

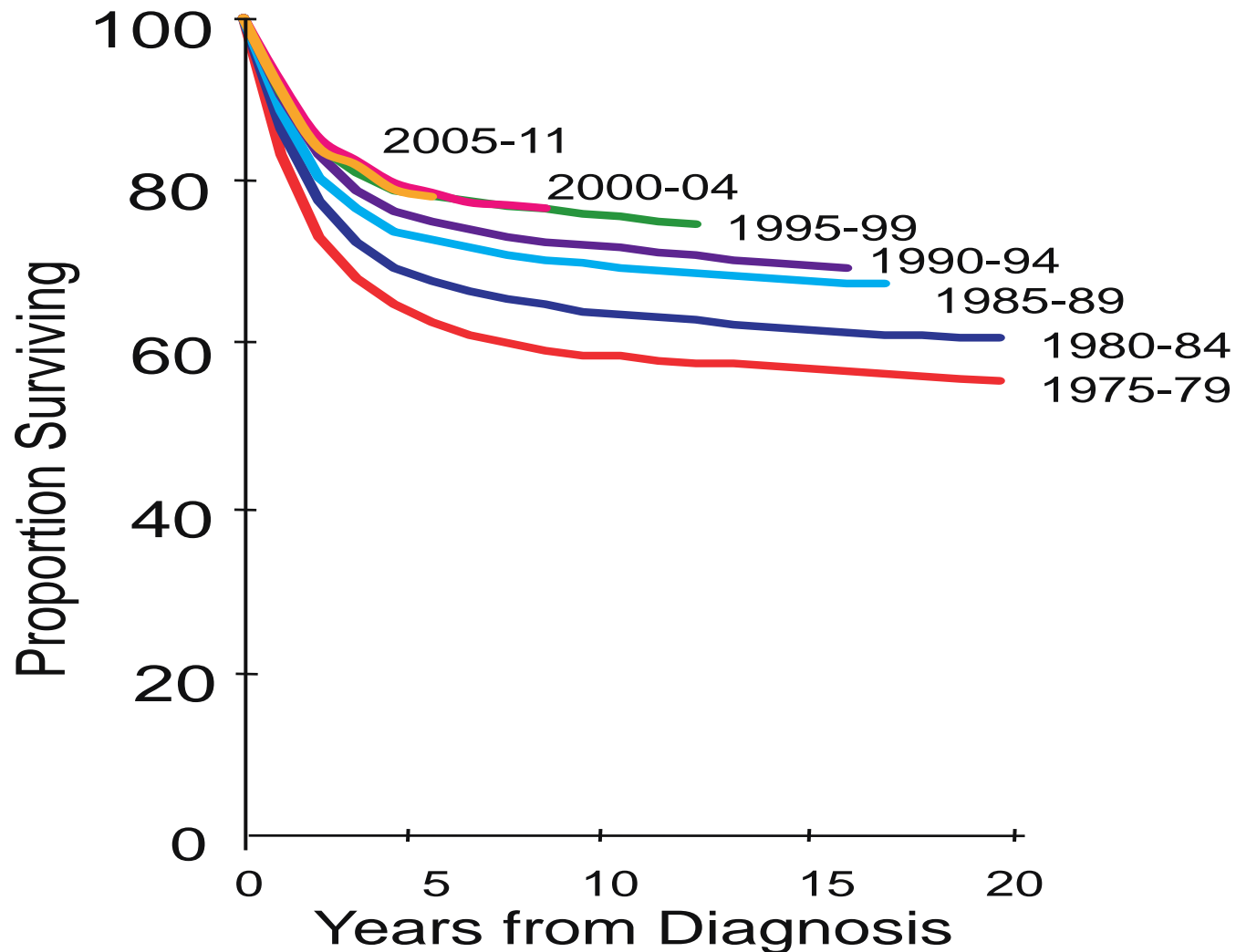


Health after Childhood Cancer:
Lessons from Pediatric Cancer Cohorts

Overview

- Epidemiology of pediatric cancer survivorship
- How a pediatric cancer cohort can inform care of newly diagnosed children with cancer and long-term survivors
- What are the unique features of the St. Jude Lifetime Cohort Study?
- What are the key early lessons from St. Jude LIFE?

Cancer Survival, 0-14 years SEER Program 1973-2012



- >80% of children with a malignancy will achieve five-year survival
- Cancer treatment-related effects contribute to high burden of morbidity and increase risk of premature mortality

Pediatric Cancer Survivor Cohort Investigations

- Characterization of long-term survivor health is challenging as cancer treatment-related toxicities may occur decades after exposure in aging survivors.
- Outcomes in adults treated for childhood cancer are mostly limited to self-report, registry or administrative sources.
- True prevalence of clinically ascertained cancer-related toxicities and impact on long-term survivor health has not been well studied.
- Several groups have established cancer survivor cohort studies with the goal of characterizing survivors at risk for adverse outcomes.

Pediatric Cancer Survivor Cohort Investigations

Pediatric Cancer Cohorts

Childhood Cancer Survivor Study (CCSS)	British CCSS	Swiss CCSS	LESS	French LEA
French-British Cohort	ALiCCSS	Dutch LATER	St. Jude Lifetime Cohort	PETALE Study

Limitations related to:

- Inclusion of survivors from single institution or nation
- Enrollment restrictions by age (e.g., < 15, < 17 years)
- Lack of representation of pediatric cancers (e.g., single or restricted diagnoses)
- Reliance on self-reported outcomes with limited validation of health events
- Reliance on registry/administrative data with limited collection of patient-reported outcomes or treatment data
- Limited or no collection of biological specimens
- Lack of longitudinal follow-up

St. Jude Lifetime Cohort (established 2007)

Eligibility:

- Diagnosis of childhood cancer
- Treatment at St. Jude Children's Research Hospital
- Survival of at least five years from diagnosis

Participation involves comprehensive clinical assessment (3-4 days)

- Self-report of behavioral, medical and psychosocial outcomes
- Laboratory and diagnostic testing of organ function
- Standardized neurocognitive and performance testing

Comprehensive Phenotyping of SJLIFE Participants

- Demographic
- Survey
 - Home
 - Health Habits
 - Psychosocial
 - Psychosexual
 - Food Frequency
- Laboratory evaluations
 - Blood
 - Urine
- Health events
- Surgical procedures
- Chemotherapy doses
- Radiation fields/doses
- Diagnostic studies
 - Echocardiogram
 - Electrocardiogram
 - Pulmonary fxn tests
 - Bone mineral density
- Special datasets
 - Neurocognitive
 - Performance lab
 - Genetic
 - WGS 30X
 - WES 100X
 - National death Index

Validation of Medical Outcomes

- Surveys are reviewed prior to SJLIFE visits to identify serious health outcome previously unknown
- Medical releases are obtained from study participants during visit for these health outcomes
- Records are requested from outside institutions to verify outcome
- Records are received and reviewed by study nurse
- Outcomes validated by medical records are added to the research database
- National Death Index search performed to supplement Cancer Registry follow-up.

Severity Grading Late/Chronic Health Events

- Severity grading of health events by Modified Common Terminology Criteria for Adverse Events (CTCAE):
 - Defined how clinical management (e.g., medical or surgical intervention) will be considered in grading
 - Defined conservative diagnostic ranges to avoid over-diagnosis
 - Provided definition and severity grading for conditions not in CTCAE
 - Specified objective clinical parameters for severity grading
 - Used same rubric: 1 - mild; 2 – moderate; 3 – severe/disabling; 4 – life-threatening; 5 – fatal.

St. Jude Lifetime Cohort

Objectives:

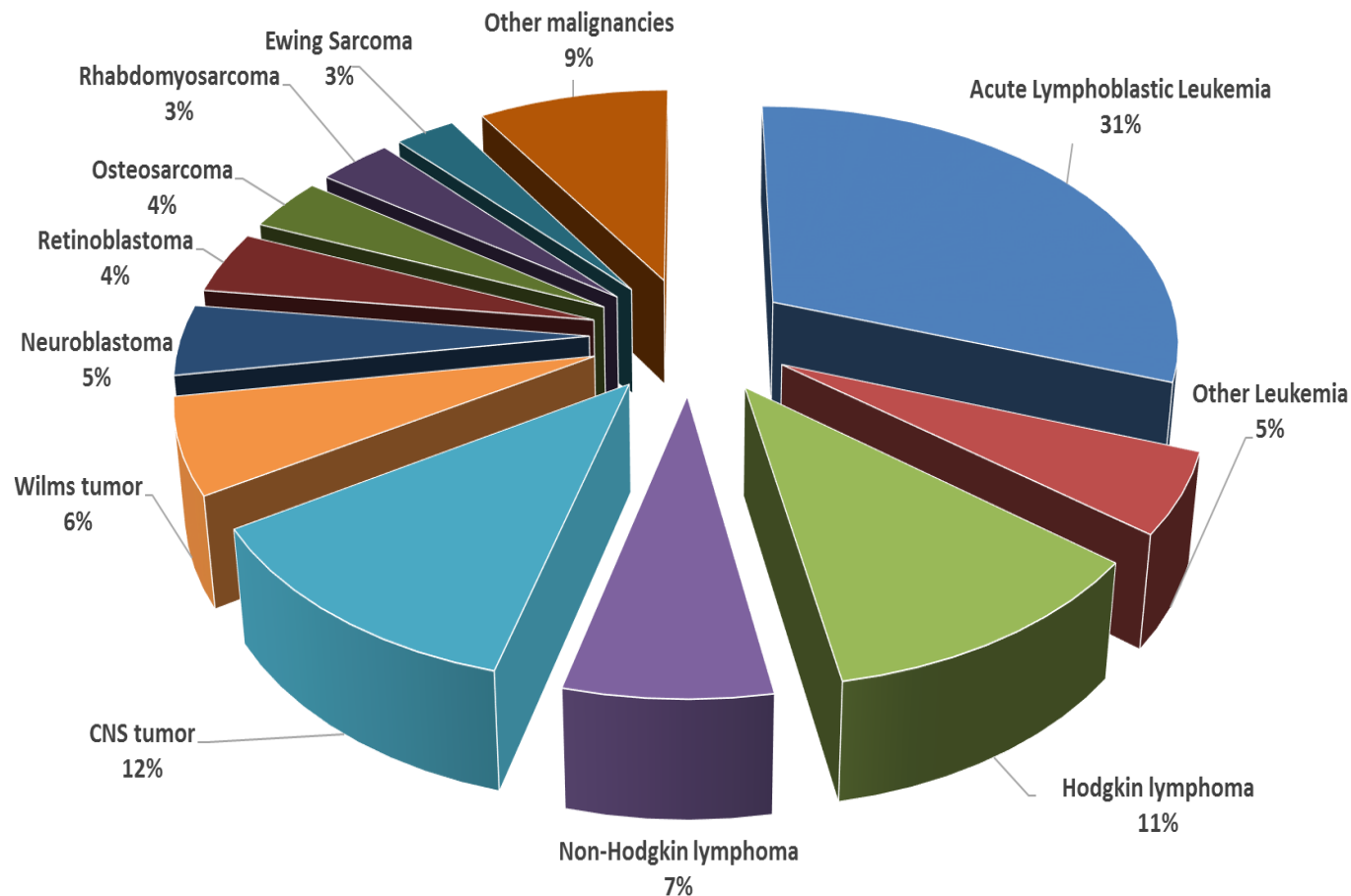
- To establish a lifetime cohort of childhood cancer survivors
- To facilitate longitudinal clinical evaluation of health outcomes in aging adults surviving pediatric cancer

Aims:

