Pediatric Cancer Survivorship

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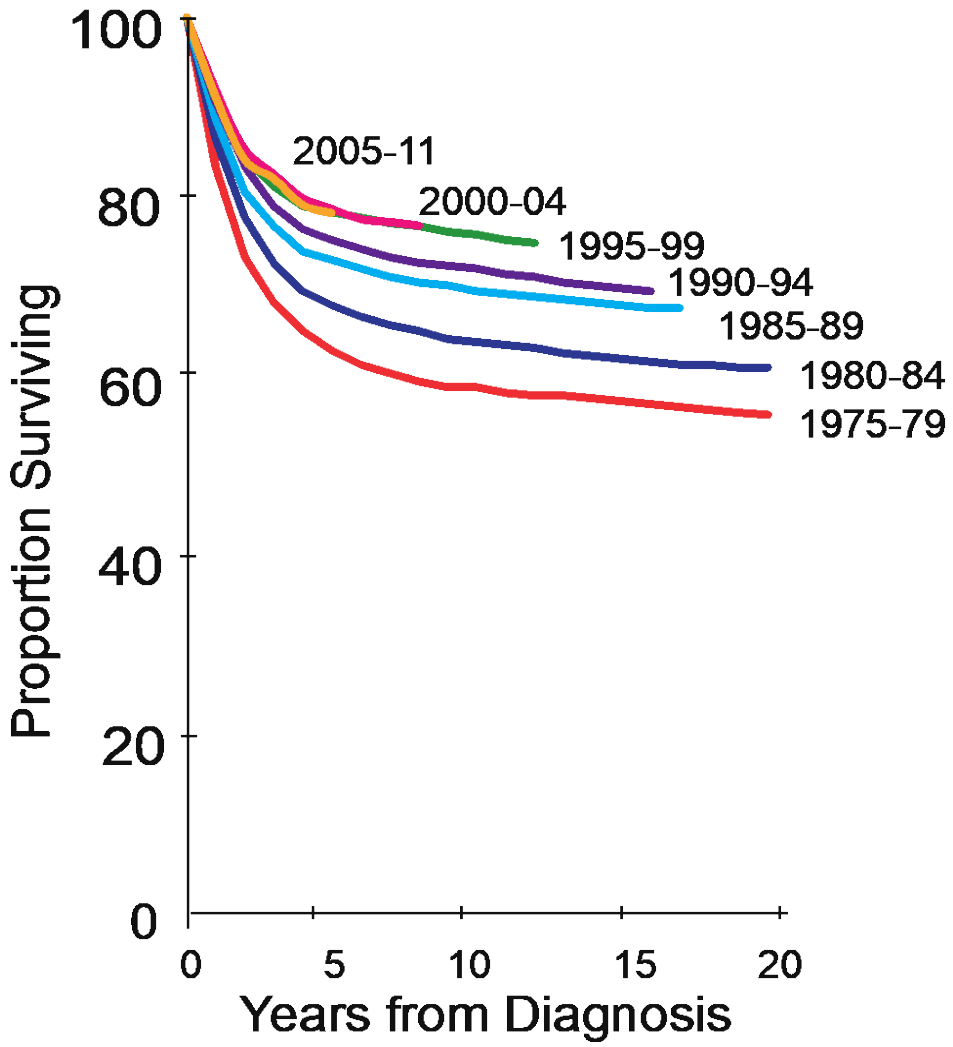
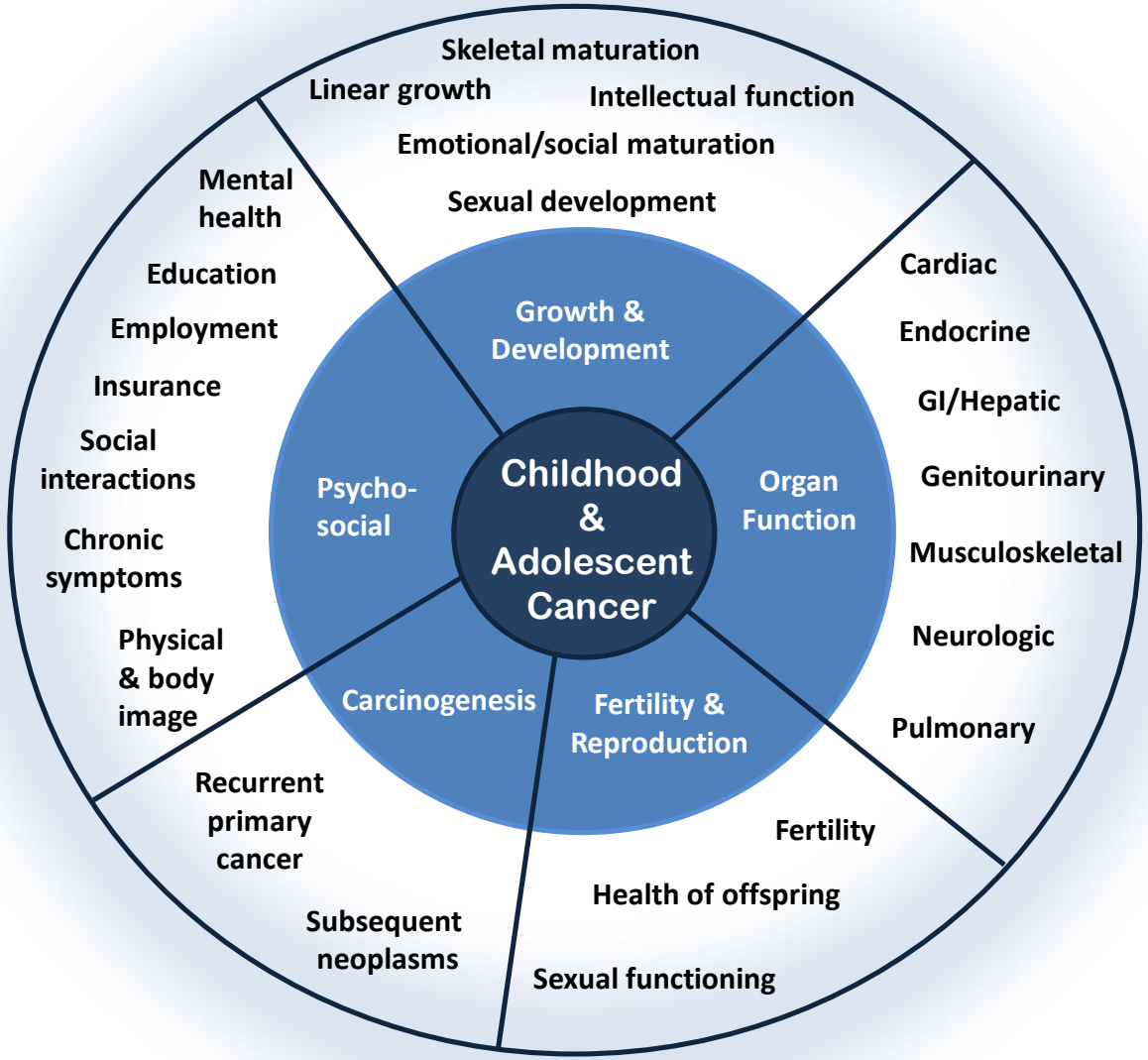
Childhood Cancer Survivors



- 10,590 diagnosed annually in the US
- >85% of children with a malignancy will achieve five-year survival
- In 2020, estimated to exceed 500,000 survivors
- 1 in 750 in US is a childhood cancer survivor
- High morbidity, premature mortality

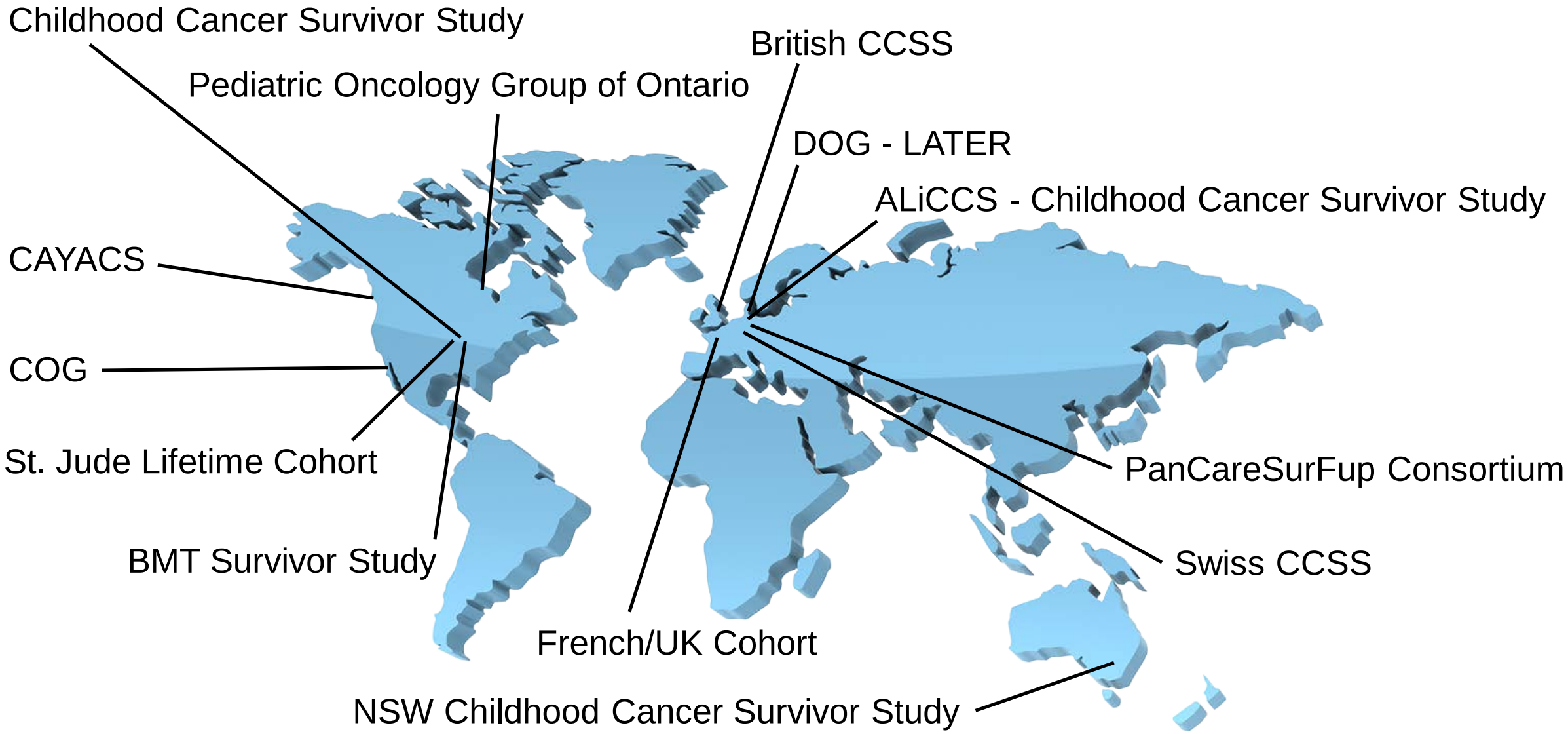
Source: SEER, Nat Rev Cancer 2014

Spectrum of Health-related and Quality of Life Outcomes



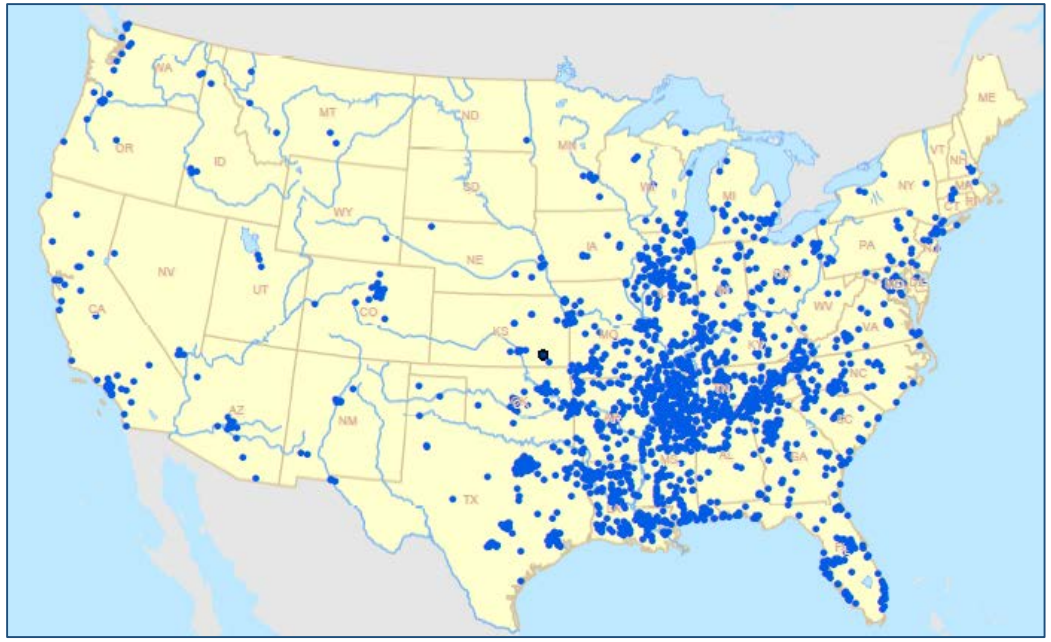
Robison and Hudson. *Nat Rev Cancer*, 2014

