Chronic Disease Working Group

CCSS Investigator Meeting 2015

Kevin Oeffinger

Charles (Chuck) Sklar

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Chronic Disease Working Group

- Next 10 yrs of CCSS may be more significant than the previous 10 yrs
- CCSS (and the CDWG) is a team sport
- CCSS is a unique resource for chronic disease research
- Early Career Investigators can (still) thrive in CCSS

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Chronic Disease Working Group

- AOI / Concept Proposals (pages 43-47)
- Organ systems / exposures / outcomes
- CTCAE update
- Selected publications since last meeting
- Career Development Awards
- Selected current analyses
- Intervention studies (w/ Cancer Control WG)
- Future directions

Chronic condition categories	Therapeutic exposures	Cancer groups
Vision	Radiation	ALL
Hearing	Body areas	AML
Speech	Dosimetry	Other leukemia
Endocrine	Chemotherapy	Medulloblastoma
Respiratory	Yes/no	Other CNS
Cardiac	Cumulative dose	Hodgkin lymphoma
Gastrointestinal	CED	NHL
Renal	Doxo-equivalent	Neuroblastoma
Musculoskeletal	Combinations	Wilms tumor
Neurologic	Surgery	Soft tissue sarcoma
Other hematologic		Osteosarcoma
Infection		Ewing sarcoma

Common Terminology Criteria for Adverse Events

- Original NEJM analysis: 114 conditions
- Aging / expansion cohort: exponential increase in the number of conditions
- Universal need for standardized grading that is generalizable, transparent, and can be refined
- CTCAE task force: Sklar, Hudson, Nathan, Armstrong, Chow, Tonorezos, Mostoufi-Moab, Wells, Gibson, Smith, Barnea, Stratton, Leisenring

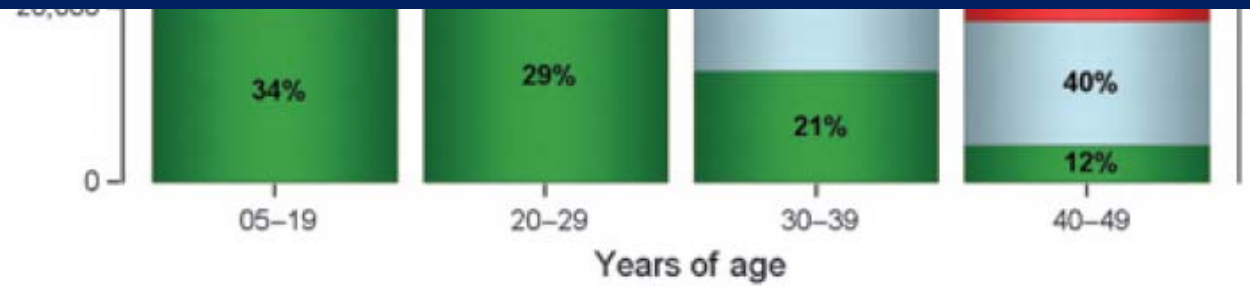
Selected Publications
2013-2015

CEBP REPORT

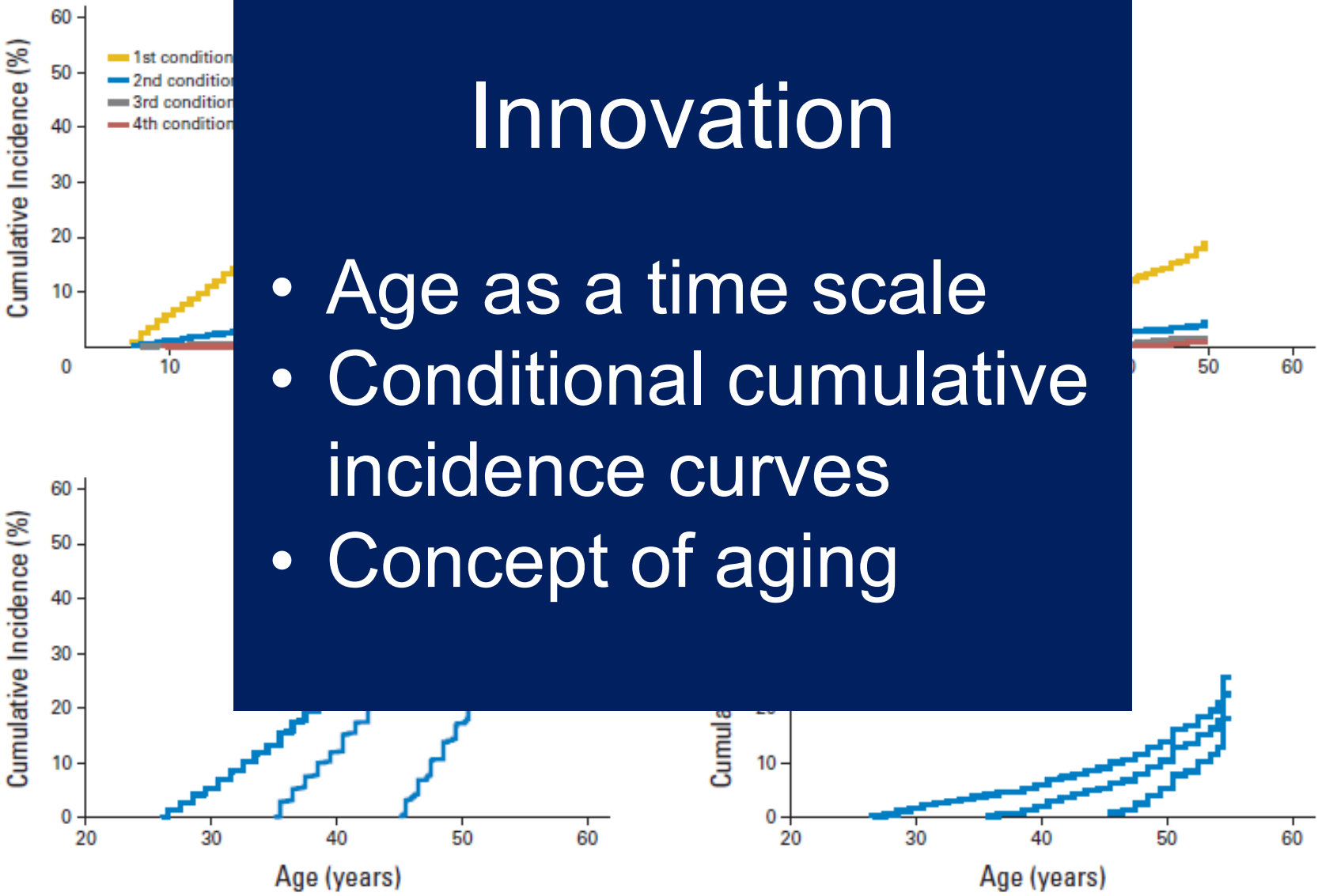
Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity