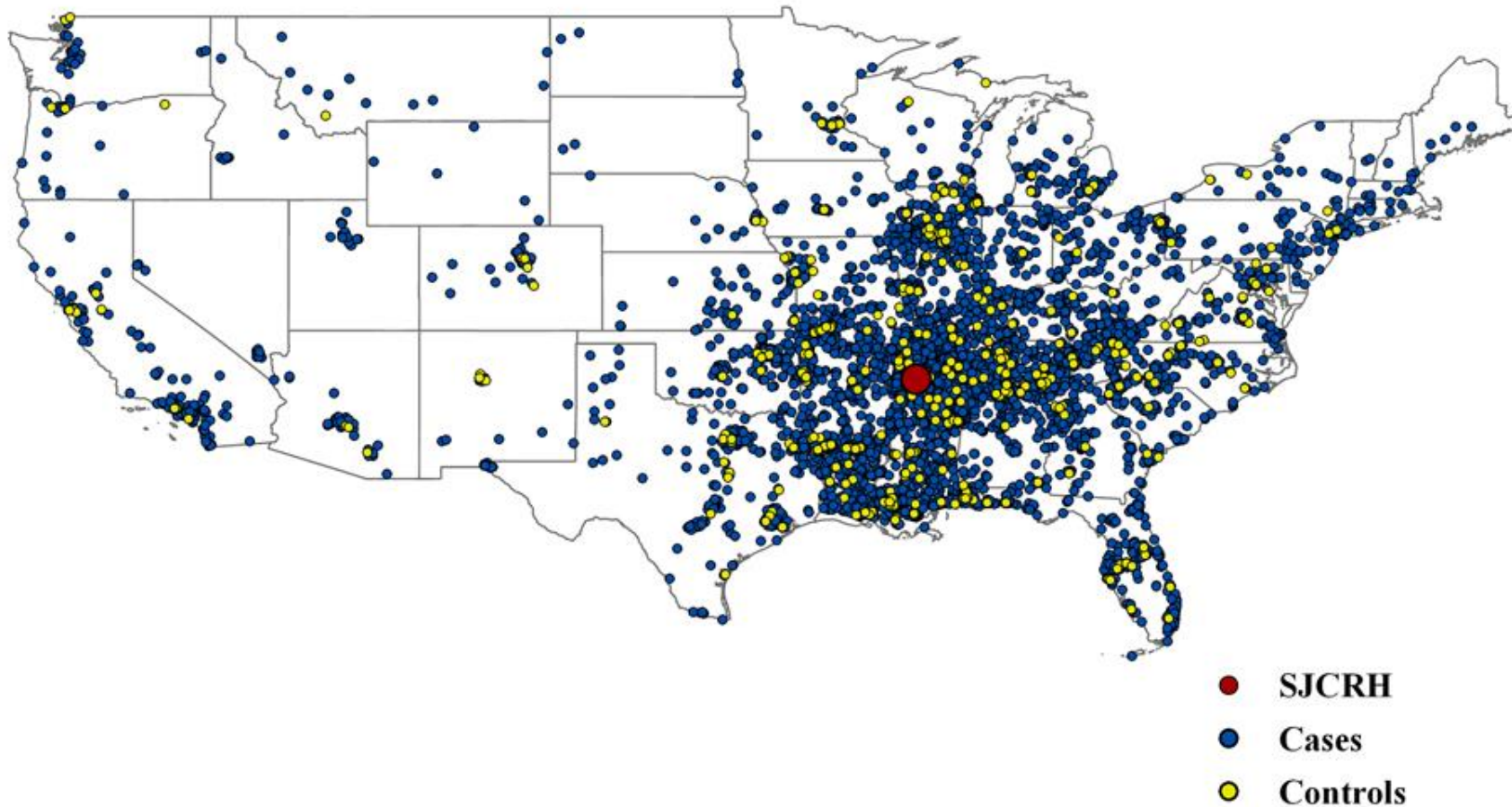
- To determine prevalence and latency of late effects
- To identify multifactorial predictors of adverse outcomes
- To develop risk profiles for adverse health outcomes across the age spectrum
- To use data to guide health screening and risk-reducing interventions

Diagnostic Groups for Campus Visit

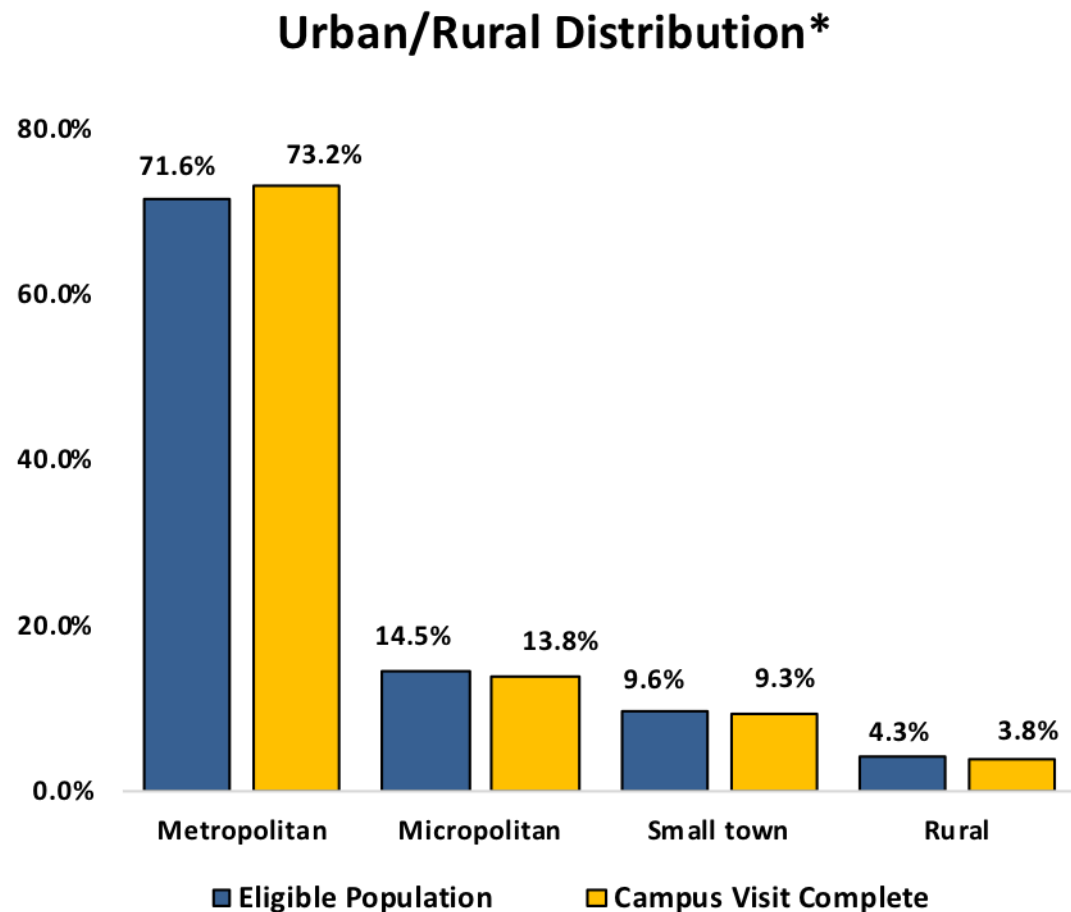
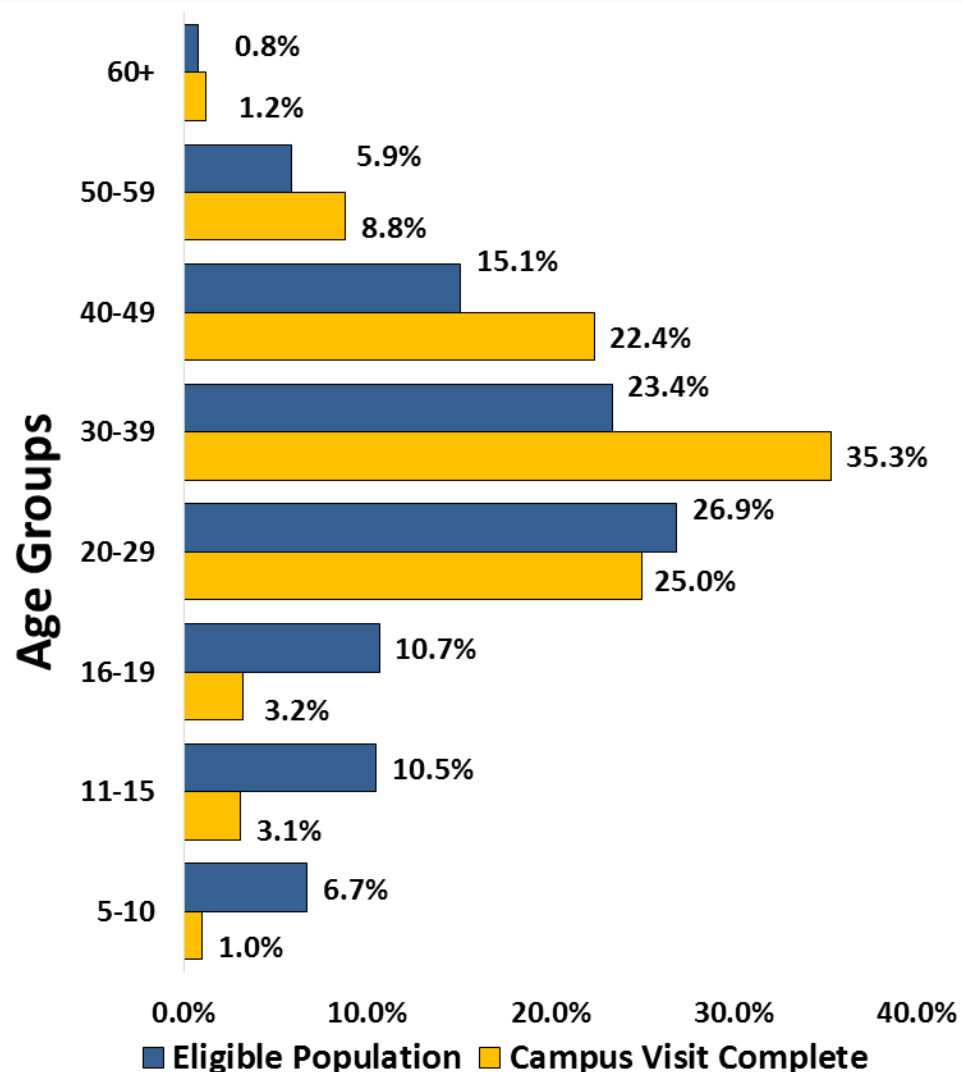
- Completed evaluation (10/2019)
5046 survivors ≥ 1 evaluation
672 community controls
- “Agreed to participate” rate:
> 90% contacted
> 80% eligible
> 90% for campus evaluation
- Average evaluation: 3 to 4 days



