficiencies in any of these components (if they exist), should be identified by peer review.
  - PI can be required by Program to address the deficiency thru a competitive process.

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Plan for Continuation of CCSS

- Request approval to reissue a letter RFA for 5 years of funding at $4.38 million/year for a total $21.9 million (10% increase)
- Co-sponsorship from DCCPS, DCEG, DCP
- Additional Evaluation criteria to include:
  - Completion of expanded cohort and merger with initial cohort; maintenance of both
  - Timely conception, implementation and conduct of intervention studies
  - Development of strategies by organ system
  - Development and conduct of hypothesis-testing molecular genetic studies
  - Identification and collaboration with other childhood cancer survivor groups internationally
  - Successful training/mentorship

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New Oppportunities

- Use of biorepository data to test pharmacogenomic/genetic risk factors for toxicity;
- Use of this cohort to address questions of the impact of ethnic/racial diversity on survivor outcome;
- Gain new insights into the incidence of and risk factors for, very late occurring events within an aging population of childhood cancer survivors (initial cohort);
- Ensure documentation of exposures and outcomes for the next generation of treated childhood cancer survivors;
- Use of this well defined population to conduct intervention studies to reduce later life morbidity and premature mortality;

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Justification for 10% increase over previous award

- Increased work load to recruit the expanded survivor and sibling cohorts
  - *HIPAA*
  - *Ability to make direct contact through mail and telephone*
  - *Mobility of study population and increased ethnic/racial diversity*
  - *Heightened sensitivity to confidentiality*
- Increasing difficulty and costs associated with follow-up and retention
  - *Ability to make direct contact through mail and telephone*
  - *Mobility of study population*
  - *Heightened sensitivity to confidentiality*
- Enhancement of the biorepository
  - *Improved quality of stored DNA (Oragene)*
  - *Increased quantity of stored DNA (multiple collections)*
  - *Increasing number of second cancers requiring tissue and blood collection*
- Increased use of the resource requiring additional biostatistical support
  - *High volume of requests for information and development of proposals*
  - *Higher volume of ancillary study proposals*
  - *Increased complexity of data analyses as data matures (longitudinal analyses)*
- Increased data management effort
  - *Requirements to harmonize data from expanded and initial cohorts*
  - *Complexity of internal data element checks and quality control edits*

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CCSS Intervention-based Research

Current studies

- Survivor based tobacco quit-line: Randomized study of two approaches for smoking cessation(R01 CA127964)
- Promotion of Breast Screening: Randomized study of female survivors at high risk for radiation-induced breast cancer(R01 CA134722)
- Promotion of cardiac screening: Randomized study of survivors at high risk for treatment associated CHF (R01 NR011322)

Potential Future Studies

Obesity prevention, chemoprevention, adherence to medical screening, sun exposure prevention, promotion of cardiovascular health

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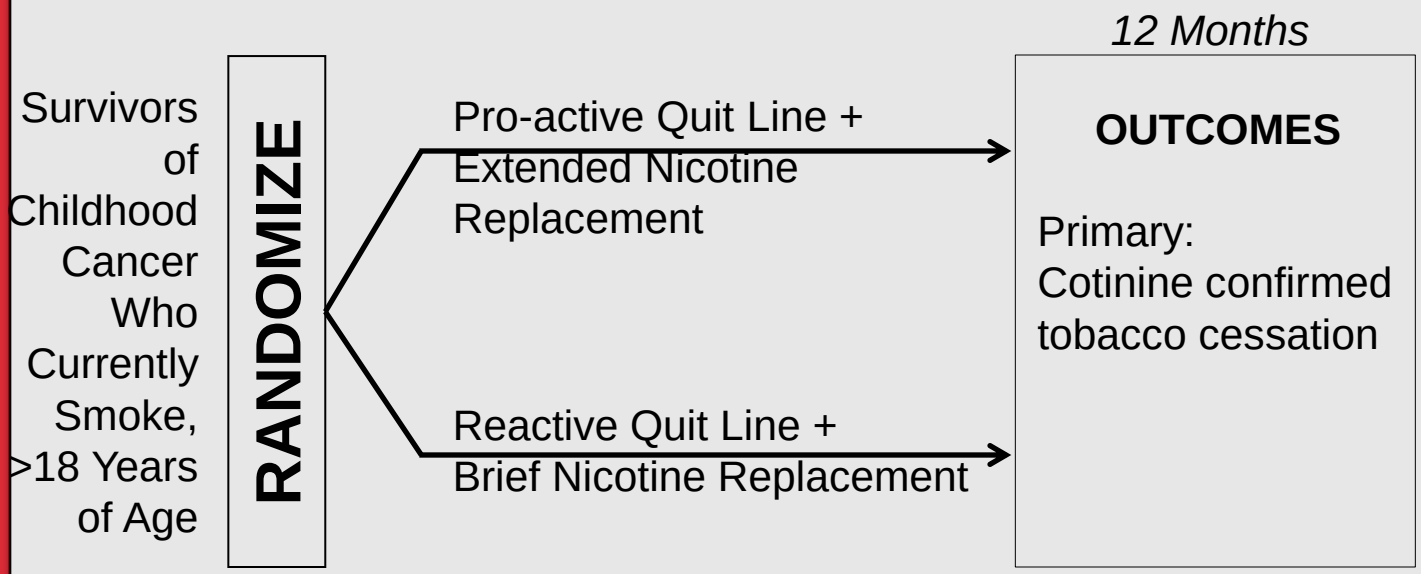
Selected Ancillary Studies

