

Chronic Disease Working Group

A Report from the Childhood Cancer Survivor Study

CCSS Investigator Meeting – June 2021

- Epidemiology of chronic health conditions (i.e., vital organ dysfunction)
 - Adapted CTCAE grading of conditions (grades 1-5)
 - Focus on “accelerated aging”
 - Inform guidelines of late effects surveillance
- Prediction models for select outcomes
 - Collaboration with Epi, Genetics, Psychology WG’s
- Ancillary studies designed to improve ascertainment & mitigate development of serious health conditions
 - Collaboration with Cancer Control & Intervention WG

Working Group Membership

CCSS

Individual

Kevin Oeffinger (co-chair)
Eric Chow (co-chair)
Charles (Chuck) Sklar (Ex-officio)
Saro Armenian
James Bates
Louis (Sandy) Constine
Danielle Friedman
Rebecca Howell
Melissa Hudson
Wendy Leisenring
Aaron McDonald
Sogol (Goli) Mostoufi-Moab
Daniel Mulrooney
Kayla Stratton
Emily Tonorezos
Elizabeth (Beth) Wells
Brent Weil
Christopher Weldon

Expertise

Primary care
Pediatric oncology
Pediatric endocrinology
Pediatric oncology
Radiation oncology
Radiation oncology
General pediatrics
Radiation dosimetry
Pediatric oncology
Biostatistician
CCSS Project Director
Pediatric endocrinology / oncology
Pediatric oncology
Biostatistician
Internal medicine
Pediatric neurology
Surgery
Surgery

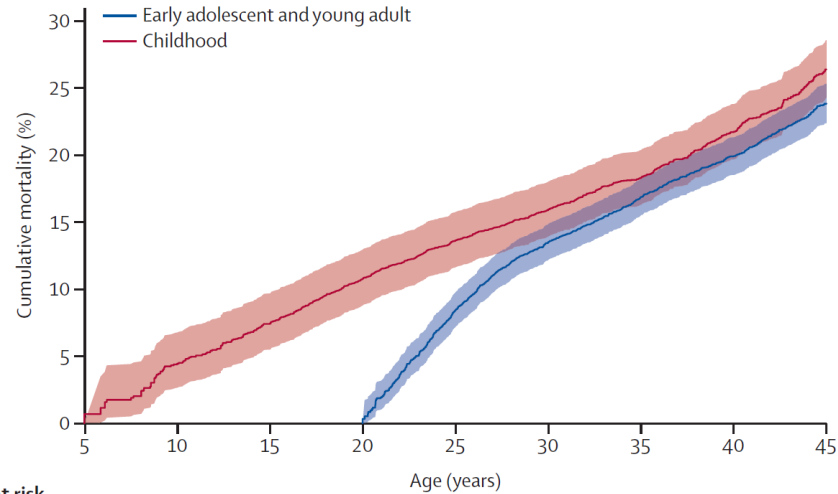
*Monthly calls to review
concepts / analyses,
discuss priorities*

Working Group Progress

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- 14 New AOs (since 6/2019 investigator meeting)
- 10 Concepts in development (not yet approved)
- 26 Analyses/manuscripts in process
- 13 Published/in press (since 6/2019)