Geographical Distribution – Eligible Population



Characteristics Eligible Population vs. Campus Visit



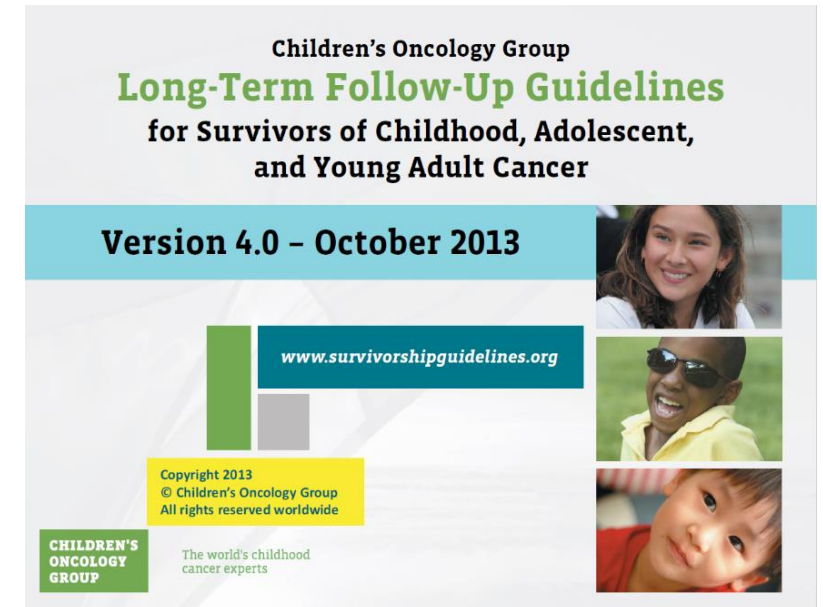
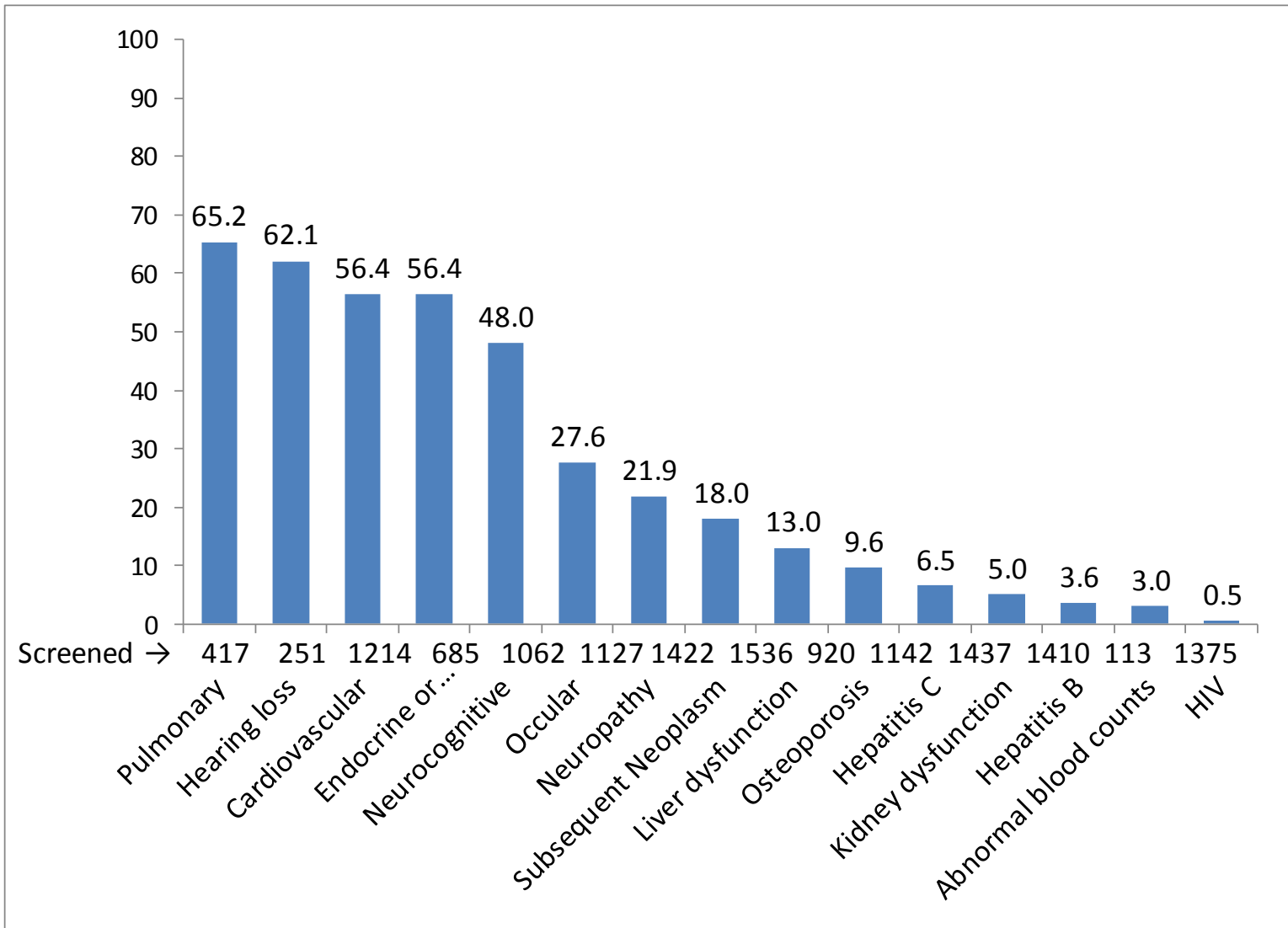
*Based on USDA Rural-Urban Commuting Area (RUCA) Codes linked to census tract of residence



Lesson #1

Childhood cancer survivors have substantial undiagnosed (subclinical) organ dysfunction.

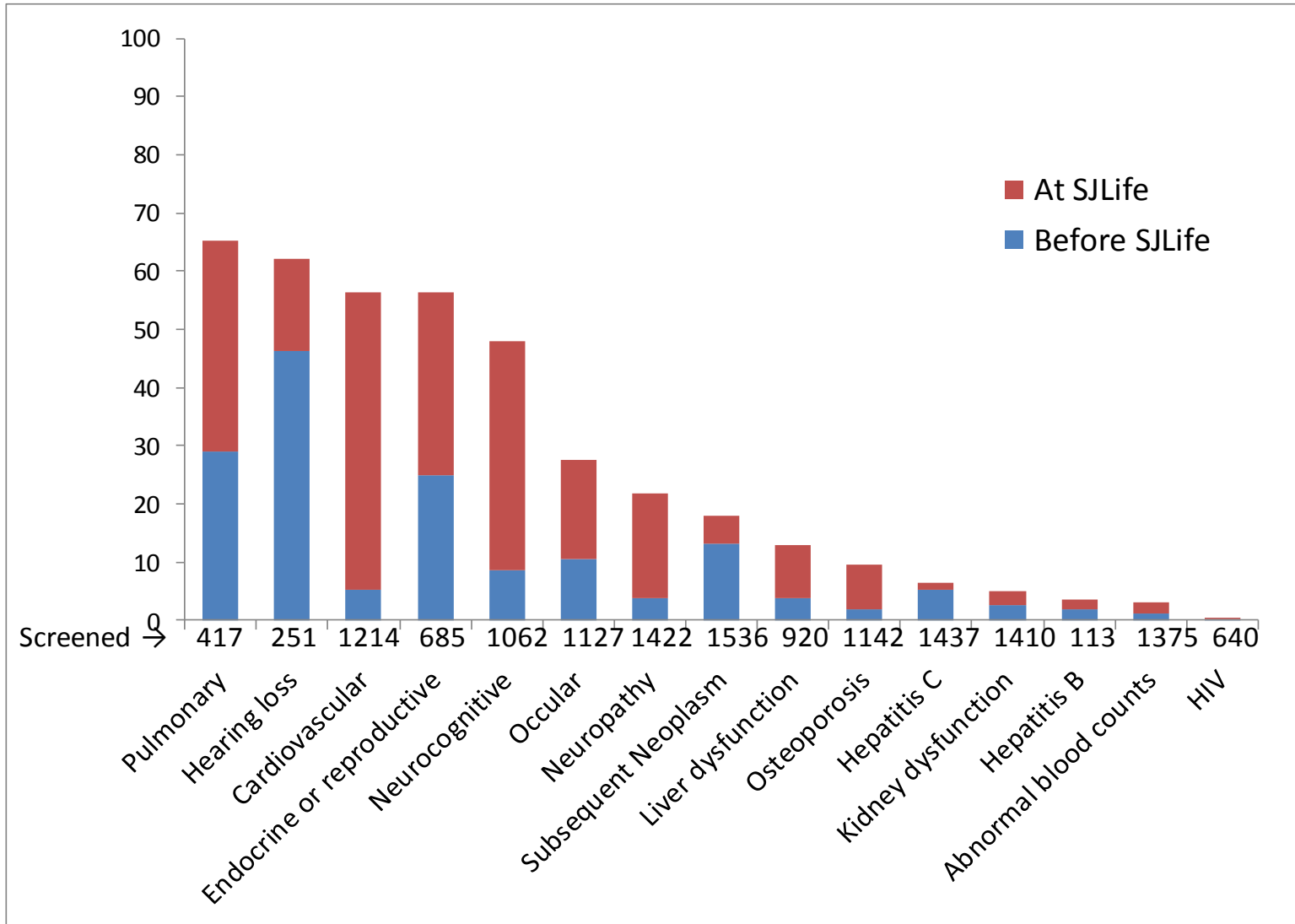
Prevalence of Late Effects following Risk-Based Screening



Screening based on
previous treatment for
childhood cancer

Hudson/Ness et al, JAMA, 2013

Prevalence of Late Effects following Risk-Based Screening



Yield $\geq 20\%$ at risk

- Pulmonary function deficits
- Heart valve abnormalities
- Cognitive deficits
- Dyslipidemia
- Hypothalamic-pituitary disorders