Pediatric Cancer Survivorship Research

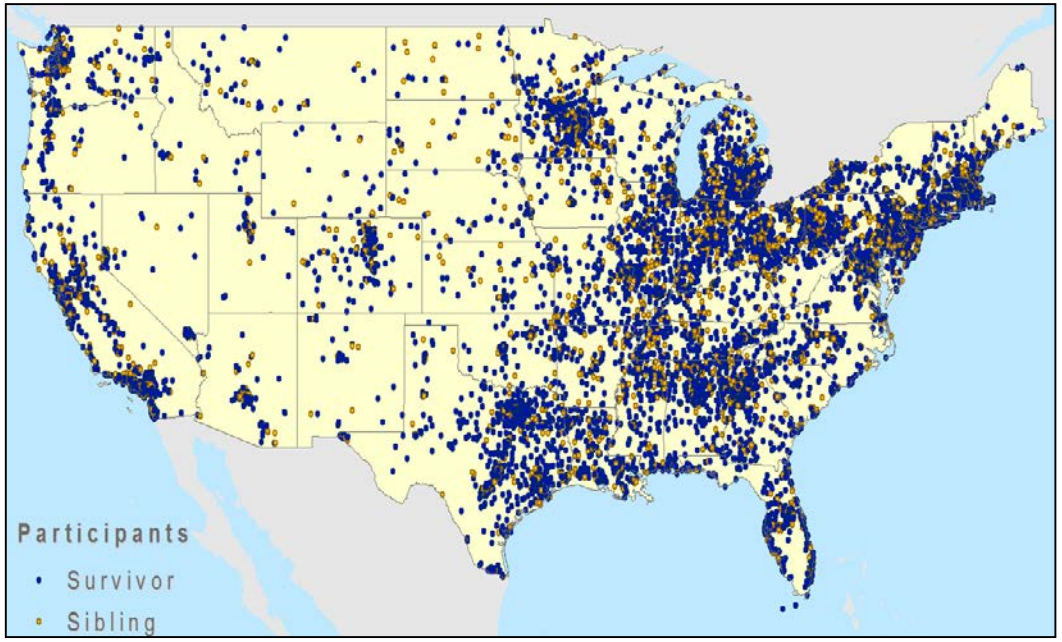


Pediatric Cancer Survivor Cohorts

SJLIFE
St. Jude Lifetime Cohort
U01 CA195547 (MPI: Hudson/Robison)
8245 Survivors (6000+ clinically assessed)



CCSS
Childhood Cancer Survivor Study Cohort
U24 CA55727 (PI: Armstrong)
35,937 Survivors (24,500+ participants)



Chronic Health Conditions
Cumulative Incidence vs. Burden

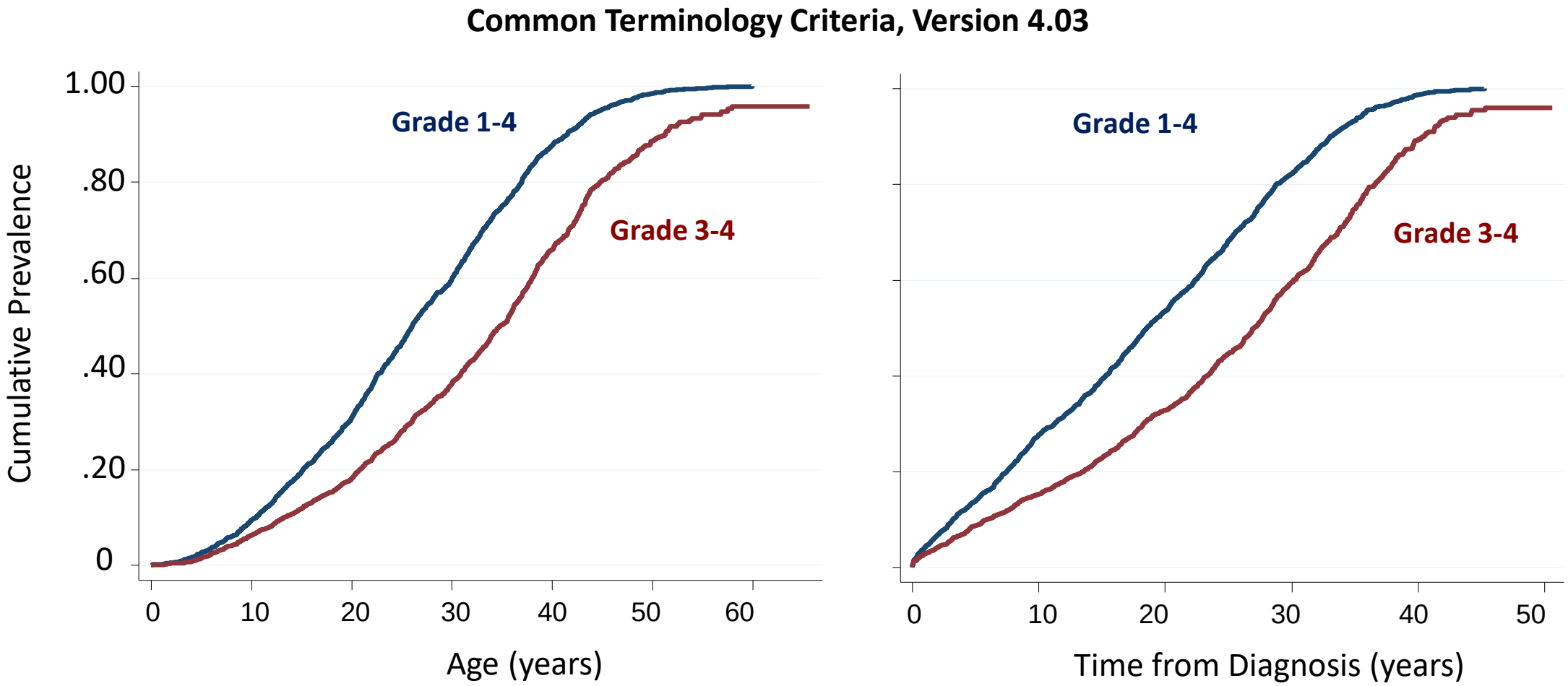
Hudson, Ness, et al. JAMA, 2013

At age 45 years it is estimated that…… 95.2% will have at least one chronic health condition and 80% will have a serious/disabling or life-threatening chronic health condition

Bhakta et al, Lancet, 2017

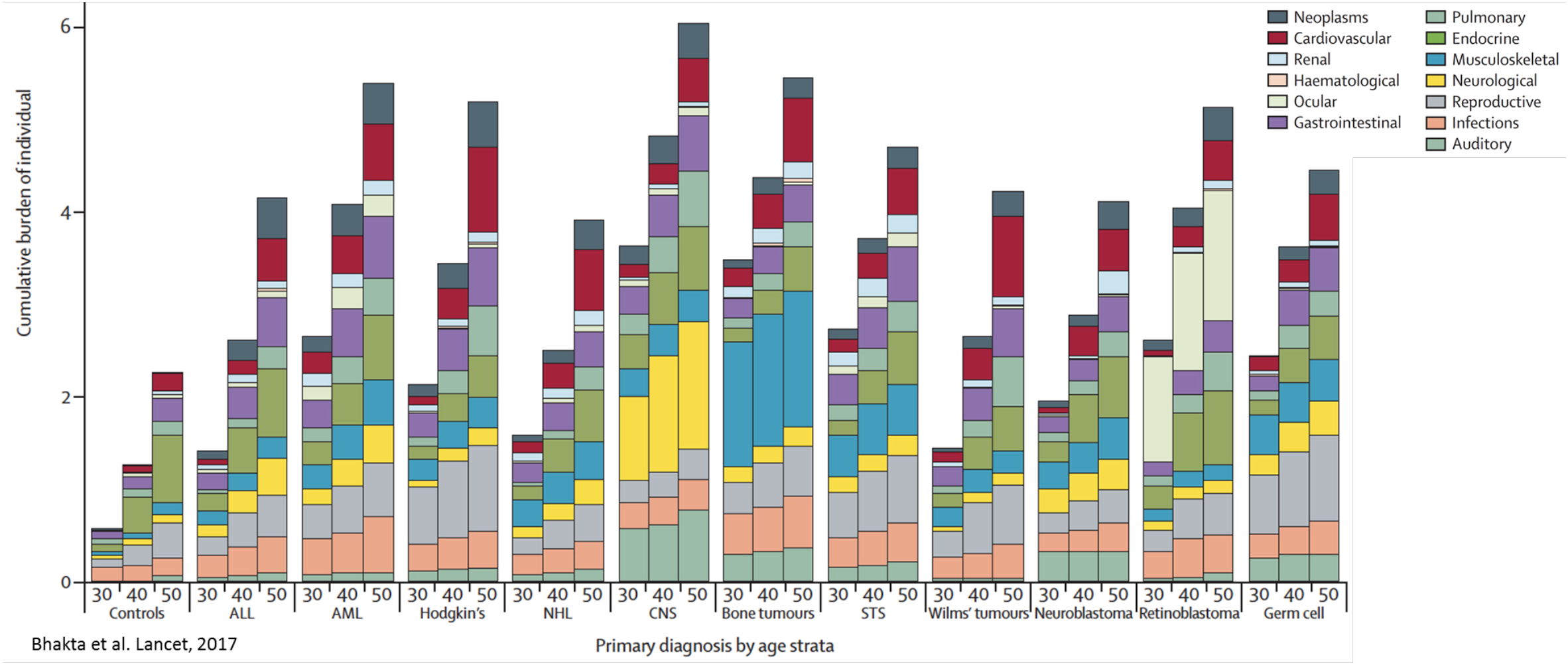
By age 40….. on average a survivor will have 12 chronic conditions, 3 of which will be serious/disabling, life-threatening, or fatal