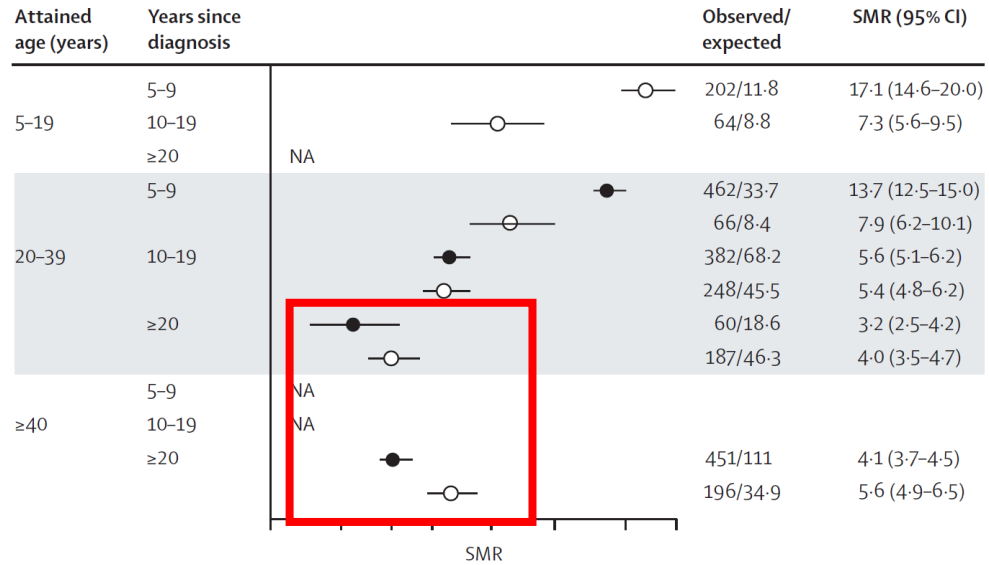
Featured Study: AYA Outcomes



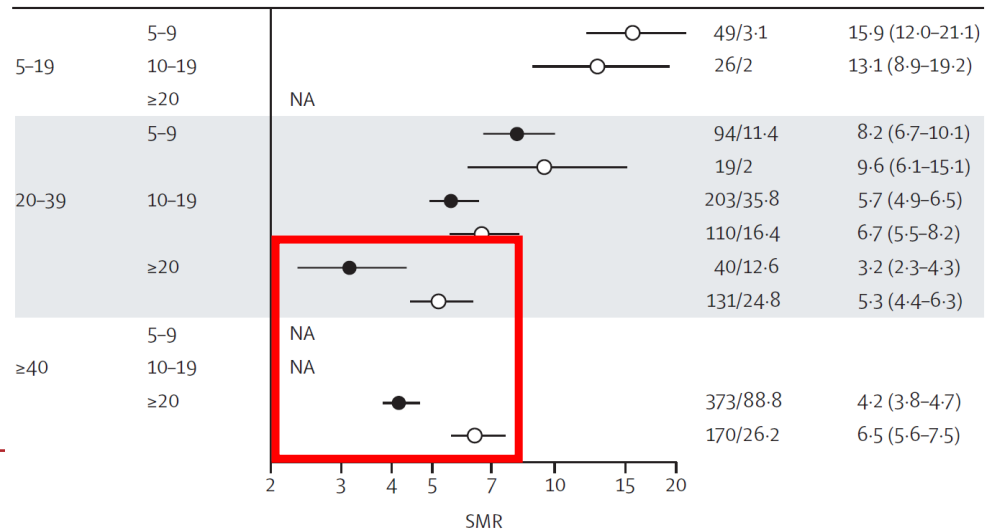
Number at risk	Age (years)								
Early adolescent and young adult	NA	NA	NA	296	4925	5218	4313	3382	2553
Childhood	141	1221	2770	5388	4825	3919	2872	2002	1060

Relative to childhood cancer survivors (<15yo), AYA survivors (15-20yo) appeared to have decreased risks of mortality and chronic conditions over time (esp. 20+yrs after cancer)

A All-cause mortality

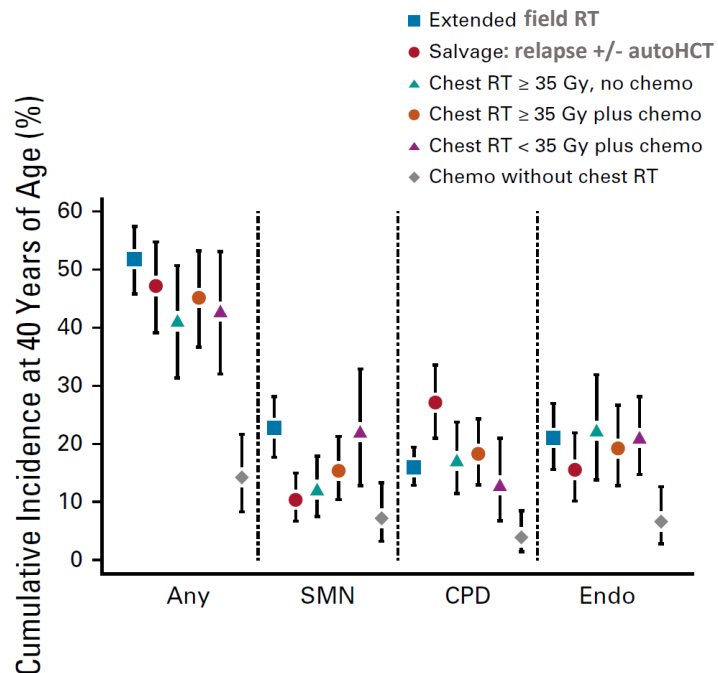
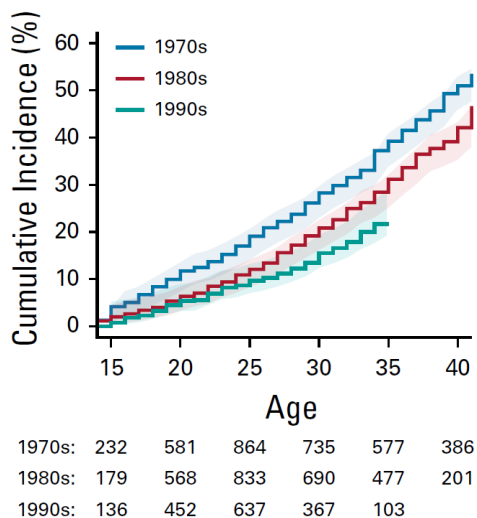


