St. Jude Children's Research Hospital
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The Cost of Cure:
understanding late effects after childhood cancer to improve quality survival

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Objectives

- Describe the spectrum of late effects after treatment of childhood cancer, including the impact of late effects on duration and quality of survival.

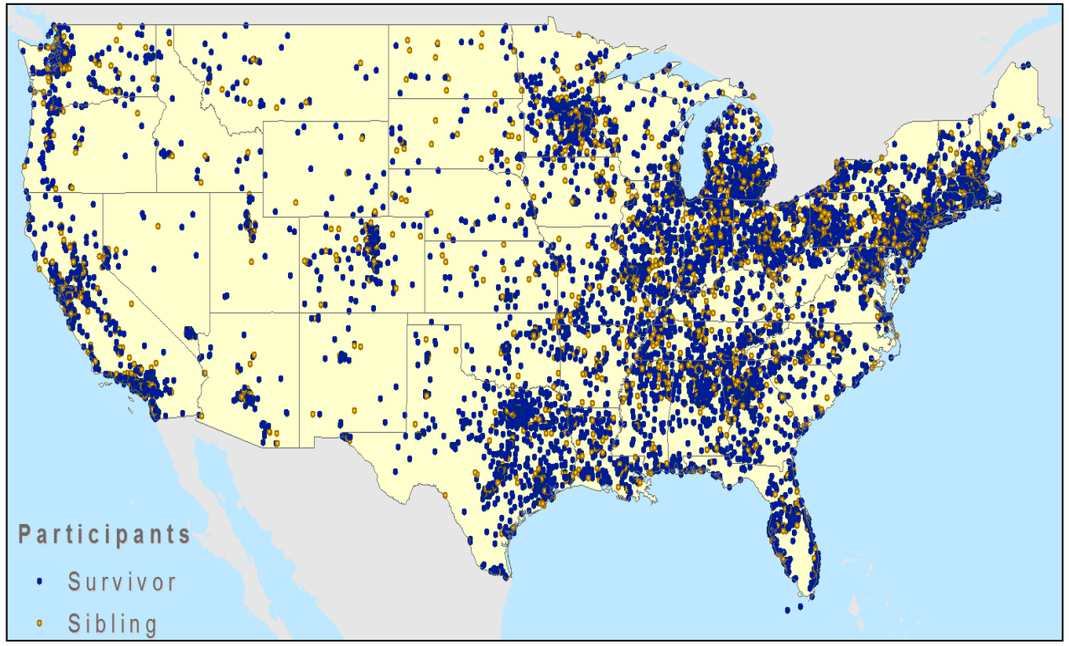
- Present associations between treatment exposures, modifiable risk factors, and late health outcomes.

- Discuss recommendations for evidence-based survivorship care with a focus on risk-based screening by treatment exposures.

NCI-Funded Survivor Cohorts

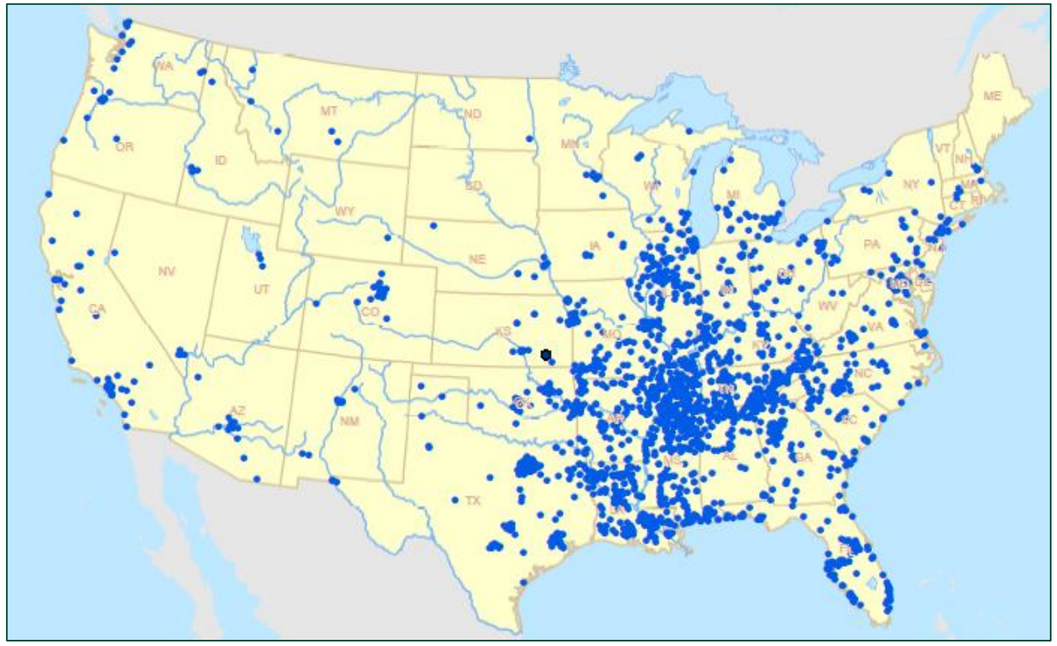
CCSS

Childhood Cancer Survivor Study Cohort
U24 CA55727 (PI: Armstrong)
38,036 Survivors (25,665 participants)



SJLIFE

St. Jude Lifetime Cohort
U01 CA195547 (MPI: Hudson/Ness)
10,020 Survivors (6000+ clinically assessed)



NCI-Funded Survivor Cohorts

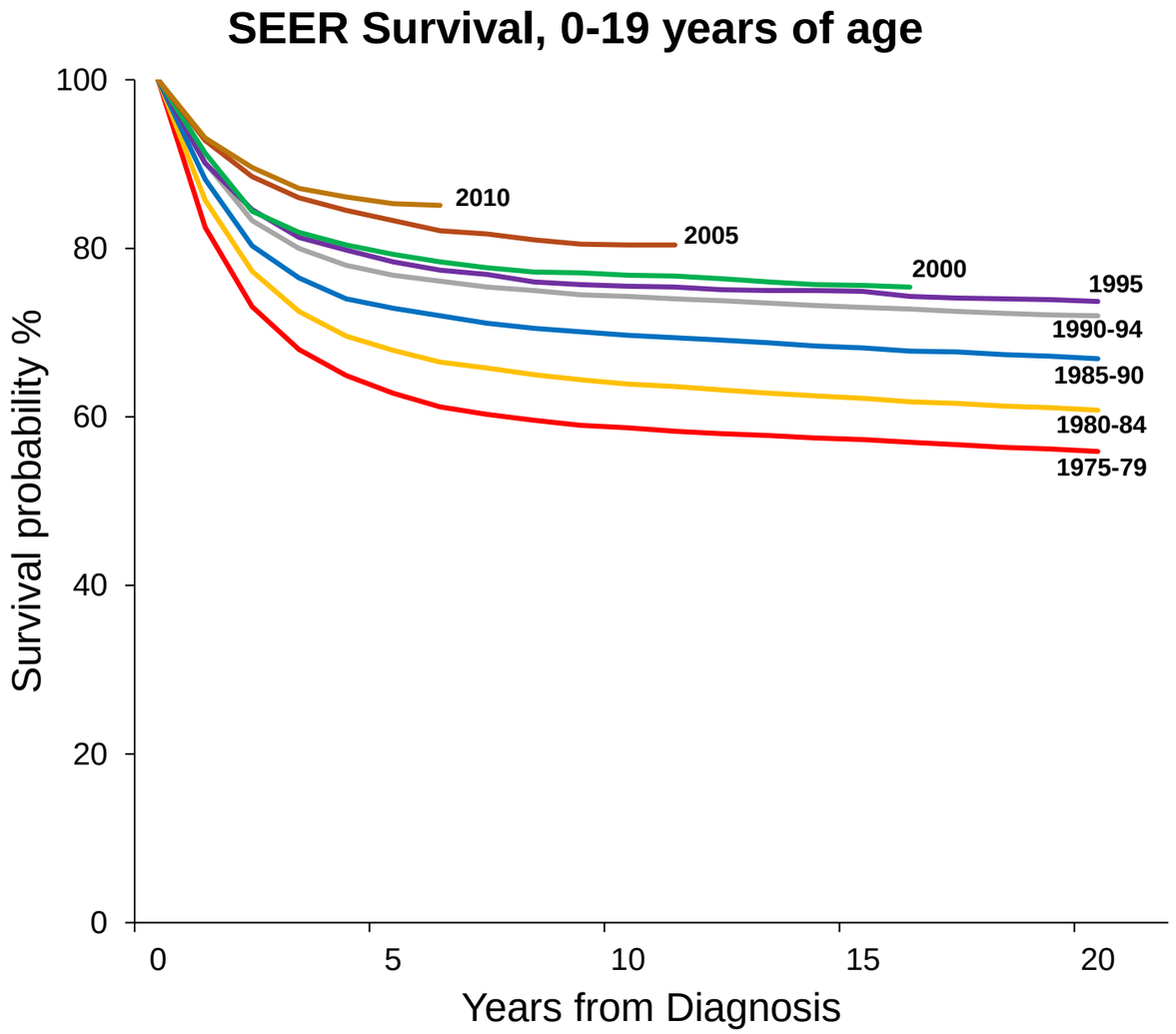
Characteristic	CCSS (Dx 1970 - 1999)	SJLIFE (Dx 1962 - 2012)
Cohort size	38,036 (25,665 active participants)	10,020 (6000+ participants to date)
Entry criteria	≥5 years from diagnosis	≥5 years from diagnosis
Age at cancer diagnosis	<21 years	<25 years
Cancers	Leukemia, CNS, HL, NHL, neuroblastoma, soft tissue sarcoma, Wilms, bone tumors	All diagnoses
Study design	Retrospective cohort with prospective follow-up, hospital-based	Retrospective cohort with prospective follow-up, hospital-based
Methods of contact	Surveys	Clinic visits including surveys
Comparison population	Siblings, general population	Frequency-matched community controls, general population
Therapeutic exposures	>90%	100%
Ascertainment methods	Self-report, pathology reports, NDI	Med. assessment, self-report, med. record, NDI
Collection of germline DNA	>60%	>95%

Case

A 40-year-old young woman with a history of Hodgkin lymphoma whose treatment included doxorubicin (250 mg/m^2) followed by 21 Gy mediastinal radiation at age 16 is being seen today in your clinic. She has not received regular follow-up and was last seen at age 35.

- What do you expect her risk for chronic conditions and early death to be?
- How is that impacted by prior treatment? Lifestyle? Comorbid conditions?
- What about recommended screening? Prevention or early treatment?

Childhood Cancer Survival



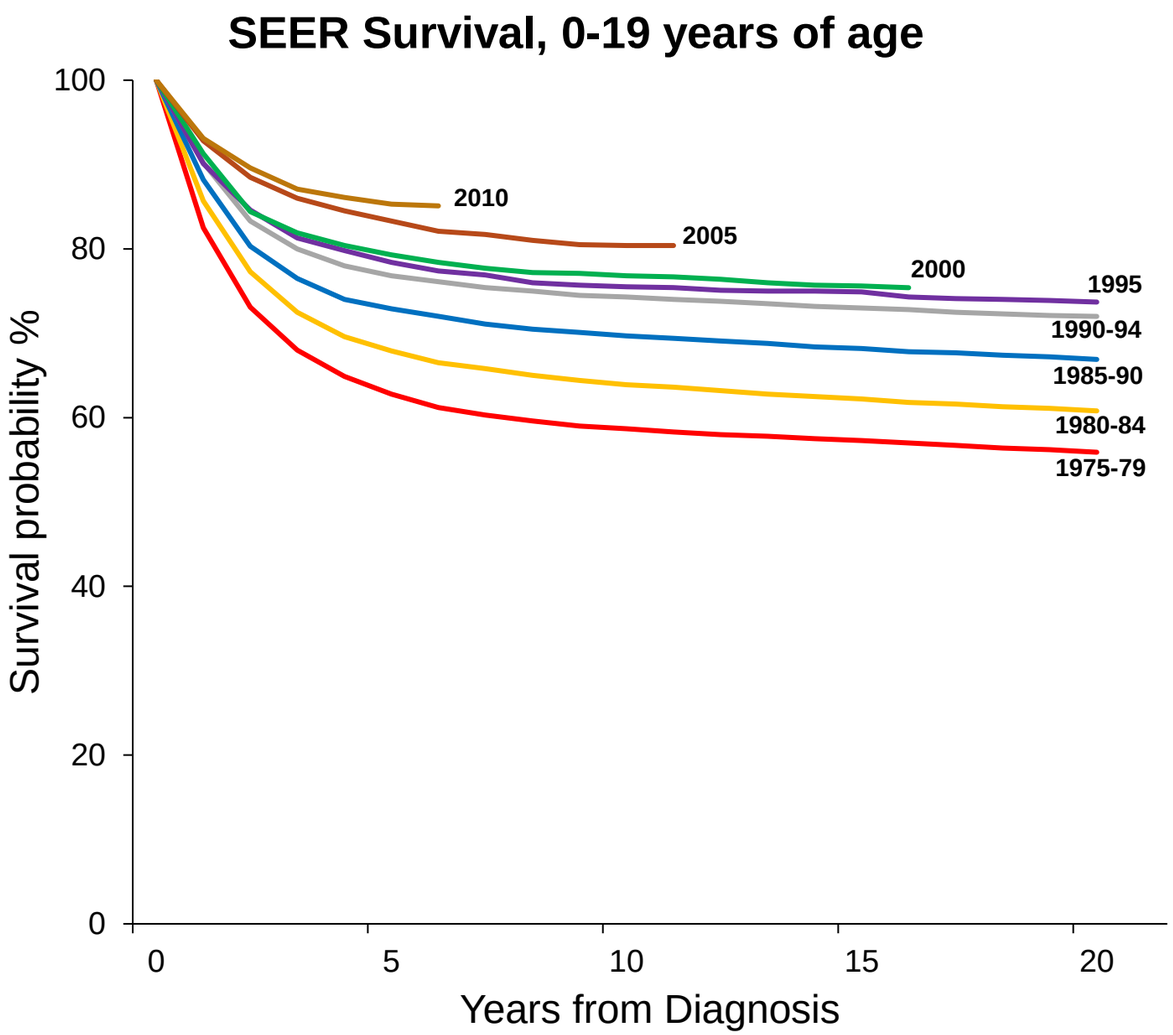
Survivorship Statistics

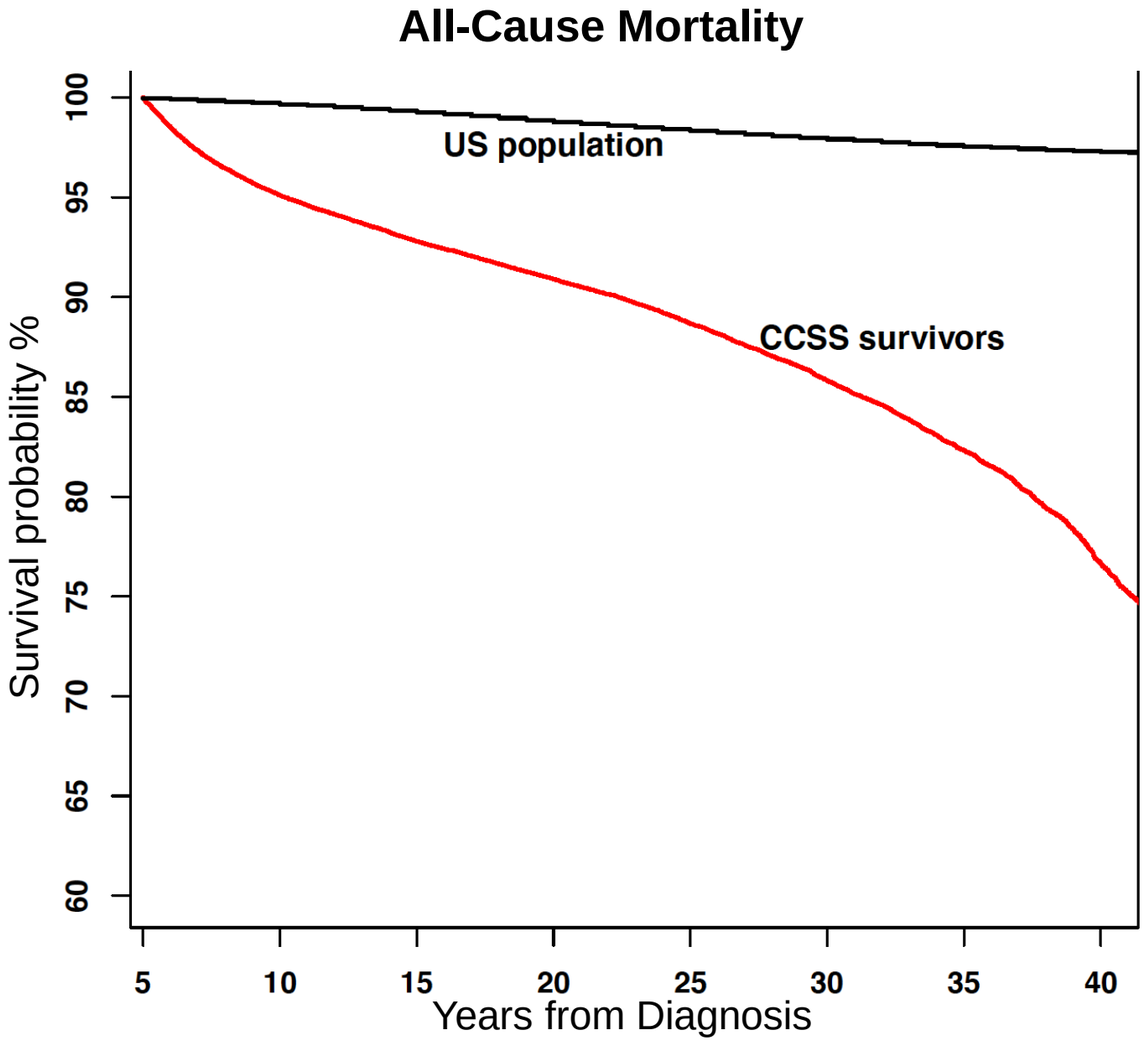
- >85% of children with a malignancy will achieve five-year survival
- By 2040, estimated 580,000 survivors
- 1 in 750 in US is a childhood cancer survivor

Howlader N, SEER Cancer Statistics Review 1975-2016. Ehrhardt et al., *Nat Reviews Clin Oncol,* 2023.

Childhood Cancer Survival and Late Mortality

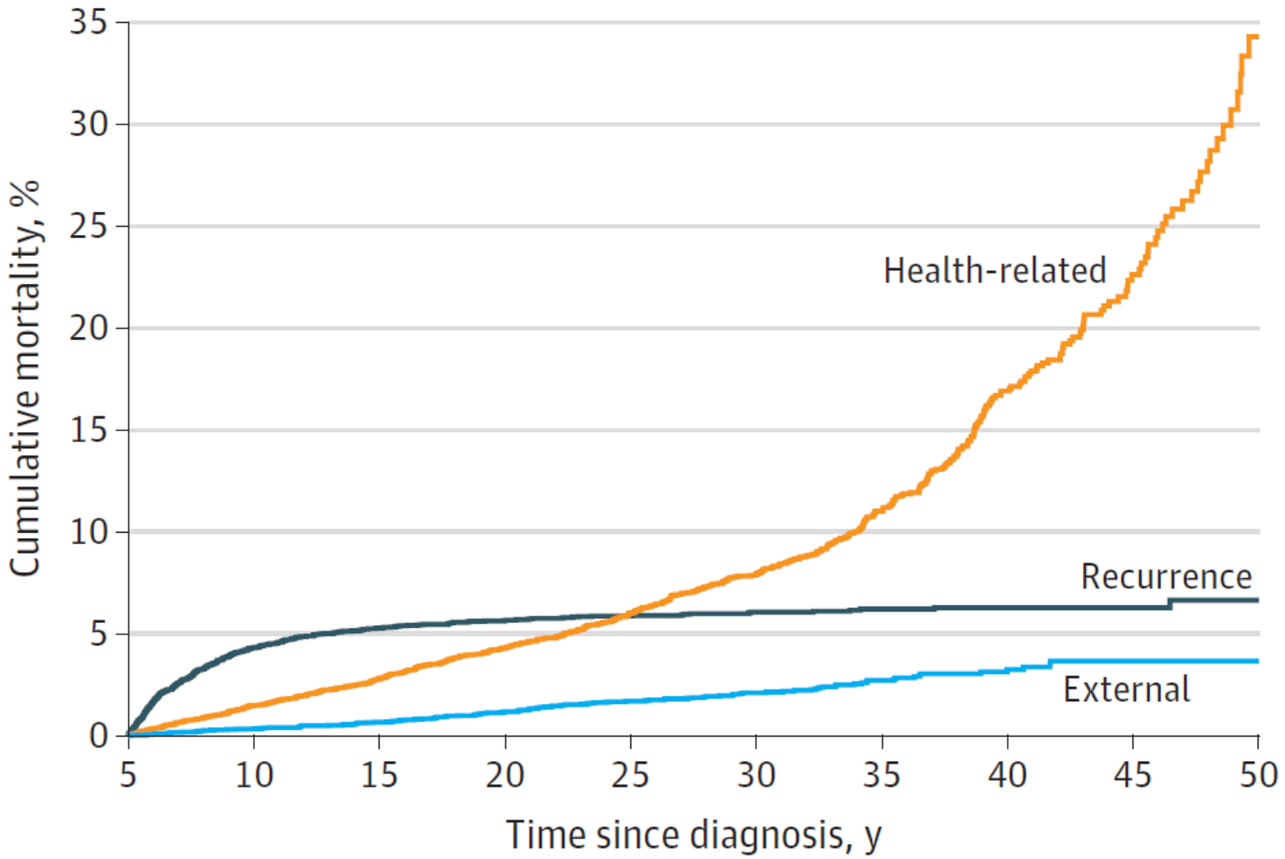
CCSS





Howlader N, SEER Cancer Statistics Review 1975-2016. Dixon et al, *Lancet* 2023.