Siobhan M. Phillips[1], Lynne S. Padgett[2], Wendy M. Leisenring[3], Kayla K. Stratton[3], Ken Bishop[2], Kevin R. Krull[4], Catherine M. Alfano[2], Todd M. Gibson[4], Janet S. de Moor[2],

- NCI / SEER and CCSS
- Innovative strategy to estimate burden of morbidity in United States
- Representativeness of the CCSS cohort
- Potential for economic and policy evaluations



Aging and Risk of Chronic Conditions

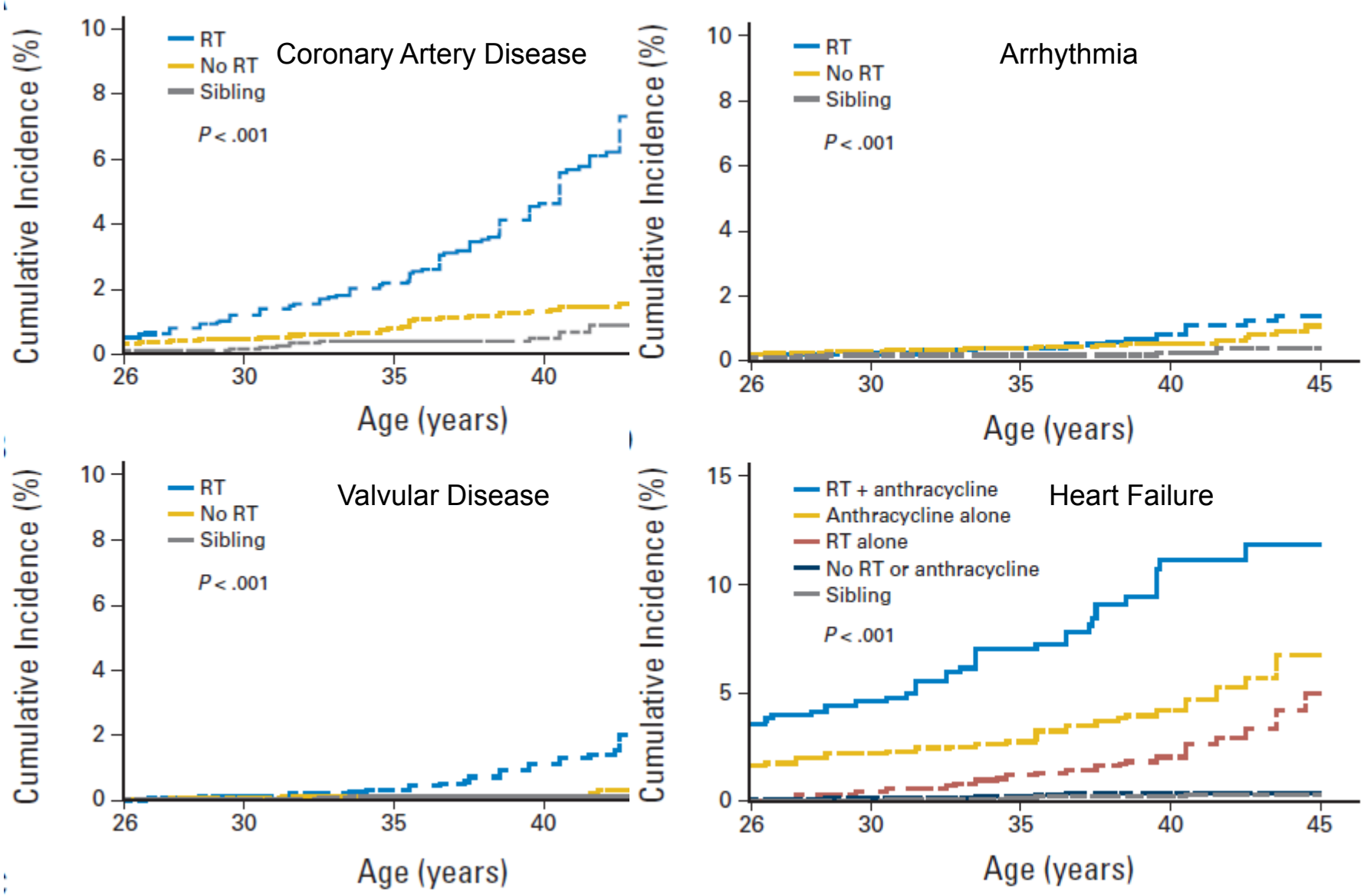


Innovation

- Age as a time scale
- Conditional cumulative incidence curves
- Concept of aging

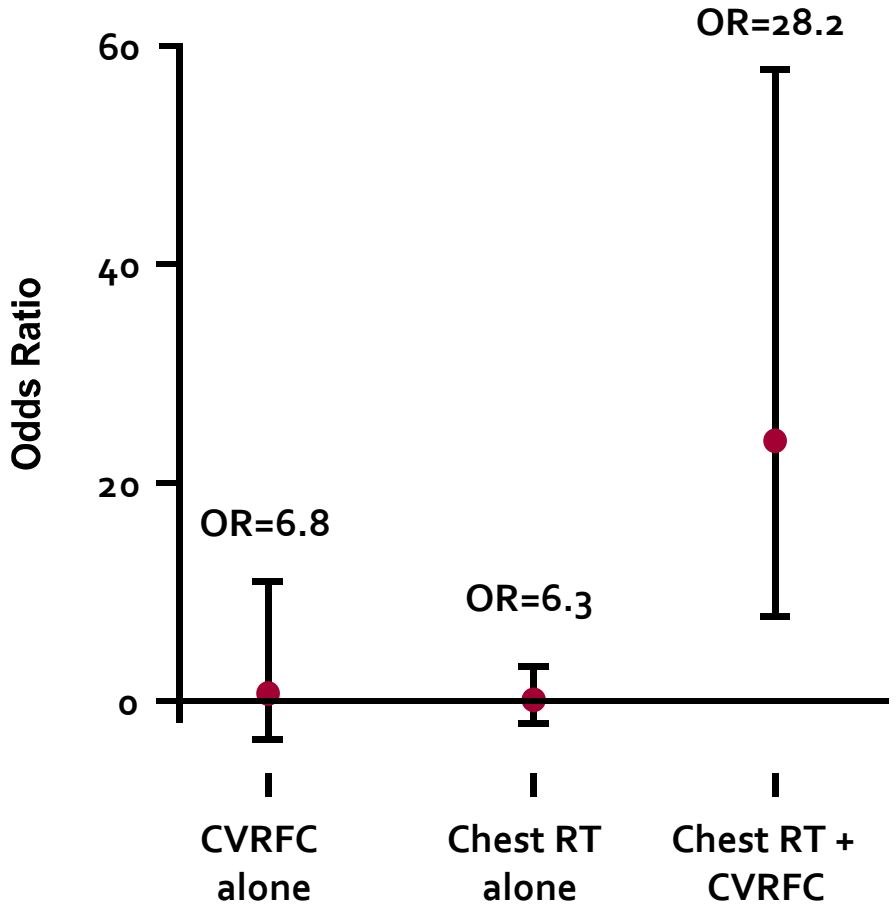
Armstrong GT, et al. J Clin Oncol, 2013

Risk of Grade 3-5 Cardiac Events



Armstrong G, et al. J Clin Oncol, 2013

Risk of Coronary Artery Disease Major Event Interaction between Chest RT and CVD Risk Factors

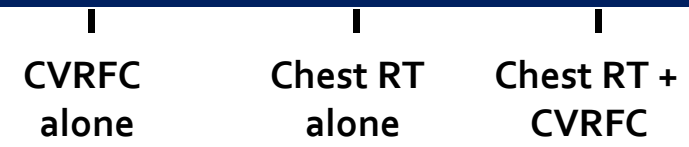


Armstrong G, et al. J Clin Oncol, 2013

Risk of Coronary Artery Disease Major Event
Interaction between Chest RT and CVD Risk Factors

Interaction between treatment exposure * comorbidities

Opportunity with longitudinal design to begin to investigate time sequence of comorbidities leading to outcome