Tobacco Quit Line Intervention Trial

Robert Klesges (St. Jude Children's Research Hospital)

This R01 funded randomized study is designed to determine efficacy of a tobacco quit line for survivors of childhood cancer who currently smoke cigarettes.



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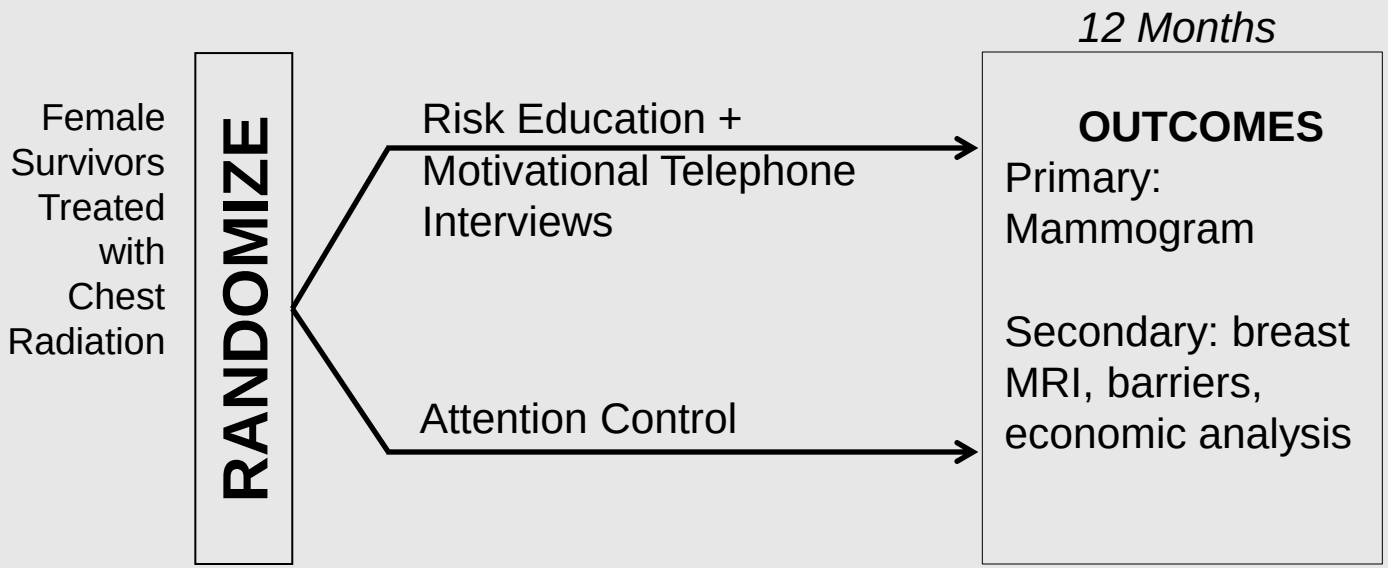
Selected Ancillary Studies

Breast Screening Intervention Trial

Kevin Oeffinger (Memorial Sloan-Kettering Cancer Center)

This R01 funded randomized study is designed to determine efficacy of a stepwise two-component intervention on mammography rates among survivors at high-risk for breast cancer.