Cumulative Prevalence of Chronic Health Conditions



Cumulative Burden by Organ System

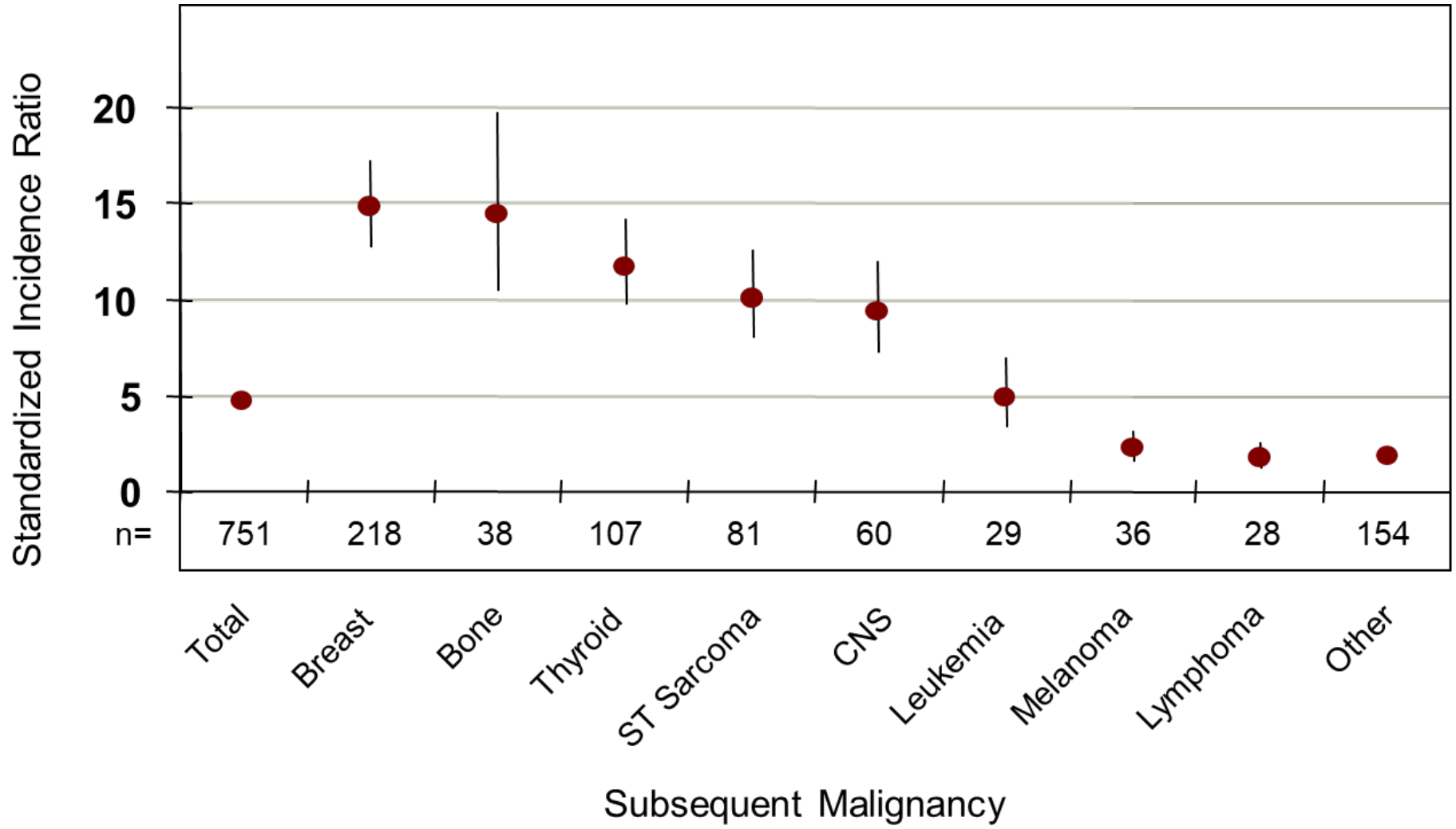
Grade 3-5* Chronic Health Conditions



Bhakta et al. Lancet, 2017

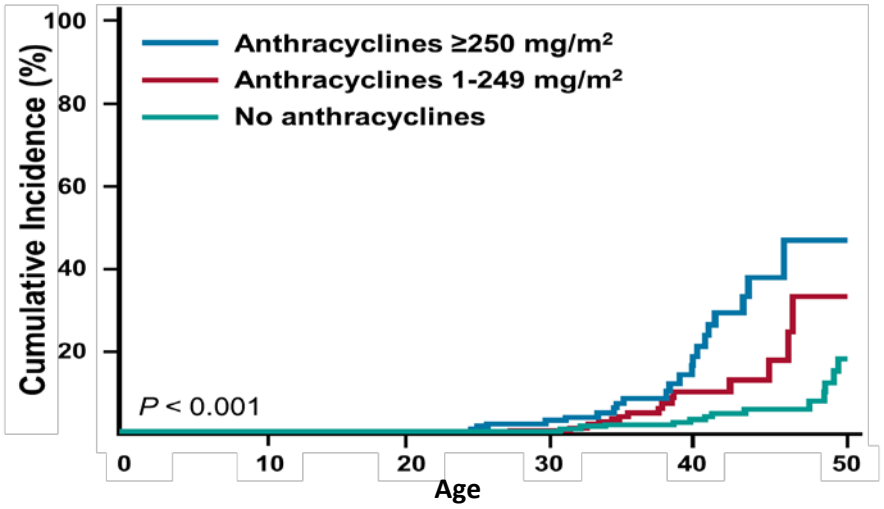
Childhood Cancer Survivor Study

Second Neoplasms Among 5+ Year Survivors of Childhood Cancer



Defining Risks for Secondary Breast Cancer

Ehrhardt et al, J Clin Oncol, 2019



Variable		Total Cohort (n=1,332) (45 with breast cancer) HR	95% CI
Breast cancer predisposition	None	1.0	
	≥1 gene mutation	**23.0**	**(7.3 - 72.2)**
Chest radiation (Gy)	None	1.0	
	>0 to <10	0.7	(0.2 - 2.8)
	10 to <20	2.4	(0.4 - 15.0)
	≥20	**7.6**	**(2.9 - 20.4)**
Alkylating agents (mg/m^2)	None	1.0	
	>0 to 5,999	1.0	(0.4 - 2.6)
	≥6,000	**0.4**	**(0.2 - 0.9)**
Anthracyclines (mg/m^2)	None	1.0	
	1-249	**2.6**	**(1.1 - 6.2)**
	≥250	**13.4**	**(5.5 - 32.5)**

- 1332 clinically assessed female SJLIFE survivors
- Multivariable models evaluating breast cancer risk for radiation, chemotherapy, cancer predisposition genetics

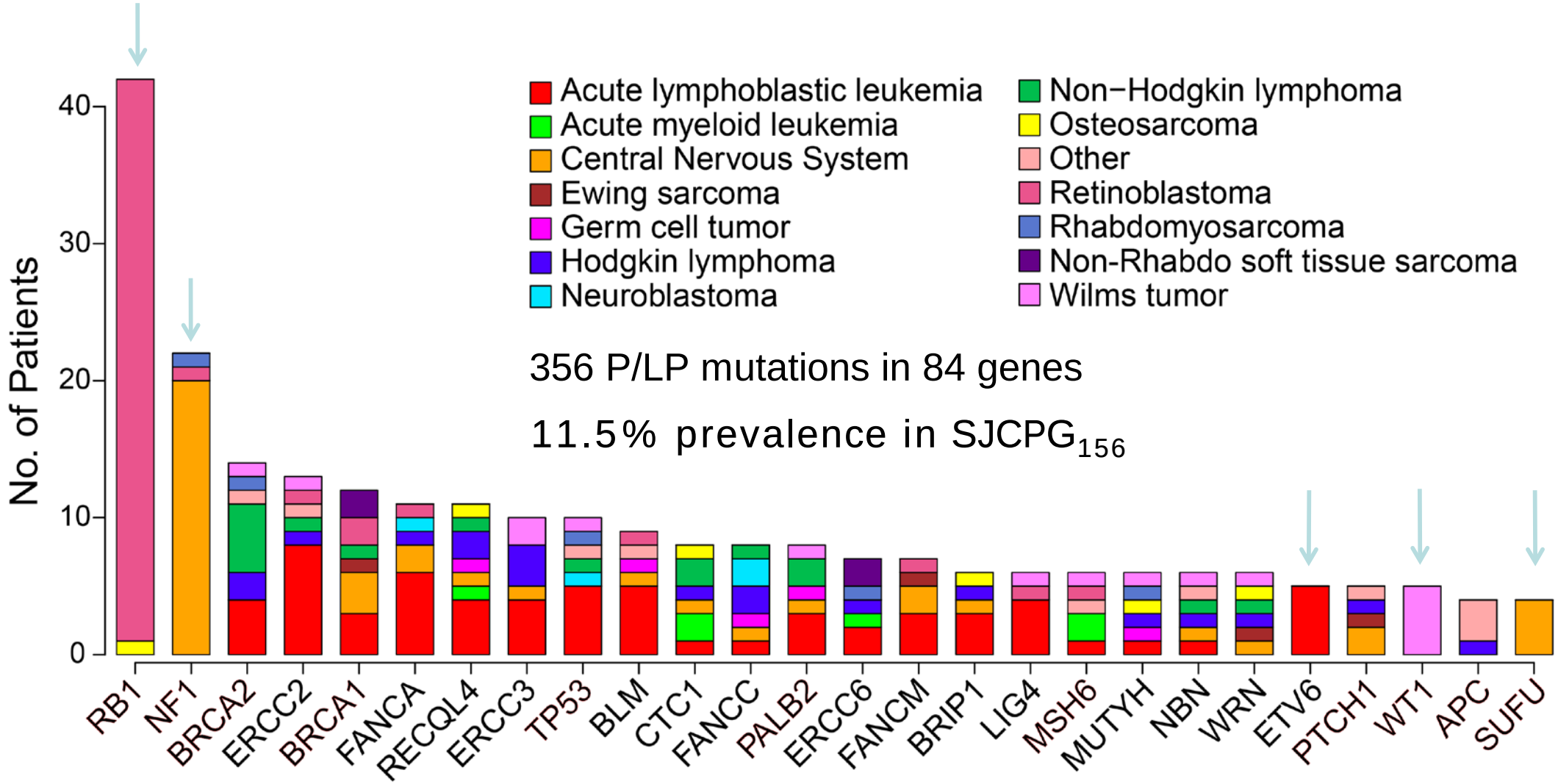
Independent risks:

23-fold risk pathogenic/likely pathogenic mutation in breast cancer predisposition gene

7-fold risk chest radiation >20 Gy

13-fold risk cumulative anthracycline >250 mg/m^2

Frequency Distribution of Germline Mutations



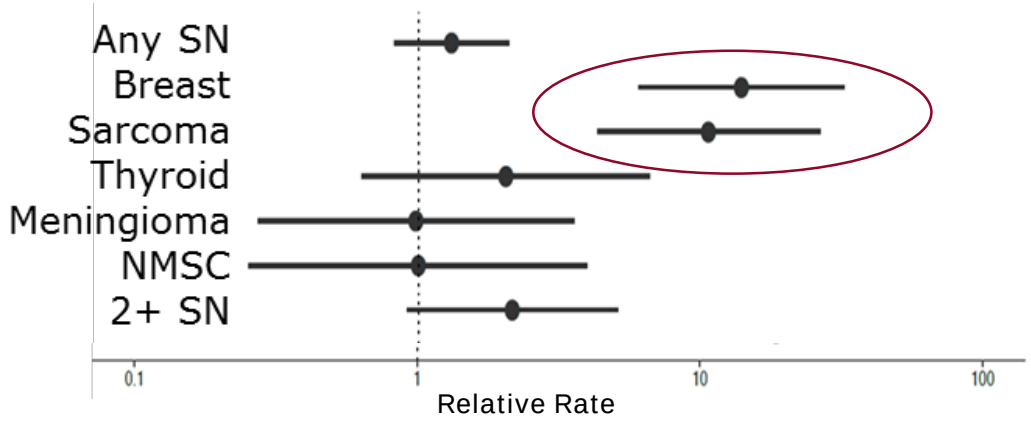
Z. Wang, C. Wilson, et al., JCO, 2018

Cancer Predisposition and Subsequent Malignancies

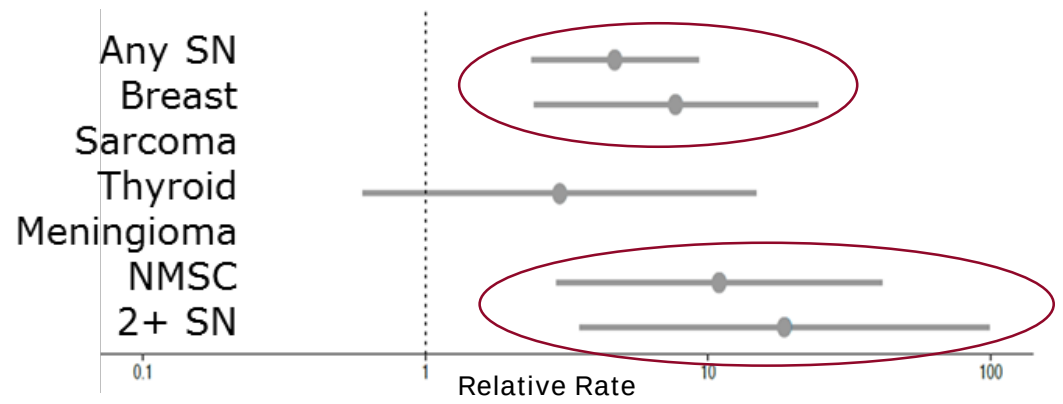
Pathogenic/Likely Pathogenic Mutation

5.8% prevalence in $SJCPG_{60}$ (autosomal dominant inheritance with high penetrance)

Irradiated



Non- Irradiated



Conclusion

"The findings support referral of all survivors for genetic counseling for potential clinical genetic testing, which should be prioritized for nonirradiated survivors with any SN and for those with breast cancer or sarcoma in the field of prior irradiation."