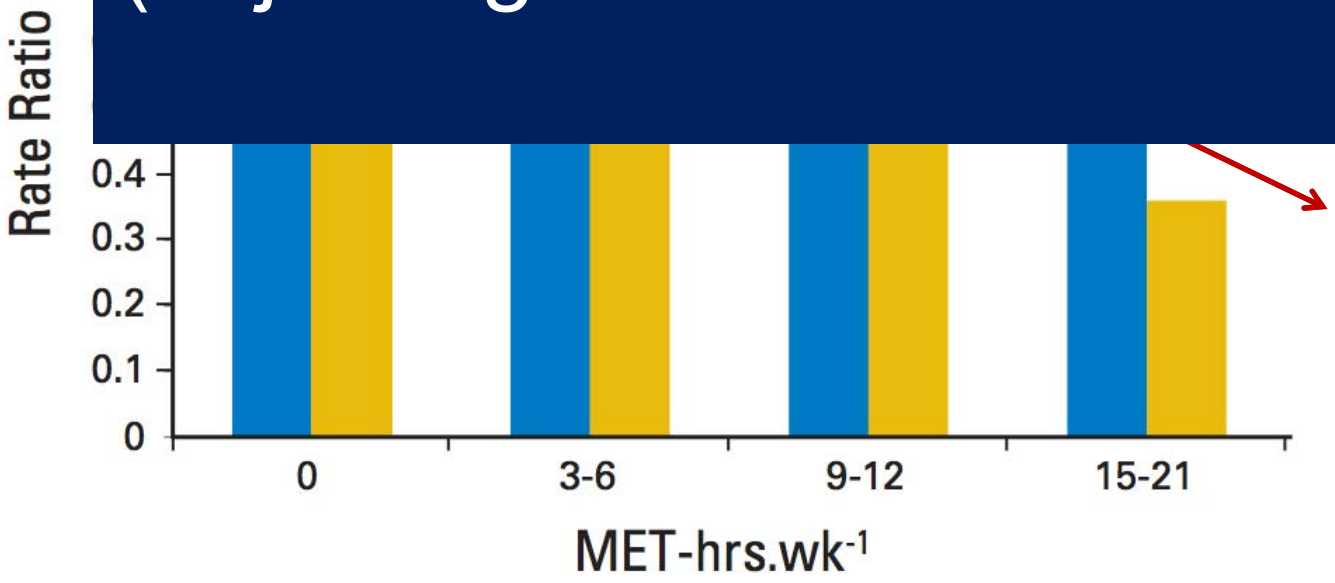
Armstrong G, et al. J Clin Oncol, 2013

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Exercise and Risk of Major Cardiovascular Events in Adult Survivors of Childhood Hodgkin Lymphoma: A Report From the Childhood Cancer Survivor Study

Lee W. Jones, Qi Liu, Gregory T. Armstrong, Kirsten K. Ness, Yutaka Yasui, Katie Devine, Emily Tonorezos, Luisa S

Lifestyle*Exposure
(adjusting for chronic morbidity)



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Indivi
Cance

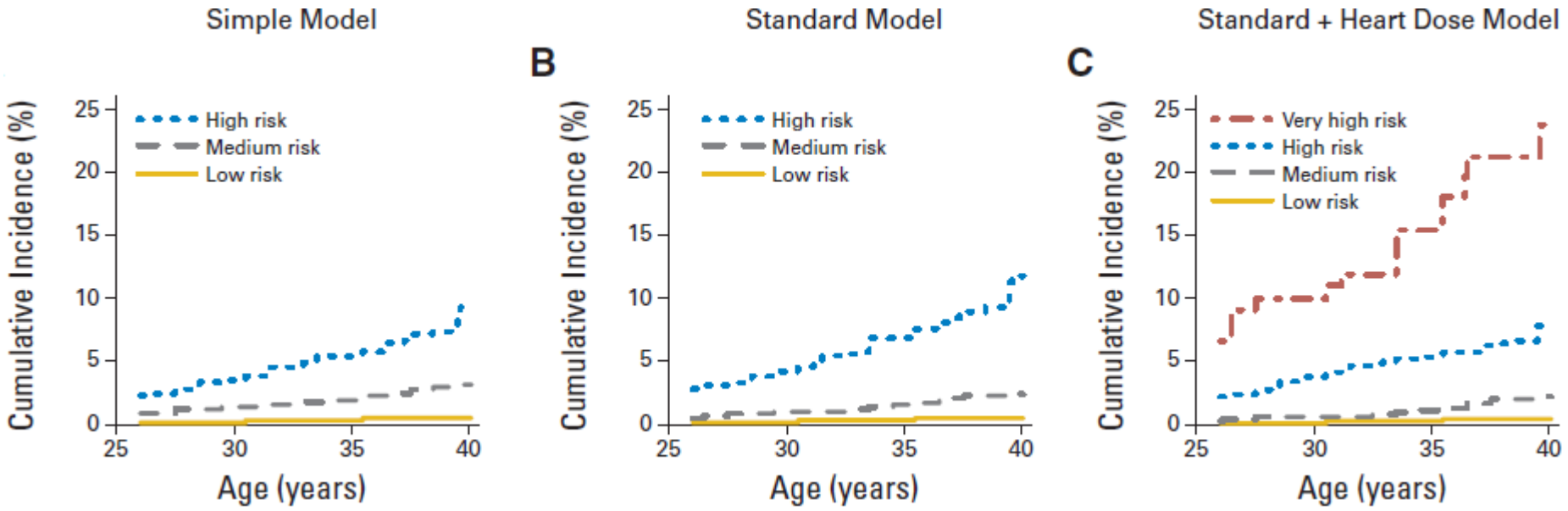
Eric J. Cho
William L.
Daniel A.
Helena J. v