Causes of Late Mortality

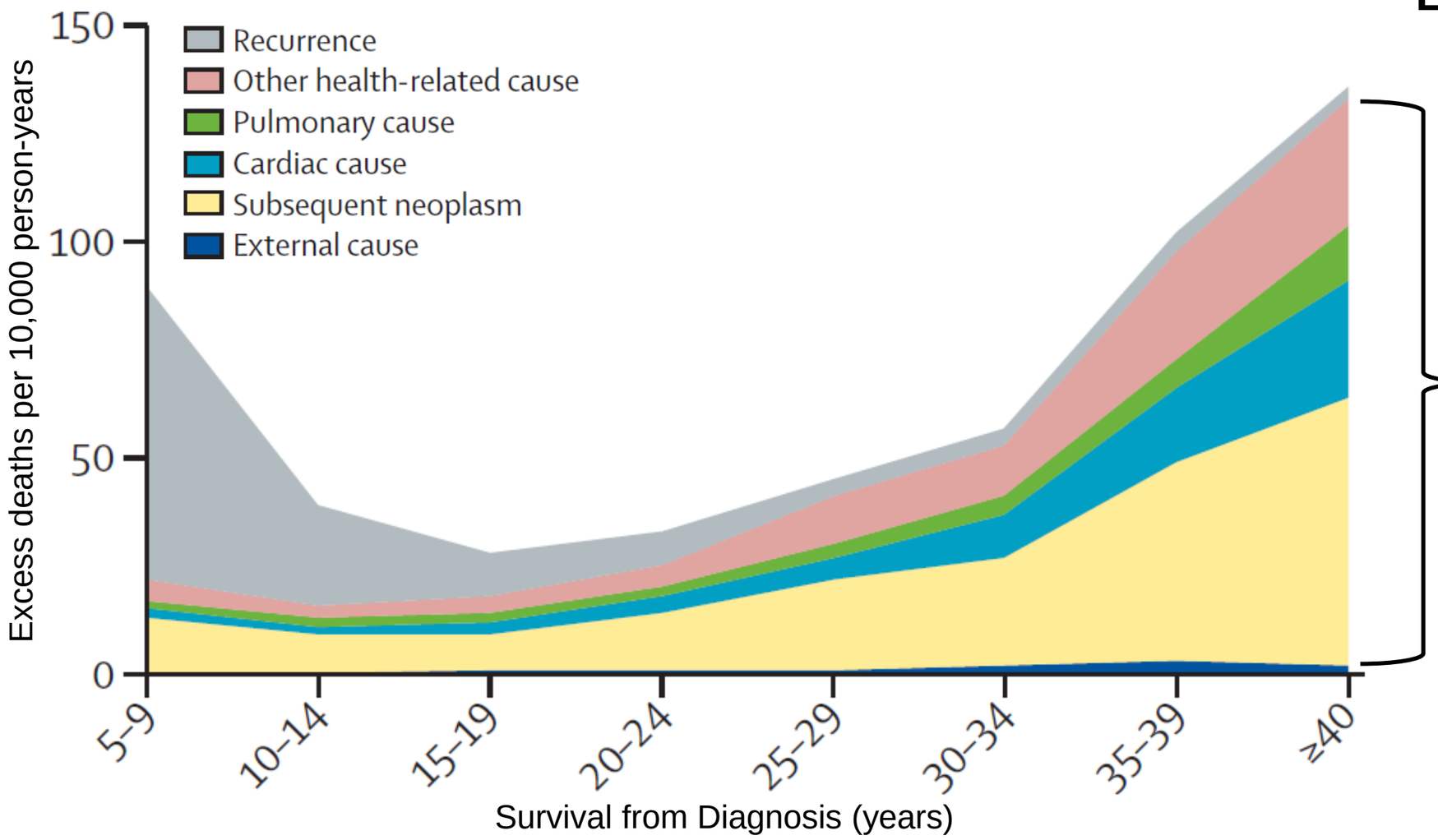


- By 25 years from cancer diagnosis, deaths due to chronic health conditions, including cardiovascular disease, exceed those due to primary cancer.

Ehrhardt et al, *JAMA Network Open* 2023.

Excess Death in Survivors of Childhood Cancer

CCSS



Excess deaths per 10,000 person years (95% CI)

≥40 years

All-cause:
138 (117 - 161)

Health-related:
131 (111 - 153)

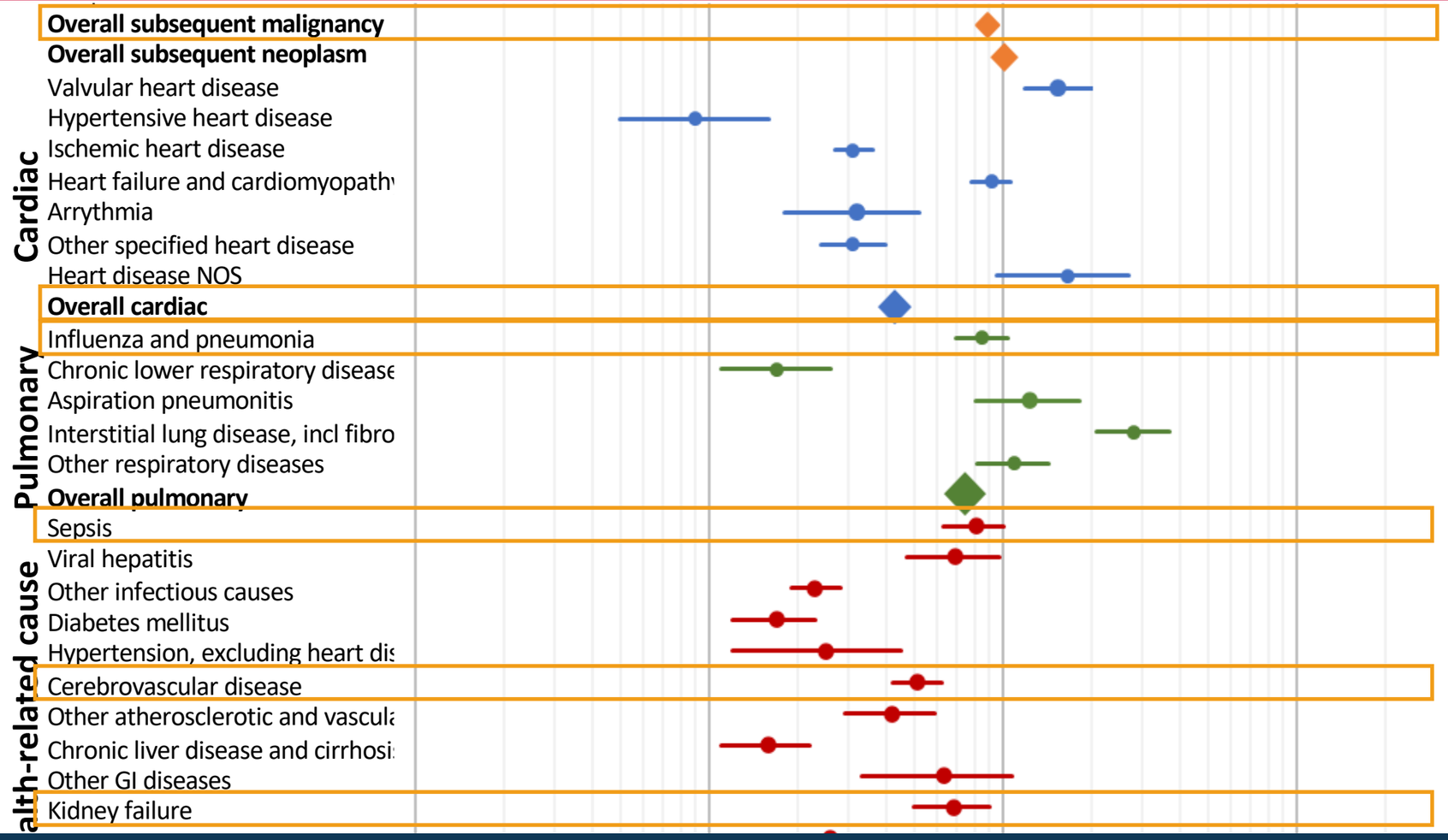
Cardiac:
27 (18 – 38)

Stroke:
10 (5 – 17)

Dixon et al, *Lancet* 2023.

Discrete Causes of Death Compared to US Population

CCSS



SMR (95% CI)

SMN: 8.9 (8.5 – 9.4)

Heart disease: 4.3 (3.9 – 4.7)

Flu & pneumonia: 8.5 (6.9 – 10.4)

Sepsis: 8.1 (6.3 – 10.1)

Stroke: 5.1 (4.2 – 6.2)

Kidney failure: 6.8 (5.0 – 9.0)

Survivors are dying at a ***younger age*** and ***higher rate*** from the same leading causes of death in the general population.

Childhood Cancer Survival

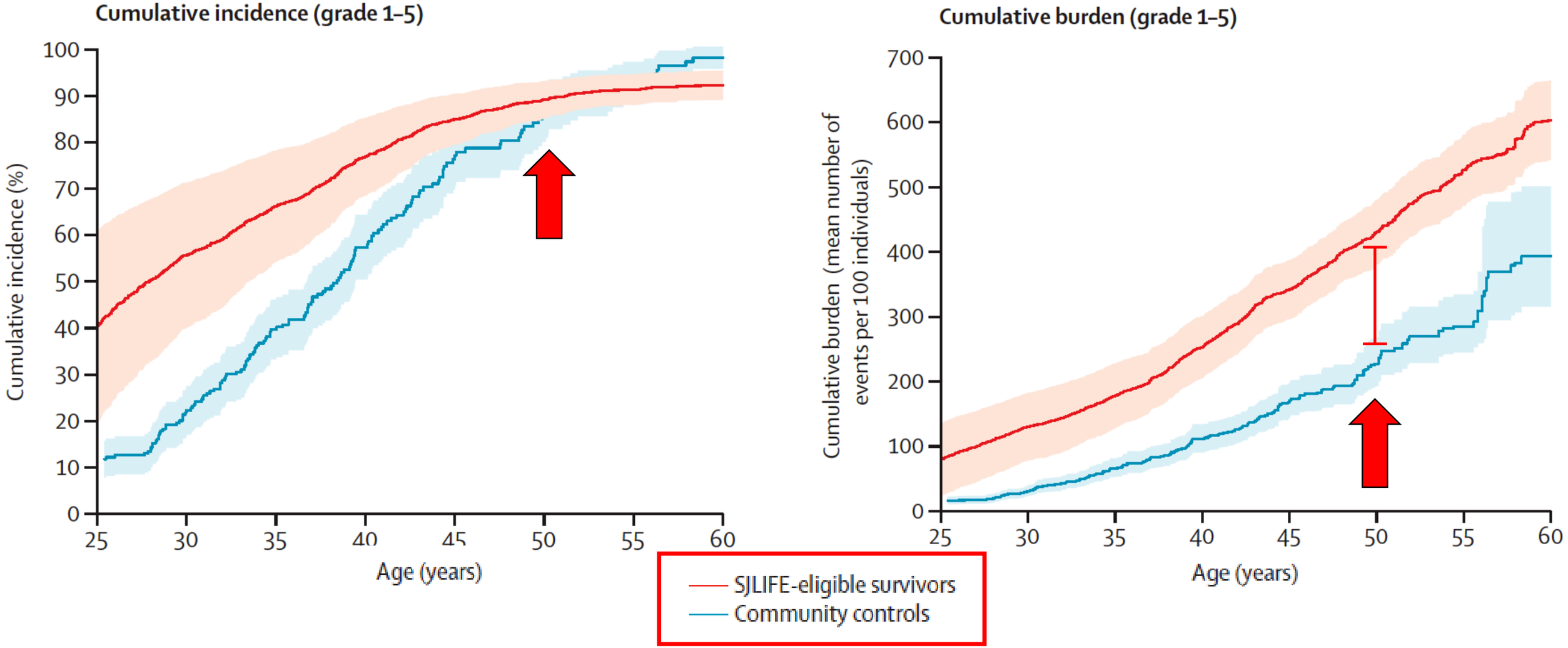
Cohort Size/Citation	≥ 1 Problem	≥ 2 Problems	Severe Problems
290 *Eur J Cancer 1998;34:694-8*	**58%**	**32%**	**–**
288 *AJPHO 1994;16:143-52*	**69%**	**–**	**21%**
96 *Cancer 2000;88:1687-95*	**69%**	**36%**	**30%**
10,397 *NEJM 2006;355:1572-82*	**67%**	**33%**	**33%**
1,713 *JAMA 2013;309:2371-2381*	**95.5%**	**–**	**80.5%**

Modified from Bhatia 2006

Cumulative Incidence vs Cumulative Burden

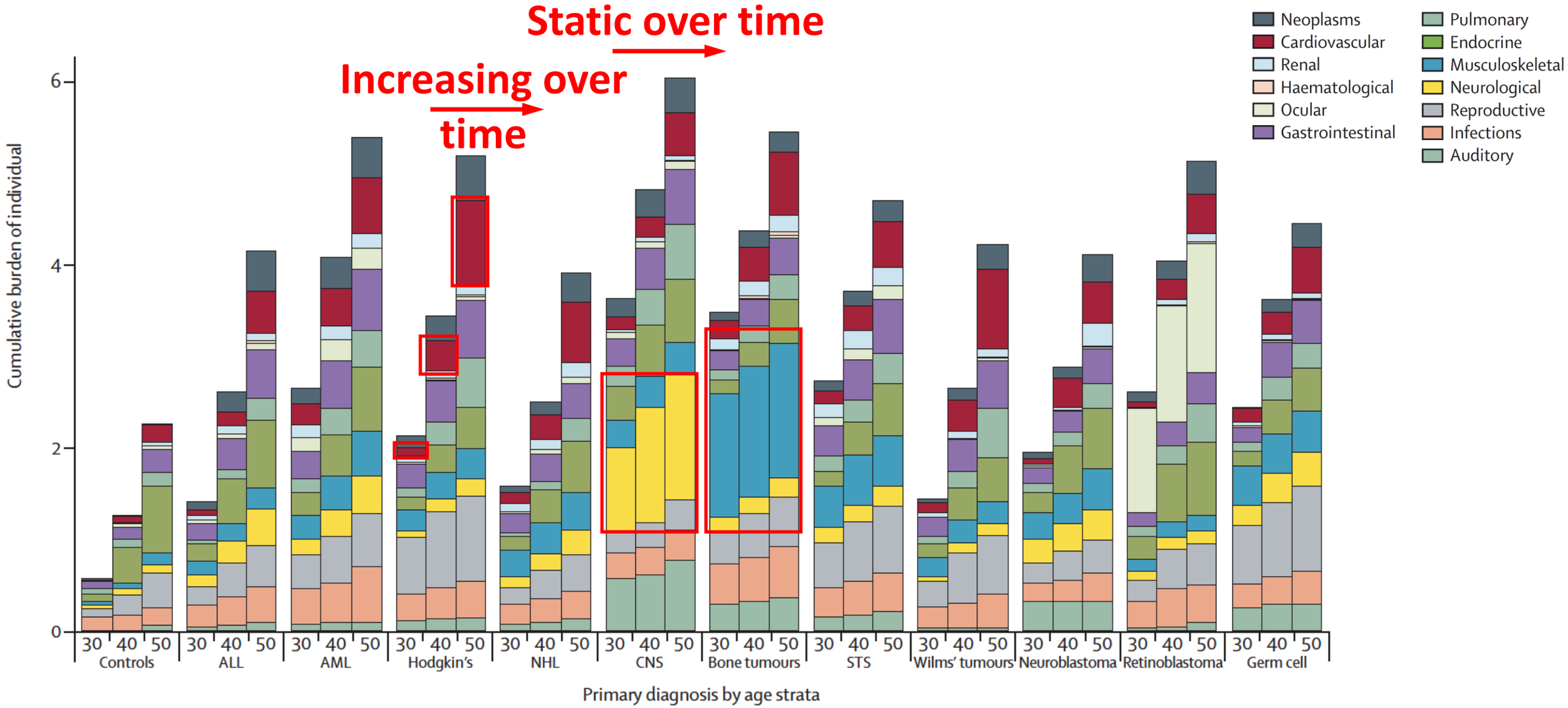
St. Jude LIFE
St. Jude for Life

Cardiovascular Conditions in SJLIFE Hodgkin Lymphoma Survivors



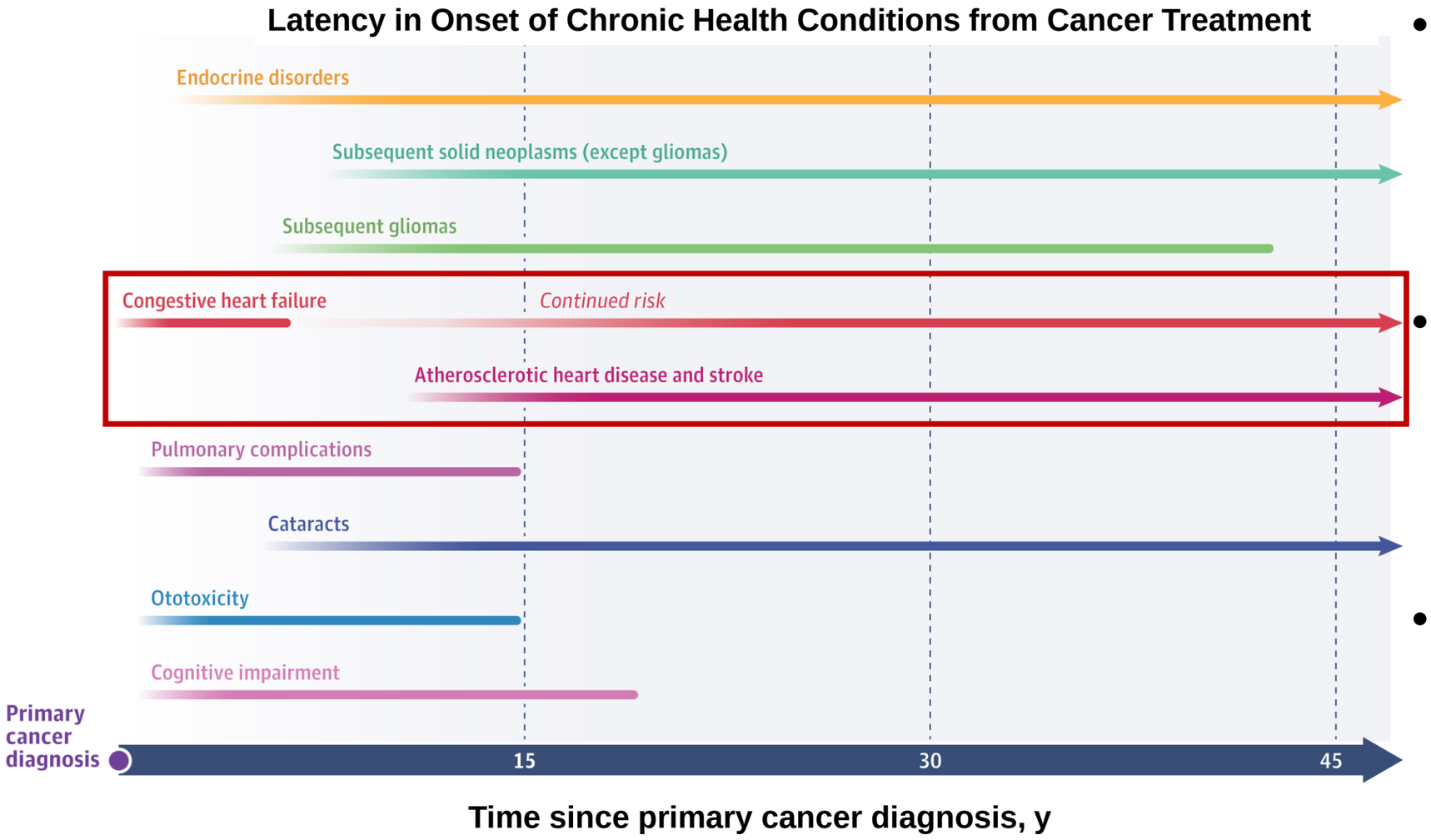
Bhaktia et al, *Lancet Oncol* 2016.

Cumulative Incidence vs Cumulative Burden



Bhaktia et al, *Lancet* 2018.

Latency of Chronic Condition Onset



- Latency period from treatment exposure varies for treatment-related chronic conditions.
- In general, radiation-related late effects have a longer latency period and occur within the radiation field.
- Dose, age at exposure, genetics, and comorbid conditions augment risk.

Bhatia et al, *JAMA* 2023.