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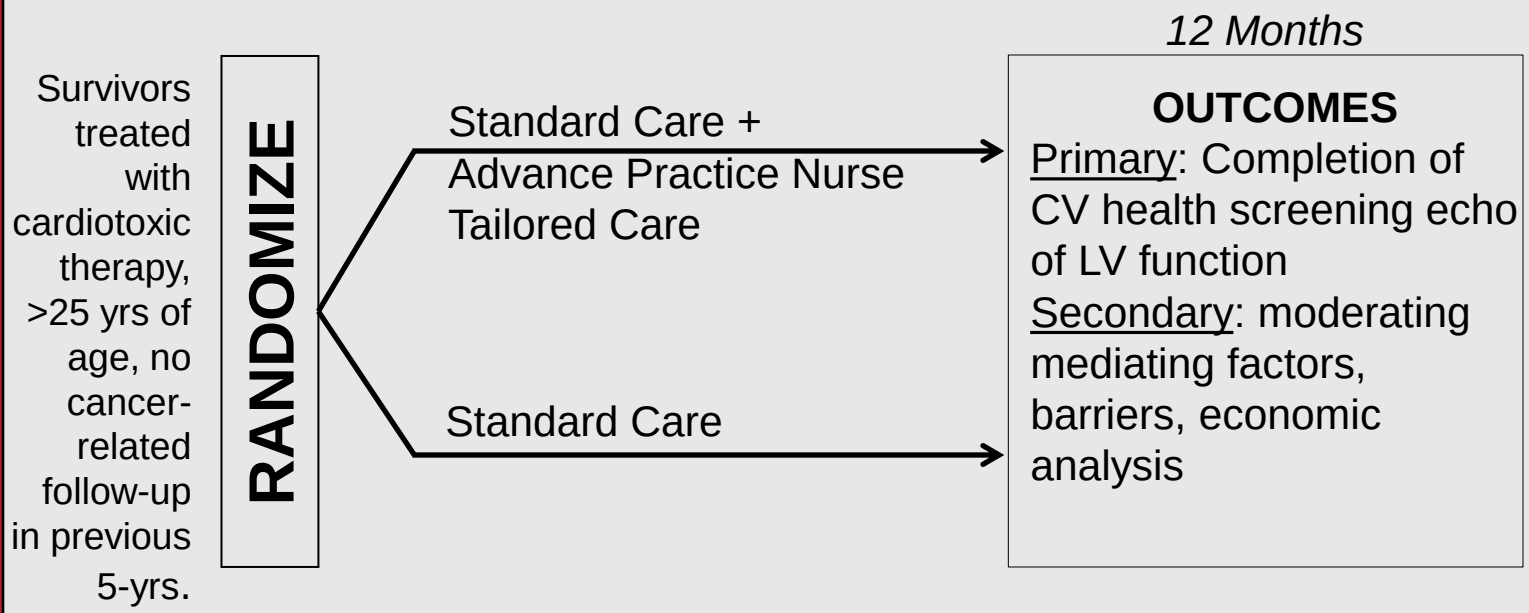
Selected Ancillary Studies

Cardiovascular Screening Intervention Trial

Melissa Hudson/Cheryl Cox (St. Jude Children's Research Hosp)

This R01 funded randomized study is designed to determine efficacy of two interventions to increase cardiovascular screening among high-risk survivors.