B Non-recurrent, health-related causes



Black Circle: AYA
Open Circle: Childhood

Featured Study: Hodgkin outcomes 1970-99



Cumulative Incidence by 30yrs of age

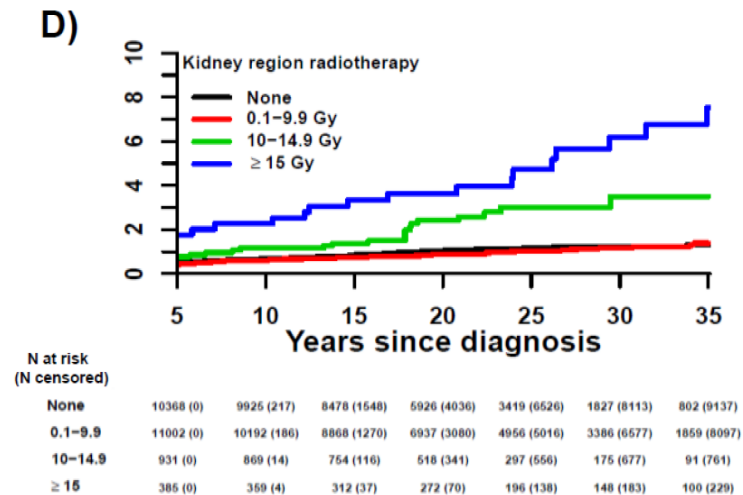
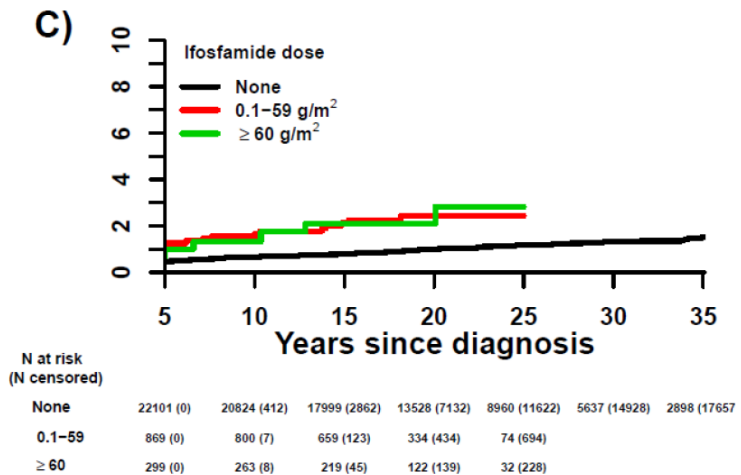
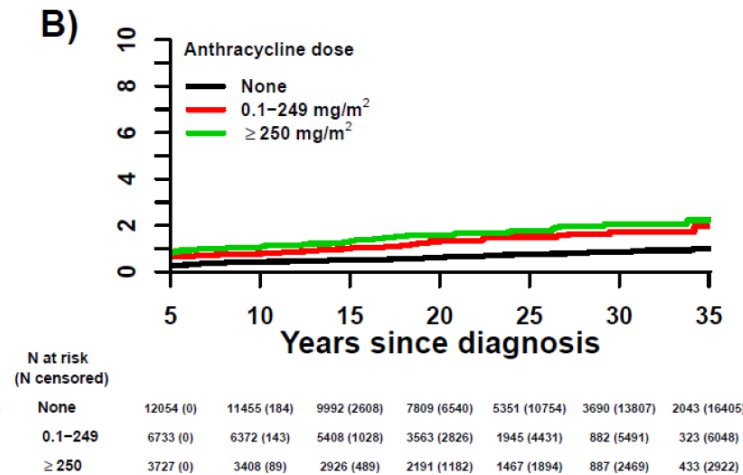
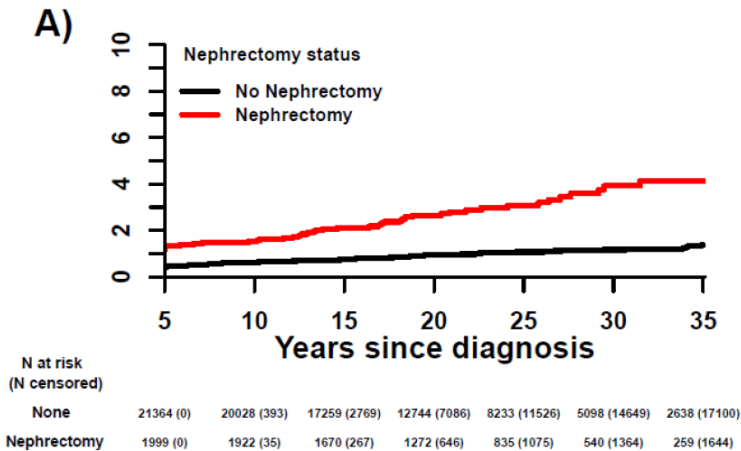
Tx group	Any grade 3-5	SMN	CV/Pulm	Endo
Contemporary tx* (AHOD0431 / AHOD0031)	15%	5%	8%	7%
Chemo w/o chest RT	8%	5%	3%	3%
Salvage tx	29%	5%	12%	12%
Chest RT 35+Gy	25%	6%	7%	13%