International Collaboration

Childhood Cancer Survivor Study
Emma Children's Hospital
National Wilms Tumor Study
St. Jude Lifetime Cohort

Table 3. CHF Risk Scores and Corresponding Model Discrimination and Predictive Power*

Characteristic	Simple Model†	Standard Model	Heart Dose Model
Sex			
Male	0	0	0
Female	1	1	1
Age at diagnosis, years			
< 5	1	2	2
5-9	0	1	1
10-14	0	0	1
≥ 15	0	0	0
Anthracycline, mg/m^2			
None	0	0	0
Any	3	—	—
< 100	—	1	2
100-249	—	3	3
≥ 250	—	4	4
Chest or heart RT, Gy‡			
None	0	0	0
Any	3	—	—
< 5	—	0	0
5-14	—	2	1
15-34	—	2	3
≥ 35	—	4	4



https://ccss.stjude.org/your-resource/calculators-and-other-tools/ccss-chf-risk-calculator.html

ORIGINAL RESEARCH | Annals of Internal Medicine

Cost-Effectiveness of the Children's Oncology Group Long-Term Follow-up Screening Guidelines for Childhood Cancer Survivors at Risk for Treatment-Related Heart Failure

F. Lennie Wong, PhD; Smita Bhatia, MD, MPH; Wendy Landier, PhD, RN; Liton Francisco, BS; Wendy Leisenring, ScD; Melissa M. Hudson, MD; Gregory T. Armstrong, MD; Ann Mertens, PhD; Marilyn Stovall, PhD; Leslie L. Robison, PhD; Gary H. Lyman, MD, MPH; Steven E. Lipshultz, MD; and Saro H. Armenian, DO, MPH

Conclusion: The COG guidelines could reduce the risk for heart failure in survivors at less than $100 000/QALY. Less frequent screening achieves most of the benefits and would be more cost-effective than the COG guidelines.

ORIGINAL RESEARCH | Annals of Internal Medicine

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Annals of Internal Medicine | ORIGINAL RESEARCH

Routine Echocardiography Screening for Asymptomatic Left Ventricular Dysfunction in Childhood Cancer Survivors: A Model-Based Estimation of the Clinical and Economic Effects

Jennifer M. Yeh, PhD; Anju Nohria, MD; and Lisa Diller, MD

Conclusion: Current recommendations for cardiac assessment may reduce CHF incidence, but less frequent assessment may be preferable.

ORIGINAL RESEARCH | Annals of Internal Medicine

Cost-Effectiveness of the Children's Oncology Group Long-Term Follow-up Screening Guidelines for Childhood Cancer Survivors at Risk for Treatment-Related Heart Failure

- For many / most screening tests in cancer survivors, we will not be able to conduct RCT to assess for a reduction in mortality
- Will need to rely upon micro-simulation / cost-effectiveness models to inform us regarding the trade-offs of different decisions

Jennifer M. Yeh, PhD; Anja Nohria, MD; and Lisa Diller, MD

Conclusion: Current recommendations for cardiac assessment may reduce CHF incidence, but less frequent assessment may be preferable.

Doxorubicin-Equivalent Dose

Historical doxorubicin equivalence ratios

(based on hematologic toxicity)

Group(s) using referenced ratio	Doxorubicin	Daunorubicin	Idarubicin	Epirubicin
Children's Oncology Group (v4.0)	1	1	5	0.67
Childhood Cancer Survivor Study	1	1	3	
Dutch Childhood Oncology Group LATER	1	1		0.67