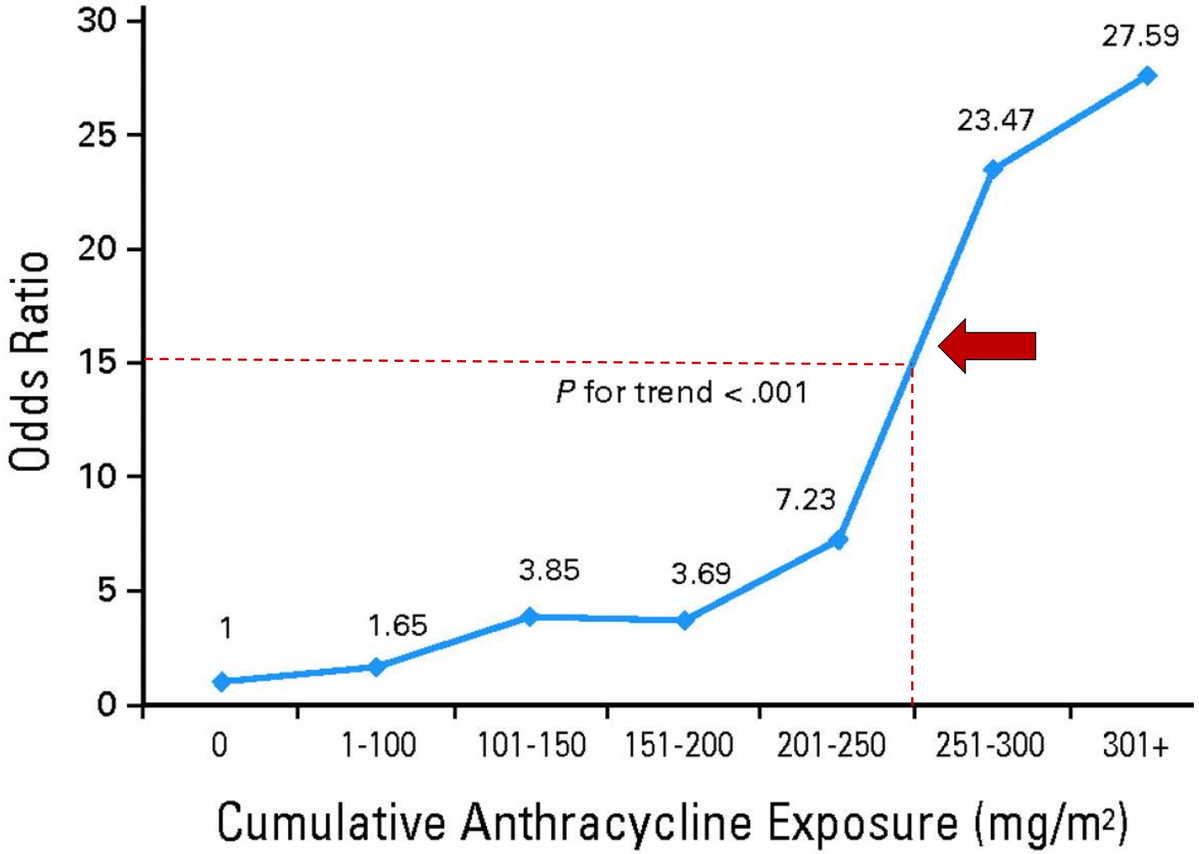
Case

A 40-year-old young woman with a history of Hodgkin lymphoma whose treatment included doxorubicin (250 mg/m^2) followed by 21 Gy mediastinal radiation at age 16 is being seen today in your clinic. She has not received regular follow-up and was last seen at age 35.

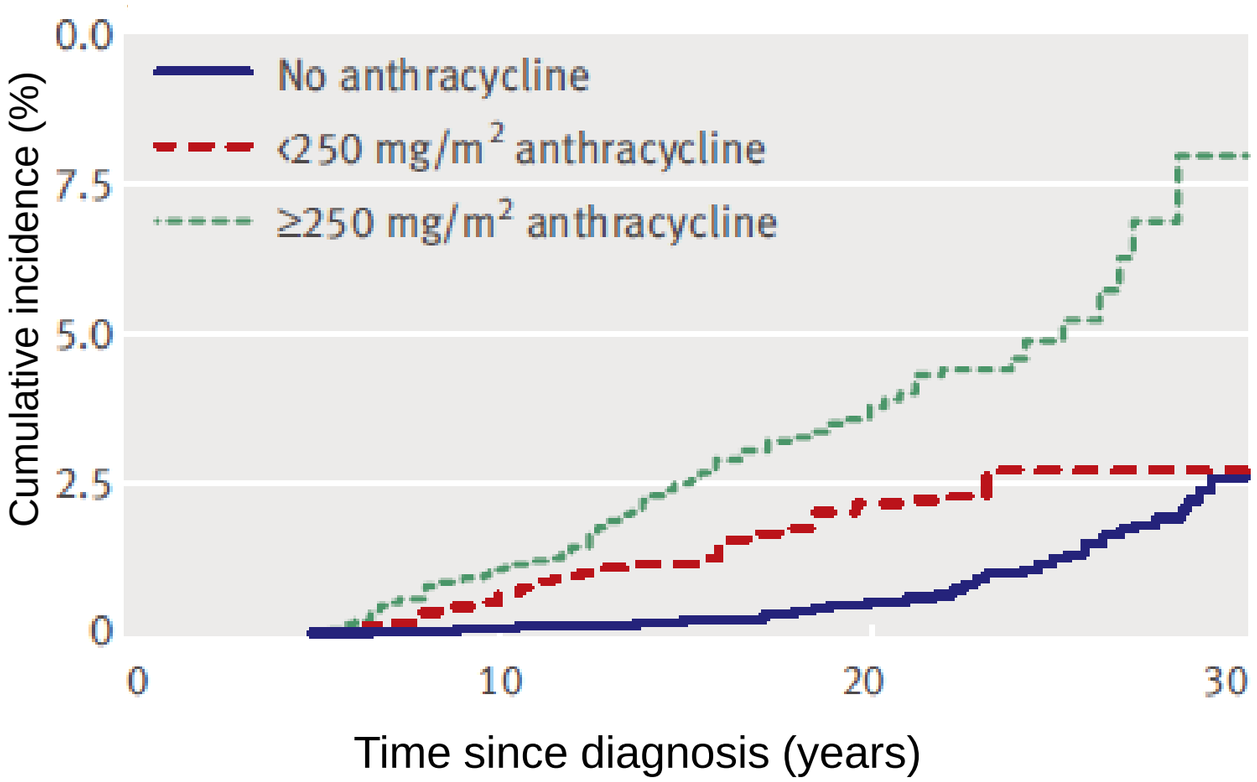
- How is risk impacted by prior treatment? Focused on cardiotoxicity and second cancer.

Anthracycline Cardiomyopathy and Dose Response

Cardiomyopathy Risk by Dose



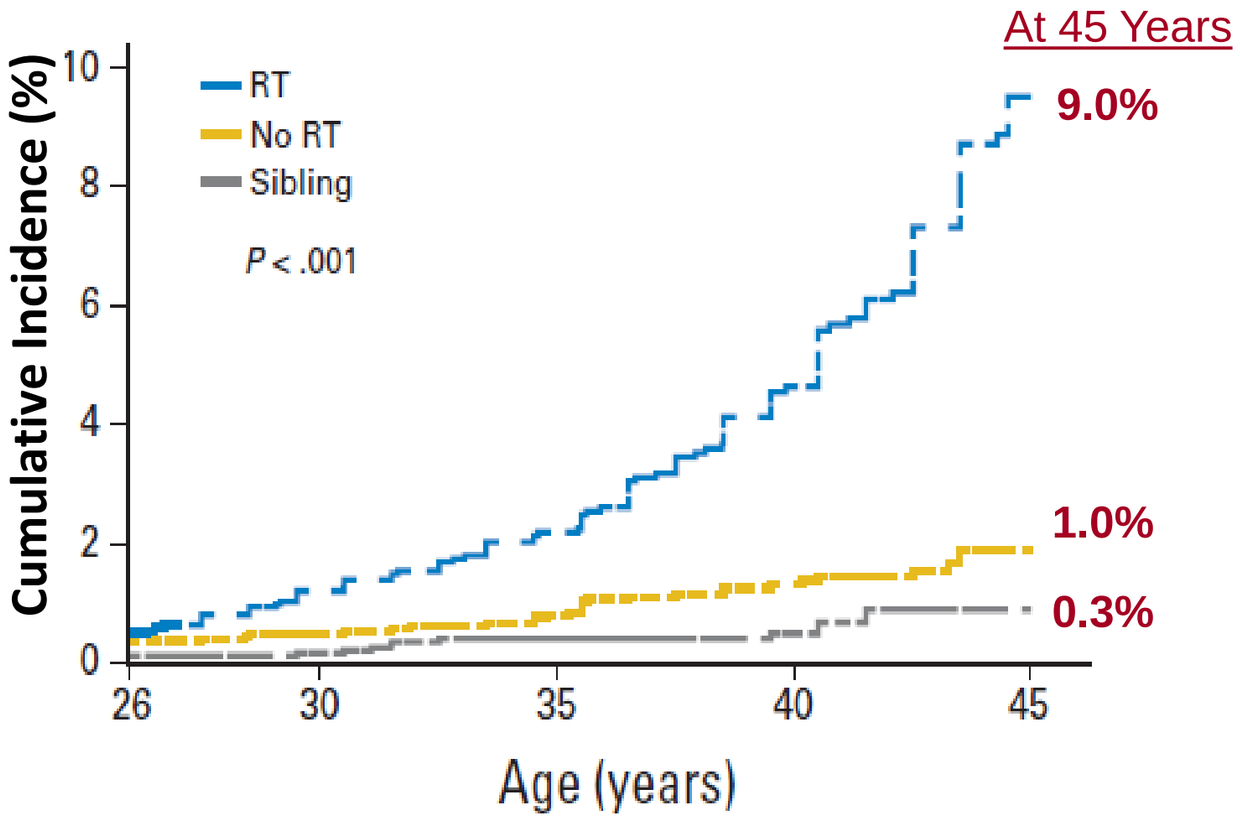
Heart Failure Cumulative Incidence



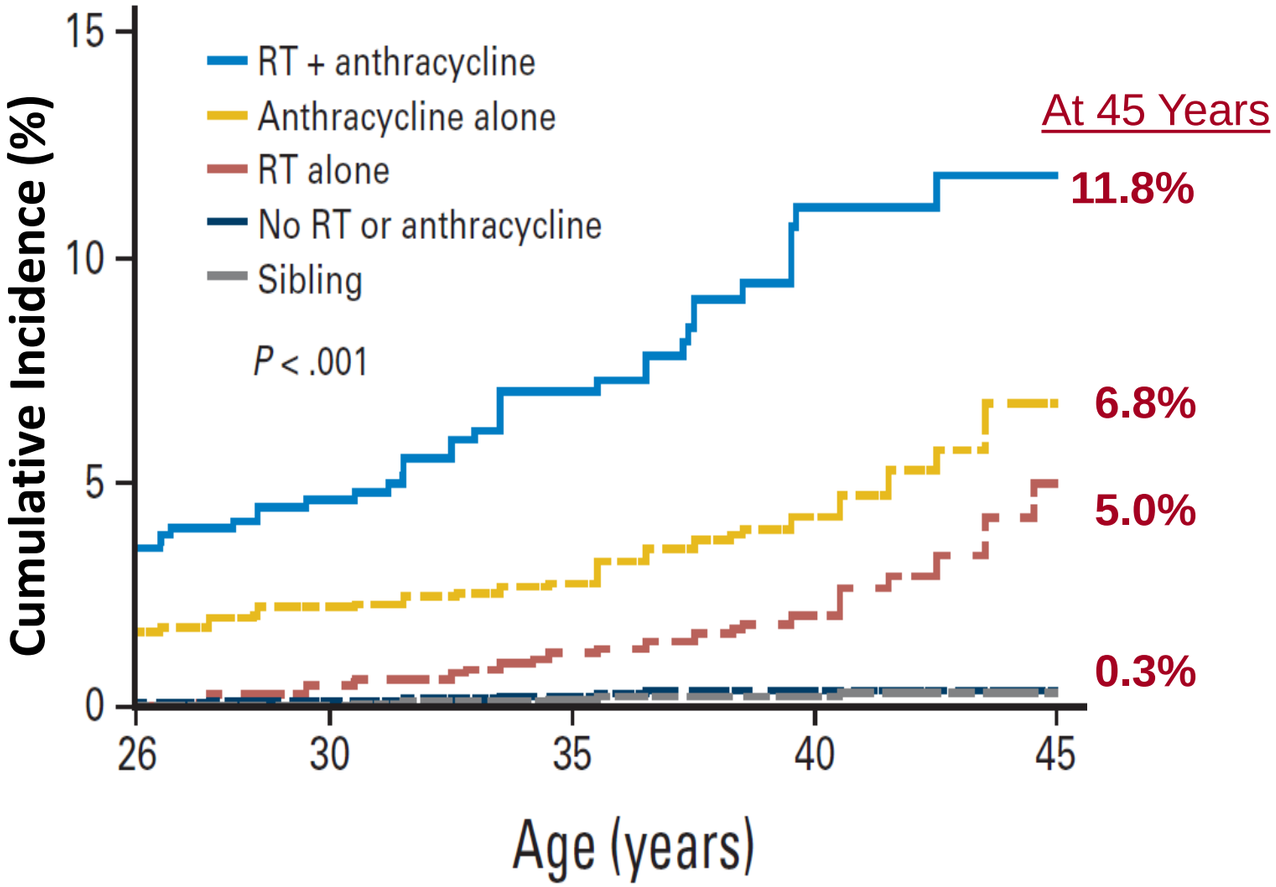
Blanco et al, *J Clin Oncol* 2012. Mulrooney et al, *BMJ* 2009.

Radiation Exposure and Cardiotoxicity

CAD in CCSS Participants



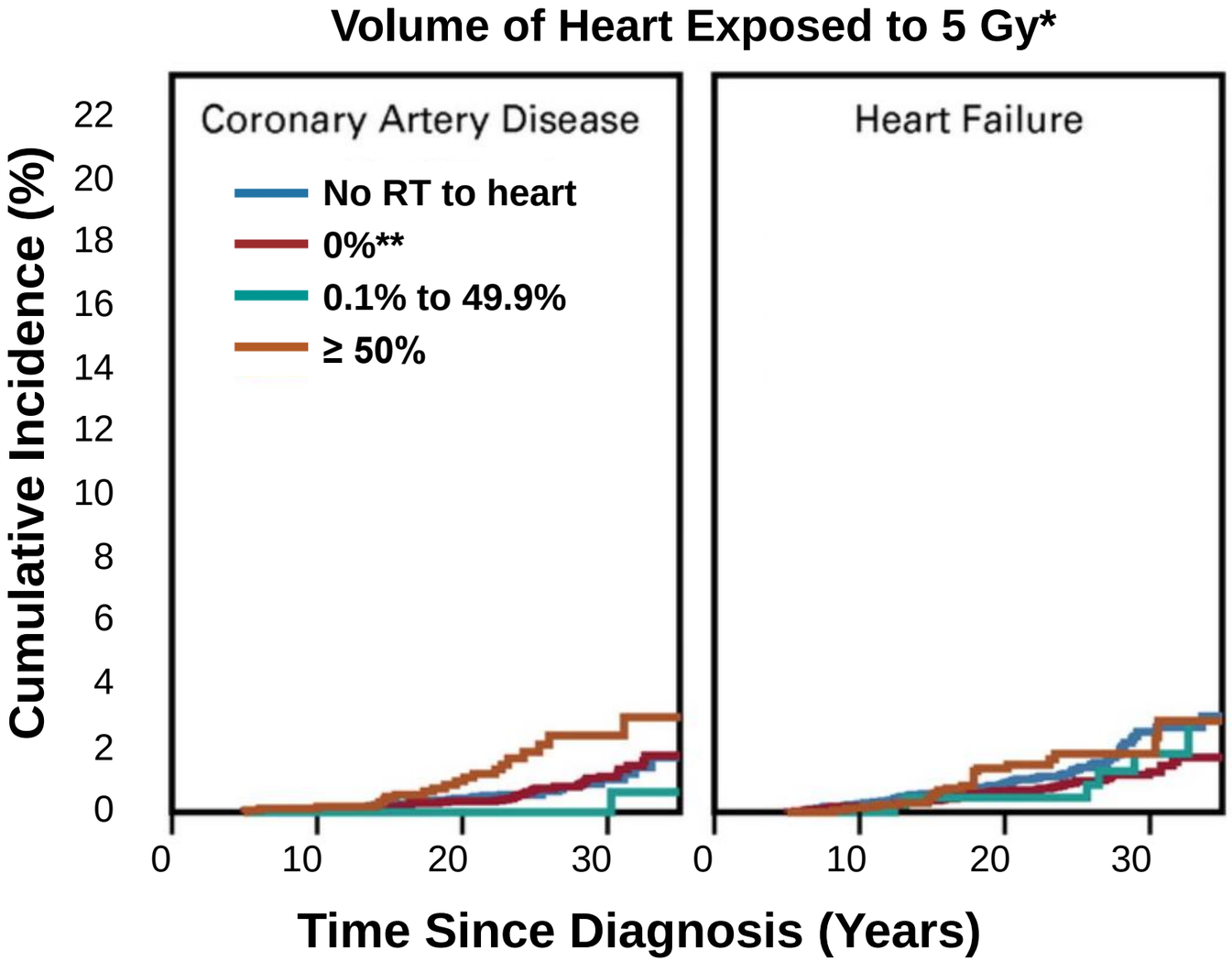
Heart Failure in CCSS Participants



Armstrong, et al. *J Clin Oncol*, 2013.

Dose Response of Radiation-related Cardiotoxicity

CCSS



- Low to moderate doses (5.0 to 19.9 Gy) of radiation to large cardiac volumes (≥ 50% of the heart) were associated with an increased rate of coronary artery disease (RR 2.3, 95% CI 1.3-4.0)

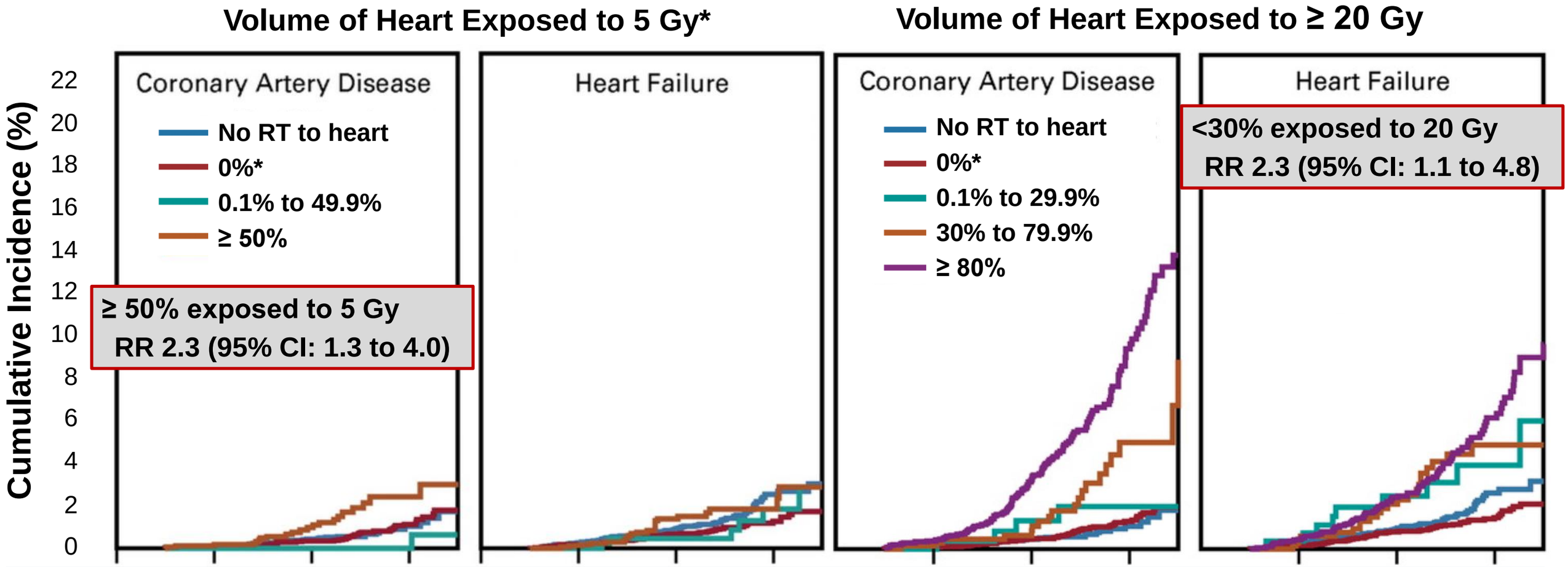
- Multivariable analyses adjusted for demographic factors, smoking, and other treatment including anthracyclines.

Bates, et al. *J Clin Oncol*, 2019.

* - maximum radiation dose to heart <20 Gy (**<5 Gy)

Dose Response of Radiation-related Cardiotoxicity

CCSS



Low dose radiation to a ***large volume*** and **moderate to high dose** radiation to a ***small volume*** were each associated with increase in risk**.**

Bates, et al. *J Clin Oncol*, 2019.