Yield 10%-20% at risk

- Hearing loss
- Ocular toxicity
- Neuropathy

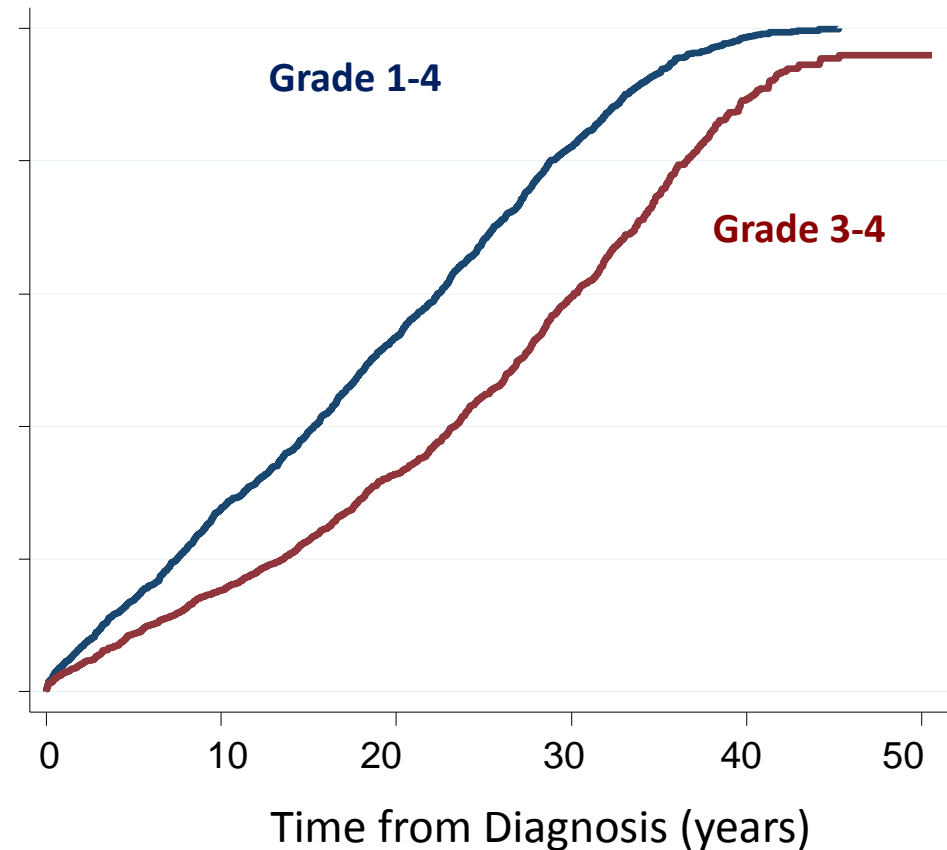
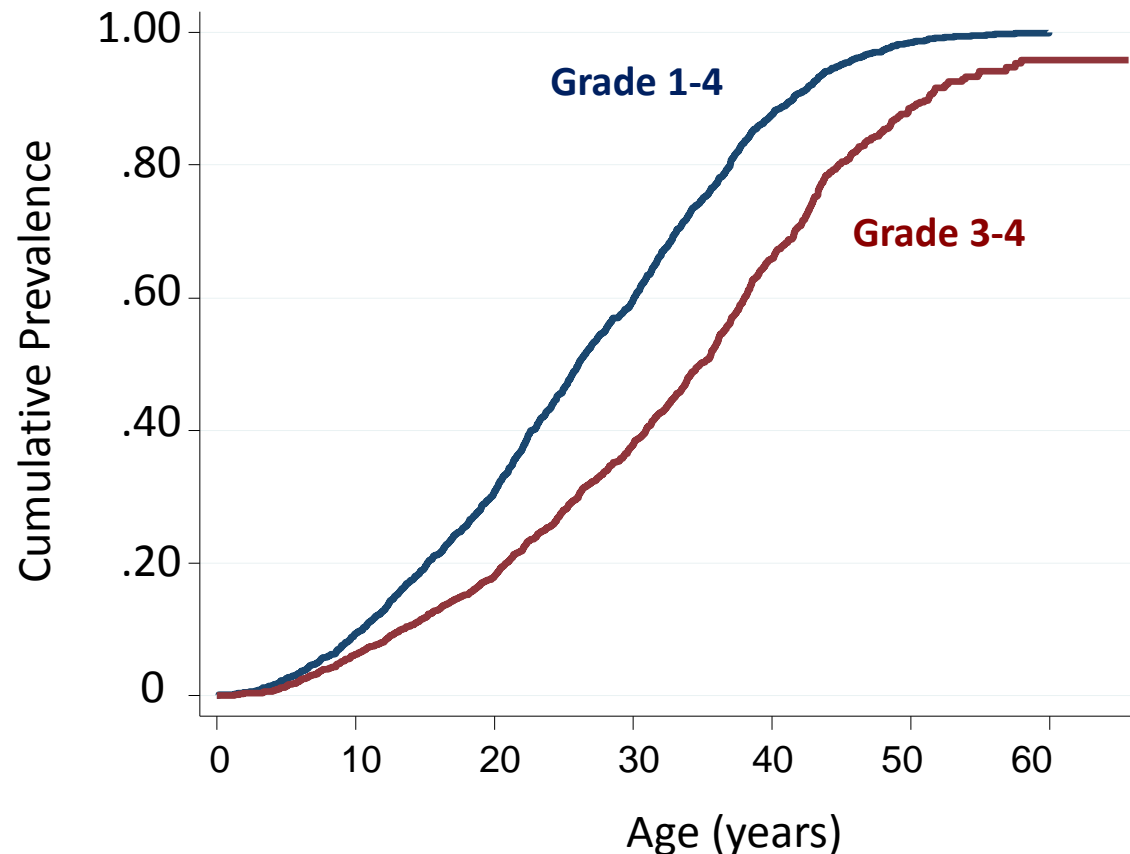


Lesson #2

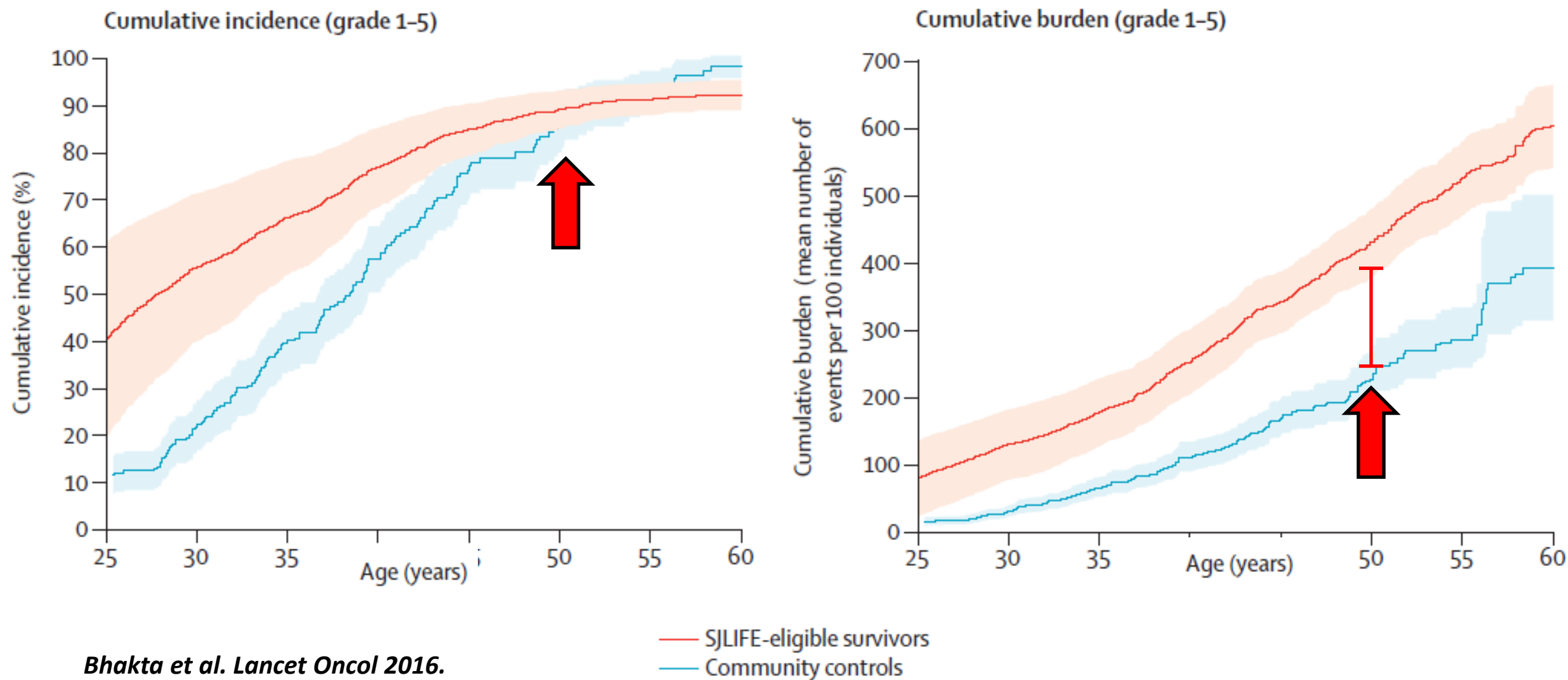
Previous studies have underestimated the chronic disease burden of childhood cancer survivors

Cumulative Prevalence of Chronic Health Conditions: Clinically assessed in SJLIFE participants

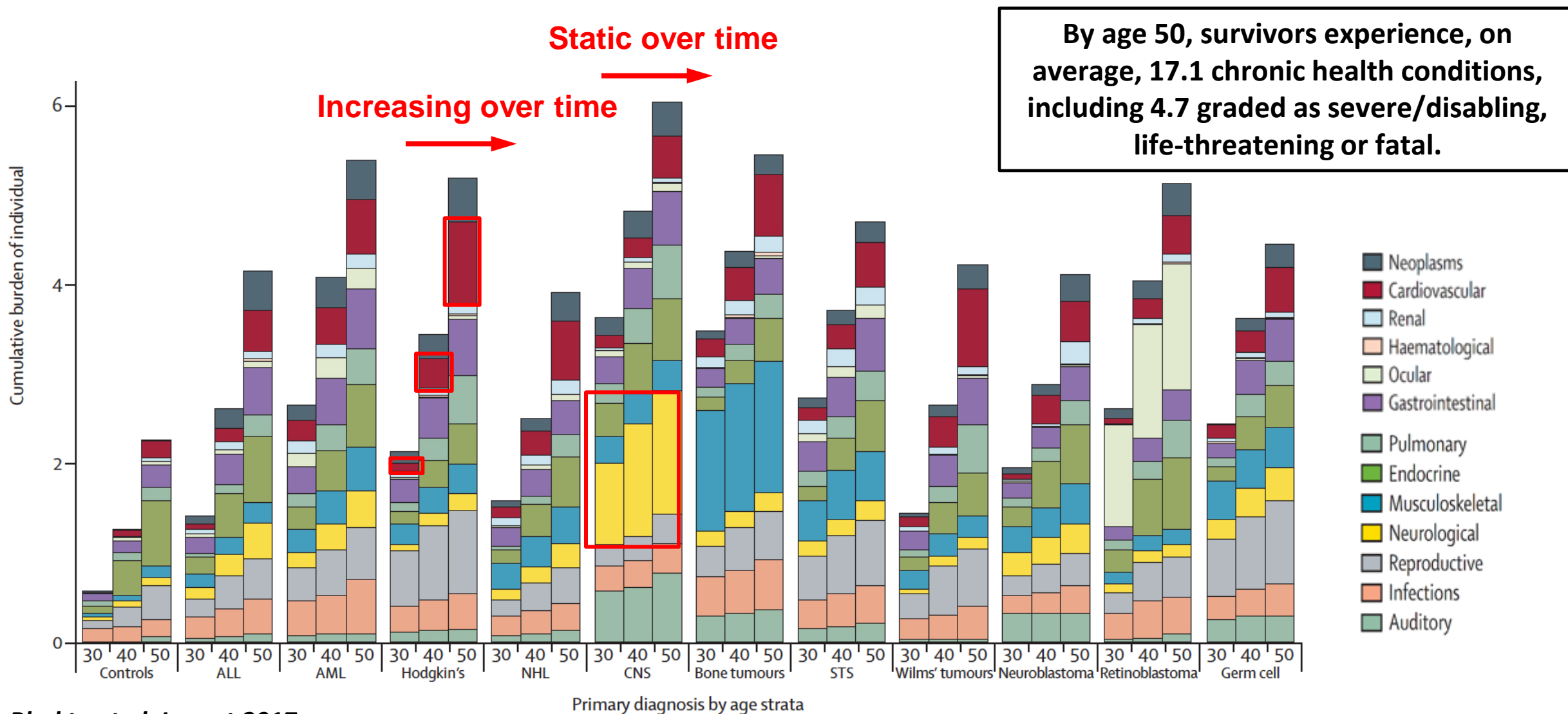
N=1713; median age 32 years; median time from diagnosis 25 years