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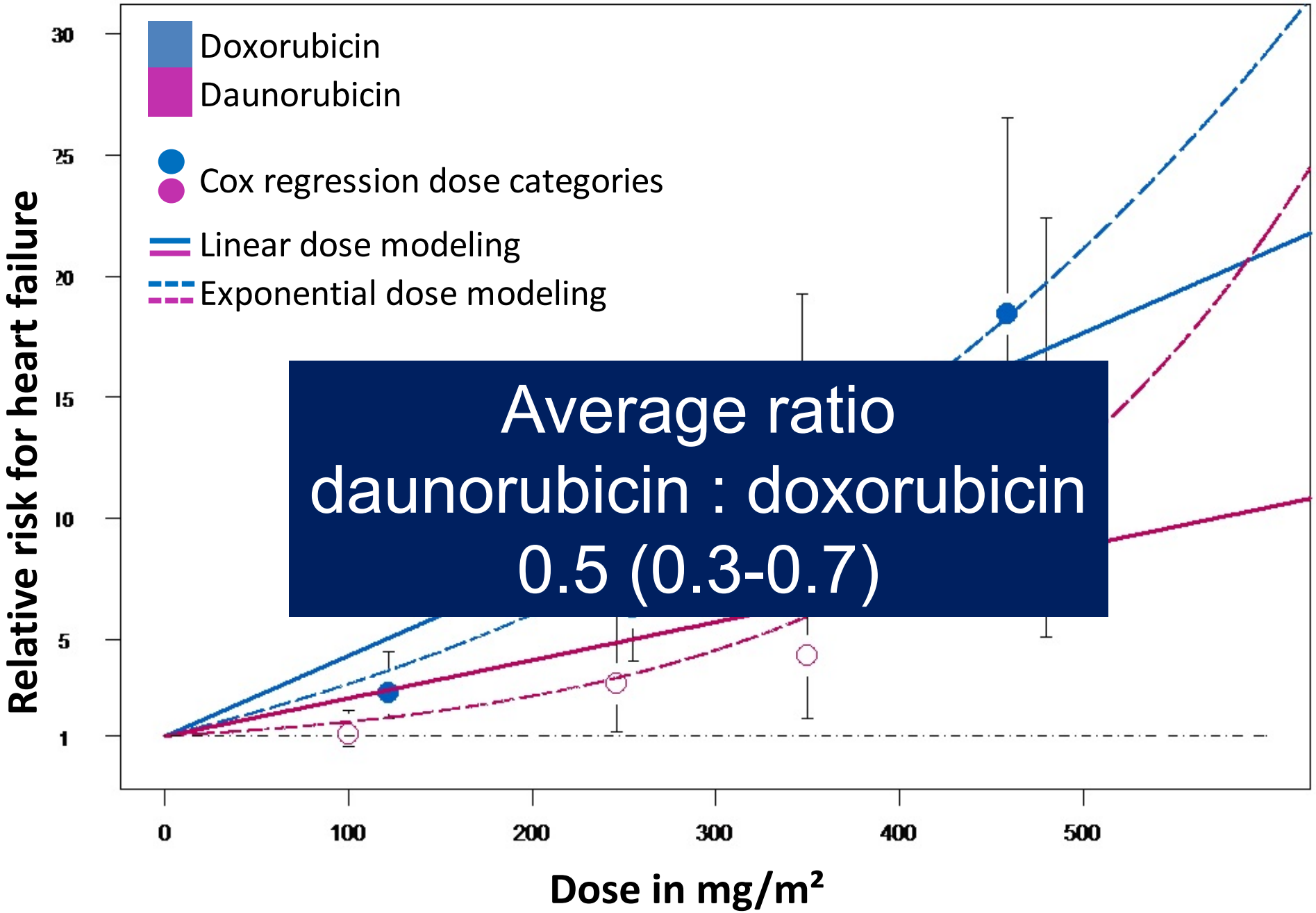
Doxorubicin-Equivalent Dose

His
(ba

International Collaboration (2)

Childhood Cancer Survivor Study
Emma Children's Hospital
National Wilms Tumor Study
St. Jude Lifetime Cohort

Grou refere				n
Child (v4.0				
Child Study				
Dutch Childhood Oncology Group LATER	1	1		0.67



Feijen L, et al. J Clin Oncol, in press

VOLUME 32 · NUMBER 35 · DECEMBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Increasing Cardiomyopathy Screening in At-Risk Adult Survivors of Pediatric Malignancies: A Randomized Controlled Trial

Melissa M. Hudson, Wendy Leisenring, Kayla K. Stratton, Nina Tinner, Brenda D. Steen, Susan Ogg, Linda Barnes, Kevin C. Oeffinger, Leslie L. Robison, and Cheryl L. Cox

Validated outcomes:

- Cardiomyopathy (10%)
- Global hypokinesia with normal EF (4%)
- Diastolic dysfunction (8%)
- Pulmonary hypertension (4%)
- Left ventricular hypertrophy (4%)

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Cyclophosphamide-Equivalent Dose

- Develop method for quantifying alkylating agent exposure that does not depend on study dose distribution and normalizes for individual agent exposure.
- Dose equivalents based on published hematological toxicity data when available.

Drug	Dose (mg/m^2)
Cyclophosphamide	100
Ifosfamide	409
Procarbazine	117
Chlorambucil	7
BCNU	6.7
CCNU	6.3
Nitrogen mustard	1
Busulfan	11.3
Thio-TEPA	2