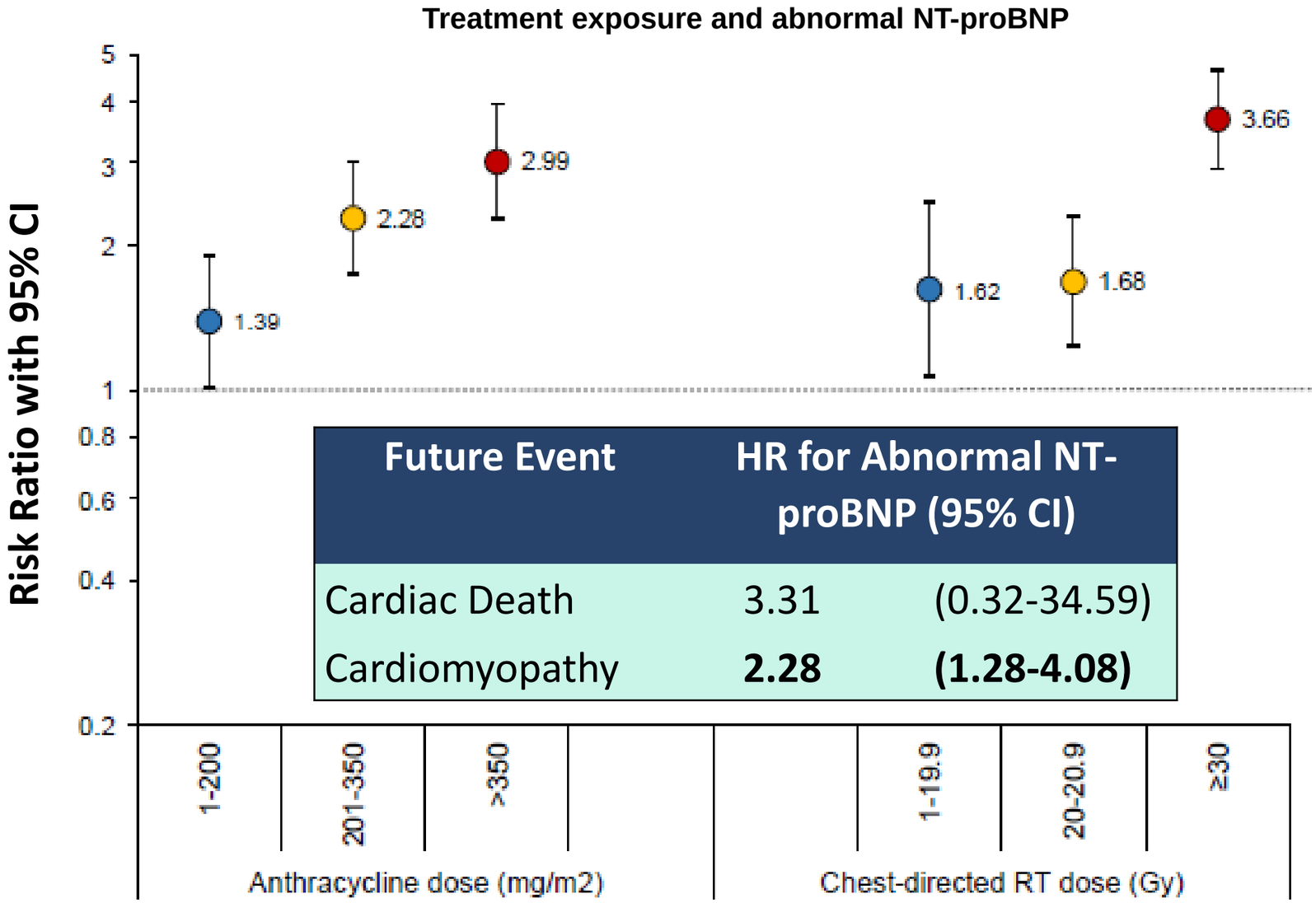
* - maximum radiation dose to heart <20 Gy (**<5 Gy)

Refining Risk using Cardiac Biomarkers

Individually NT-proBNP, BNP or Troponin-T are not adequate to identify cardiomyopathy.

Abnormal NT-proBNP is associated with cardiotoxic therapy exposure in a dose-dependent manner.

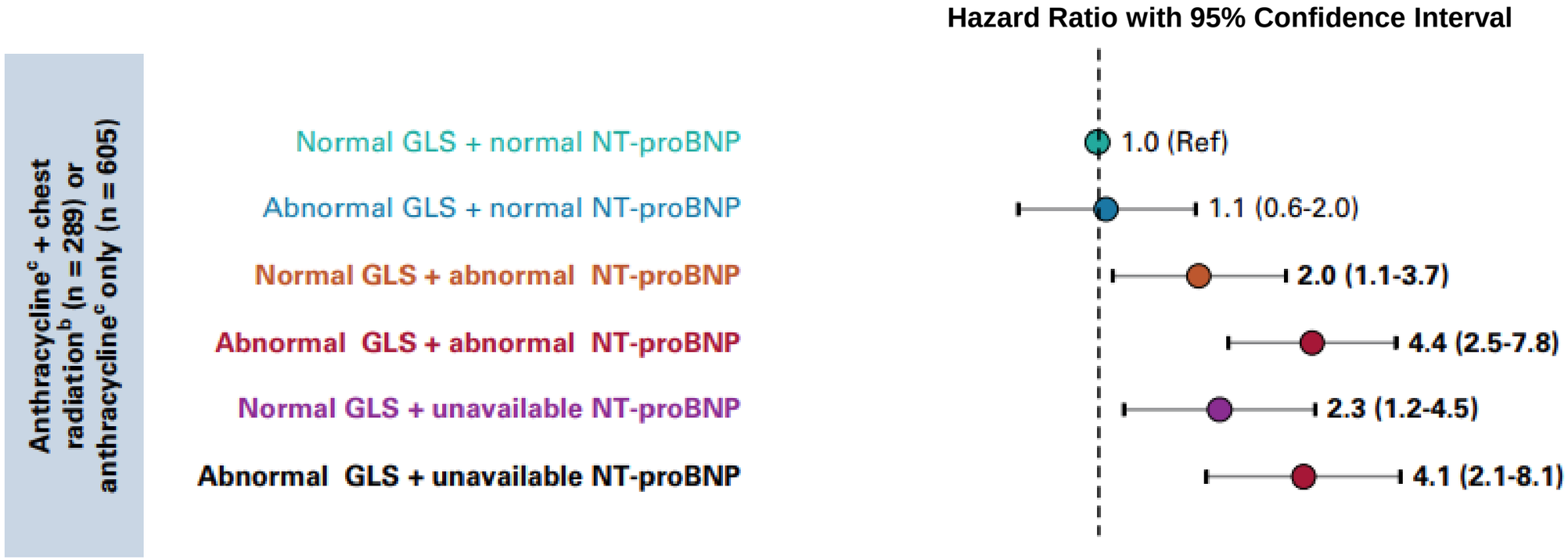
Among survivors with normal LVEF, abnormal NT-proBNP is associated with *future* cardiomyopathy.



Future Event	HR for Abnormal NT-proBNP (95% CI)	
Cardiac Death	3.31	(0.32-34.59)
Cardiomyopathy	**2.28**	**(1.28-4.08)**

Dixon, et al. *Cancer* 2021.

Refining Risk using Echocardiogram and Cardiac Biomarkers



Combination of echocardiogram (using GLS) and NT-proBNP further refines risk.

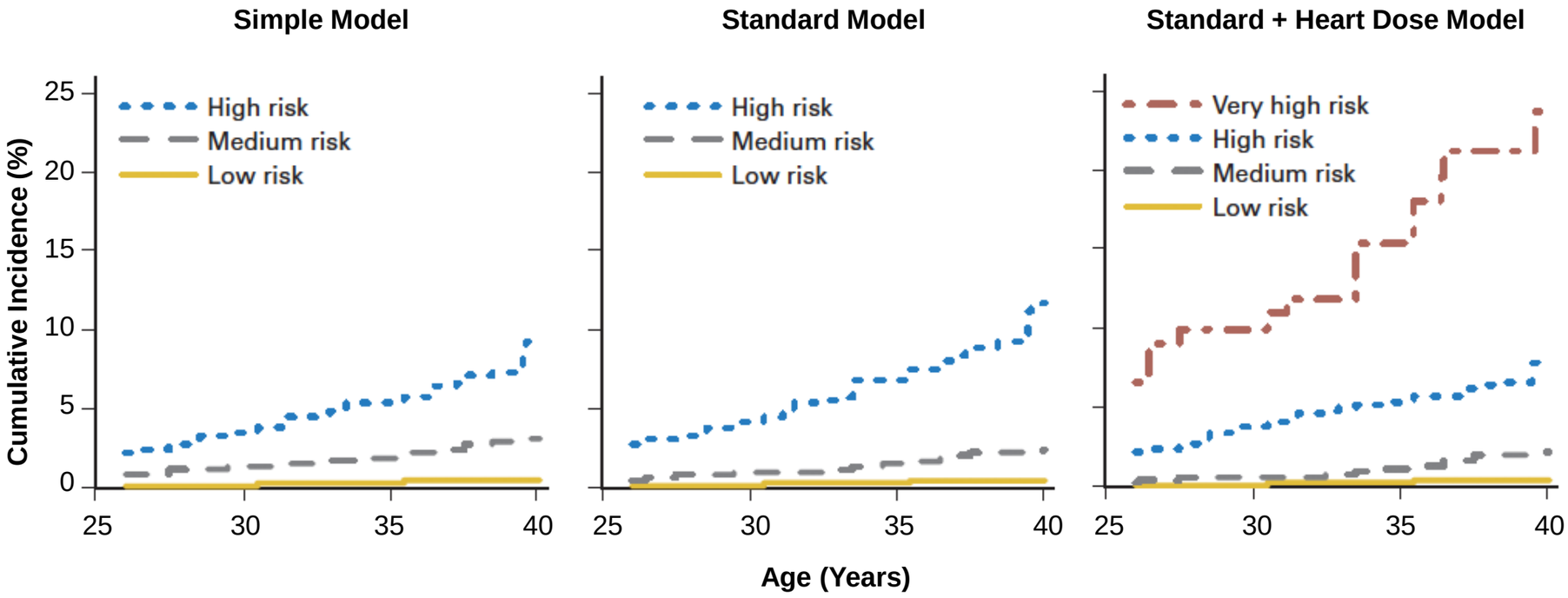
Among survivors in IGHG moderate- to high-risk groups, those with both abnormal NT-proBNP and GLS at baseline had a ***4-fold increase in risk*** of future cardiomyopathy.

Ehrhardt et al. *J Clin Oncol,* 2024.

Risk Prediction in Childhood Cancer Survivors

CCSS

Cumulative Incidence of Heart Failure in Childhood Cancer Survivors



Simple: Anthracycline exposure and chest RT as binary (Yes/No) variable.

Standard: Cumulative doses of anthracycline and chest RT.

Heat Dose: Cumulative dose of anthracycline and cardiac radiation dosimetry.

*All models include sex and age at diagnosis.

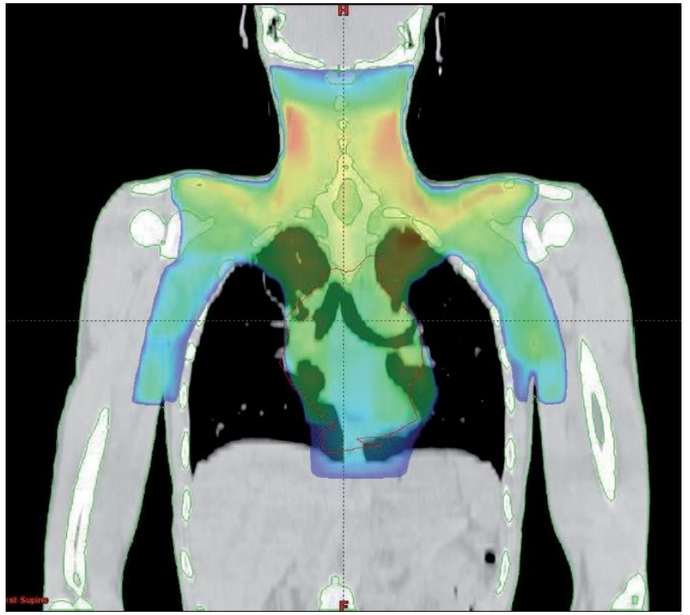
Chow, et al *J Clin Oncol* 2015.

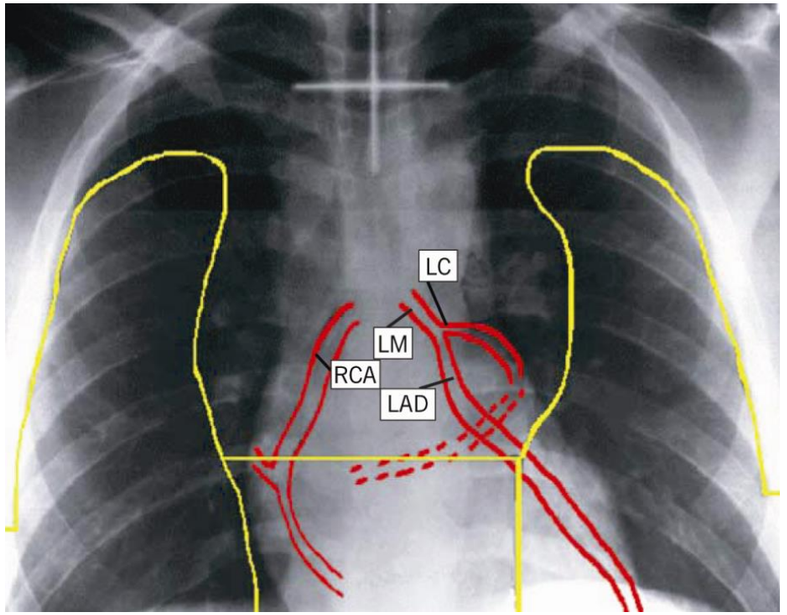
Risk Prediction in Childhood Cancer Survivors

CCSS

40-year-old female Hodgkin survivor exposed to 250 mg/m^2 anthracyclines and 21 Gy chest radiation.

BP 130/80, HDL 50, LDL 100, TG 120
Hgb A1c 5.5%, no smoking history, no current medication use.





American College of Cardiology atherosclerotic cardiovascular disease (ASCVD) risk calculator

10-year risk = 0.7%

http://tools.acc.org/ascvd-risk-estimator-plus

Childhood Cancer Survivor Study Ischemic Heart Disease risk calculator

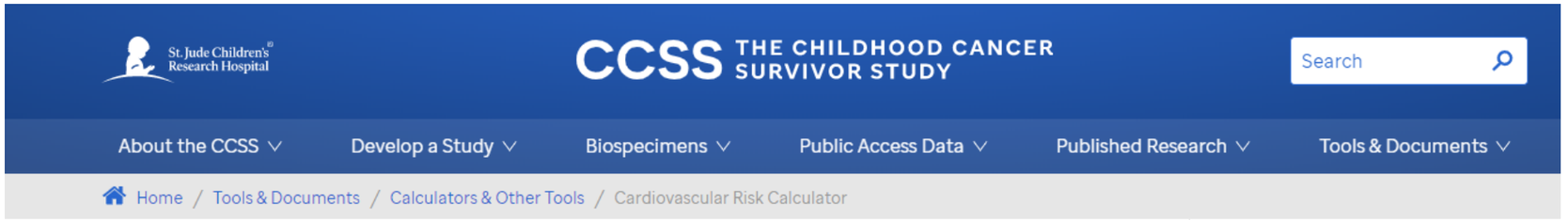
Risk at age 50 = 10.4%

https://ccss.stjude.org/tools-documents/calculators-other-tools/

Chow, et al *J Clin Oncol* 2015. Chen et al., *JNCI* 2020.

Cardiovascular Risk Calculator for Survivors

CCSS



CCSS Cardiovascular Risk Calculator

This risk assessment tool predicts risk of heart failure, ischemic heart disease, and stroke by age 50 among survivors of childhood cancer. It uses information from the CCSS papers, "Individual prediction of heart failure among childhood cancer survivors" (Chow et al., ...) and "Prediction of ischemic heart disease and stroke among childhood cancer survivors" (Chow et al, ...) , which created clinically useful models with readily available demographic and cancer treatment information. These models were designed specifically for patients who have recently completed cancer treatment (5 years from cancer diagnosis). These models have been validated in separate groups of childhood cancer survivors: Emma Children's Hospital and Academic Medical Center (Amsterdam, the Netherlands), the St. Jude Lifetime Cohort Study, and the National Wilms Tumor Study.

Depending on what level of treatment information is available, we created three different prediction models:

- Simple (if anthracycline, alkylator, platinum-agent chemotherapy, and radiation exposures to the brain, neck, and chest are known, but not the doses)
- Standard (if anthracycline and field-specific radiation doses are known)
- Standard+heart (if anthracycline dose and heart-specific radiation dosimetry are known)
- A subsequent analysis based on CCSS data alone (Chen et al.) extended the Standard model to survivors of childhood cancer currently ages 20 to 39 (Standard+Age), and incorporates information on diabetes, dyslipidemia, and hypertension status.

To determine one's risk of cardiovascular disease using these models, please enter the information below **(All fields are Required)**:

Related Information

Acute Ovarian Failure Risk Prediction Calculator

Breast Cancer Probability Calculator

Kidney Failure Calculator

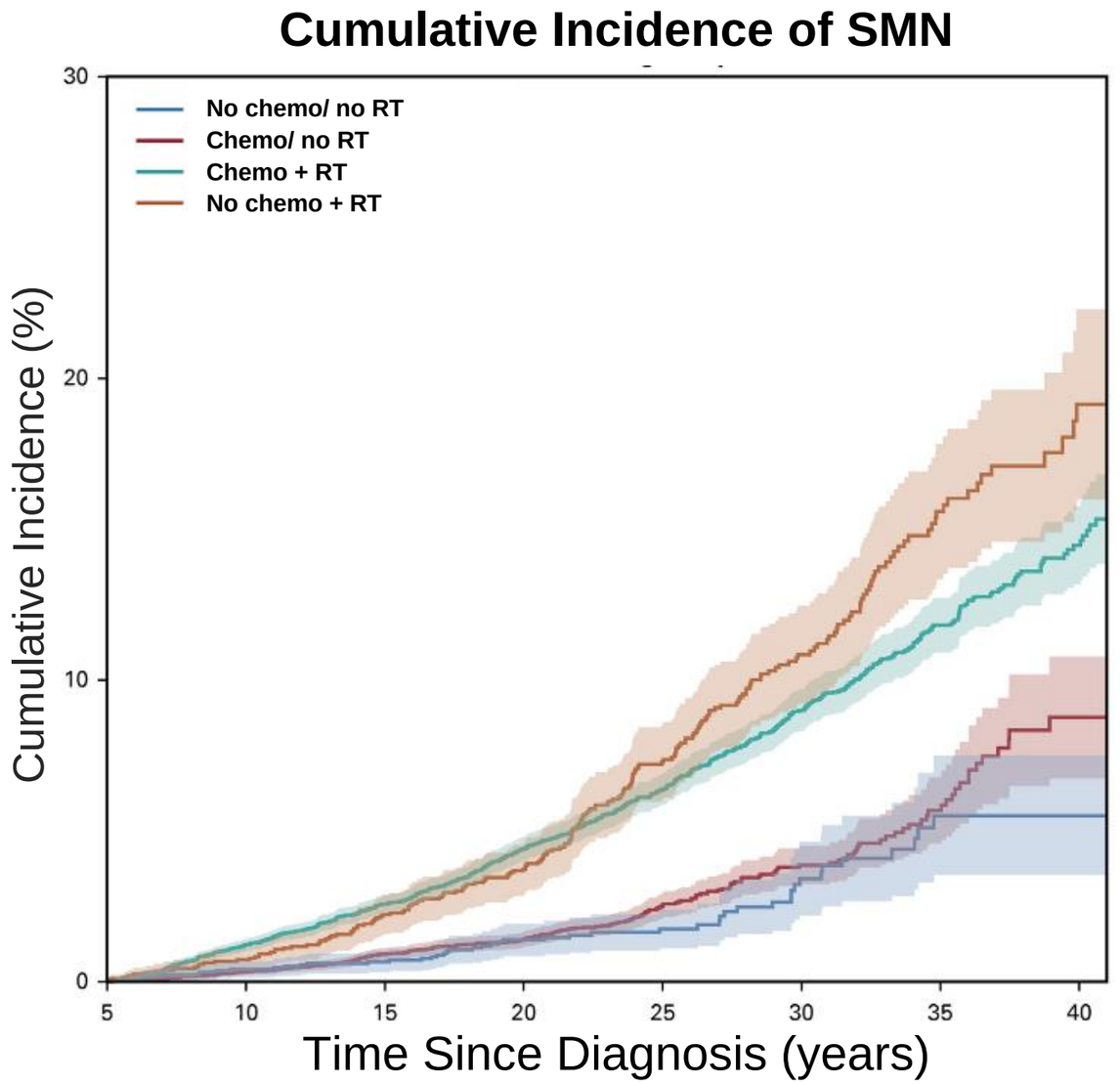
Risk Calculator
ccss.stjude.org

Chow, et al *J Clin Oncol* 2015. Chen et al., *JNCI* 2020.

Second Malignant Neoplasms in Survivors

CCSS

- Second malignant neoplasms are the most frequent cause of late-mortality in long-term survivors.
- Even decades after cancer, survivors have a 4-fold increase in risk for SMN after age 40.
- Breast, thyroid, melanoma and soft-tissue sarcomas are among the most common second malignancies.