Z. Wang, C. Wilson, et al., JCO, 2018

Pathogenic Germline Mutations in DNA Repair Genes

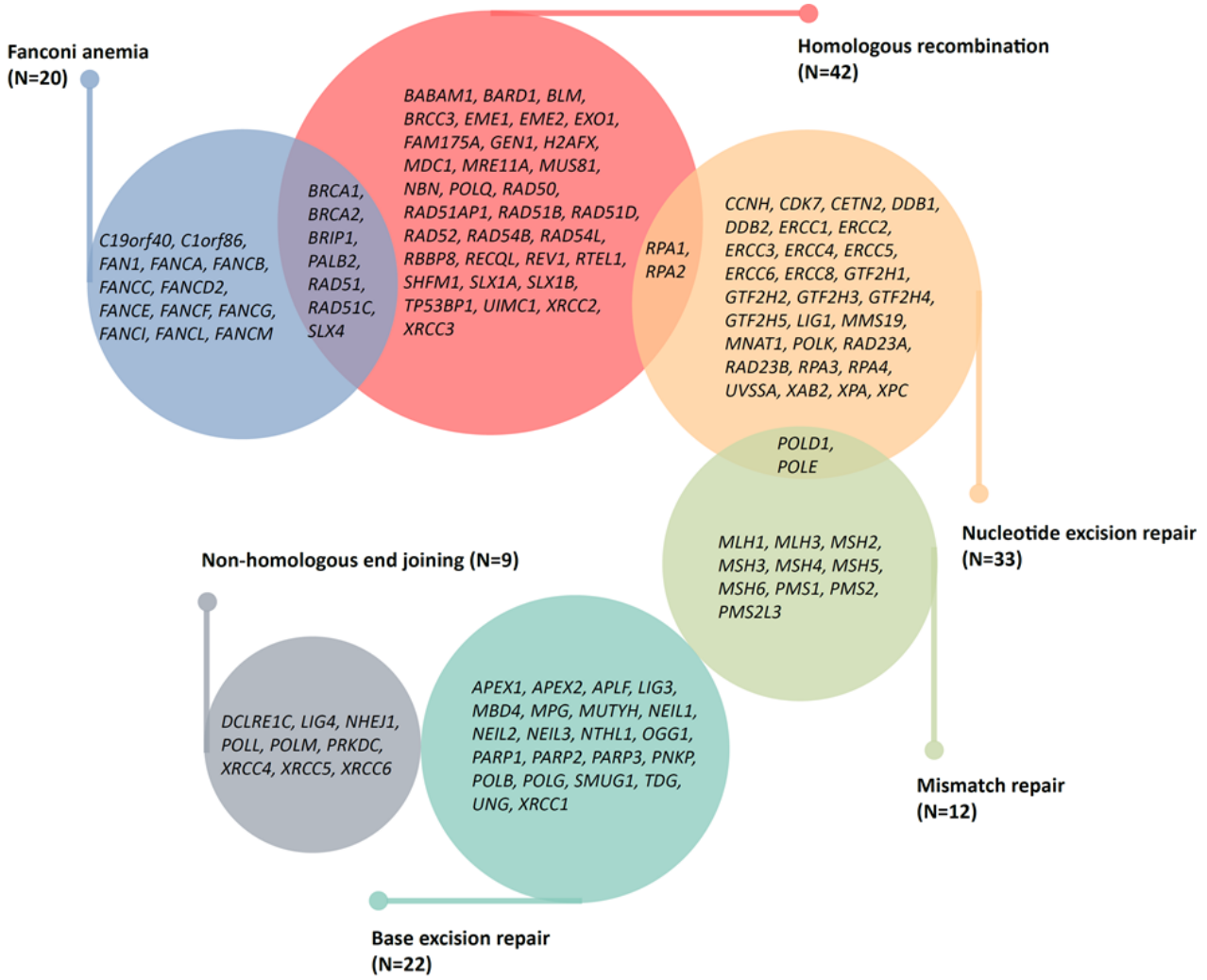
SJ Lifetime Cohort Study

4402 survivors of childhood cancer

WGS (average coverage 39X)
WES (average coverage 234X)

Median age dx 6.3 yrs (range 0-23)
Median age at follow-up 29.6 yrs (range 6-70)

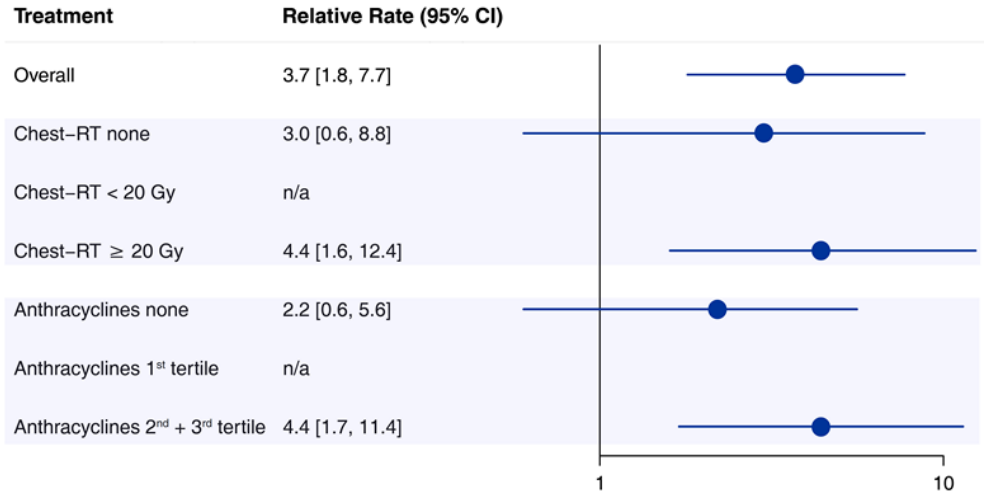
1269 SNs in 497 survivors
127 genes in 6 major DNA repair pathways



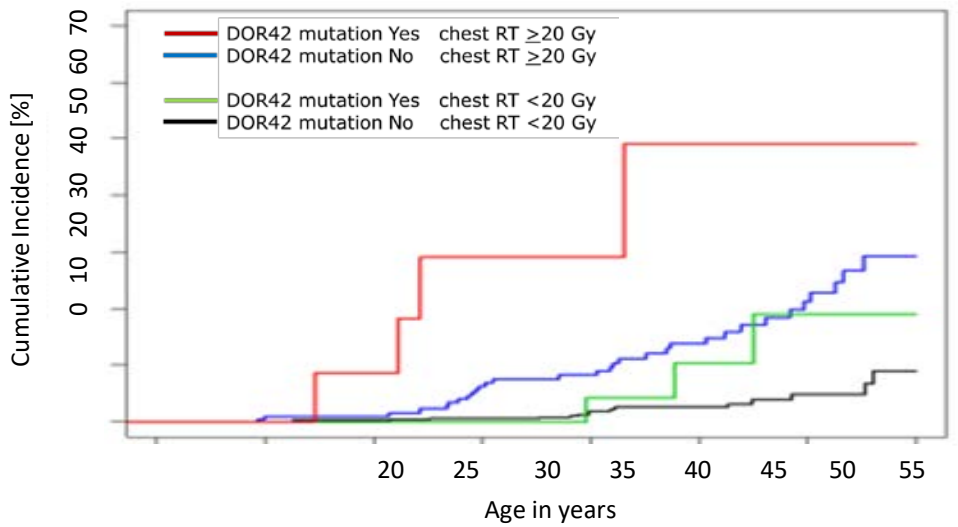
Qin N, et al. J Clin Oncol, 2020

Pathogenic Germline Mutations in DNA Repair Genes

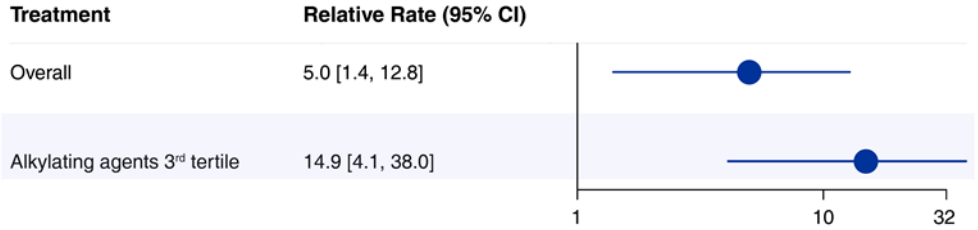
Subsequent breast cancer



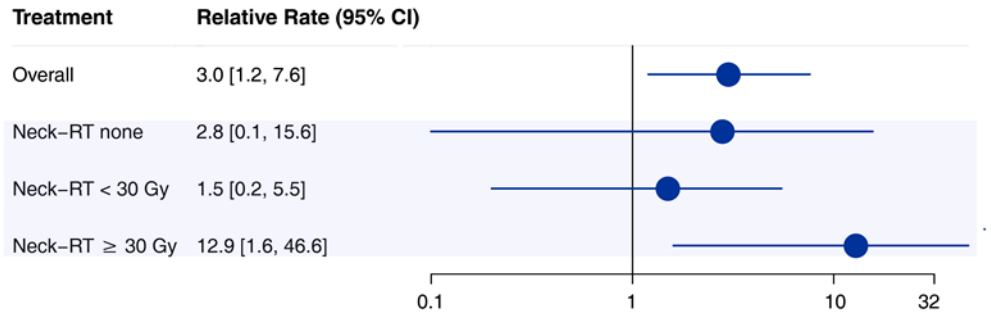
Subsequent breast cancer



Subsequent sarcoma



Subsequent thyroid cancer



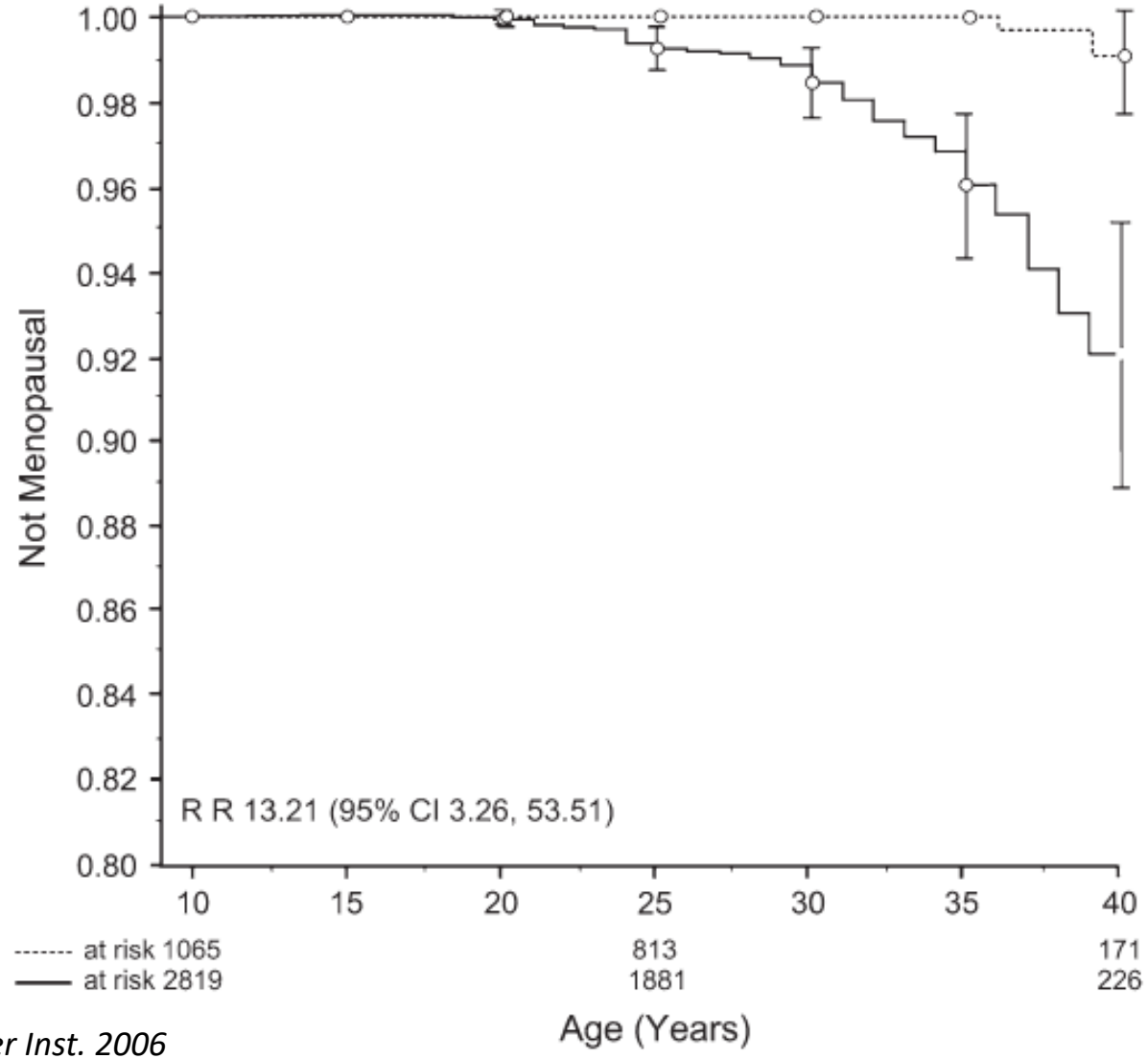
Qin N, et al. J Clin Oncol, 2020

Identifying Factors Increasing Vulnerability

Age and Risk of Ovarian Insufficiency in Childhood Cancer Survivor Study

- N = 2819 females ≥ 18 years/1065 siblings
- Premature menopause: cessation of menses before 40 years (non-surgical)
- Incidence of premature menopause
  - 8% in survivors v. 0.8% siblings
  - 13.2-fold excess risk (95% CI, 3.26-53.51)
- Risk factors for premature menopause
  - Older attained age
  - Exposure to increasing ovarian radiation dose
  - Increasing alkylating agent score
  - Diagnosis of Hodgkin lymphoma