* Dox <250 mg/m², Cytosan 2-3.9 gm/m², Vcr, Pred, RT ≤26Gy

20% reduction in decade-specific risk of grade 3-5 chronic condition

Contemporary regimens for low/intermediate risk HL associated with 40% reduction vs chest RT 35+ Gy (with Dox/CPM)

Featured Study: Late Kidney Failure



Expanded cohort enables study of rare but serious outcomes:

- 35yr cumulative incidence of late-onset kidney failure 1.7% (95% CI 1.4–1.9), n=206 (siblings, n=10)
- Data now also being adapted for risk prediction model
- Preliminary risk scores with AUC/C-statistics of 0.65/0.68 (CCSS)
- Validation risk scores 0.83/0.86 (SJLIFE) and 0.61/0.63 (NWTs) – Natalie Wu (ASCO 2021 abstract; 2020 CCSS trainee award)

Approved Concepts – Current Status

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Published since 6/2019

- Bates/Howell/Constine – **CV & RT dose volume**, JCO 2020
- Chen/Chow/Yasui – **CV risk prediction**, JNCI 2019
- Dieffenbach/Barnea – **Gallbladder disease**, Eur J Cancer 2019
- Dietz/Termuhlen – **Solid organ transplantation**, Lancet Oncol 2019
- Dixon/Nathan – **ALL** outcomes, JCO 2020
- Ehrhardt/Mulrooney – **NHL** outcomes, JCO 2019
- Fidler/Oeffinger/Hawkins – **BCCSS vs CCSS** comparisons, JNCI 2020
- Friedman/Sklar - **Diabetes & abdominal radiation**, JNCI 2019
- Madenci/Weldon – **Anorectal complications**, Cancer 2019
- Mulrooney/Armstrong - **Cardiac** outcomes update, BMJ 2020
- Oeffinger/Robison – **Hodgkin** outcomes, JCO 2021
- Rodwin/Kadan-Lottick – **Neuropathy**, CEBP 2021
- Suh/Henderson – **AYA survivor** outcomes, Lancet Oncol 2020

Analyses under peer review or final draft

- Dieffenbach/Weil – **Renal** outcomes
- Chow/Yasui – **CVRF underdiagnosis & undertreatment**
- Geiger/Srivastava/Wustrack – **Secondary amputation / limb salvage**
- Keefe/Leisenring/Ginsburg – Society for **assisted reproductive** technologies linkage