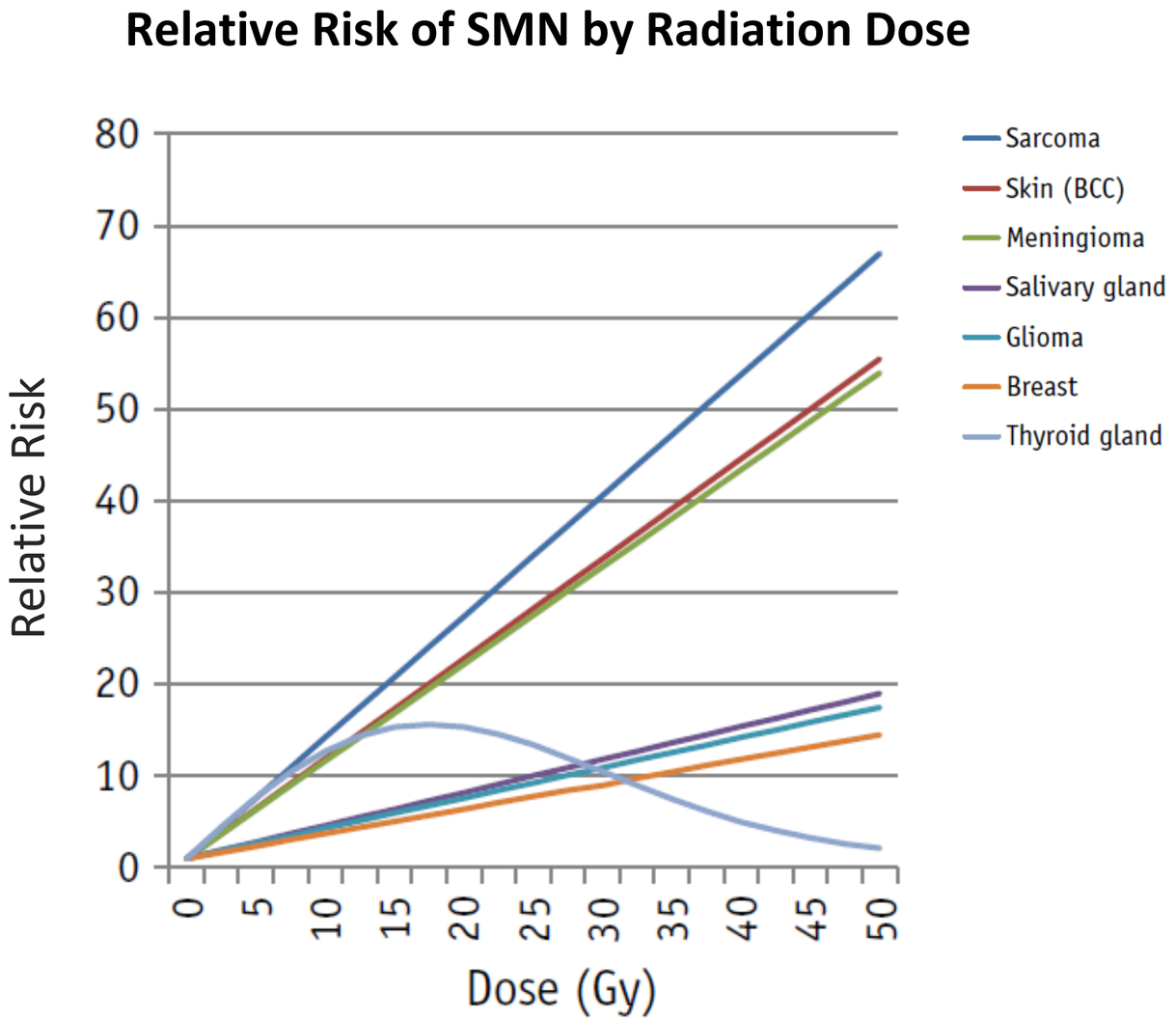


Turcotte, et al. *J Clin Oncol*, 2018. Turcotte, et al. *J Clin Oncol,* 2019.

Radiation Exposure and Second Malignancy

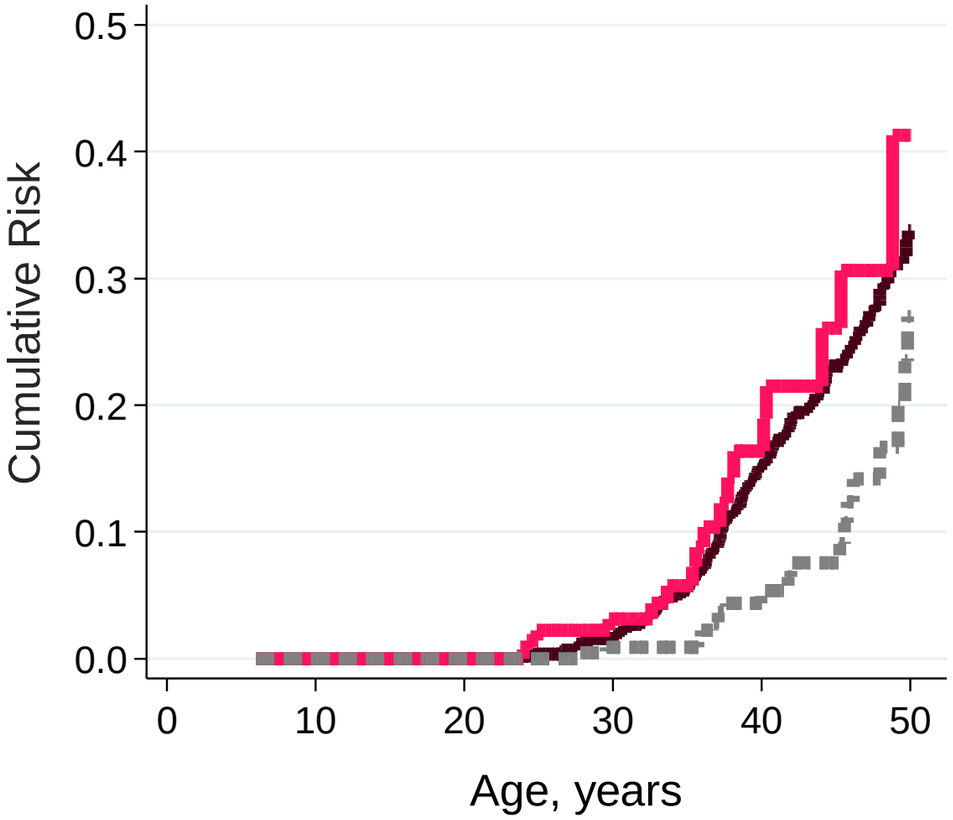
CCSS

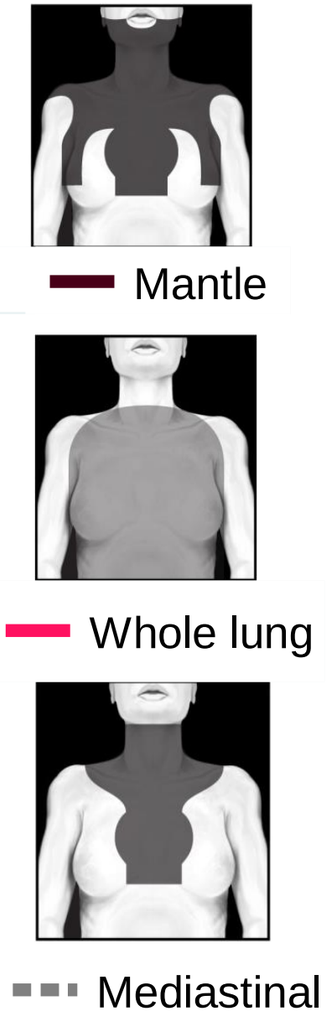
- Risk of SMN increases with increasing dose of radiation.
- For many SMNs, as radiation doses increase beyond 20-30 Gy, risk is 10 to 50 times that of general population.
- Exception is secondary thyroid cancer.



Inskip et al, *Int J Radiation Oncol Biol Phys,* 2016.

Radiation Exposure and Second Malignancy





Moskowitz et al, *J Clin Oncol* 2014. Inskip et al, *J Clin Oncol* 2009.

Anthracycline Chemotherapy and Subsequent Malignancy

- CCSS: Nested case/control, 271 women with subsequent breast cancer
- Odds ratio for breast cancer increased with cumulative anthracycline dose:
  OR per 100mg/m^2 = 1.23 (95% CI 1.09-1.3)

Breast RT Dose	Anthracyclines	
	No	Yes
	OR (95% CI)	OR (95% CI)
0 - <1Gy	1.0	1.0
1 - <10Gy	2.1 (0.9-4.8)	**3.7 (1.4-10.3)**
10+ Gy	**9.6 (4.4-20.7)**	**19.1 (7.6-48.0)**

Veiga LH, Berrington A., et al, ***JAMA Pediatr***, 2020

- SJLIFE: Anthracycline risk is **independent of genetic predisposition** for breast cancer

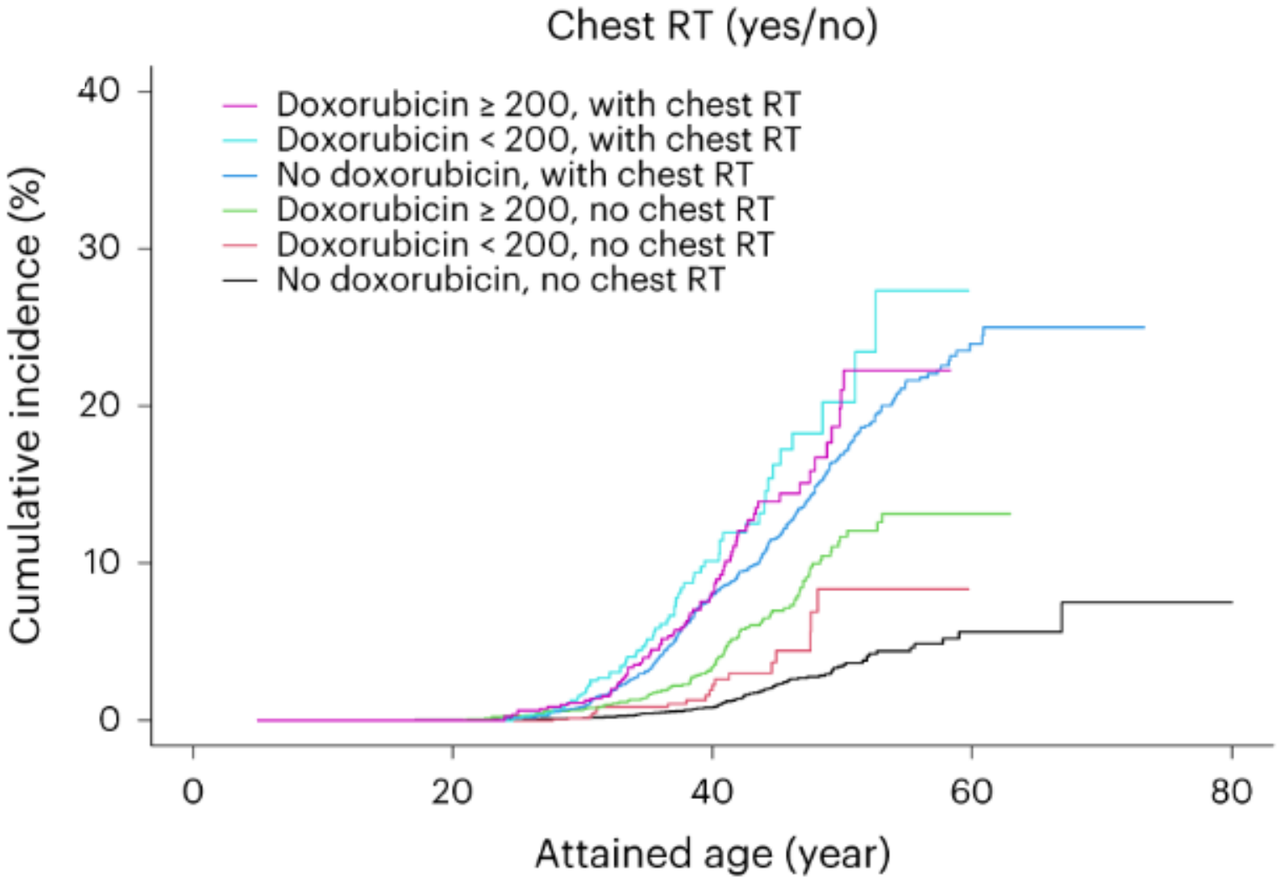
Ehrhardt M et al., ***J Clin Oncol,*** 2019

Anthracycline chemotherapy increases risk for breast cancer.

Anthracycline Chemotherapy and Subsequent Malignancy

- Pooled 17,943 female survivors from six international cohorts

- A dose-dependent risk for doxorubicin:
  - 24% increase in risk of subsequent breast cancer per 100 mg/m^2 (HR 1.24, 95% CI 1.18–1.31)
  - ≥200 mg/m^2 cumulative doxorubicin dose versus no doxorubicin (HR: 2.50 for 200–299 mg/m^2)

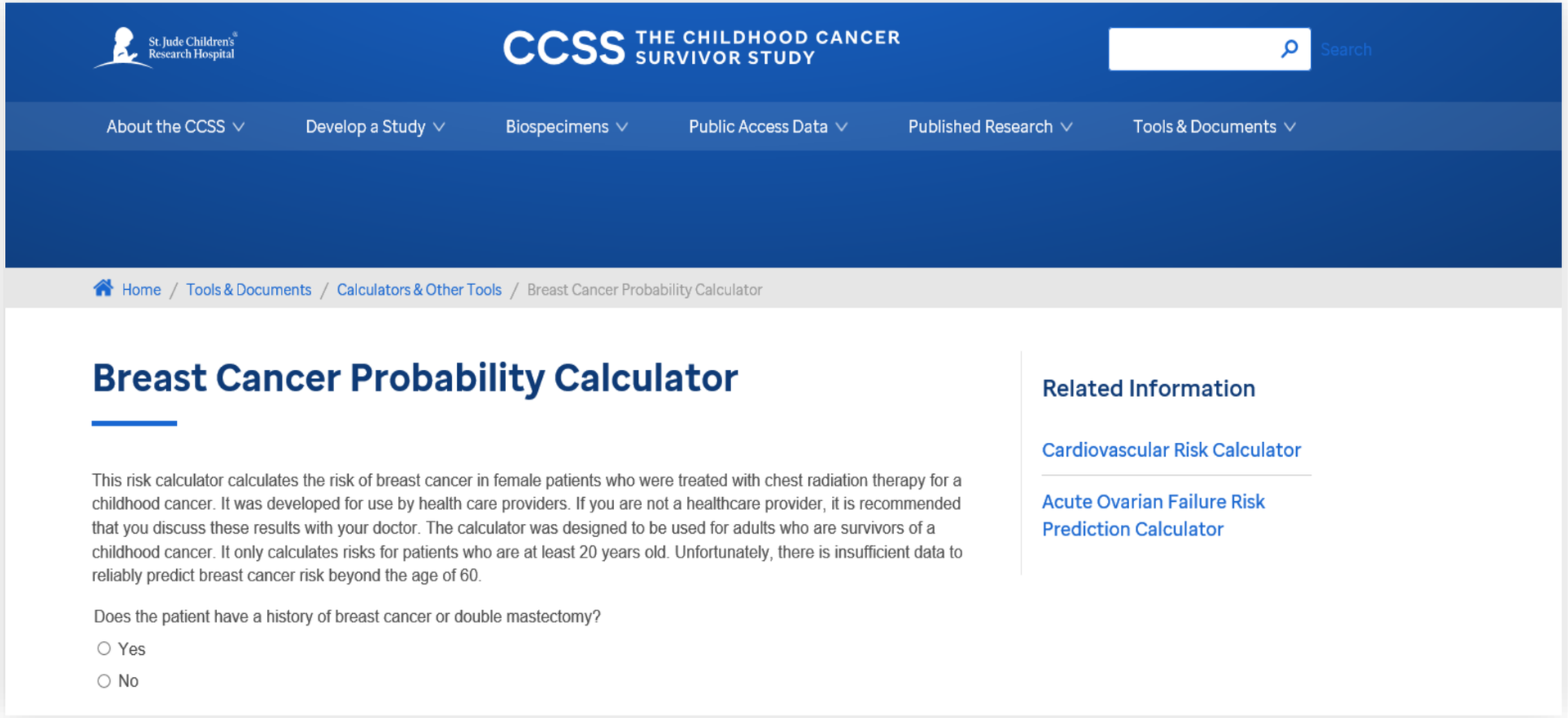


Early initiation of breast cancer surveillance may be reasonable in female survivors exposed to ≥200 mg/m2 cumulative doxorubicin dose.

Wang et al., *Nature Medicine*, 2023.

Breast Cancer Risk Prediction Calculator

CCSS



Risk Calculator
ccss.stjude.org

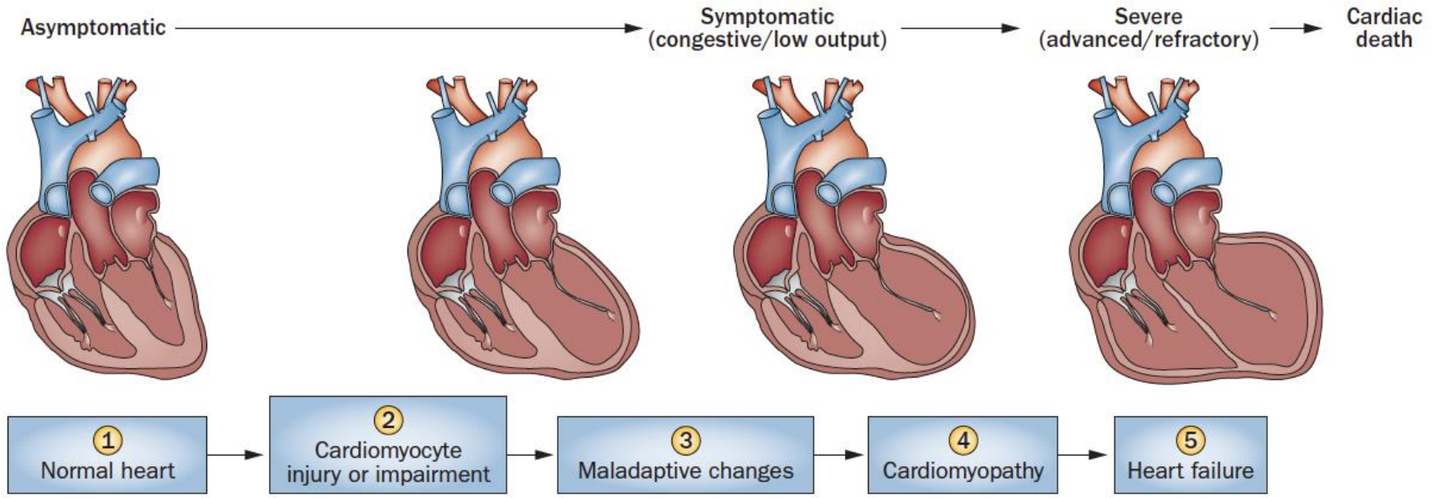
Moskowitz CS et al, J Clin Onc 2021

Case

A 40-year-old young woman with a history of Hodgkin lymphoma whose treatment included doxorubicin (250 mg/m^2) followed by 21 Gy mediastinal radiation at age 16 is being seen today in your clinic. She has not received regular follow-up and was last seen at age 35.

- What screening is recommended?

Prevention of Excess Death and Disability in Survivors



	PRIMORDIAL Prevention	PRIMARY Prevention	SECONDARY Prevention	TERTIARY Prevention
Definition [a]	An intervention aiming to prevent the development of disease risk factors	An intervention implemented before evidence of disease/injury	An intervention implemented after disease onset, but asymptomatic	An intervention implemented after established disease
Intent [a]	Eliminate causative risk factors (risk avoidance)	Mitigate causative risk factors (risk reduction)	Early identification (screening) and treatment	Prevent progression/sequelae
Cardiac Example [b]	**Risk-adapted therapy to *eliminate* radiation**	**Risk-adapted therapy to *decrease* anthracycline doses**	**Screening echos for asymptomatic left ventricular dysfunction or mammography/breast MRI for early breast cancer**	**Treat cardiomyopathy with ACE-I's and/or β-blockers Early stage breast cancer treatment**

[a] Adapted from Centers for Disease Control and Prevention: A Framework for Assessing the Effectiveness of Disease and Injury Prevention. MMWR. 1992;41(RR-3):001.

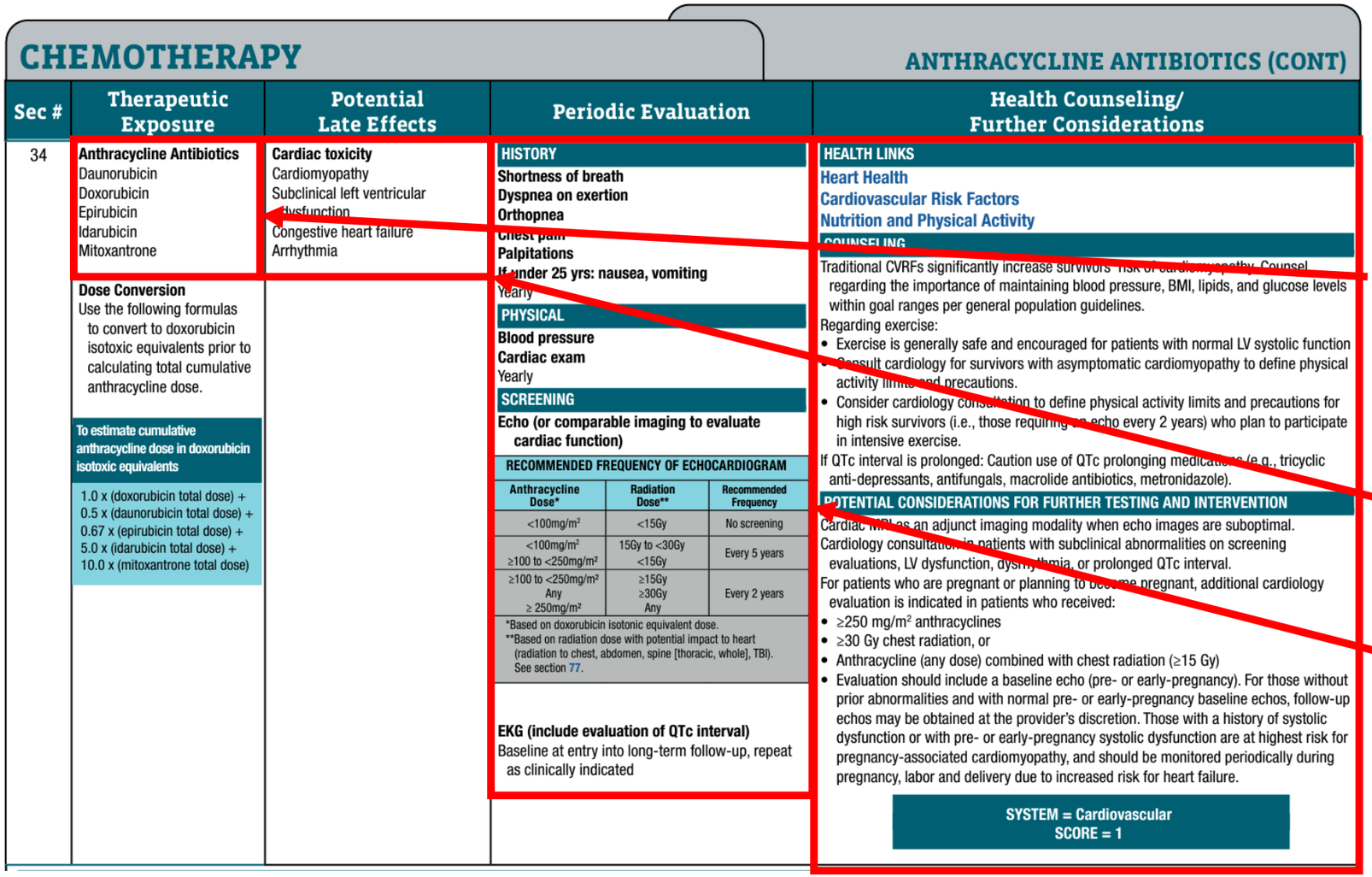
[b] Adapted from Armenian and Ehrhardt, *J Clin Oncol* 2018

Children's Oncology Group Long-Term Follow-up Guidelines

- survivorshipguidelines.org
- Updated every 5 years.
- Comprehensive literature search and grading of evidence.
- Consensus based recommendations – hybrid of evidence and expert opinion.