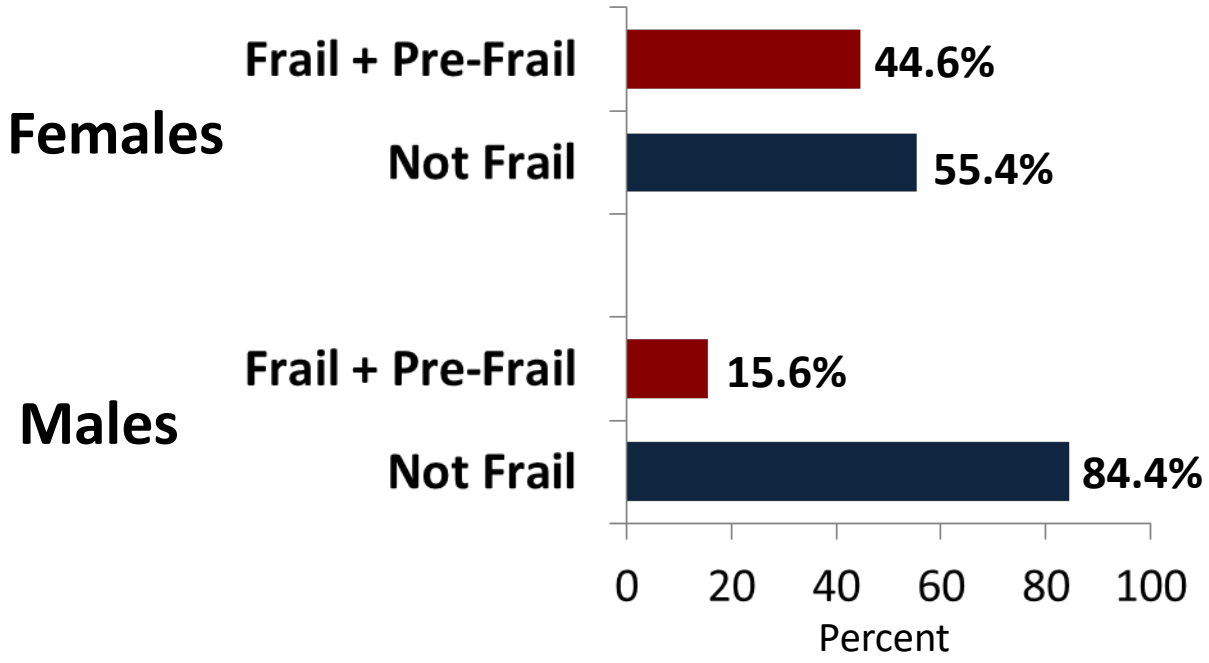
  Cumulative incidence of ~30% if treated with alkylating agents + abdominopelvic RT.



Sklar CA et al. J Natl Cancer Inst. 2006

Frailty Among Childhood Cancer Survivors

Clinical evaluation of 1922 adult survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE)
Mean age of 33.6 years



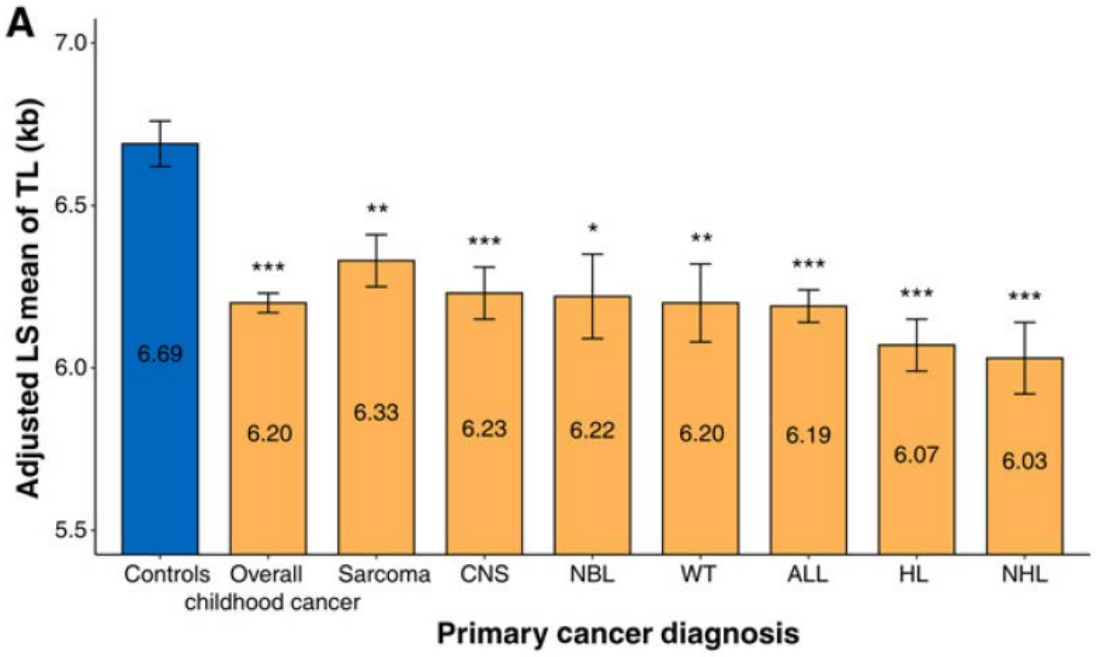
Prevalence of frailty among childhood cancer survivors, is similar to that in the general population for those greater than 65 years of age