Approved Concepts – Current Status

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Manuscript in preparation

- Esbenschade/Ness – **Cumulative Illness Rating Scale (CIRS)**
- Friedman/Oeffinger – **Neuroblastoma** outcomes
- Turcotte/Leisenring/Chow – **AML** outcomes
- Weil/Armenian – **Wilms** tumor outcomes
- Wu/Chow – **Kidney failure prediction**

Active analyses

Focused outcomes

- Asdahl – **Esophageal strictures**
- Brown – **Hearing** Impairment
- Bjornard – Female **sexual dysfunction** & chronic health condition
- Dieffenbach/Murphy/Weil/Weldon – **Late surgery** burden
- Noyd/Oeffinger – **CV** health outcomes **disparities**
- Bates/Howell/Constine – **CV substructures** and radiation outcomes

Disease-based analyses

- Beckett/Phelan/Schwartz – **Osteosarcoma** outcomes
- DeBlank – **Astrocytoma & ependymoma** outcomes
- Friedman/Phelan/Chow – BMT outcomes [**CIBMTR linkage**]
- Hingorani/Ness – **Rhabdomyosarcoma** outcomes
- Murphy – **Pelvic sarcoma** outcomes

- Yeh/Leisenring – **Microsimulation modeling** of chronic health outcomes

- Currently Funded
 - CHIP Study: Improving assessment and treatment of **cardiovascular risk factors** among childhood cancer survivors (Chow / R01 CA204378)
 - **Estimating the burden of disease** associated with late-effects among childhood cancer survivors (Yeh / ACS Research Scholar Grant)
 - **Genetic testing** to guide pediatric cancer care and follow up: using anthracycline-associated cardiac toxicity as a model for the future (Yeh / R01 CA227576)
 - Risk of adverse **cardiometabolic outcomes** after TBI (Friedman / ACS Clinician Scientist Award; CIBMTR linkage/support)
 - EMPOWER: **Predicting chronic health conditions** among female survivors (Oeffinger / R01 CA134722)
- Applying for Funding
 - SALSA – Study of Active **Lifestyle** Activation (Chow / R01 / “CHIP2”)

Current Priorities

- Complete disease-specific papers

Disease	Status
ALL	JCO 2020
AML	Manuscript drafted
Astrocytoma	Data analyses
Medulloblastoma	JCO 2019
Hodgkin	JCO 2021
Non-Hodgkin	JCO 2019
Neuroblastoma	Final analyses (ASCO 2021)
Osteosarcoma	Final analyses
Ewing	Concept being finalized
Rhabdomyosarcoma	Final analyses
Wilms	Manuscript drafted

- CTCAE update (FU5, ICD10, v4.03 to v5.0)
 - 2202 items to review, categorize, and grade
 - ICD9 – numeric
 - ICD10 – alpha numeric
 - 5-times as many diagnoses included in ICD10 than in ICD9

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Fiver Year Plan: Research Priorities

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- Improved understanding of accelerated aging
 - Case-control study of frail vs. non-frail? Healthy vs. “accelerated” aging?
- More detailed radiation organ-specific dose/volume relationships
- Exploring/analyzing late surgery dataset (whole new dimension of outcomes!)
- Risk prediction of chronic conditions, adding in genetics
 - For example, bone density (Im, 2021), CV (Bhatia, under review)
- Improved phenotyping of self-reported outcomes (and exposures)
 - mHealth methods for data collection? SALSA study (diet, physical activity, BP, wgt)
 - Linkage to other administrative datasets (e.g., SART, CIBMTR)?
 - EHR-based strategies to improve coordination with primary care? Nudges?
 - Use of biomarker/physiologic data on those with selected chronic illness?
 - Case-control studies of select key outcomes?

Discussion: Threats & Opportunities

Major Threats or Challenges:

- Reliance on self-reported chronic health conditions only
- Volume of AOs and Concepts in working group (assigning concepts to core WG members to assist)

Major Opportunities:

- More novel exposure / outcomes assessments
 - mHealth, EHR (Care Everywhere?), administrative linkages
 - Case-control study of select serious chronic condition
- More collaborative efforts with other working groups to design more complex, innovative analyses, ancillary studies
- Incorporate growing biomarker data beyond genetics into concepts, analyses