Cumulative Incidence vs. Cumulative Burden

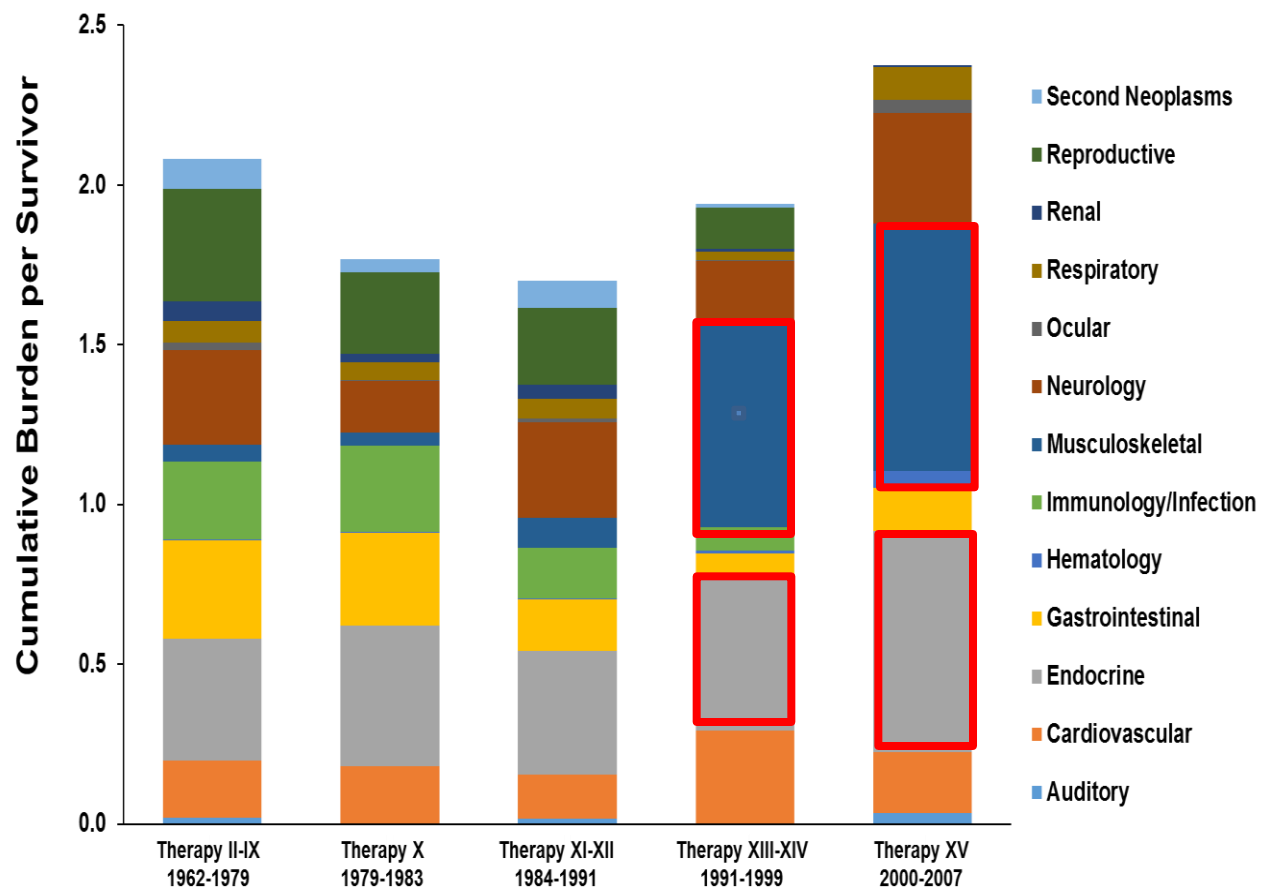


All Survivors Grade 3-5 Cumulative Burden By Organ System



Temporal Trends 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 3.2 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



Lesson #3

Childhood cancer survivors develop conditions that commonly occur in a much older population.

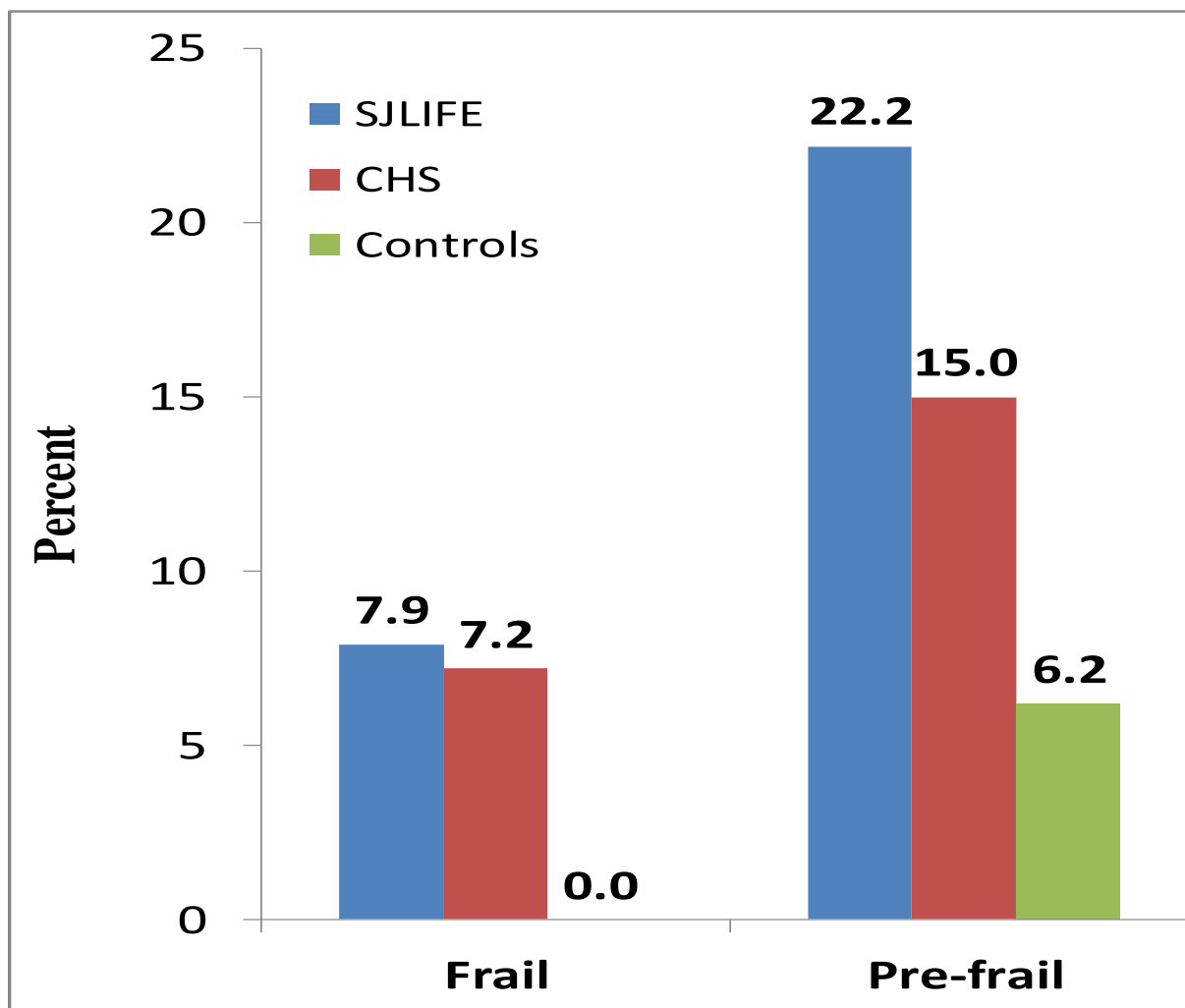
Frailty in Childhood Cancer Survivors

- Pre-frailty and Frailty are defined by a cluster of five measurements of physical state/abilities
 - Lean muscle mass - DXA and height
 - Exhaustion - Vitality subscale of the SF-36
 - Energy expenditure – Kilocalories/week (NHANES)
 - Walking speed – 15 feet, adjusted for height/sex
 - Muscle weakness – Hand grip strength, dynamometer