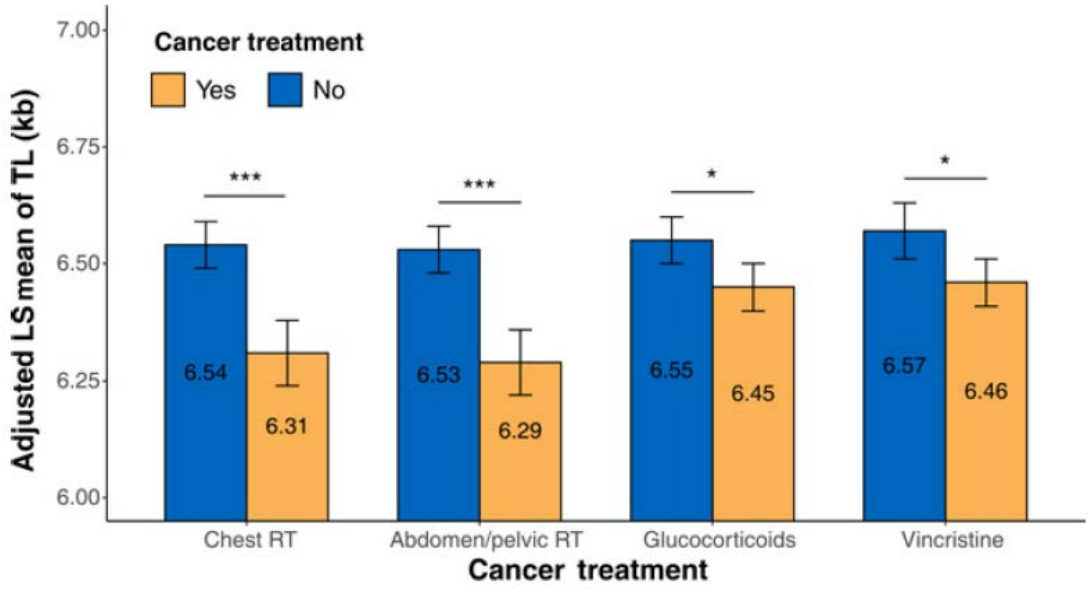
Ness et al, J Clin Oncol, 2013

Pathophysiology of Aging in Childhood Cancer Survivors

Song N, …..Wang Z, Clin Cancer Res 2020

Shortened Leukocyte Telomere Length and Cancer Treatment Exposures

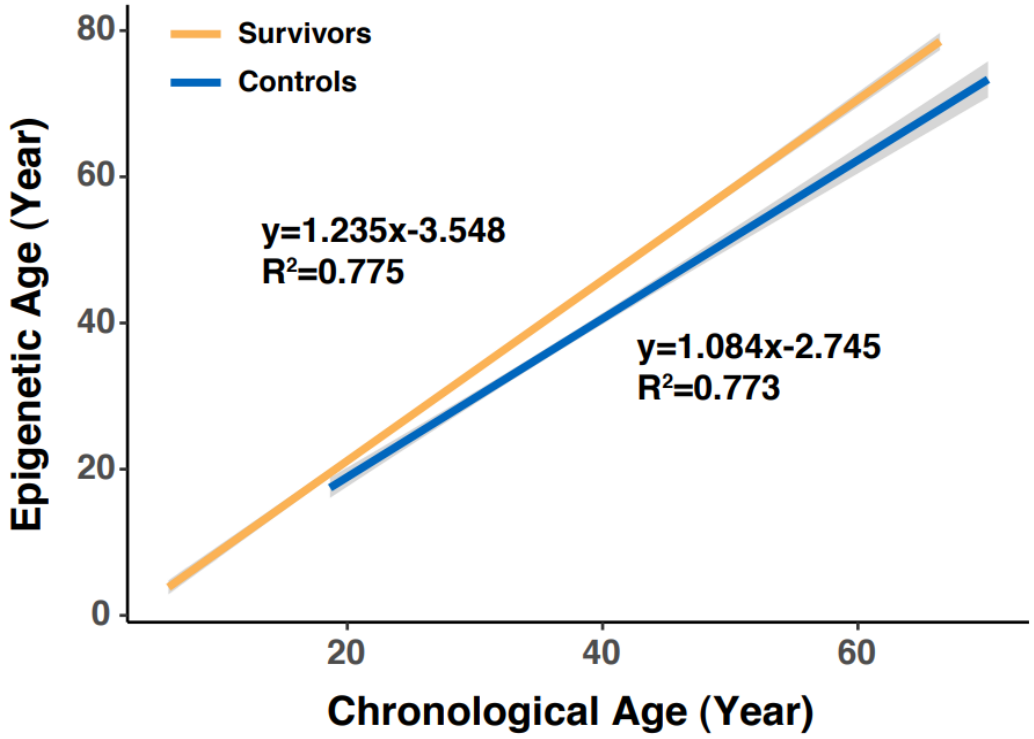


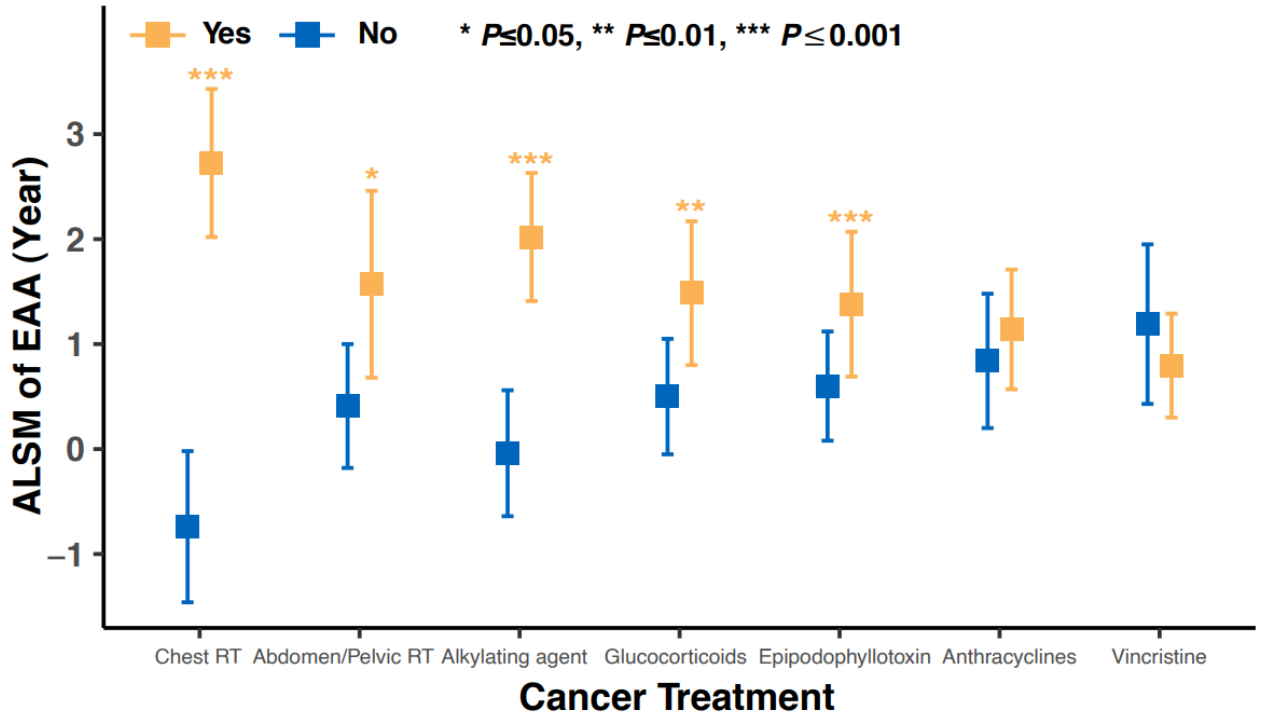


Pathophysiology of Aging in Childhood Cancer Survivors

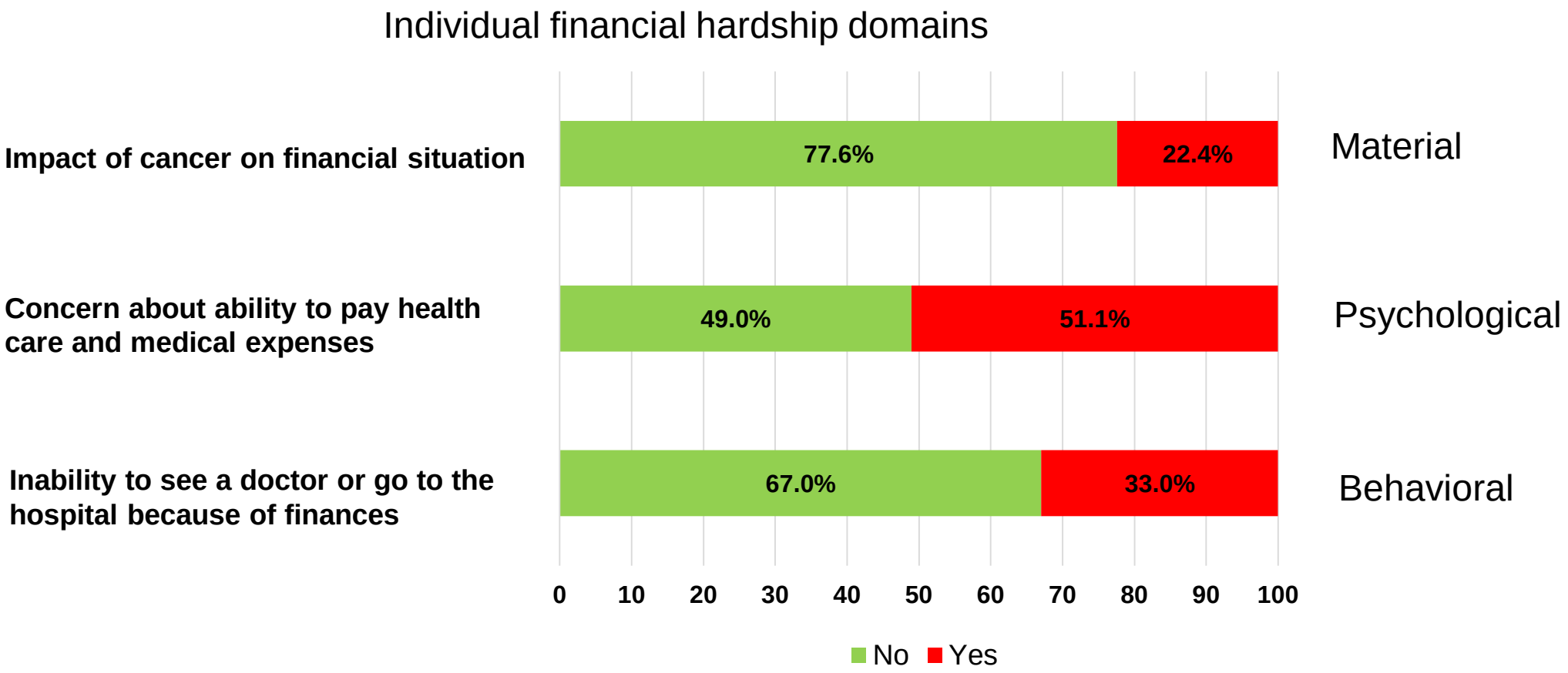
Qin N, …. Wang Z, JNCI 2020

Epigenetic Age Acceleration and Cancer Treatment Exposures



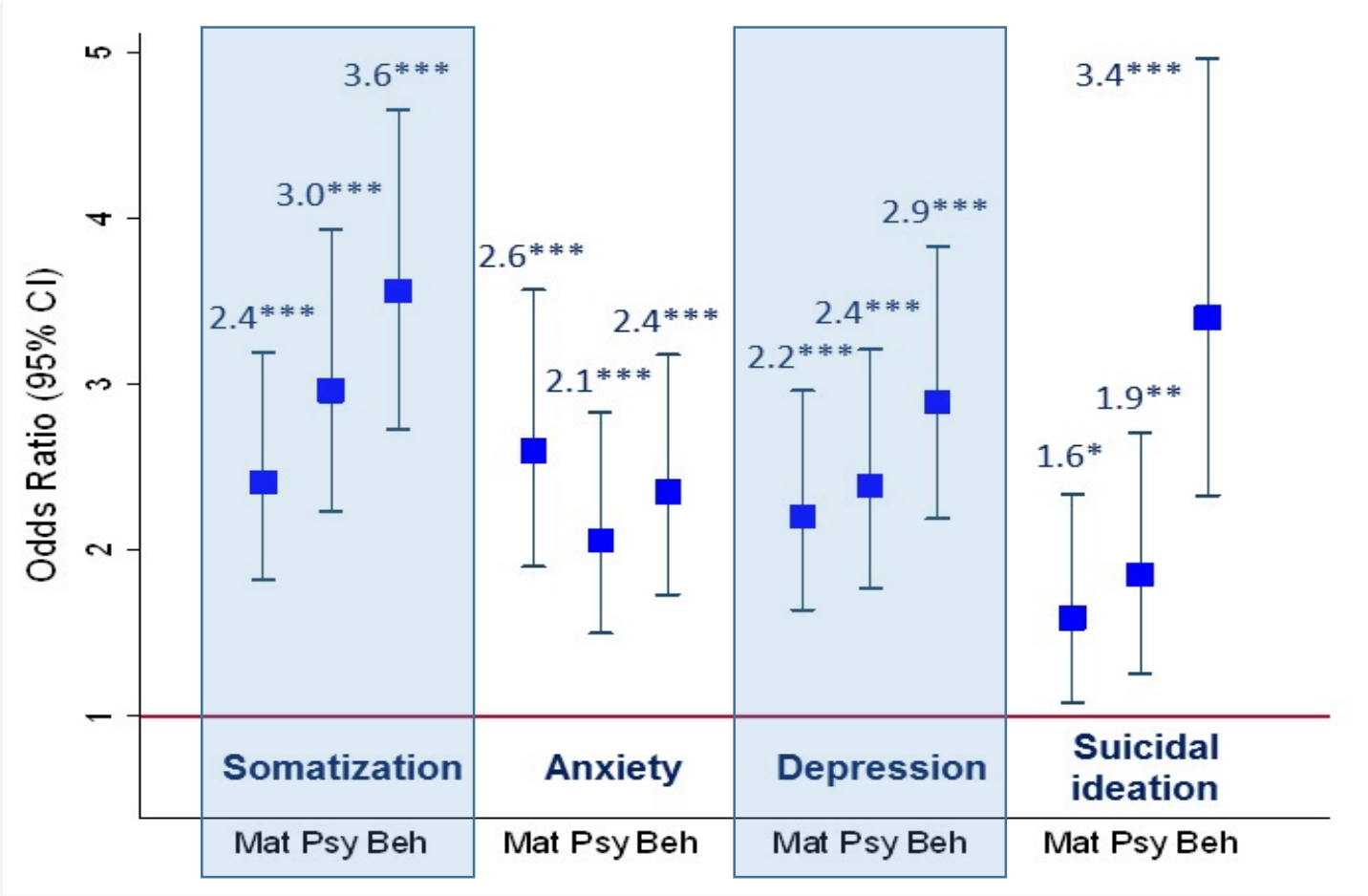


Impact of Financial Hardship on Symptoms and HRQOL



Huang et al. 2018. *JNCI*

Impact of Financial Hardship on Symptoms and HRQOL



Mat = Material hardship; Psy = Psychological hardship; Beh = Behavioral hardship

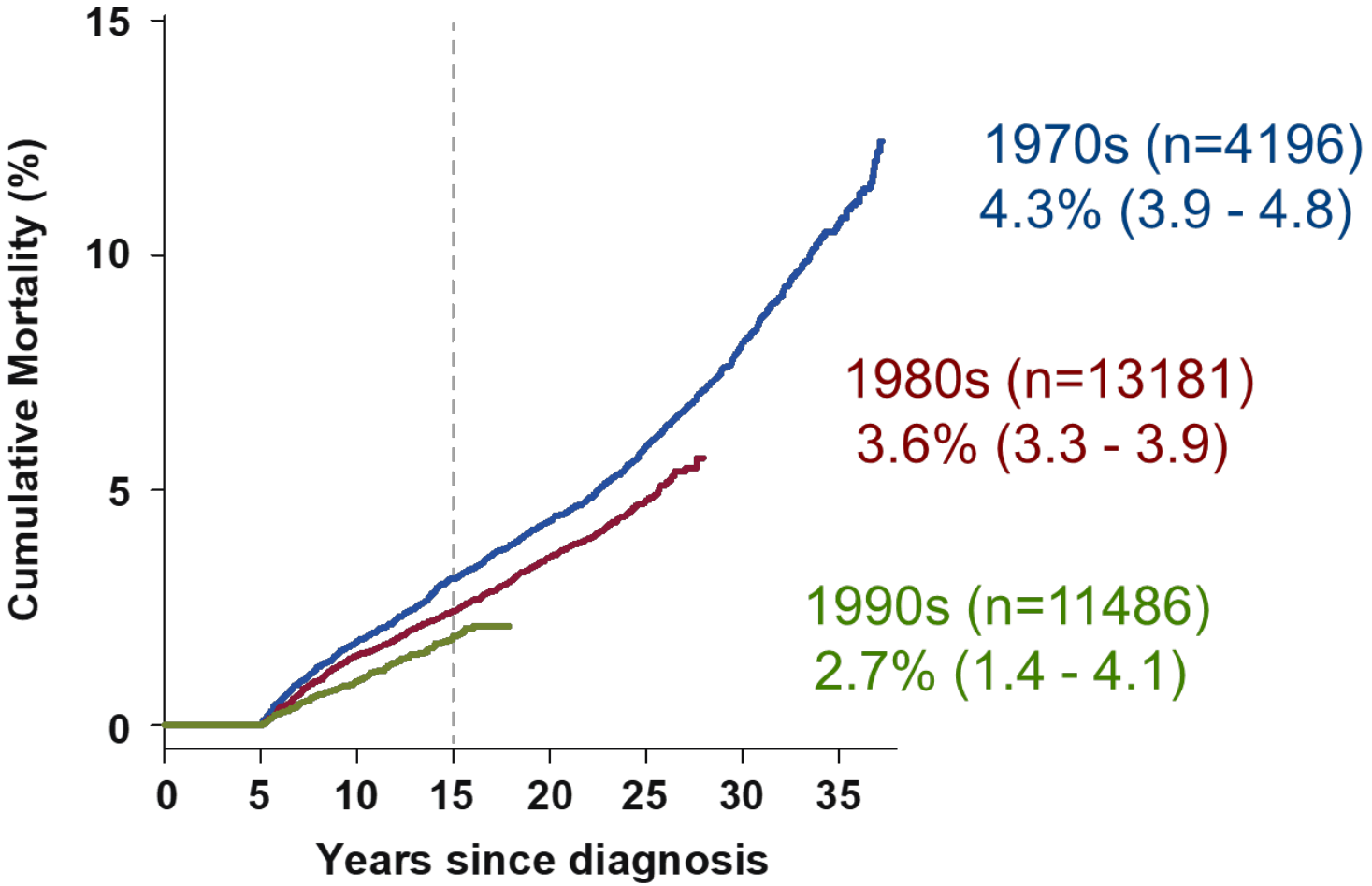
Huang et al. 2018. *JNCI*

Translating Research into Clinical Care

- Frontline therapy
  - Risk-stratification of anthracyclines, alkylating agents, radiation, etc…
- Health surveillance during and after therapy
  - Risk-based, linking exposure with acute/persistent or late effect(s)
- Counseling about cancer/treatment-related health risks
  - Informed by prevalence, dose-relationships, latency patterns, etc…
- Interventions to optimize health outcomes
  - Focused on promoting positive health behaviors, participation in health surveillance, adherence to medical management, etc…