Green DM, et al., Pediatr Blood Cancer 2014;61:53-67

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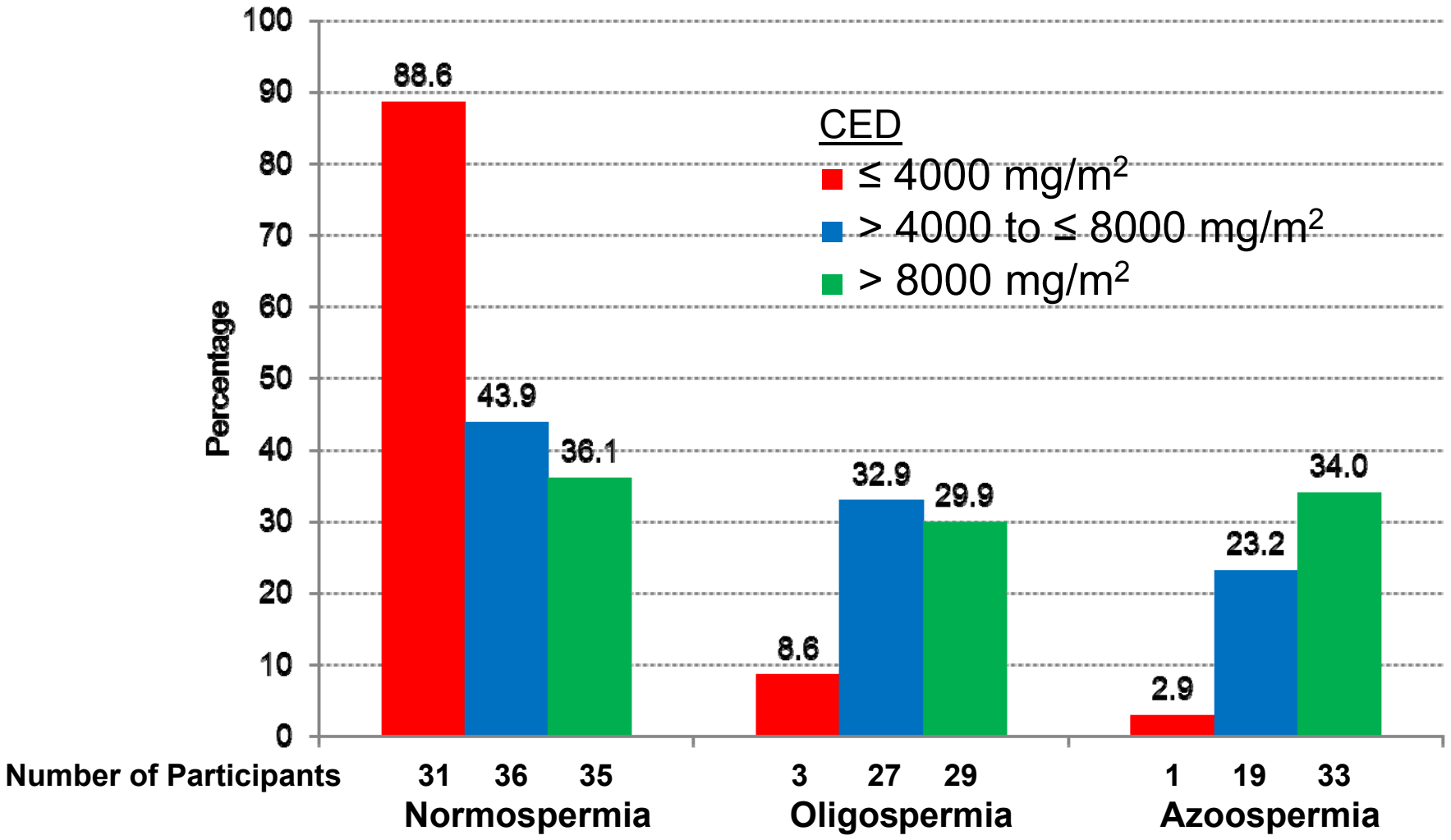
Sperm Concentration Groups by CED



Green DM, et al., Lancet Oncol 2014;15:1215-1223

Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort

Stefan Essig, Qiaozhi Li, Yan Chen, Johann Hitzler, Wendy Leisenring, Mark Greenberg, Charles Sklar, Melissa M Hudson, Gregory T Armstrong, Kevin R Krull, Joseph P Neglia, Kevin C Oeffinger, Leslie L Robison, Claudia E Kuehni, Yutaka Yasui, Paul C Nathan *Lancet Oncol* 2014; 15: 841–51

Can we predict outcomes for standard risk ALL survivors treated with contemporary therapy?

- CCSS 1970-1986, age 1.0-9.9 yrs with ALL
- Model based upon contemporary ALL therapy
- Mortality, chronic conditions, health status

Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort

Stefan Essig, Qiaozhi Li, Yan Chen, Johann Hitzler, Wendy Leisenring, Mark Greenberg, Charles Sklar, Melissa M Hudson, Gregory T Armstrong, Kevin R Krull, Joseph P Neglia, Kevin C Oeffinger, Leslie L Robison, Claudia E Kuehni, Yutaka Yasui, Paul C Nathan

Lancet Oncol 2014; 15: 841–51

	Survivors (n=556)	Siblings (n=2232)	RR or OR (95% CI)*	p value	Number needed to harm (95% CI)†
Overall chronic health disorders‡§					
Any disorder, grade 1–5	192 (48%)	1058 (51%)	1·3 (1·1 to 1·6)	0·0005	107 (81 to 193)
Any disorder, grade 3–5	51 (10%)	157 (7%)	2·0 (1·4 to 2·8)	<0·0001	415 (376 to 939)
More than one disorder, grade 1–5	156 (32%)	598 (27%)	1·6 (1·4 to 2·0)	<0·0001	136 (126 to 236)
Multiple disorder, grade 3–5	6 (1%)	18 (1%)	1·8 (0·7 to 4·8)	0·21	..

What are some of our current concepts?