Pre-frail = 2 items Frail = 3+ items

Frailty in Childhood Cancer Survivors



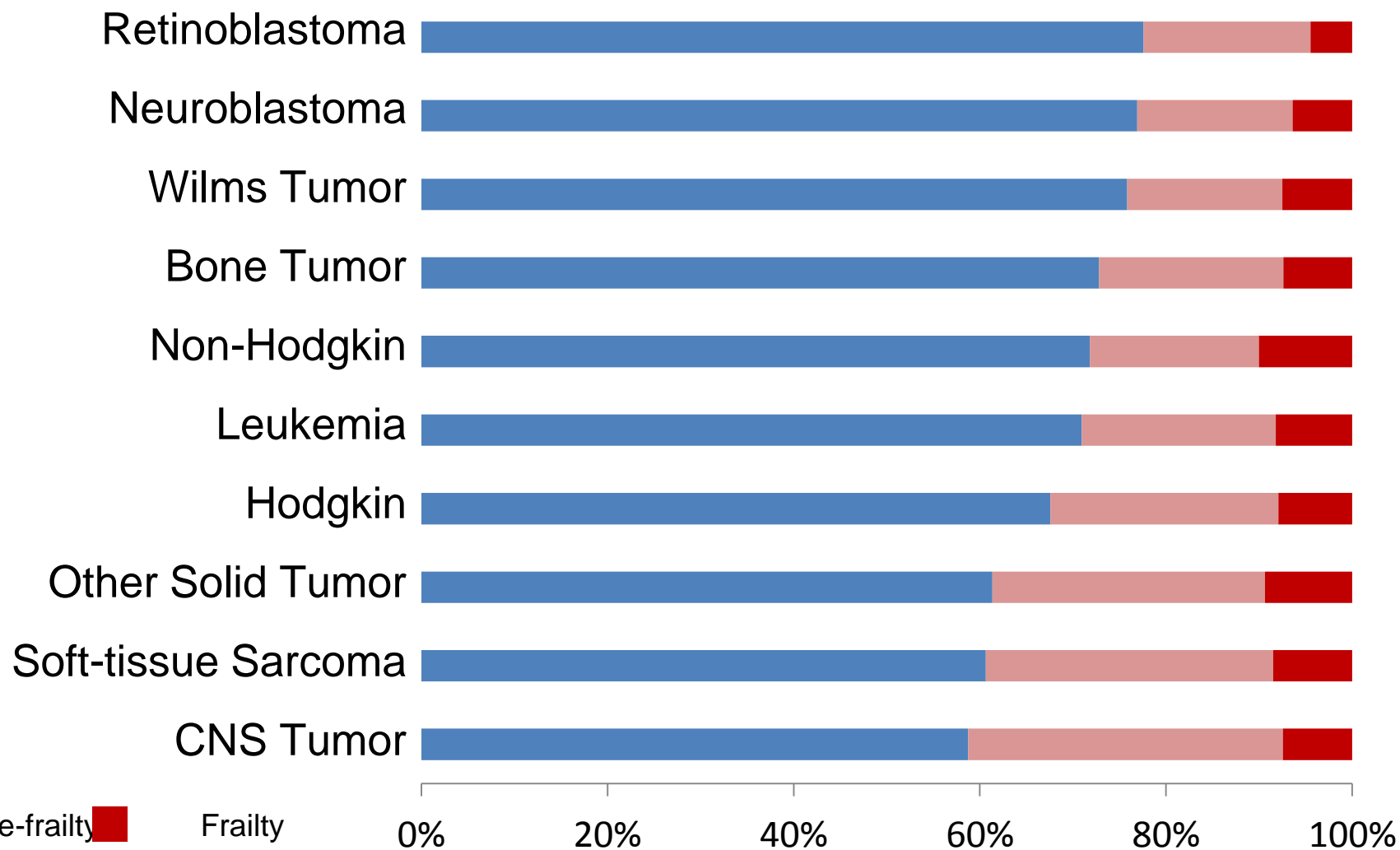
St. Jude Lifetime Cohort Study

- N=1922 (50.3% male)
- Mean age 34 years
- Mean time since Dx: 26 years

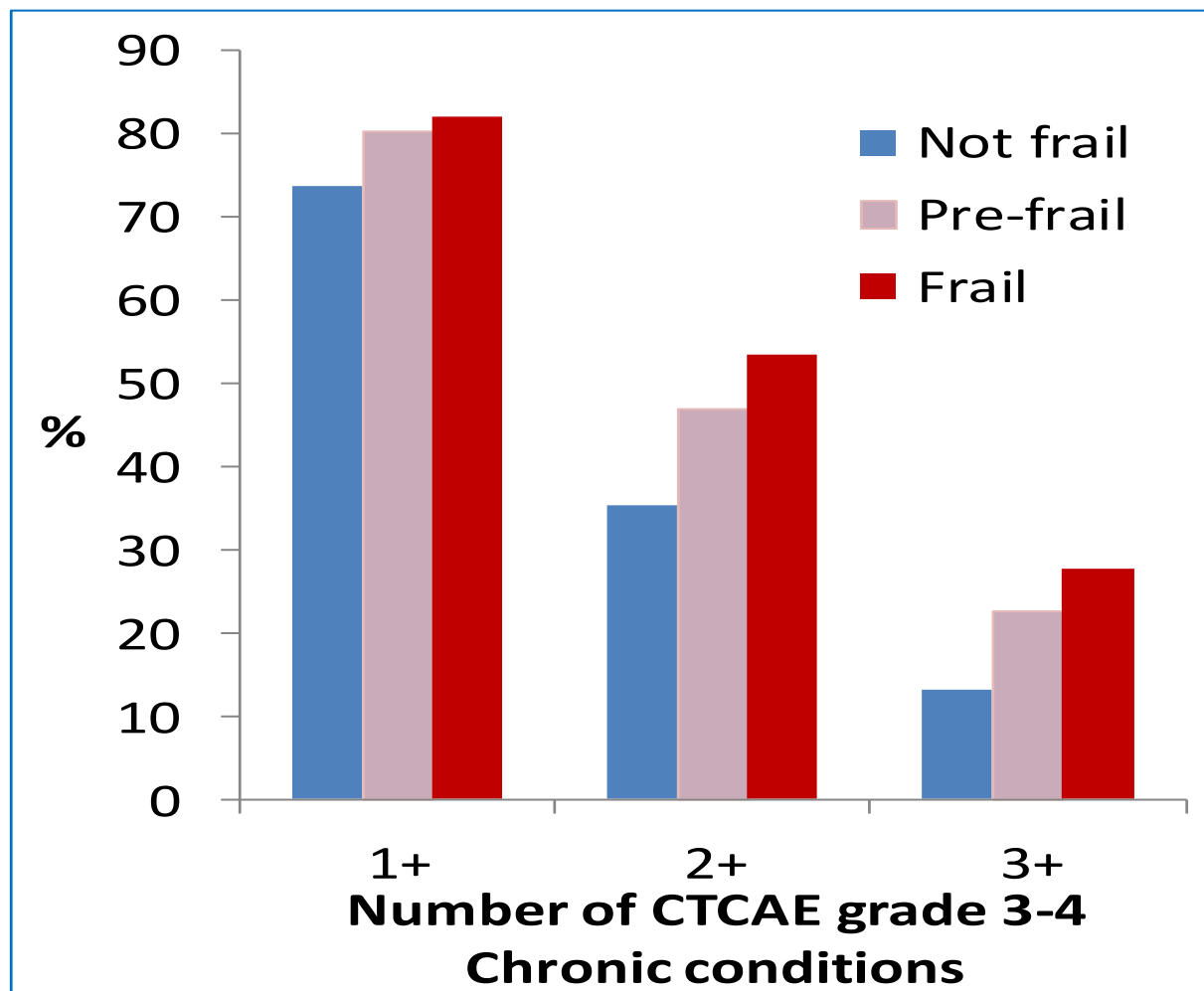
Cardiovascular Health Study (CHS): 65-101 years

Control participants: 18-50 years (mean 29 years)

Frailty Rates Varied by Cancer Diagnosis



Frailty, Chronic Health Conditions, and Mortality



Among participants who returned for a second visit, risk of developing a serious, disabling or life-threatening chronic condition (CTCAE grade 3-4), adjusting for sex and time since frailty assessment:

RR= 2.2 (95% CI 1.2-4.2)

Risk for Death by Frailty Status

	Hazard ratio	95% CI
Frailty	3.53	1.95-6.38
Age (one year increments)	1.06	1.03-1.10
Female	0.64	0.40-1.02
Non-white race	0.88	0.45-1.73
Cardiac condition	1.97	1.19-3.26
Pulmonary condition	2.32	1.38-3.89
Neurological condition	1.91	1.14-3.22
Endocrine condition	2.59	1.48-4.54

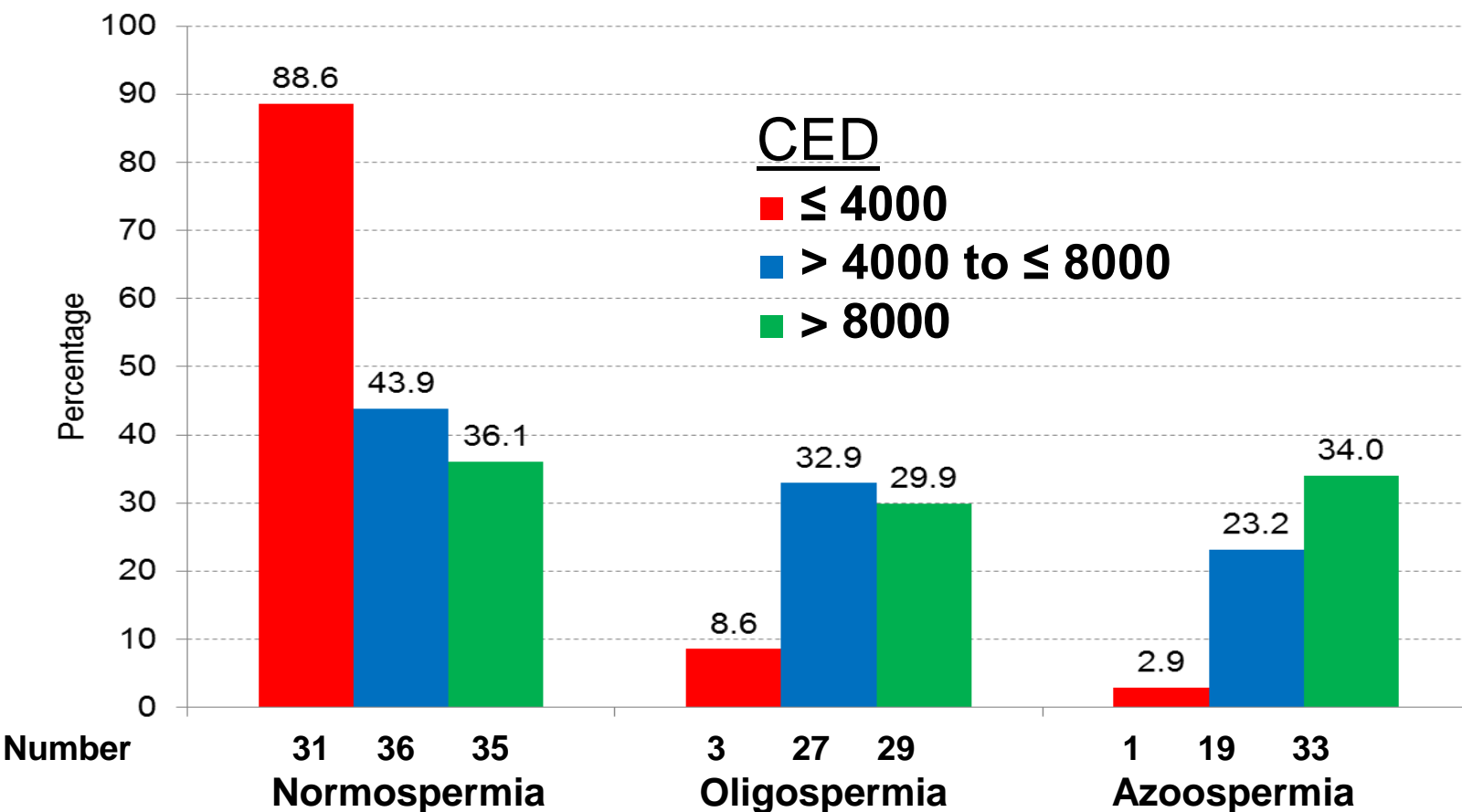
There were 77 deaths in the cohort, 17.4% among those who were frail and 4.3% among those who were not frail.



Lesson #4

Findings from late health outcomes studies can inform counseling and care of long-term survivors and newly diagnosed childhood cancer patients.

Semen Parameters and Cyclophosphamide Equivalent Dose (CED)



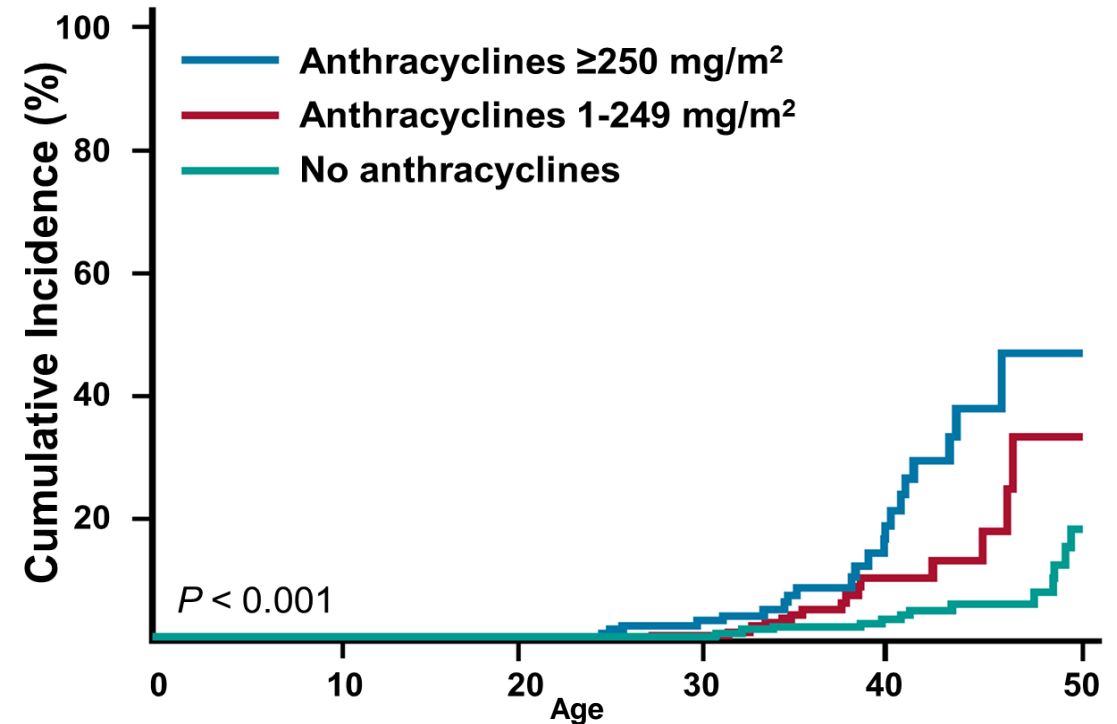
- N=214 adult males
- Median age 29 years
- Median 21 years from Dx
- Findings: azoospermia (25%); oligospermia (28%)
- CED negatively correlated with sperm concentration
- Impaired spermatogenesis less likely if $CED < 4g/m^2$