Temporal Changes in Mortality after Childhood Cancer

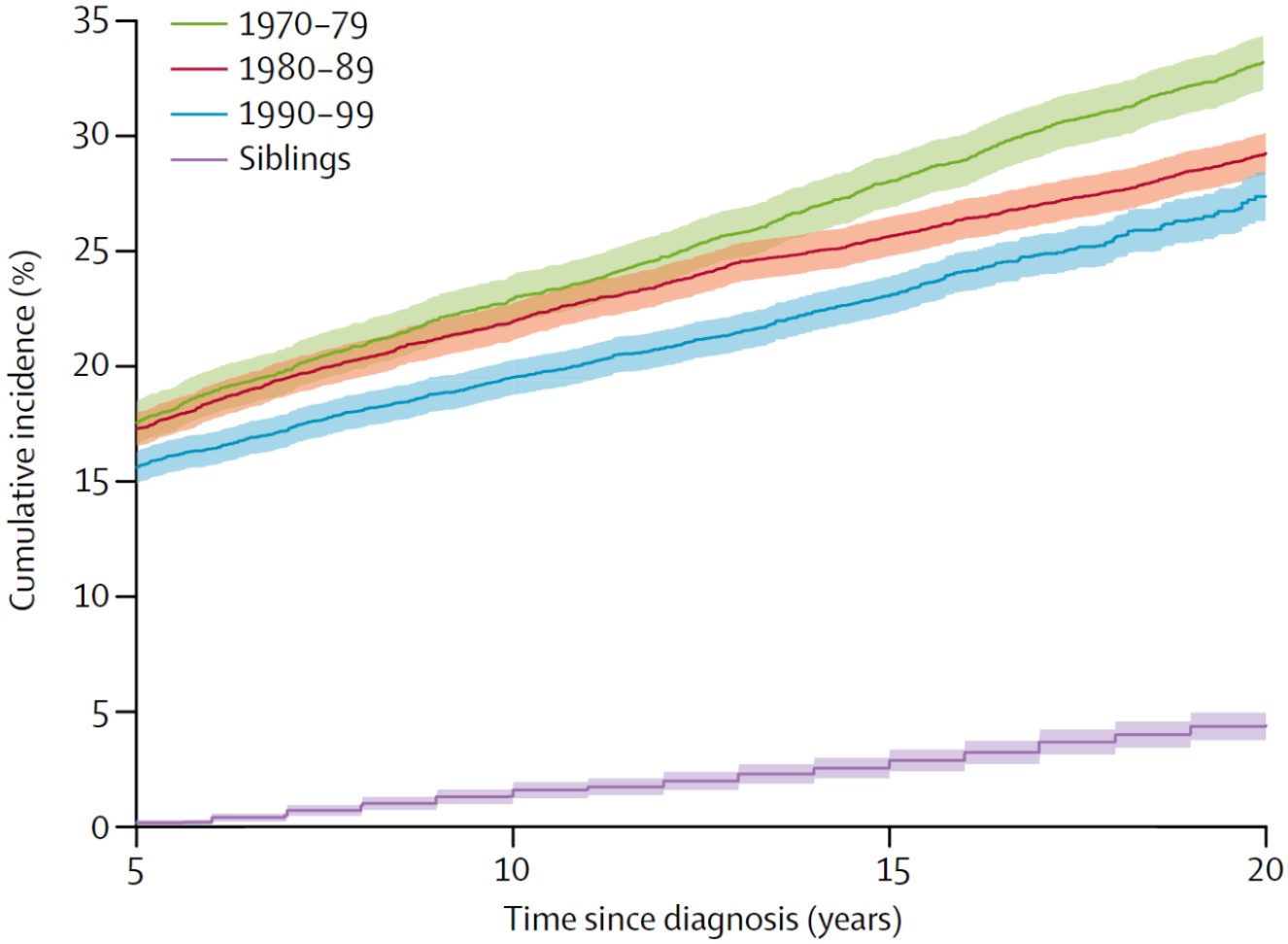
N=34033 five-year survivors
Diagnosis: 1970-1999
Median f-up: 21 years



Temporal Changes in Morbidity after Childhood Cancer

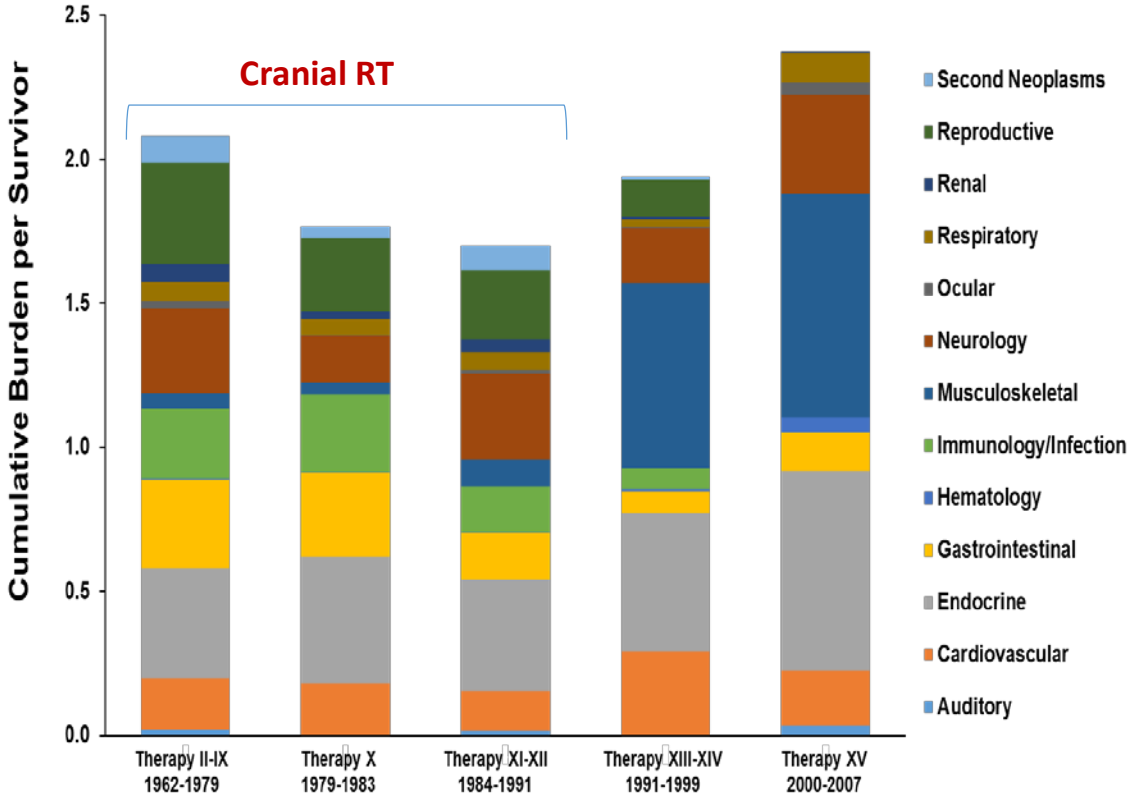
Grade 3-5 chronic health conditions

N=23,601 five-year survivors
Diagnosis: 1970-1999
Median f-up: 21 years



Temporal Patterns in Long-term Morbidity: Total Therapy ALL Trials

Cumulative Burden of Chronic Health Conditions Grade 2-4
(Moderate, Severe, Life-threatening)



- By 30 years of age, survivors experienced on average 2.3 grade 2-4 chronic health conditions
- Elimination of cranial RT did not result in an overall decline in the cumulative burden of morbidity, however:
  - For trials including cranial RT, cumulative burden of chronic health conditions involved multiple organ systems
  - After elimination of cranial RT, chronic conditions predominantly include musculoskeletal and endocrine disorders

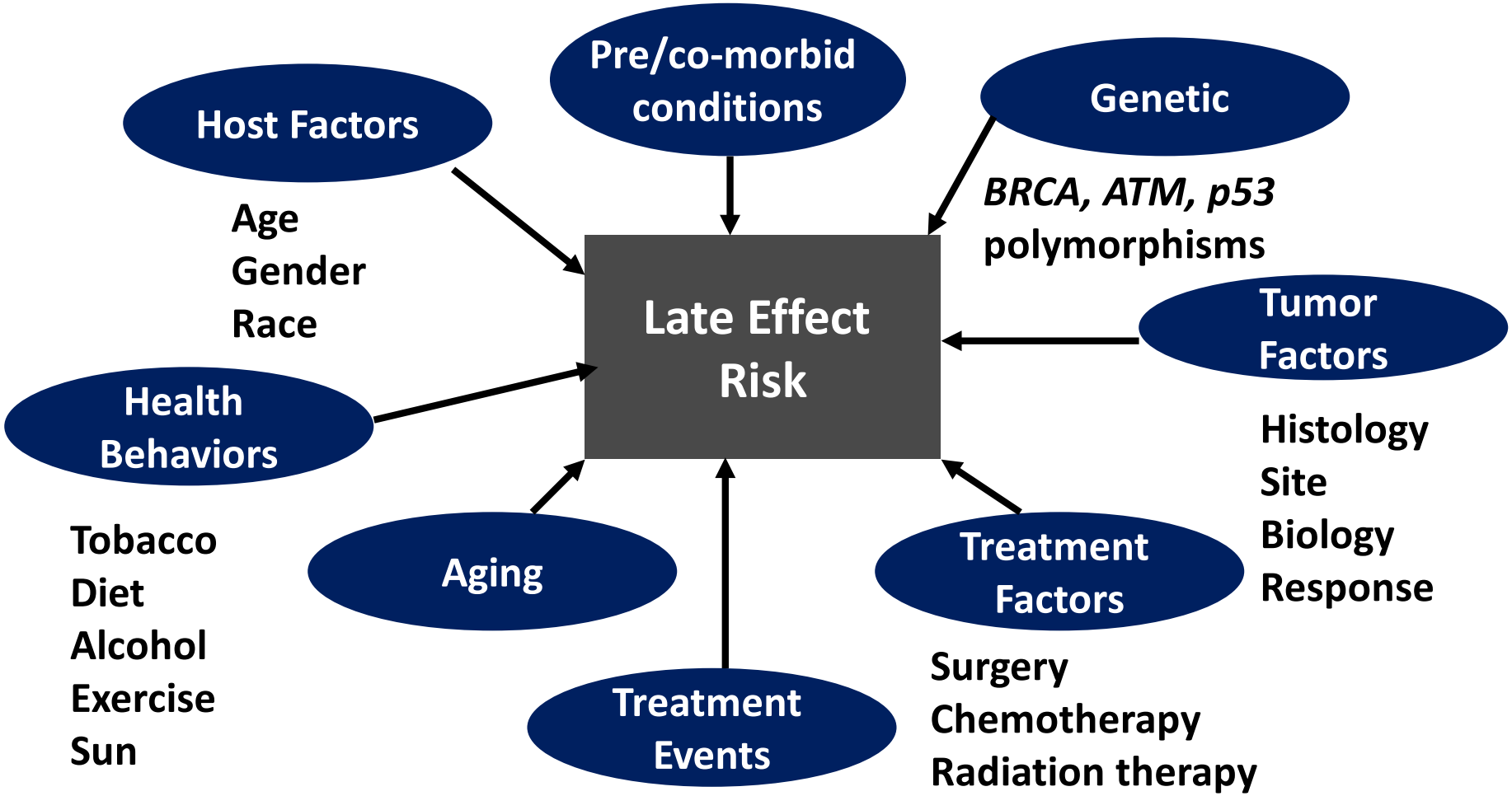
Mulrooney et al, Lancet Haematol 2019

Guiding Health Screening/Surveillance/Counseling

Other factors:

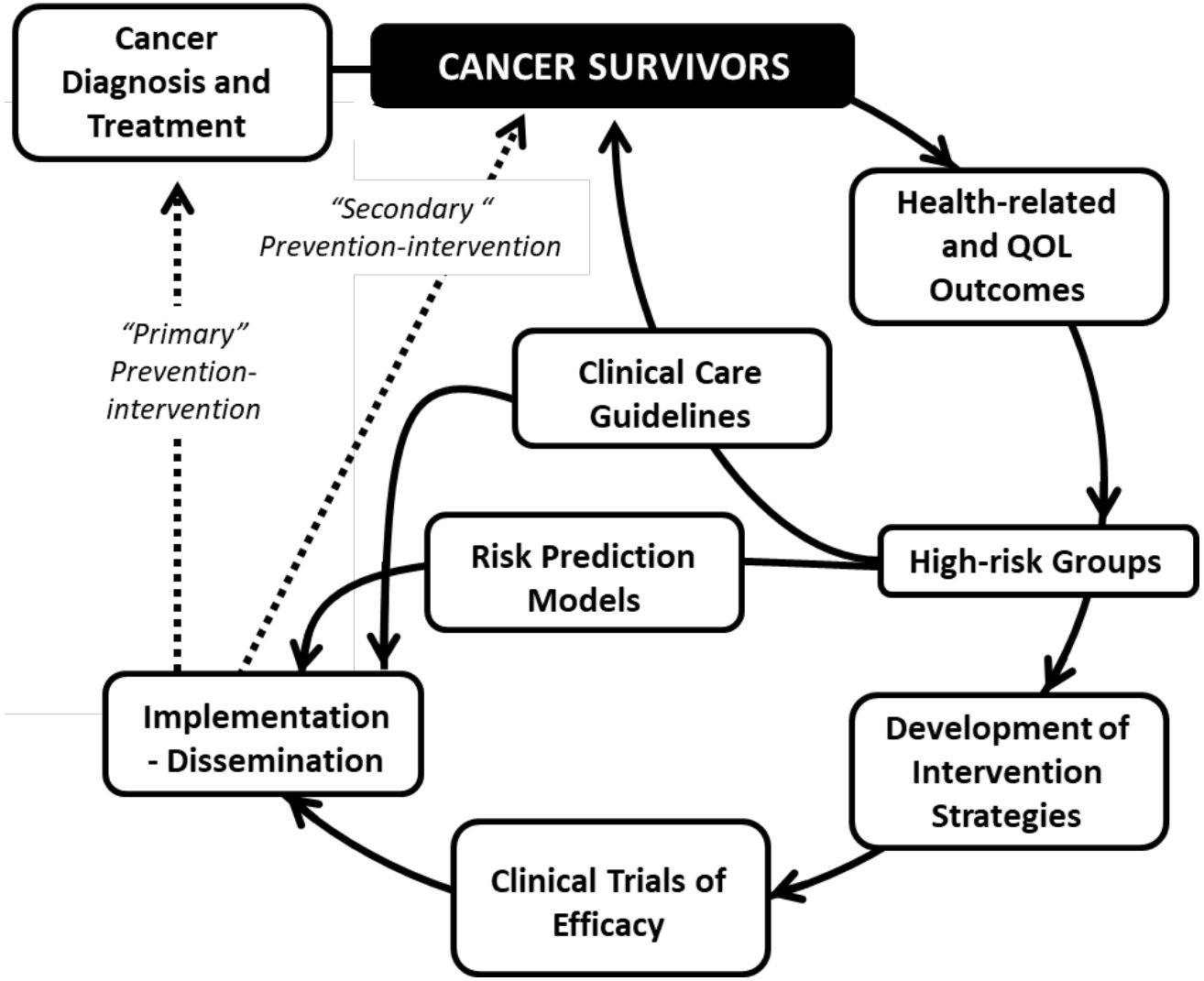
Survivor:
Health knowledge
Health perceptions
Self-efficacy
Health care access