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Percent Distributions of Cohort Characteristics Baseline to Current (2010) Participants

Characteristic	Baseline (n=14,357)	2010 (n=10,562)	Deaths (n=2124)	Drop-out (n=1672)
Male	53.7	51.9	58.7	58.7
Female	46.3	48.1	41.3	41.3
White not Hispanic	83.2	83.1	83.9	82.7
Black not Hispanic	4.7	4.5	5.2	4.8
American Indian/Alaska Native	0.6	0.6	0.4	0.7
Asian or Pacific Islander	1.2	1.2	0.8	1.3
Hispanic	2.8	2.9	2.7	2.3
Other	7.3	7.3	6.7	7.9
Unknown	0.3	0.4	0.3	0.4

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Percent Distributions of Cohort Characteristics Baseline to Current (2010) Participants

Age at Cancer Diagnosis	Baseline (n=14,357)	2010 (n=10,562)	Deaths (n=2124)	Drop-out (n=1672)
0-4 yrs	40.1	42.2	27.6	42.5
5-9 yrs	22.3	22.4	20.9	23.7
10-14 yrs	20.3	19.8	24.8	17.7
15-20 yrs	17.4	15.7	26.8	16.1

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Percent Distributions of Cohort Characteristics Baseline to Current (2010) Participants

Cancer Diagnosis	Baseline (n=14,357)	2010 (n=10,562)	Deaths (n=2124)	Drop-out (n=1672)
Acute lymphoblastic leukemia	28.9	31.4	23.6	30.7
Acute myeloid leukemia	2.5	2.5	2.7	2.3
Other leukemia	2.2	0.8	2.2	0.8
Astrocytomas	8.2	7.4	11.3	9.8
Medulloblastoma, PNET	2.7	2.4	4.3	2.3
Other CNS tumors	2.2	1.9	3.4	2.4
Hodgkins lymphoma	13.4	12.1	21.1	11.9
Non-Hodgkins lymphoma	7.5	7.8	5.5	8.1
Kidney tumors	8.8	10.0	3.8	7.2
Neuroblastoma	6.6	7.2	3.3	7.5
Soft tissue sarcoma	8.7	8.7	8.9	8.6
Ewings sarcoma	2.8	2.5	5.0	2.2
Osteosarcoma	5.1	5.1	4.7	5.8
Other bone tumors	0.4	0.4	0.2	0.4

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Percent Distributions of Cohort Characteristics Baseline to Current (2010) Participants

Cancer Therapy	Baseline (n=14,357)	2010 (n=10,562)	Deaths (n=2124)	Drop-out (n=1672)
Chemo- RT- Surg	38.7	36.7	54.4	31.0
Chemo- RT	10.2	10.9	6.4	10.3
Chemo- Surg	15.8	17.5	8.3	14.9
Chemo only	5.7	6.6	2.5	4.2
RT- Surg	10.4	10.3	12.1	8.3
RT only	0.2	0.2	0.3	0.2
Surg only	6.3	6.9	2.2	8.0
No Med Record	12.7	11.0	13.8	23.1

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New Centers to Enrich the Ethnic/Racial Diversity of the Expanded Cohort

CENTER	POPULATION
University of Chicago	41% minority Predominantly African American
Northwestern University	27% minority Predominantly Hispanic
Cook Children's	29% minority Predominantly Hispanic and African American
Children's Hospital Orange County	46% minority Predominantly Hispanic and Asian

NOTE: New Centers are considered probationary members of CCSS, pending successful registration of eligible cases and submission of abstracted medical record information (i.e., cancer therapy exposures). All activities are supported by the probationary institution and are not funded through the current CCSS award.