Breast Cancer Risk and Detection in SJLIFE

- Objectives
 - Estimate risk for secondary breast cancer within the context of chest dosimetry, genetic predisposition, and direct assessment
 - Characterize breast cancers, detection method, treatment, and diagnostic sensitivity/specificity of surveillance methods
- 1,467 female SJLIFE participants (1,343 with whole genome sequencing)
 - 9 autosomal dominant breast cancer predisposition genes (*BRCA1*, *BRCA2*, *ATM*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, *TP53*)
 - 56 women with 68 secondary breast cancers (38 invasive ductal, 26 *in situ* carcinomas, 4 other)

Breast Cancer Risk and Detection in SJLIFE

- Cumulative incidence by anthracycline exposure
 - None: 2% at 35 15% at 50 years of age
 - $\geq 250 \text{ mg/m}^2$: 7% at 35 and 46% at 50 years of age
- Anthracycline dose vs. none
 - 1-249 mg/m^2 – HR 2.9, 95%CI: 1.2-7.4
 - $\geq 250 \text{ mg/m}^2$ – HR 12.2, 95%CI: 5.0-29.7



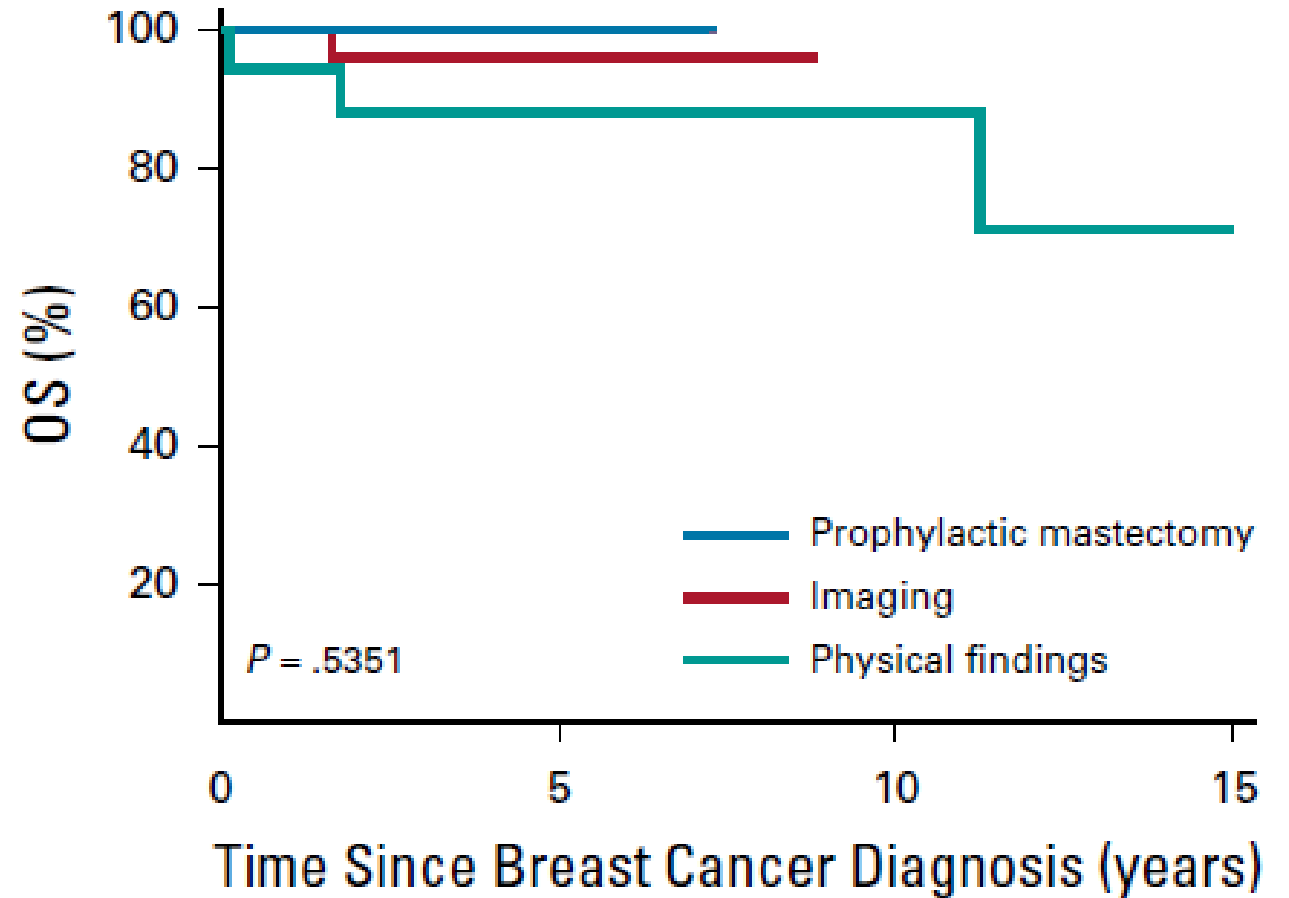
Anthracyclines and Risk for Secondary Breast Cancer

- 45 Of 1322 survivors developed breast cancer.
- Multivariable models evaluating breast cancer risk for radiation, chemotherapy, cancer predisposition genetics.
- Similar results in model excluding survivors with pathogenic/likely pathogenic mutations

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)

Breast Cancer Risk and Detection in SJLIFE

- Compared to breast cancers diagnosed by physical findings, those detected by imaging and/or prophylactic mastectomy were more likely (p 's < 0.001) to be
 - *In situ* carcinomas
 - Smaller at diagnosis
 - Without lymph node involvement
 - Treated without chemotherapy
- Trend towards lower survival rates when detected by physical findings, imaging, and prophylactic mastectomy, respectively

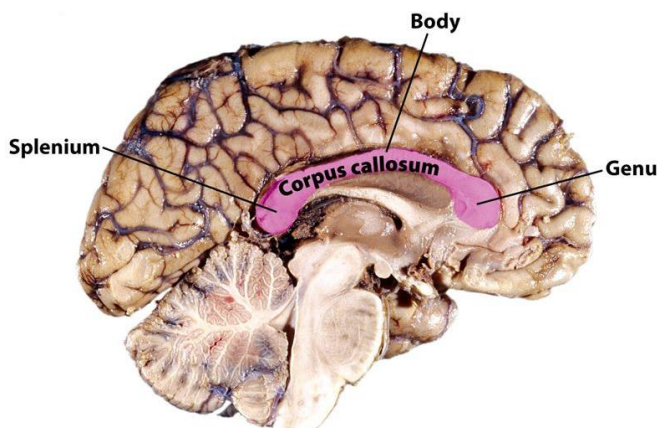


General Anesthesia and Neurocognitive Outcomes in ALL

General Anesthesia Exposures	Mean (SD)	Range
Number of anesthesia events	26.9 (6.3)	12.0 – 48.0
Cumulative hours under anesthesia	15.6 (5.7)	4.3 – 40.9

Neurocognitive Impairment	RR* (95% CI)
Propofol (per 100 mg/kg)	1.40 (1.02-1.68)
Anesthesia duration (per hour)	1.03 (1.01-1.06)

*adjusted for age at MRI, IT therapy, high-dose MTX



Impact on corpus callosum diffusivity:

- Increased in body with propofol ($p=0.01$)
- Increased in splenium with duration ($p=0.02$)

- **212 (70%) ALL survivors (median 7.7 years from diagnosis) underwent neurocognitive testing.**
- **Cognitive outcomes correlated with cumulative doses anesthetics, sedatives, analgesics, anxiolytics, and neuromuscular blockers**
- **Cumulative dose of propofol, fluranes and cumulative duration are associated with:**
 - General neurocognitive impairment
 - Worse performance on tests of attention and processing speed
 - Abnormally high diffusivity in corpus callosum
- **Processing speed correlated with diffusivity**
 - Letter Sequencing (est -0.22, $p=0.005$)
 - Digit Symbol (est -0.26, $p<0.001$)

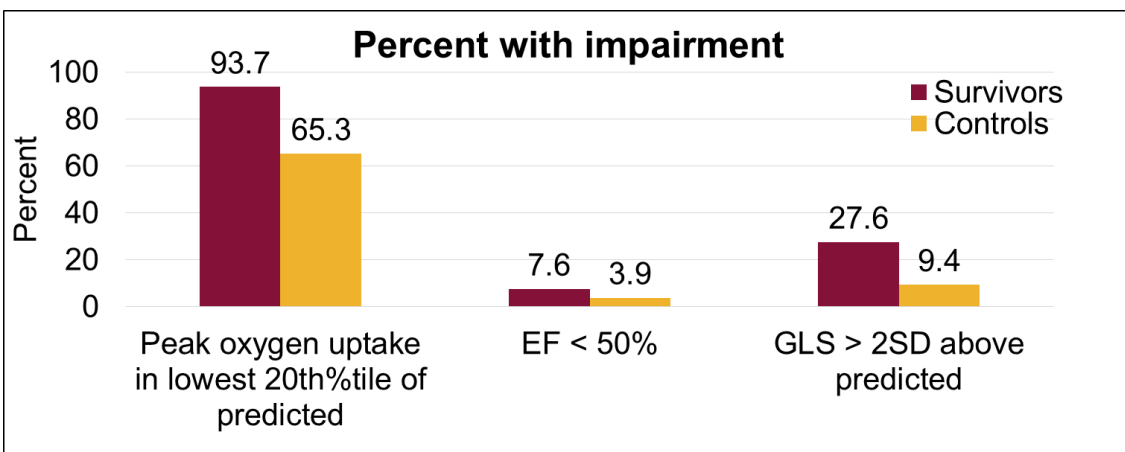


Lesson #5

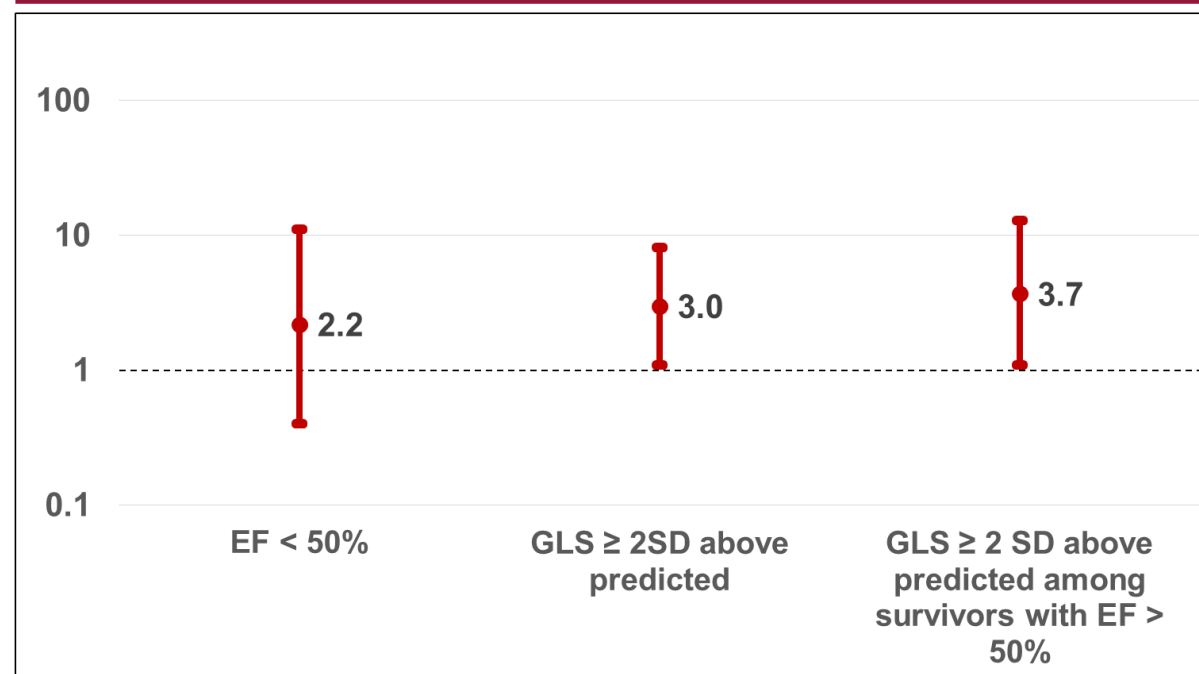
Adults treated for childhood cancer may benefit from novel surveillance measures that facilitate early detection and opportunities for intervention.