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Career Development Award

- Sogol (Goli) Mostoufi-Moab (2013)

  Overall risk of Chronic Endocrine Disorders in Adult Survivors of Childhood Cancer
- Danielle Novetsky Friedman (2015)

  Impact of radiation dose to the pancreas on subsequent risk of diabetes mellitus
- Adam Esbenshade (2015)

  Using the Cumulative Illness Rating Scale to characterize the burden of chronic conditions
- Miranda Fidler (2015)

  Comparison of risks for mortality and subsequent cancers in the CCSS and the BCCSS

Fertility following Contemporary Chemotherapy in Childhood Cancer Survivors

Eric Chow

- Determine if more contemporary chemotherapy agents and treatment combinations, specifically those that include ifosfamide and platinum-containing agents, are associated with a differential likelihood of male and female fertility compared with regimens that do not contain these agents among the entire CCSS population.
- Apply classification and regression tree (CART) methods to determine which chemotherapy agents and agent-dose combinations will be most strongly associated with a lower likelihood of fertility.

Contemporary Risk-Adapted Therapy for Hodgkin Lymphoma: What are the Trade-Offs?

Kevin Oeffinger

1. Estimate all-cause and cause-specific mortality for 5+ year survivors of Hodgkin lymphoma diagnosed 1970-1999 and compare by era of therapy and by major treatment groupings.
2. Determine the incidence of chronic health conditions and compare by era of therapy and by major treatment groupings.
3. Estimate risks of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions) with contemporary HL therapy - use data from CCSS to create groups with similar exposures to two contemporary Children's Oncology Group (COG) protocols – AHOD 0031 and AHOD 0431.
4. Merge data with Dutch HL cohort to look more closely at treatment exposures and trade-offs (combined data almost 5,500 HL survivors).

EQUAL

Emily Tonorezos

- 24-month RCT comparing the effect of a web- and telephone-based weight loss intervention (led by *Healthways at Hopkins*) to general information about weight loss and healthy living (control).
- Calculate the effect of the diet and physical activity intervention, compared to self- directed weight loss, on three key metabolic biomarkers:
  - *a. Fasting insulin*
  - *b. Leptin:adiponectin ratio*
  - *c. Small, dense LDL*

Improving treatment of cardiovascular risk factors in childhood cancer survivors

Eric Chow – R01 grant application in review

1. Determine the prevalence of underdiagnosis and undertreatment of conventional CV risk factors (i.e., hypertension, dyslipidemia, and diabetes) among CCSS participants predicted to be either high (n=600) or low risk (n=200) for future serious CV disease (i.e., ischemic heart disease, cardiomyopathy/heart failure) on the basis of their original cancer treatment exposures (e.g., chest radiotherapy, anthracycline doses).

Improving treatment of cardiovascular risk factors in childhood cancer survivors

Eric Chow – R01 grant application in review

2. Among survivors found to be underdiagnosed or undertreated (Aim 1), in a randomized controlled design, compare changes in blood pressure, lipid, and blood glucose values from baseline to 1-year between those receiving the intervention (providing clinical results and survivorship care plans [SCPs] to participants and their healthcare providers, supplemented by clinician-led remote counseling sessions with participants to review SCP contents and teach CV risk factor self-management strategies) vs. control (providing clinical results to participants and their healthcare providers; can receive the full intervention on a delayed basis).

Refining Risk-based Follow-up Guidelines To Improve Childhood Cancer Survivorship

Jennifer Yeh – R01/ACS grant applications in review

1. Develop a Childhood Cancer Survivorship Simulation Model
2. Estimate the lifelong magnitude and heterogeneity in disease burden associated with late effects among childhood cancer survivors
3. Assess the comparative effectiveness of secondary cancer screening strategies to improve long-term outcomes among at-risk survivors

Where are we going?

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Collaboration is a Requirement

- Between CCSS Working Groups
- With other cohort studies / investigators
- Engaging non-CCSS specialists
- Collaboration enriches both the science and the impact of the results

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Impactful / Practice Changing Research

- Treatment*Lifestyle*Comorbidity*Genetic Variant
- Newer chemotherapy combinations (or larger numbers) with and without radiation
- More contemporary radiation doses and fields
- Risk prediction / micro-simulation / cost-effective
- How chronic conditions predict psychosocial outcomes - how psychosocial outcomes predict future morbidity
- Innovative longitudinal analyses
- Interventions to reduce selected morbidities and overall burden of morbidity

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Key Questions

- Do lifestyle changes influence the development of chronic diseases? (pathway analysis)
- What are the key factors explaining variance in hearing loss among childhood cancer survivors treated with cisplatin?
- What are the key chronic diseases that contribute to accelerated aging?
- Kevin, what about analyzing __ cancer group?
- Has reduction in whole brain / posterior fossa radiation dose with concurrent chemotherapeutic intensification resulted in better long-term outcomes among medulloblastoma survivors?

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What about case-control studies?

- Ancillary studies to gather more detailed information / international or large collaborations
- Neurologic sequelae associated with a meningioma
- Hypertension post radiation – kidney / renal artery dose, comorbidities (insulin resistance, obesity), and genetic variants
- Cardiovascular disease in long-term survivors who had established growth hormone deficiency during childhood

Thanks
(to the many, many investigators
working on chronic disease projects)

Questions?