Landier et al, *J Clin Oncol* 2004.

Children's Oncology Group Long-Term Follow-up Guidelines



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
34	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: nausea, vomiting** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **Echo (or comparable imaging to evaluate cardiac function)**	**HEALTH LINKS** Heart Health Cardiovascular Risk Factors Nutrition and Physical Activity **COUNSELING** Traditional CVRFs significantly increase survivors' risk of cardiomyopathy. Counsel regarding the importance of maintaining blood pressure, BMI, lipids, and glucose levels within goal ranges per general population guidelines. Regarding exercise: • Exercise is generally safe and encouraged for patients with normal LV systolic function • Consult cardiology for survivors with asymptomatic cardiomyopathy to define physical activity limits and precautions. • Consider cardiology consultation to define physical activity limits and precautions for high risk survivors (i.e., those requiring an echo every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution use of QTc prolonging medications (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echo images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, LV dysfunction, dysrhythmia, or prolonged QTc interval. For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: • ≥250 mg/m² anthracyclines • ≥30 Gy chest radiation, or • Anthracycline (any dose) combined with chest radiation (≥15 Gy) • Evaluation should include a baseline echo (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echos, follow-up echos may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy, and should be monitored periodically during pregnancy, labor and delivery due to increased risk for heart failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Dose Conversion
Use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose.

To estimate cumulative anthracycline dose in doxorubicin isotoxic equivalents

1.0 x (doxorubicin total dose) +
0.5 x (daunorubicin total dose) +
0.67 x (epirubicin total dose) +
5.0 x (idarubicin total dose) +
10.0 x (mitoxantrone total dose)

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
<100mg/m²	<15Gy	No screening
<100mg/m² ≥100 to <250mg/m²	15Gy to <30Gy <15Gy	Every 5 years
≥100 to <250mg/m² Any ≥ 250mg/m²	≥15Gy ≥30Gy Any	Every 2 years

*Based on doxorubicin isotonic equivalent dose.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 77.

EKG (include evaluation of QTc interval)
Baseline at entry into long-term follow-up, repeat as clinically indicated

- Organized around risk-based exposure and appropriate follow-up care.
- Exposure specific sections can be found, with corresponding agents listed.
- Pertinent late effects are individually listed.
- Suggested evaluations are outlined pertinent to the exposure and degree of risk.
- Other considerations and the level of evidence are given.

Guideline Harmonization Across Groups

St. Jude Children's Research Hospital

Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies

PanCareSurFup

CHILDREN'S ONCOLOGY GROUP *Foundation*

International Guideline Harmonization Group for Late Effects of Childhood Cancer

Children's Cancer and Leukaemia Group

Working together to beat childhood cancer

DCOG LATER

Longterm effects after childhood cancer

SIGN

Scottish Intercollegiate Guidelines Network

Cardiomyopathy Monitoring Recommendations

International Guideline Harmonization Group Risk Groups and Surveillance Recommendations

Risk	Anthracycline (mg/m^2)	Chest RT (Gy)	Anthracycline (mg/m^2) + chest RT (Gy)	Is screening recommended?	Interval
High	≥ 250	≥ 30	≥ 100 and ≥ 15	Yes	2 years
Moderate	100 to < 250	15 to < 30	–	Maybe	5 years
Low	> 0 to < 100	> 0 to < 15	–	No	No screening

*Beginning no later than 2 years after completion of therapy

Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent , and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Ehrhardt et al., *Lancet Oncol* 2023.

Breast Cancer Screening Recommendations

International Guideline Harmonization Group Risk Groups and Surveillance Recommendations

Exposure	Dose	Is screening recommended?	Interval	Modality	Initiation
Chest RT (Gy)	≥ 10	Yes	Annually	Mammography and breast MRI	Age 25 or 8 years from RT, whichever comes last
Chest RT (Gy) **Abdominal RT exposing breast**	<10 Gy --	Maybe Shared Decision			
Anthracycline*	≥ 250 (200)	No			

*Inconsistent/inadequate evidence at the time of recommendation.

Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group

Mulder et al., *J Clin Oncol* 2020.

IGHG Publications for Late-Effects Screening

- Methodology (*Pediatr Blood Cancer* 2013)
- Breast cancer (*Lancet Oncol* 2013, *J Clin Oncol* 2020)
- Cardiomyopathy (*Lancet Onc*ol 2015, 2023)
- Dexrazoxane Cardioprotection (*Lancet Child & Adolescent Health* 2022*)*
- Premature ovarian insufficiency (*J Clin Oncol* 2016)
- Fertility preservation (*Cancer* 2016)
- Male gonadotoxicity *(Lancet Oncol 2017)*
- Thyroid cancer *(Cancer Treat Rev 2018)*
- Ototoxicity *(Lancet Oncol* 2019)
- Meningioma surveillance (*J Neuro-Oncol* 2020)
- Cancer-related fatigue (*J Cancer Surviv* 2020)
- Obstetrical care (*Am J Obstet Gynecol* 2020)
- Fertility preservation series (female, male, ethics) (*Lancet Oncol* 2021)
- Meningioma (*Lancet Oncol* 2021)
- Coronary artery disease (*Eur J Cancer* 2021)
- Bone mineral density (*Lancet Diabetes Endocrinol* 2021)
- Hepatotoxicity (*Cancer Treat Rev* 2021)
- Education/employment (*Cancer* 2022)
- Pituitary deficiencies (*Endocrine Reviews* 2022)
- COVID-19 survivorship statement (*Pediatr Blood Cancer* 2020)
- Mental health *(Lancet Oncol* 2022)

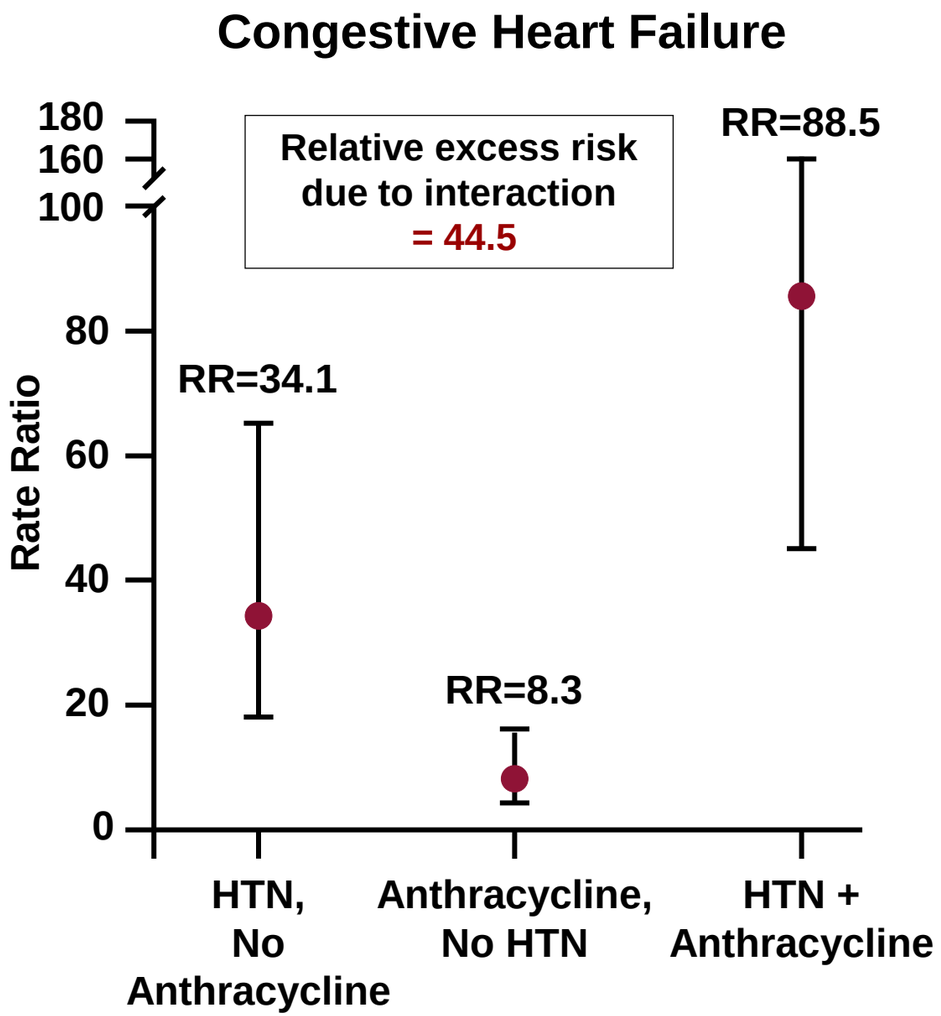
Case

A 40-year-old young woman with a history of Hodgkin lymphoma whose treatment included doxorubicin (250 mg/m^2) followed by 21 Gy mediastinal radiation at age 16 is being seen today in your clinic. She has not received regular follow-up and was last seen at age 35.

- How is that impacted by lifestyle factors and comorbid conditions?

Cardiotoxicity and Modifiable Risk Factors

CCSS



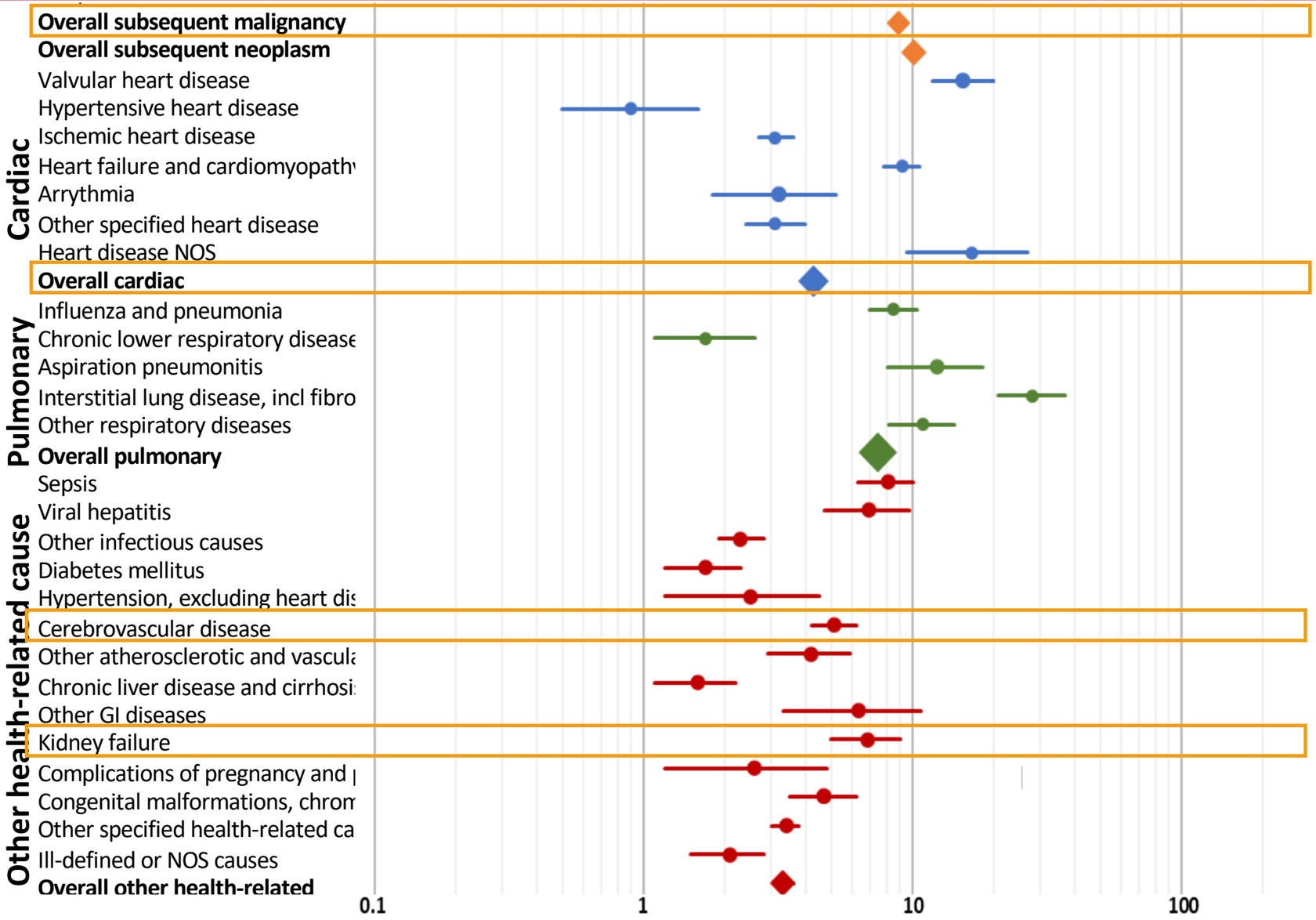
- Among survivors exposed to cardiotoxic therapy, modifiable cardiovascular risk factors are associated with an increased risk of major cardiac events.

- Similar effects were seen for CAD and valvular heart disease among those exposed to chest radiation.

Armstrong, et al. *J Clin Oncol*, 2013.

Discrete Causes of Excess Death in Survivors

CCSS



What is the impact of potentially modifiable risk factors including health behaviors in this population with cancer treatment exposure?

Potentially Modifiable Risk Factors

CCSS

Lifestyle factors

- Smoking status
- Alcohol use
- Physical activity
- Obese/underweight

Traditional Cardiovascular Risk Factors (CVRFs)

- Hypertension
- Diabetes
- Dyslipidemia

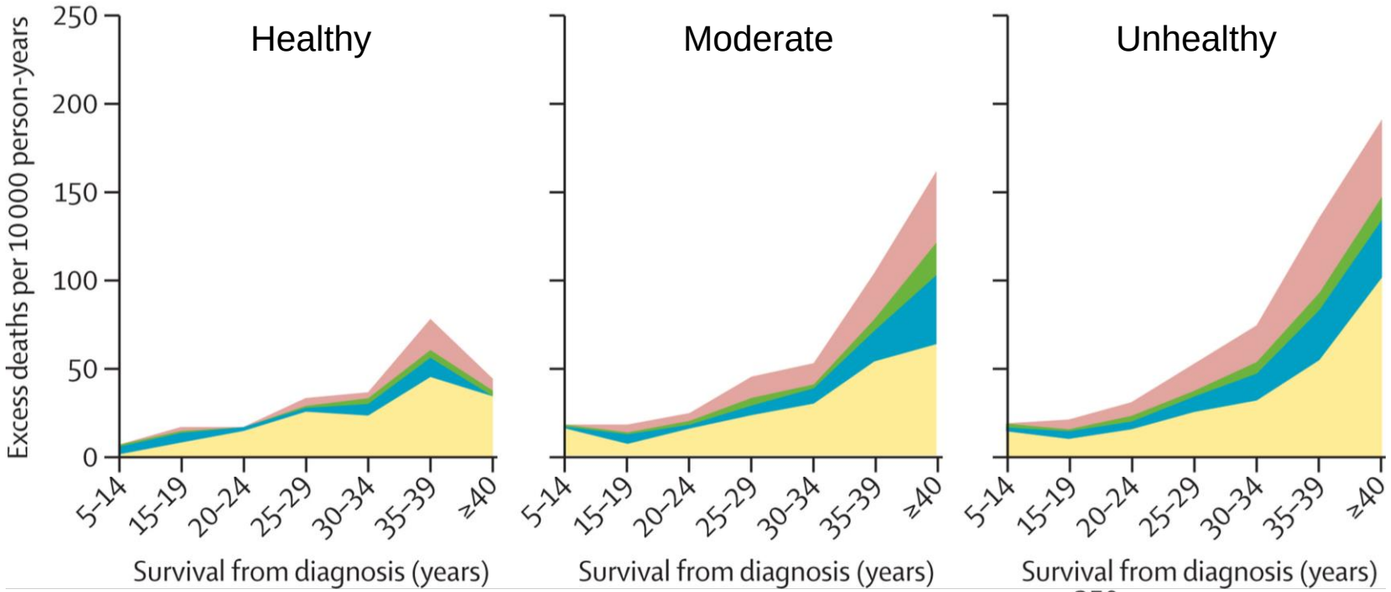
Lifestyle factors assessed at each time-point, assigned a score 0 (unhealthy) or 1 (healthy) and summed to create a total lifestyle score (0-4), categorized below

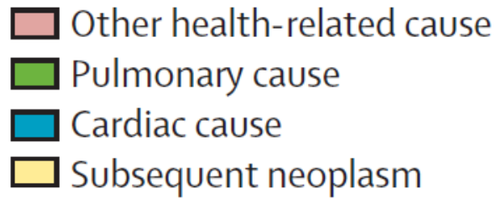
Modifiable lifestyle category	Score range
Unhealthy	0 – 2.0
Moderately healthy	2.5 – 3.0
Healthy	3.5 – 4.0

Dixon et al, *Lancet* 2023.

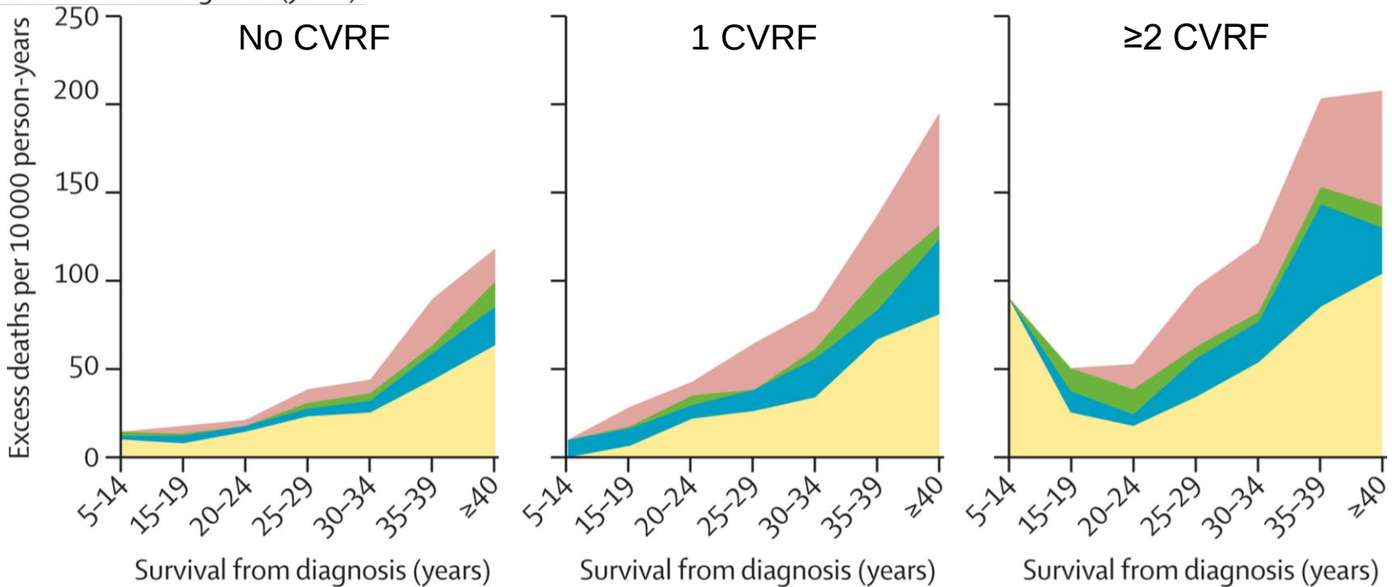
Excess Death in Survivors of Childhood Cancer

CCSS





Unhealthy lifestyle and presence of hypertension or diabetes were each associated with a **20-40% increase** in risk of health-related mortality, independent of prior cancer treatment.