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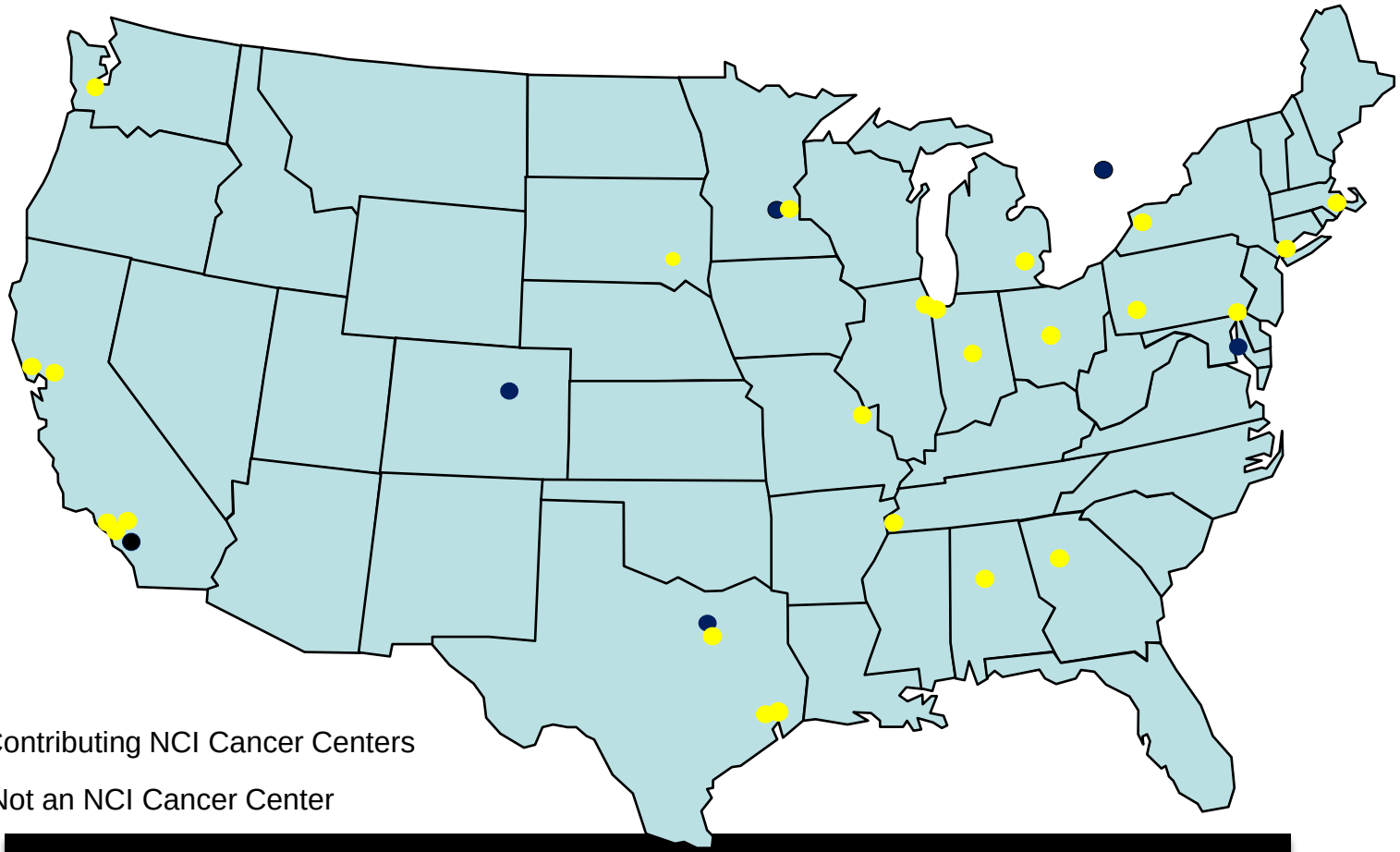
Contributing Centers by NCI-designated Cancer Center Status



SURVIVORS	NCI – CANCER CTRS	Non-CANCER CTRS
Initial Cohort (Baseline)	12,280 (86%)	2,092 (14%)
Expanded Cohort (Eligible)	14,804 (84%)	2,921 (16%)

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Evaluation Findings

- The CCSS cohort itself is perhaps the most important product of the study.
- Interviewees noted that the CCSS was the **first** cohort of pediatric cancer survivors ever assembled at this scale, and it remains the **largest** cohort of its type in the world.
- The original cohort successfully enrolled 14,370 out of 20,879 eligible survivors diagnosed between 1970 and 1986 as well as 3,737 siblings. An equal number of survivors diagnosed between 1987 and 1999 have been targeted for the expansion, and over 5600 had been enrolled.

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Evaluation Findings: CCSS Is A Valuable Resource

- **General agreement among interviewees that the CCSS is an example of a large cohort study that has greatly advanced knowledge.**
  - Cohort has helped to quantify risks of second malignancies and other late effects in survivors of pediatric cancers (CCSS participants).
  - CCSS is acknowledged as a pioneering effort and also as a model and inspiration for current efforts to build comparable cohorts in other countries (leaders in survivorship field).
  - Favored support of current cohort to obtain data on aging such as CV effects, Type II Diabetes, osteoporosis as well as the expansion cohort
  - CCSS Outcome Evaluation is not warranted