Myocardial Strain and Impaired Exercise Capacity

- Describe exercise capacity and cardiac function
- Determine cardiac measure associated with impaired exercise



Relative odds of impaired exercise tolerance by indicator of cardiac function



From separate models adjusted for age, sex, race, fev¹, isokinetic quadriceps strength, score on the mTNS, smoking status, physical activity

- Abnormal global longitudinal strain, but not ejection fraction, is associated with impaired exercise capacity.
- Global longitudinal strain should be considered in screening guideline.



Lesson #6

Precision medicine will have a
role in survivorship care.

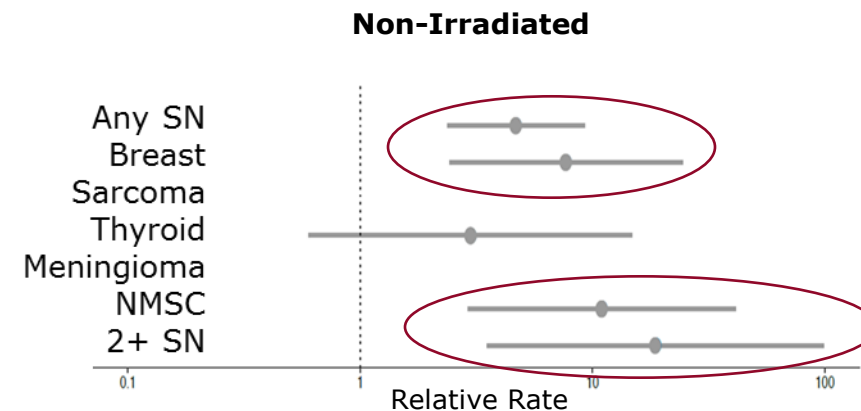
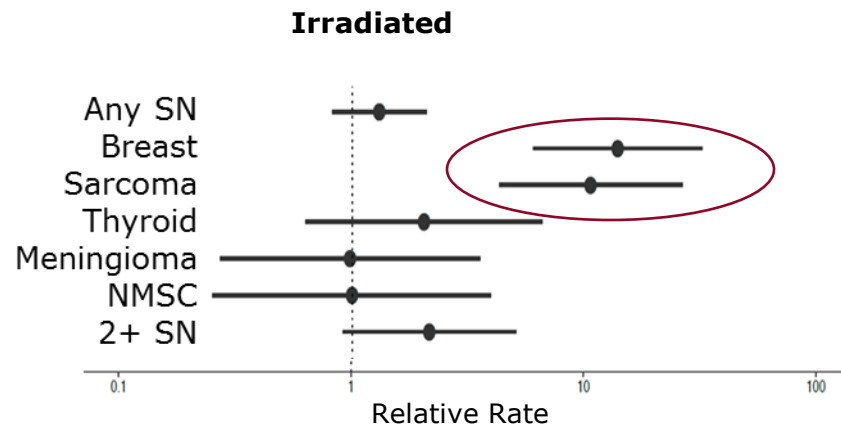
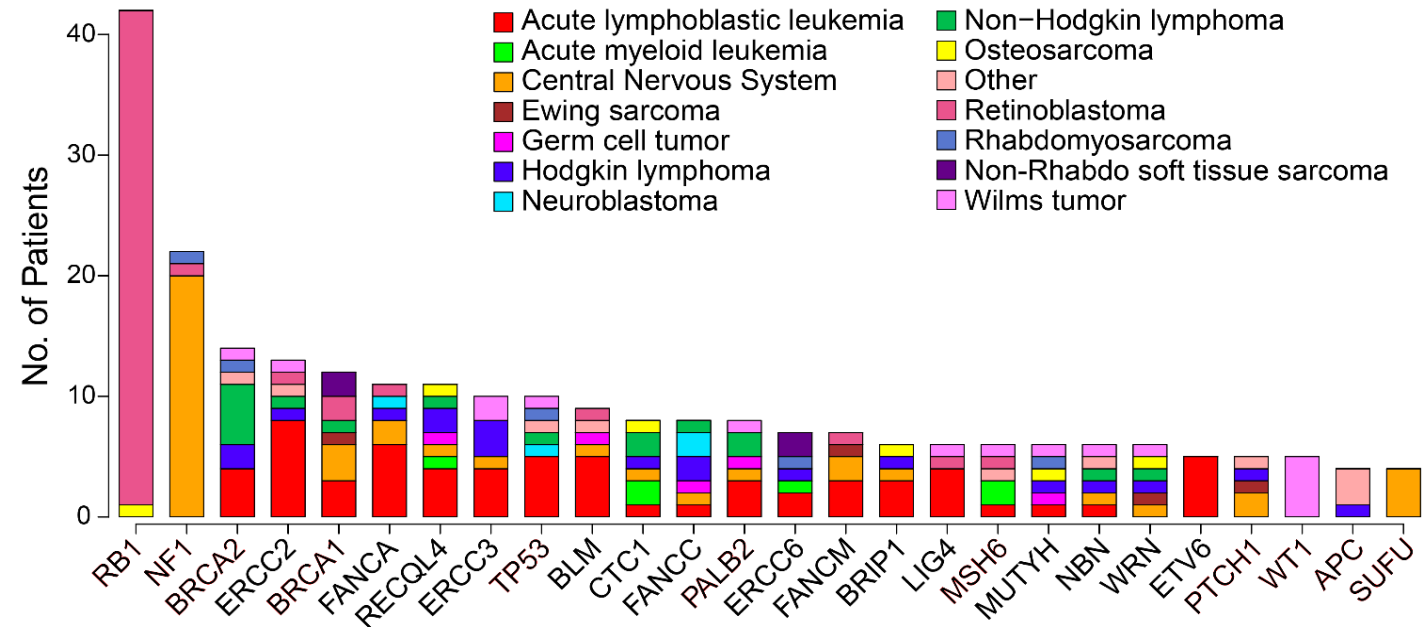
Cancer Predisposition and Subsequent Neoplasms

N=3006 survivors

14.6% developed one or more subsequent neoplasm (1120 SN in 439 survivors)

5.8% with pathogenic/likely pathogenic mutation in SJCPG₆₀ (autosomal dominant inheritance with high penetrance)

Wang/Wilson et al. J Clin Oncol, 2018



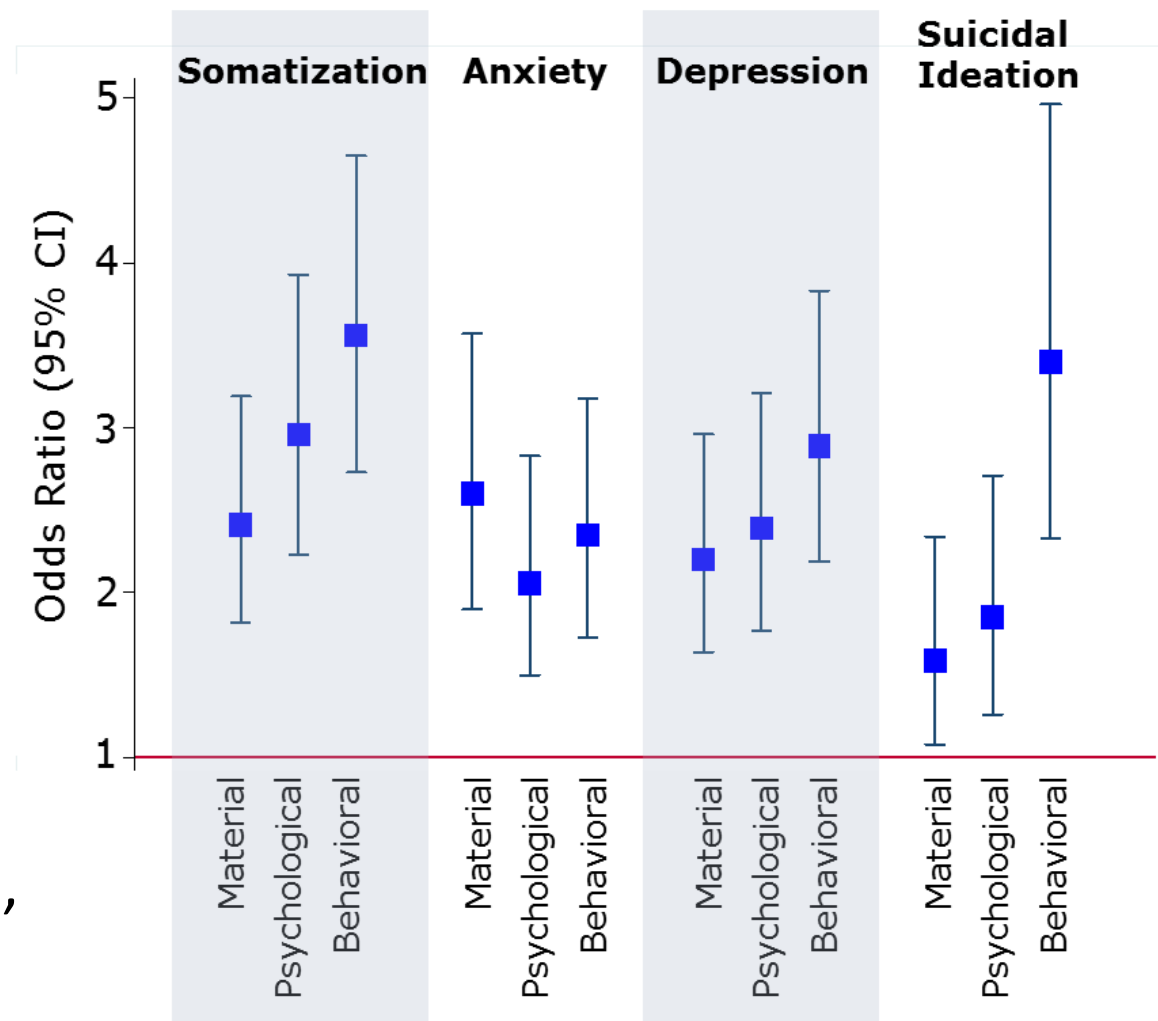


Lesson #8

Childhood cancer has substantial psychosocial repercussions in adulthood.

Consequences of Financial Hardship

- Outcomes reported by 2811 survivors:
Financial situation
Health care affordability/accessibility
Life insurance/retirement planning
Physical/emotional symptoms
Health related quality of life
- Prevalence of hardship:
22% Material hardship
30% Coping/behavioral hardship
51% Psychological hardship
- Hardship associated with risk of somatization, anxiety, depression, and suicidal ideation



Clinical Implications and Future Directions

- There is a critical need to develop interventions to preserve health across survivorship.
- Collaboration is required to evaluate rare outcomes and replicate findings.
- Understanding perspectives of survivors/families and community clinicians will facilitate delivery of optimal survivor care.

Thank You & Acknowledgements



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