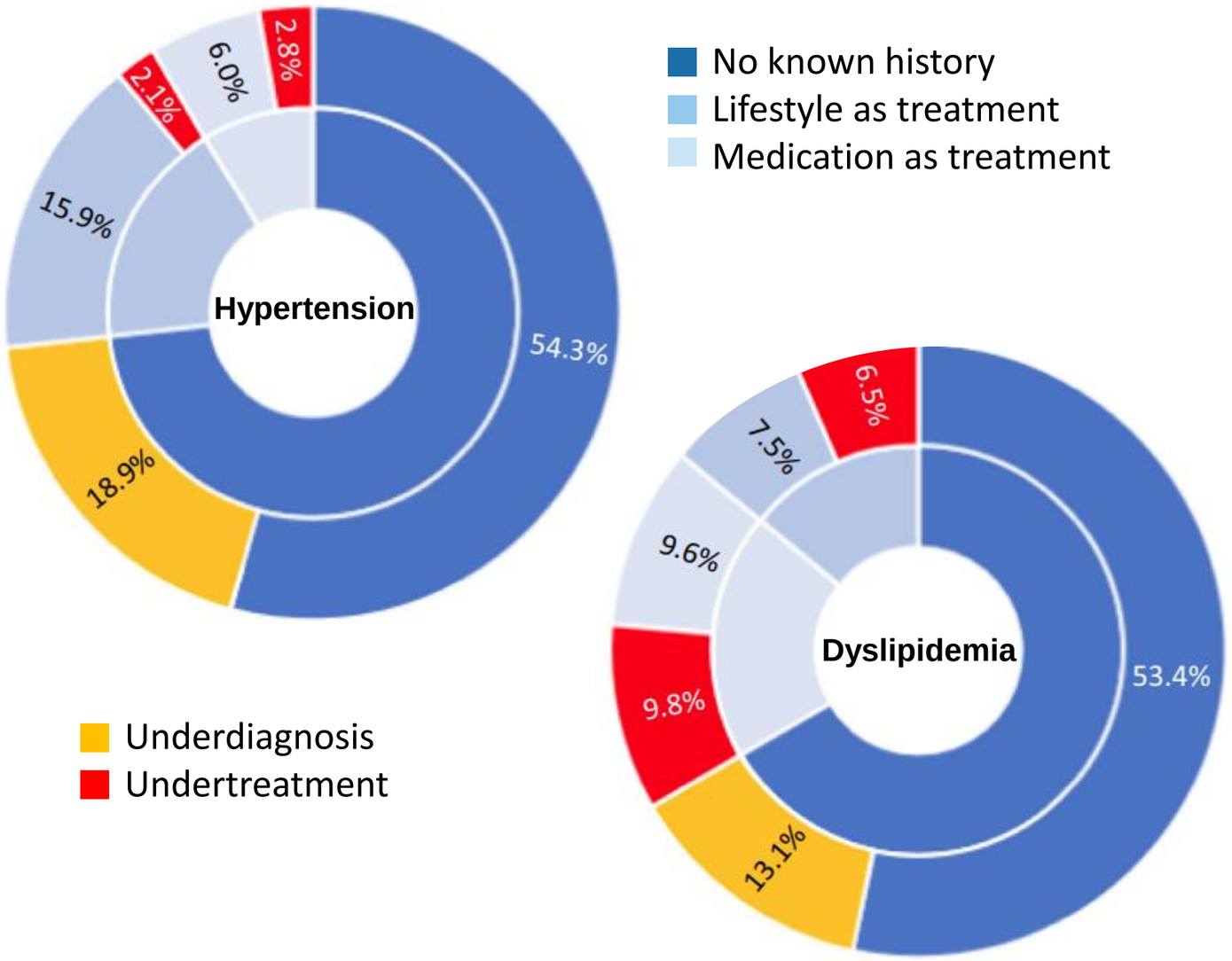


Dixon et al, *Lancet* 2023.

Underdiagnosis and Undertreatment of Risk Factors

CCSS

- Over 500 survivors evaluated for hypertension, dyslipidemia and diabetes or prediabetes.
- 1 in 4 survivors had an undiagnosed condition.
- 1 in 5 survivors had a known condition that was undertreated.

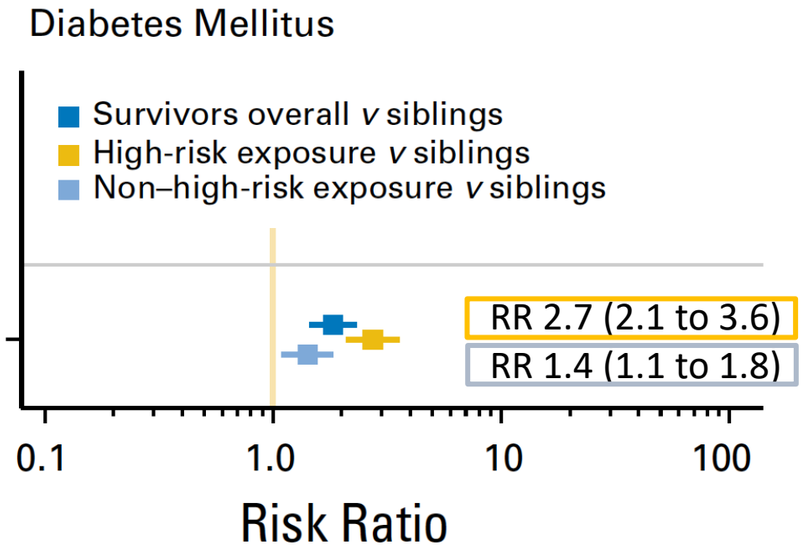


Chow, et al *JAHA* 2022.

Prediabetes as a Modifiable Risk Factor

Survivors have twice the risk of diabetes, and a younger age of onset, compared to siblings.

Prediabetes is a well-defined state of impaired glucose homeostasis that confers an increased risk for diabetes.

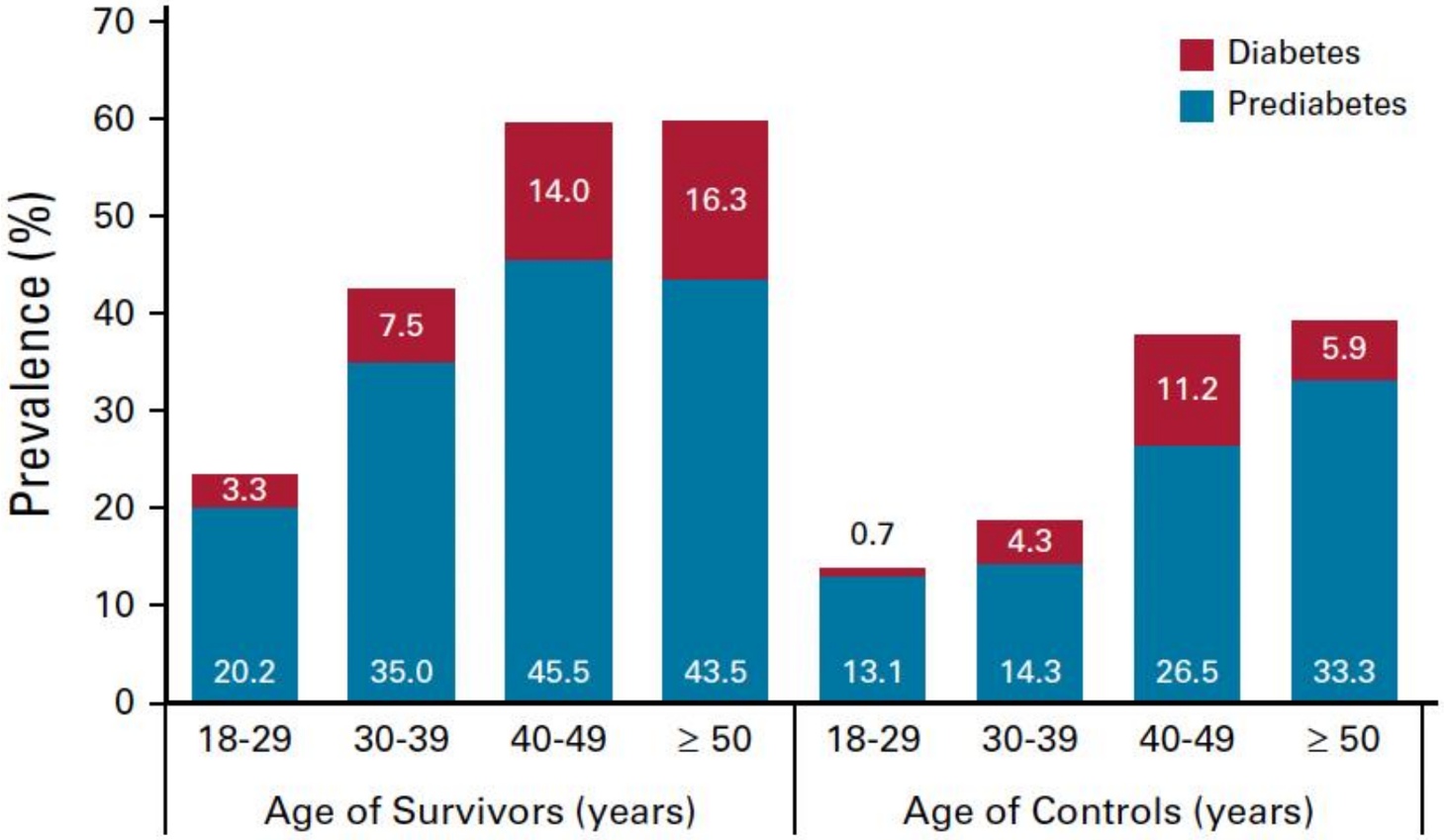


Laboratory Test	Prediabetes Range
Fasting Plasma Glucose	100 – 125 mg/dL
Hemoglobin A1c	5.7% – 6.4%

Gap: Unknown prevalence of prediabetes and associated risk for health outcomes in survivors.

Meacham. *Arch Int Med,* 2009 169:1381-8. Mostoufi-Moab. *J Clin Oncol*, 2016 34:3240-7. Friedman. *JNCI J Natl Cancer Inst,* 2020;112(5). de Vathaire. *Lancet Oncol*, 2012;13(10):1002-1010.

Prediabetes and Diabetes by Age



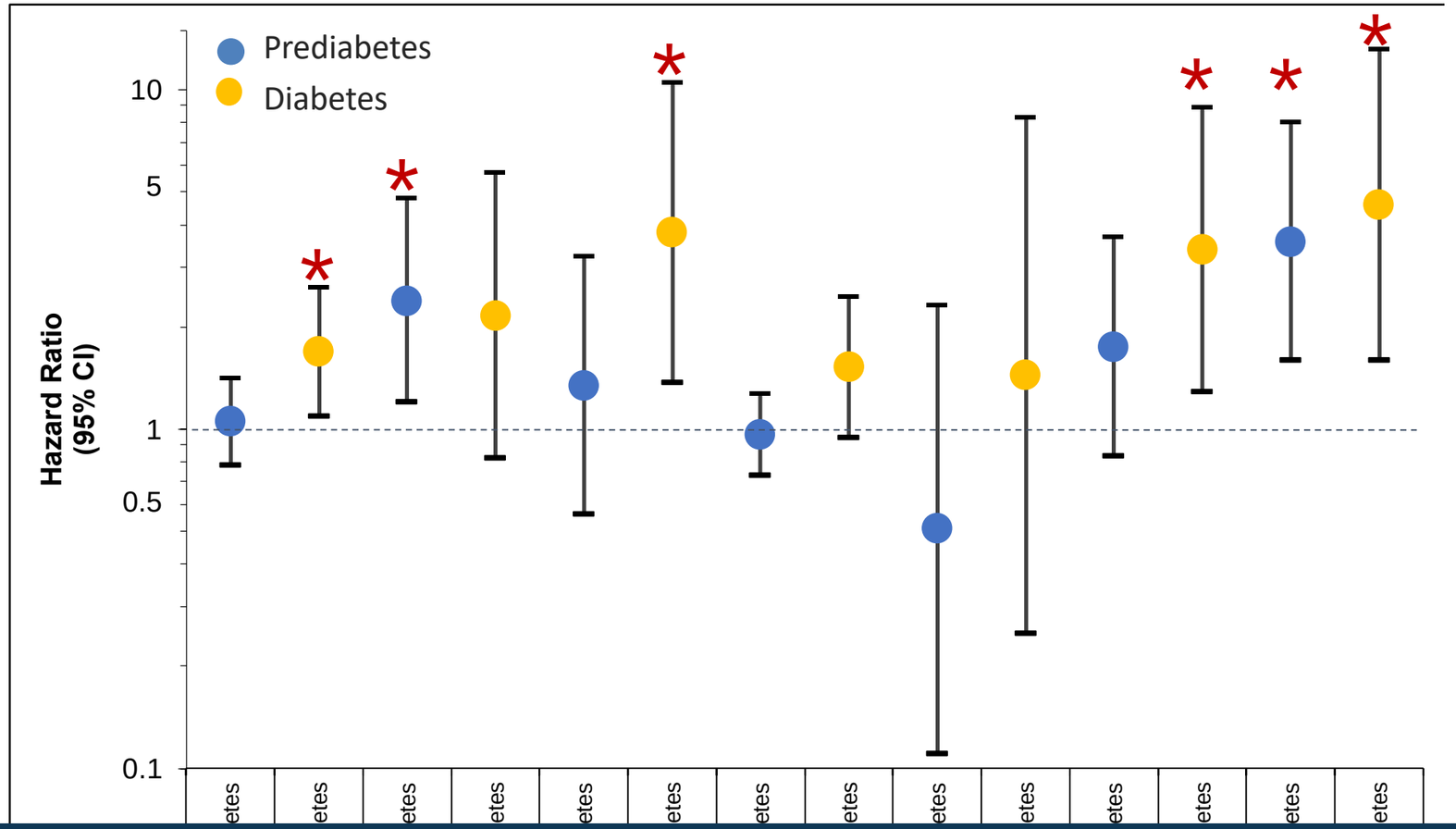
Prediabetes was assessed by laboratory values among SJLIFE participants.

The prevalence of prediabetes was significantly higher among survivors than controls at all ages.

More than 1/3 of survivors over the age of 30 years who were assessed had prediabetes.

Dixon, et al. *J Clin Oncol*, 2024.

Risk of Future Comorbidities by Diabetes Status



All models adjusted for age at evaluation, sex, race/ethnicity and BMI-category.

Added adjustment for each condition included relevant treatment exposure and modifiable cardiovascular risk factors (hypertension and/or dyslipidemia).

Prediabetes is a prevalent and potentially modifiable risk factor for cardiovascular and renal morbidity in survivors and may be a target for intervention.

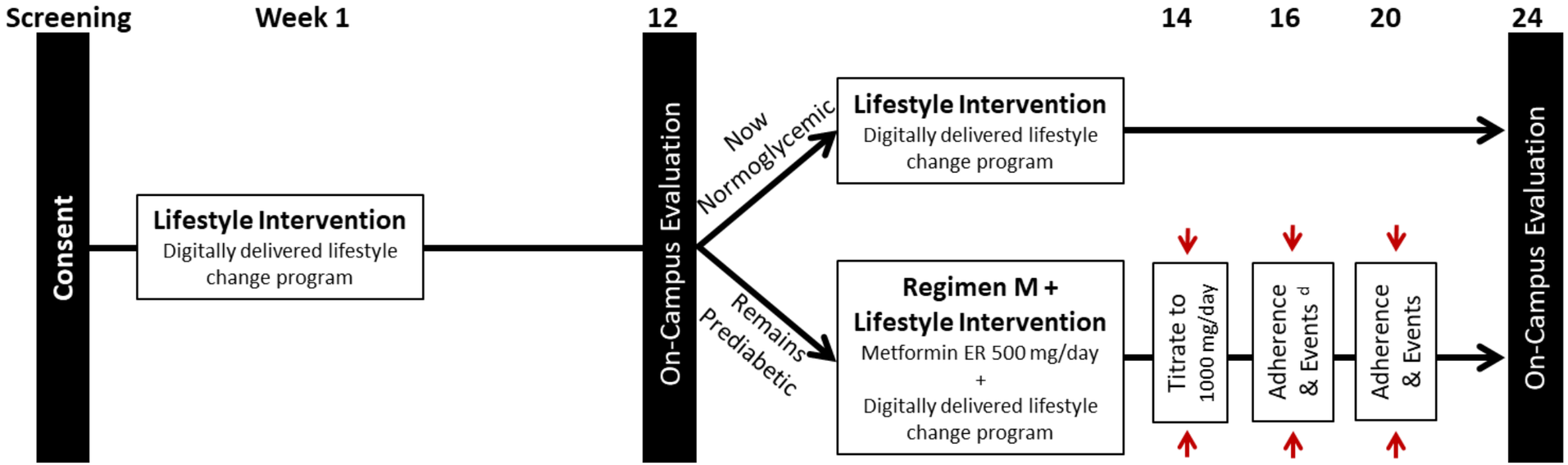
PREDM: A Pilot Intervention for *Diabetes* Prevention in Prediabetic Survivors

St. Jude LIFE
St. Jude for Life

Primary Aim: Establish feasibility and safety of a combined metformin and mHealth lifestyle intervention, and identify preliminary evidence for efficacy

Primary Endpoint: Treatment adherence

Secondary Endpoints: Safety and adverse events (CTCAE), Glycemic control (FPG and HbA1c), and insulin resistance



National Cancer Institute R21CA2617130; PI Dixon/Ness

St. Baldrick's FOUNDATION
Conquer Childhood Cancers

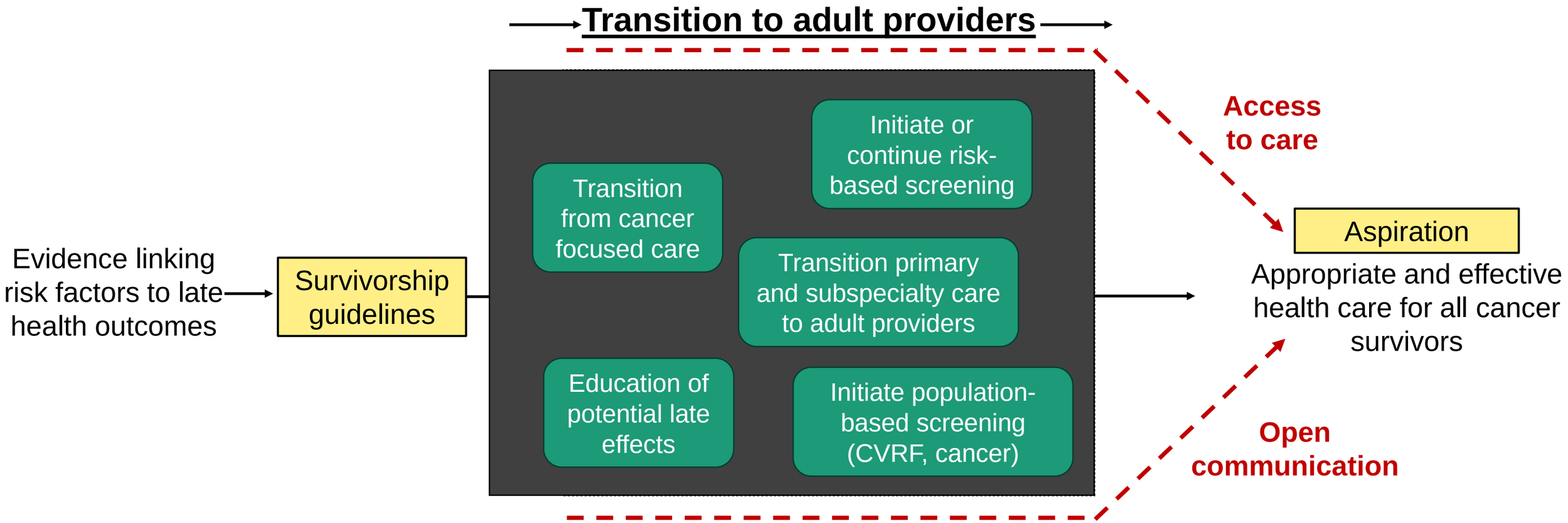
CONQUER CANCER®
THE ASCO FOUNDATION
CAREER DEVELOPMENT AWARD

Case

A 40-year-old young woman with a history of Hodgkin lymphoma whose treatment included doxorubicin (250 mg/m^2) followed by 21 Gy mediastinal radiation at age 16 is being seen today in your clinic. She has not received regular follow-up and was last seen at age 35.

- How might we improve the chances that this survivor receives guideline recommended care?

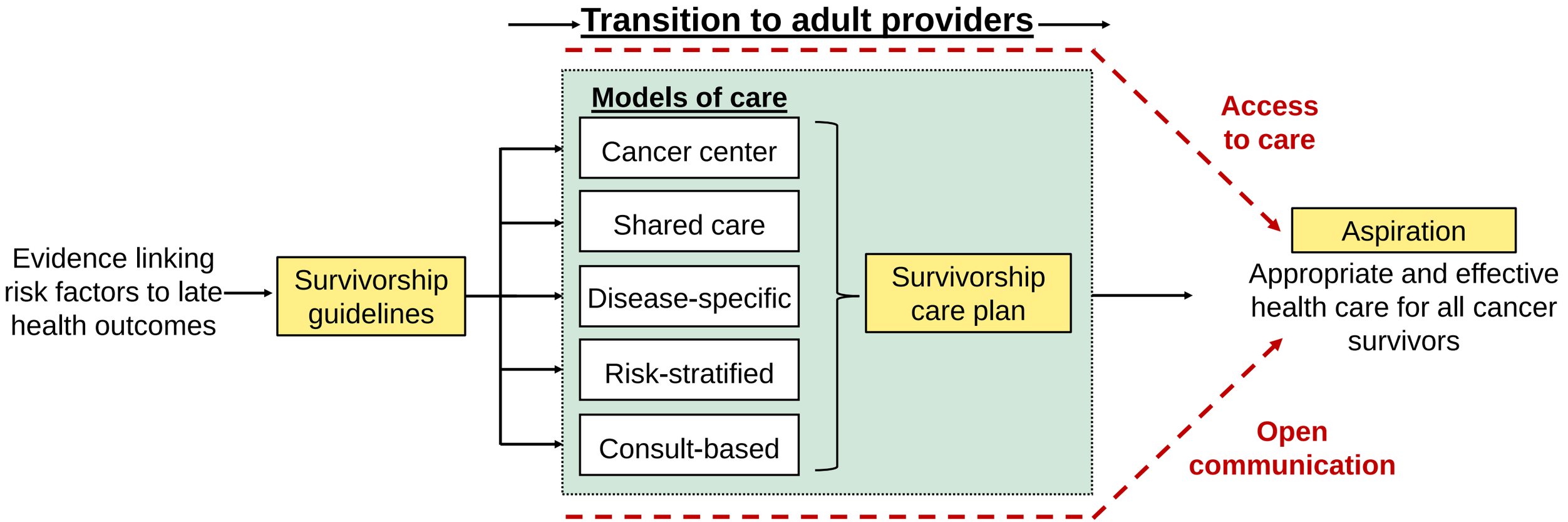
Survivorship Care Continuum



2006 Institute of Medicine ***From Cancer Patient to Cancer Survivor: Lost in Transition*** recommended all cancer patients receive care summary and follow-up plan → survivorship care plans

Dixon et al. *CA Cancer J Clin,* 2018.