Provider:
Education/training
Experience
Perceptions
Access to resources
Access to survivor health history

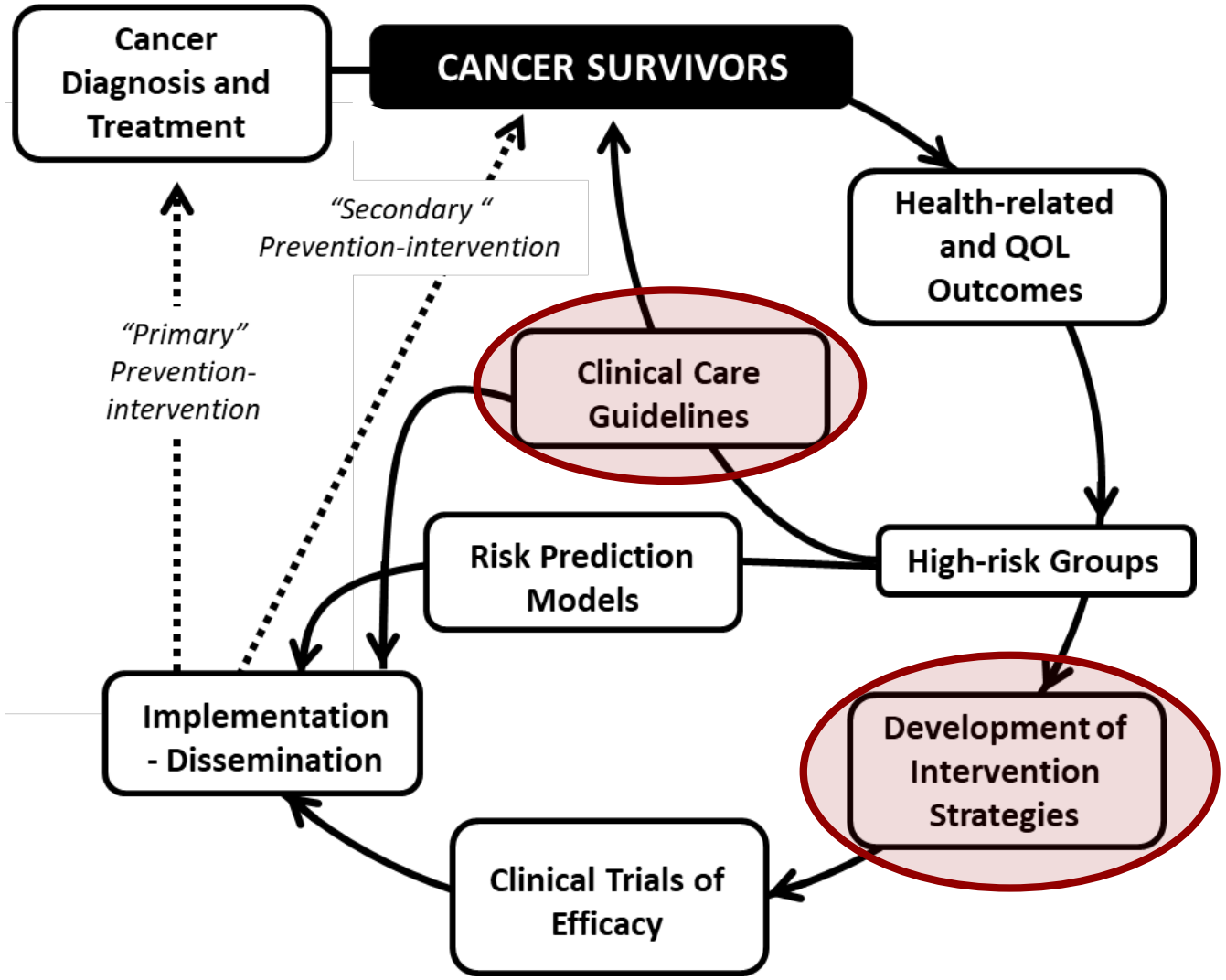


Hudson M. Cancer. 2005

Pediatric Cancer Survivorship

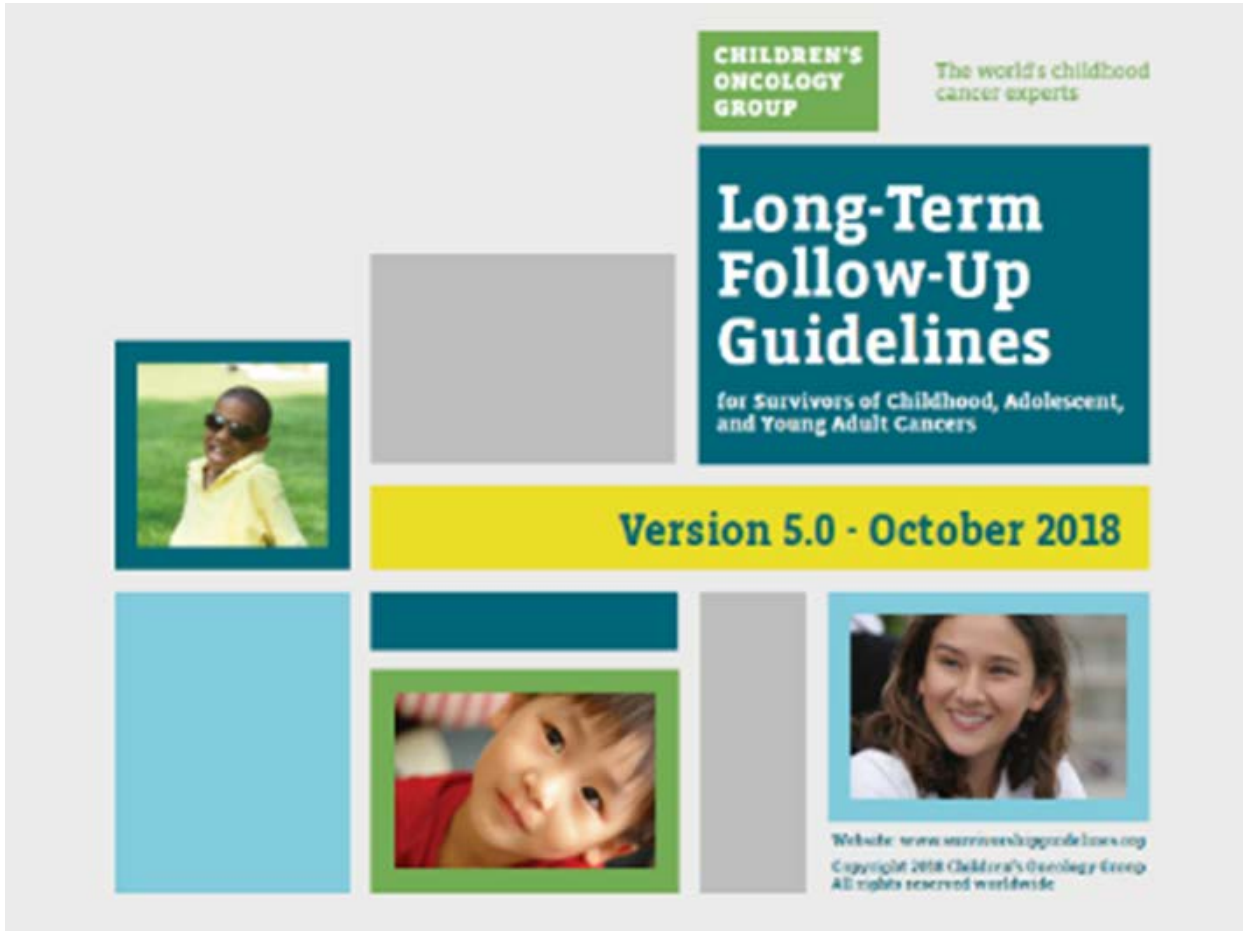


Pediatric Cancer Survivorship



Children's Oncology Group

Long-term Follow-up Guidelines



Evidence-based health surveillance guidelines, available since 2003, and "essential" to delivery of high quality survivorship care have not been effectively implemented.

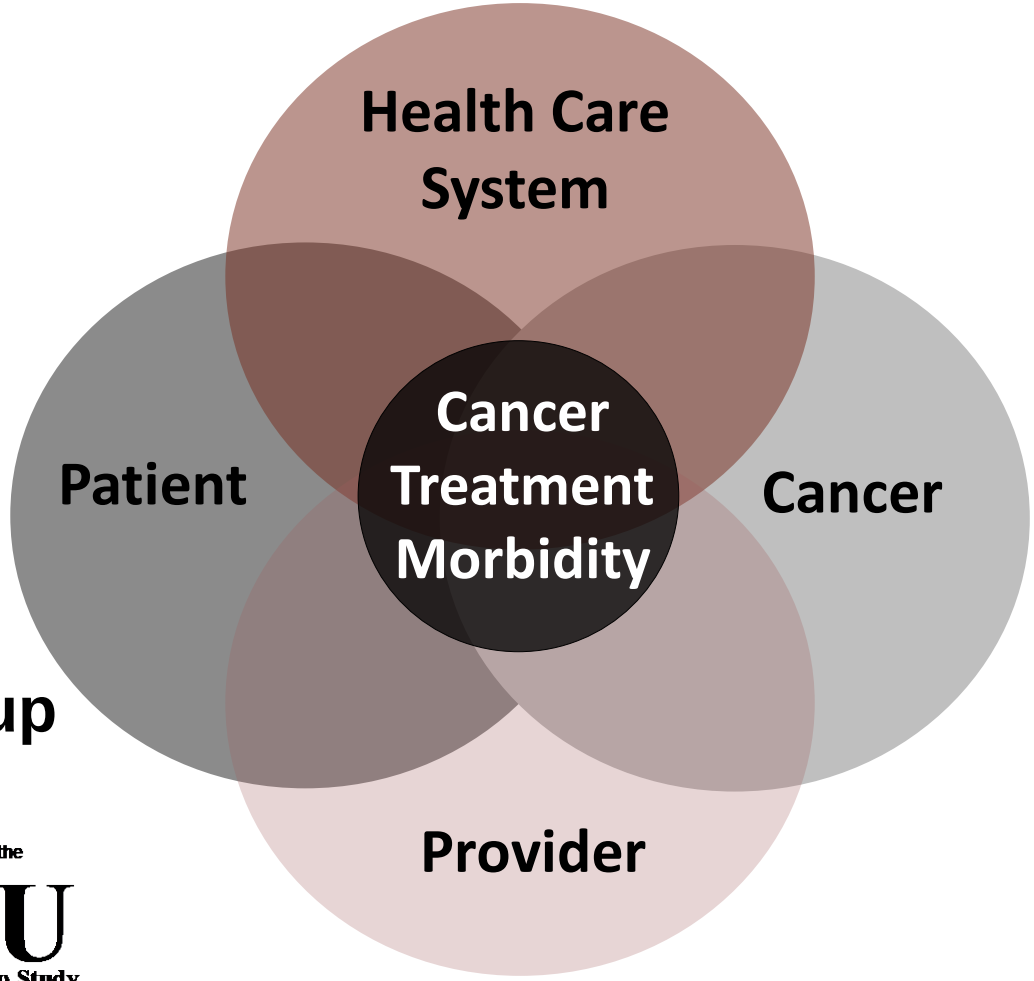
Informing Interventions to Optimize Outcomes

EQUAL

Health behaviors

Health knowledge

Adherence to follow-up



Provider education

Access to health care

Early detection

ECHOS
Healthy Hearts After Childhood Cancer

A new program of the
LTFU
Long-term Follow-up Study

ASK about skin cancer

Addressing Knowledge Gaps in Survivorship

- Long-term and late effects of contemporary treatment
  - Risk-adapted, personalized
  - Novel targeted agents
- Impact of screening and early detection of late effects on mortality
- Interventions to promote healthy aging of growing survivor population
- Interventions to optimize survivorship care

Gaps in Knowledge Regarding Long-term Outcomes: Theoretical Framework