Survivorship Care Continuum

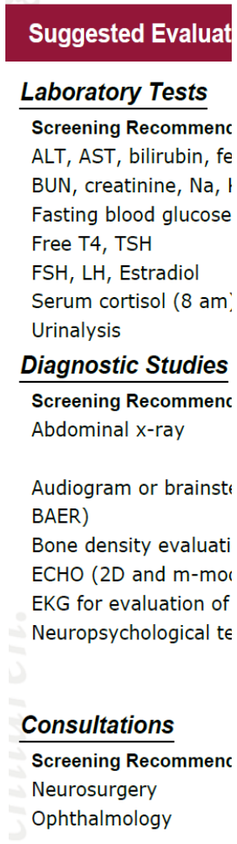


2006 Institute of Medicine ***From Cancer Patient to Cancer Survivor: Lost in Transition*** recommended all cancer patients receive care summary and follow-up plan → survivorship care plans

Dixon et al. *CA Cancer J Clin,* 2018.

Survivorship Care Plans (SCPs)

- Cancer diagnostic information
- Cumulative treatment exposures
- Cancer-related health risks
- Risk-based screening recommendations
- Major clinical events
- Transfusion history
- Health behaviors modifying risk
- Family history



Suggested Evaluat

Laboratory Tests

Screening Recommenc

ALT, AST, bilirubin, fe
BUN, creatinine, Na, I
Fasting blood glucose
Free T4, TSH
FSH, LH, Estradiol
Serum cortisol (8 am)
Urinalysis

Diagnostic Studies

Screening Recommenc

Abdominal x-ray

Audiogram or brainste
BAER)
Bone density evaluati
ECHO (2D and m-moc
EKG for evaluation of
Neuropsychological te

Consultations

Screening Recommenc

Neurosurgery
Ophthalmology

St. Jude Children's Research Hospital

Survivorship Care Plan - Research Report

August 2, 2016

St. Jude LIFE — St. Jude for Life

Date of Birth:

MRN:
Gender:

General Information

Race:
Gender:
Current Age:
Phone#:

MILLI Patient Status: Active ACT
Initial Medical Service: Neuro-Oncology
Initial Primary St. Jude MD:
Last Medical Service Visit Date:
Date of Transfer:
Last ACT Clinic Visit Date:
Affiliate: Other (Memphis)

Diagnosis

DX#	Date	Age/History	Diagnosis	Stage
1		3.7 yrs	Medulloblastoma, Posterior Fossa	Chang (M0)

Protocol Enrollments

Mnemonic	Title	On Study Date	Off Study Date	Off Therapy Date
97BANK	Protocol for Collecting, Archiving, and Distributing Human Tissue Specimens			
SJMB03	Treatment of Patients with Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor, or Atypical Teratoid Rhabdoid Tumor			
SJLTFU	Protocol for Collecting Data on Childhood Cancer Survivors			
PGEN5	Pharmacogenetic Determinants of Treatment Response in Children with Cancer			
SJLIFE	Establishment of a Lifetime cohort of Adults Surviving Childhood Cancer			

Oncology History

Start Date Resolve Date

- Diagnosis of Medulloblastoma, posterior fossa, following gross total tumor resection by craniotomy (Valley Baptist Medical Center, Harlingen, TX)
  - Treatment with combined modality SJMB03 protocol therapy including consolidation with myeloablative therapy followed by autologous hematopoietic cell rescue
  - Cranio-spinal (2340 cGy), Left cerebellum (3060 cGy), Posterior fossa tumor bed boost (180 cGy) radiation therapy (5580 cGy total cumulative dose)

Therapy

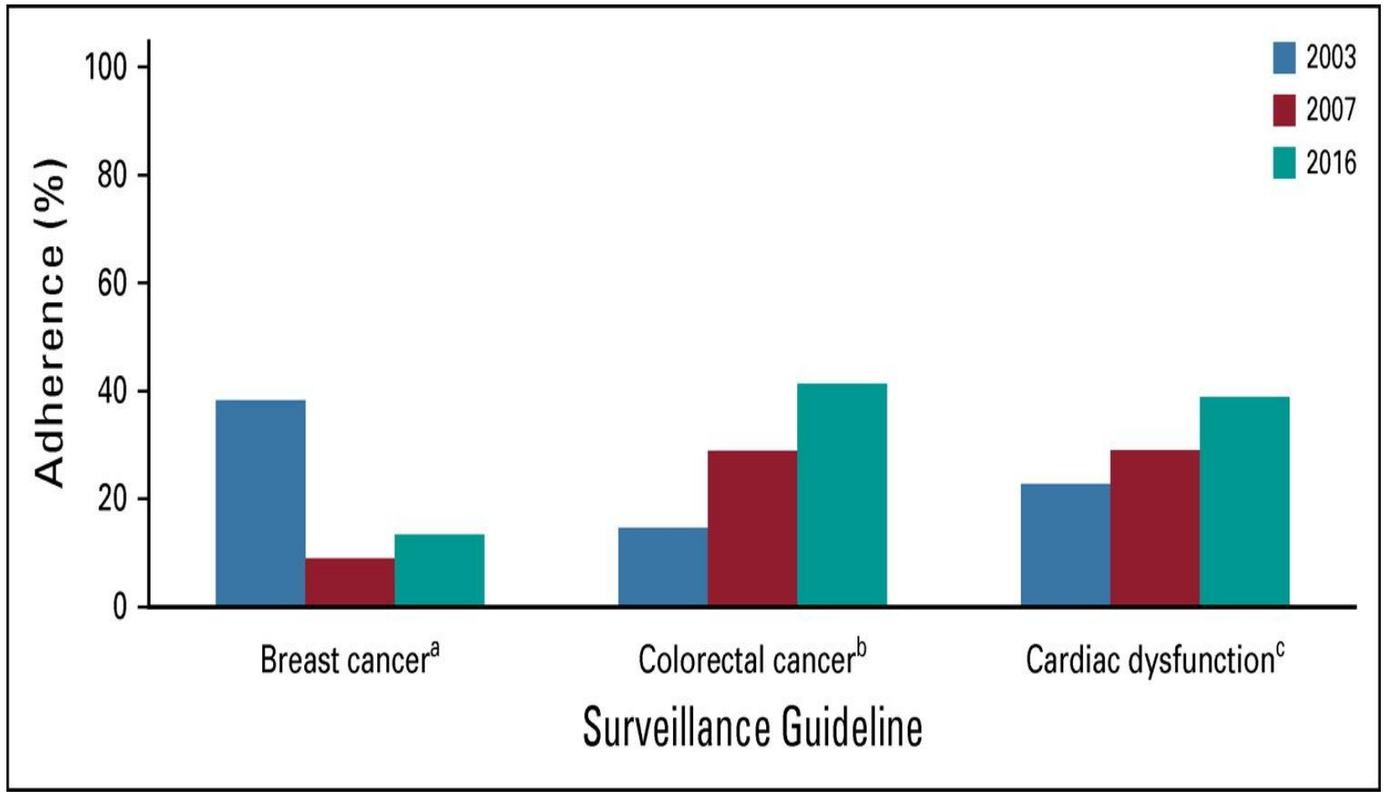
Surgeries

MRN:

SCPs and Adherence to Screening

CCSS

Screening Adherence among High-Risk Survivors



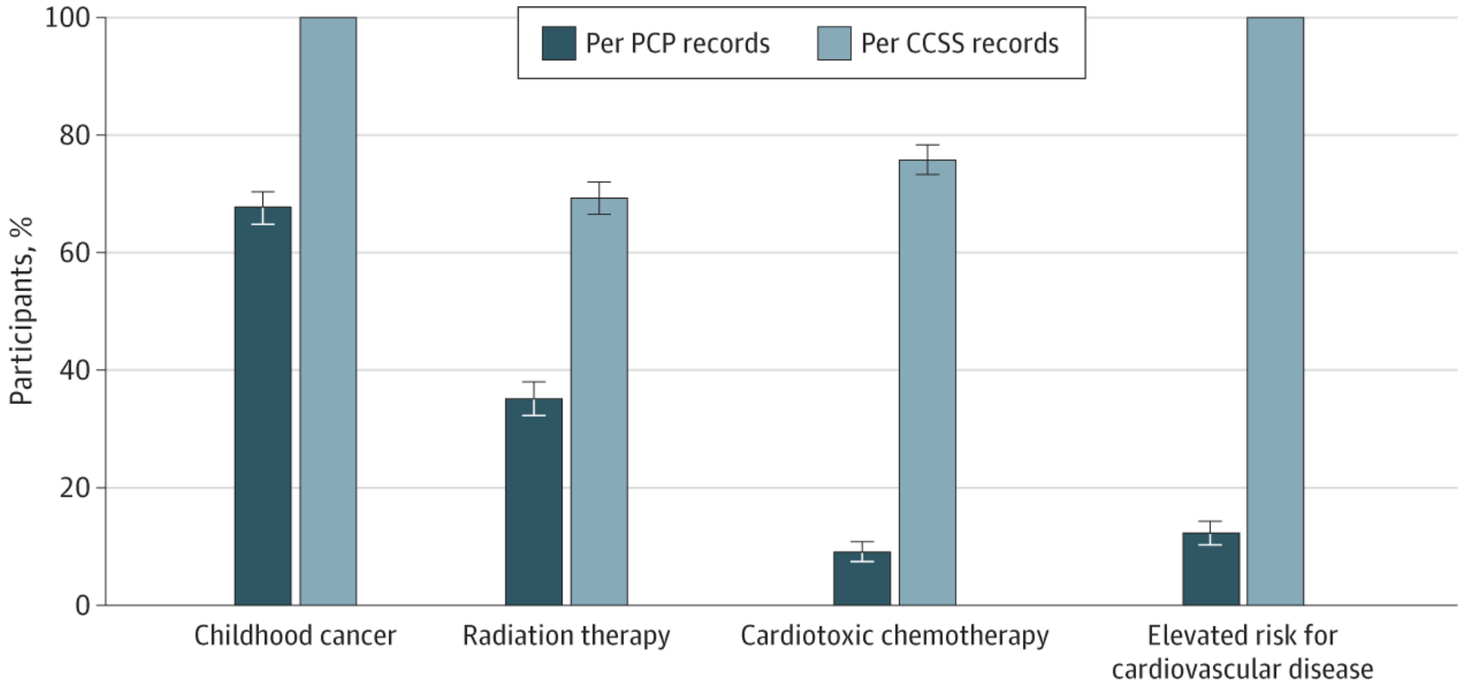
- SCP possession was generally effective at increasing adherence in high-risk survivors
  - 2.5-fold increase for breast cancer
  - 1.7-fold increase for cardiac
- Only 27% of survivors reported having a SCP

Yan AP et al. *J Clin Oncol,* 2020.

PCP and Cardiovascular Screening in Survivors

CCSS

- 293 survivors with high exposure-based cardiovascular risk (median age 40 years), 81% had PCP.
- 82% had blood pressure screening, 61% lipid testing, 66% diabetes screening, 22% echocardiogram.
- <5% had referenced survivorship care plan.



Documentation of increased CV disease risk and need for late-effects screening were each independently associated with up-to-date cardiovascular disease screening.

Ohlsen, et al *JAMA Network Open, 2023*.

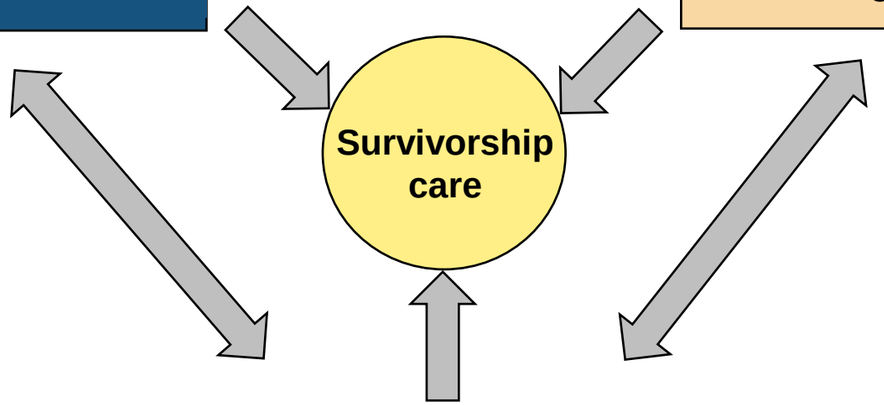
Barriers to Survivorship Care Delivery

Survivor Factors

- Self-efficacy
- Cognitive status
- Health knowledge
- Health risk perceptions
- Insurance status/healthcare access

Provider Factors

- Practice setting
- Survivorship education/training
- Access to survivorship resources
- Perceptions regarding preventive care
- Knowledge or access to individual survivor health history

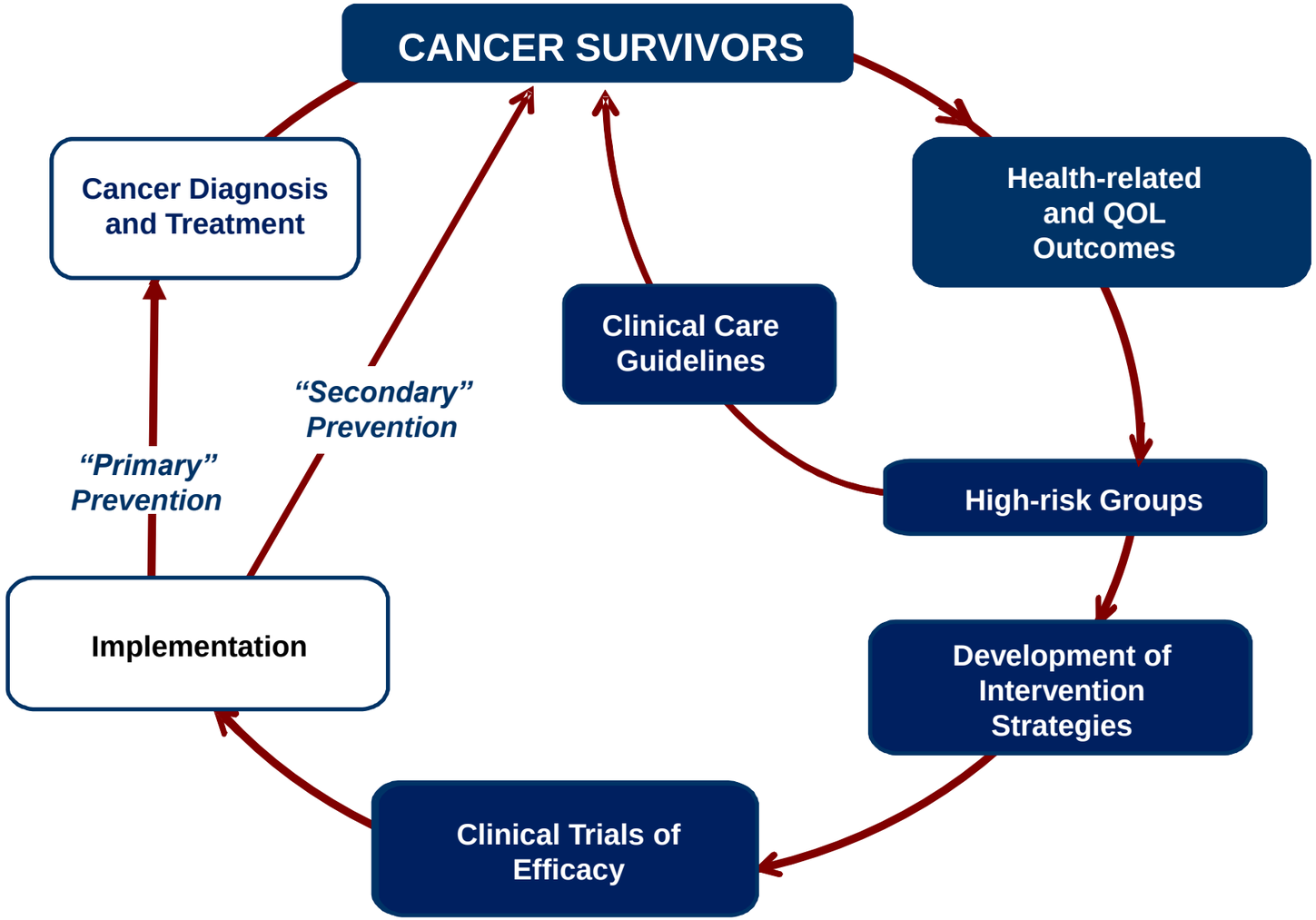


Health Care System Factors

- Models of survivorship care
- Financing and payment policies
- Health information management systems and information sharing
- Organization and access to subspecialty/psychosocial providers
- Insurance coverage and benefits (especially psychosocial and rehabilitation services)

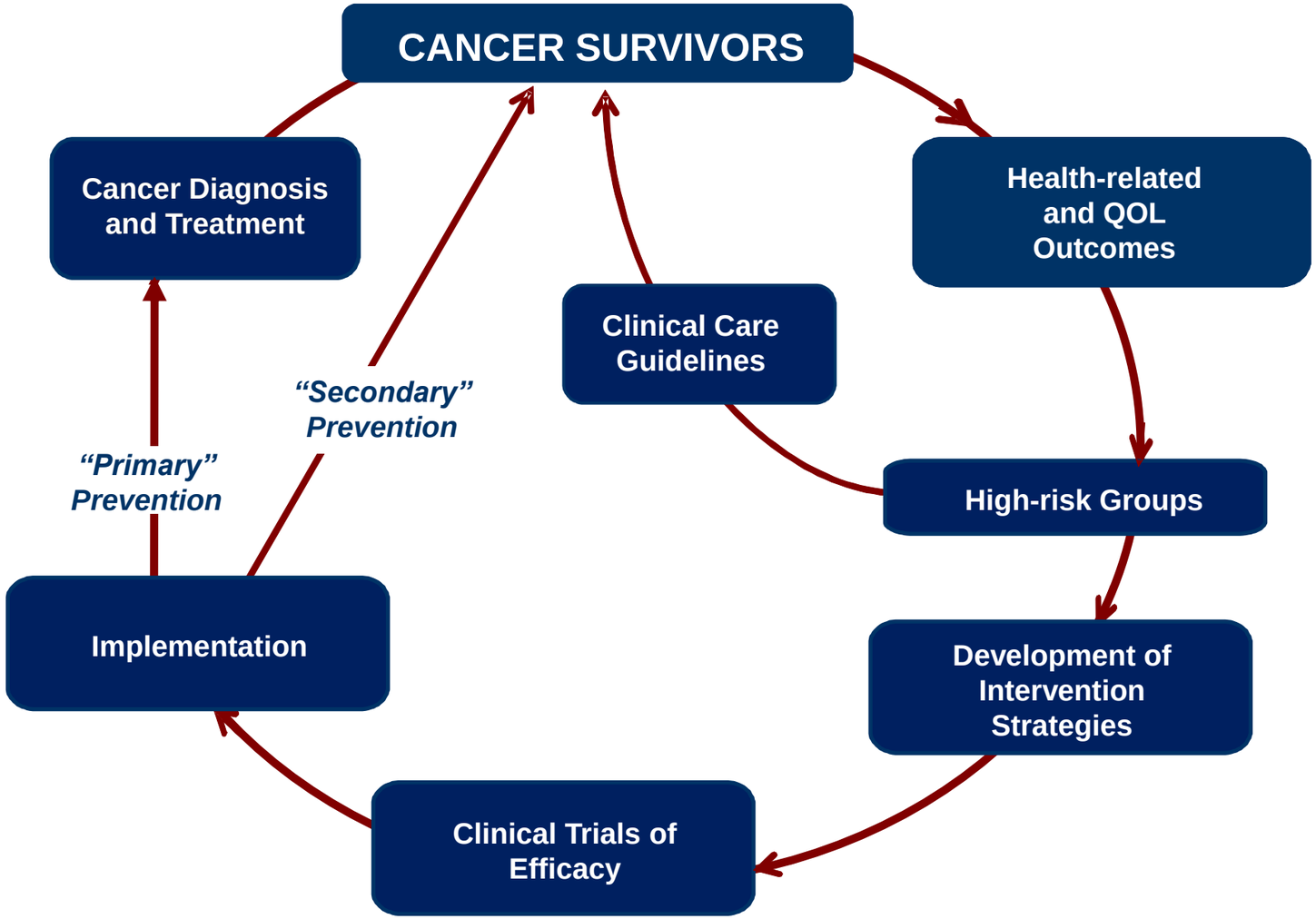
Dixon et al. *CA Cancer J Clin,* 2018.

Reducing the Cost of Cure through Research



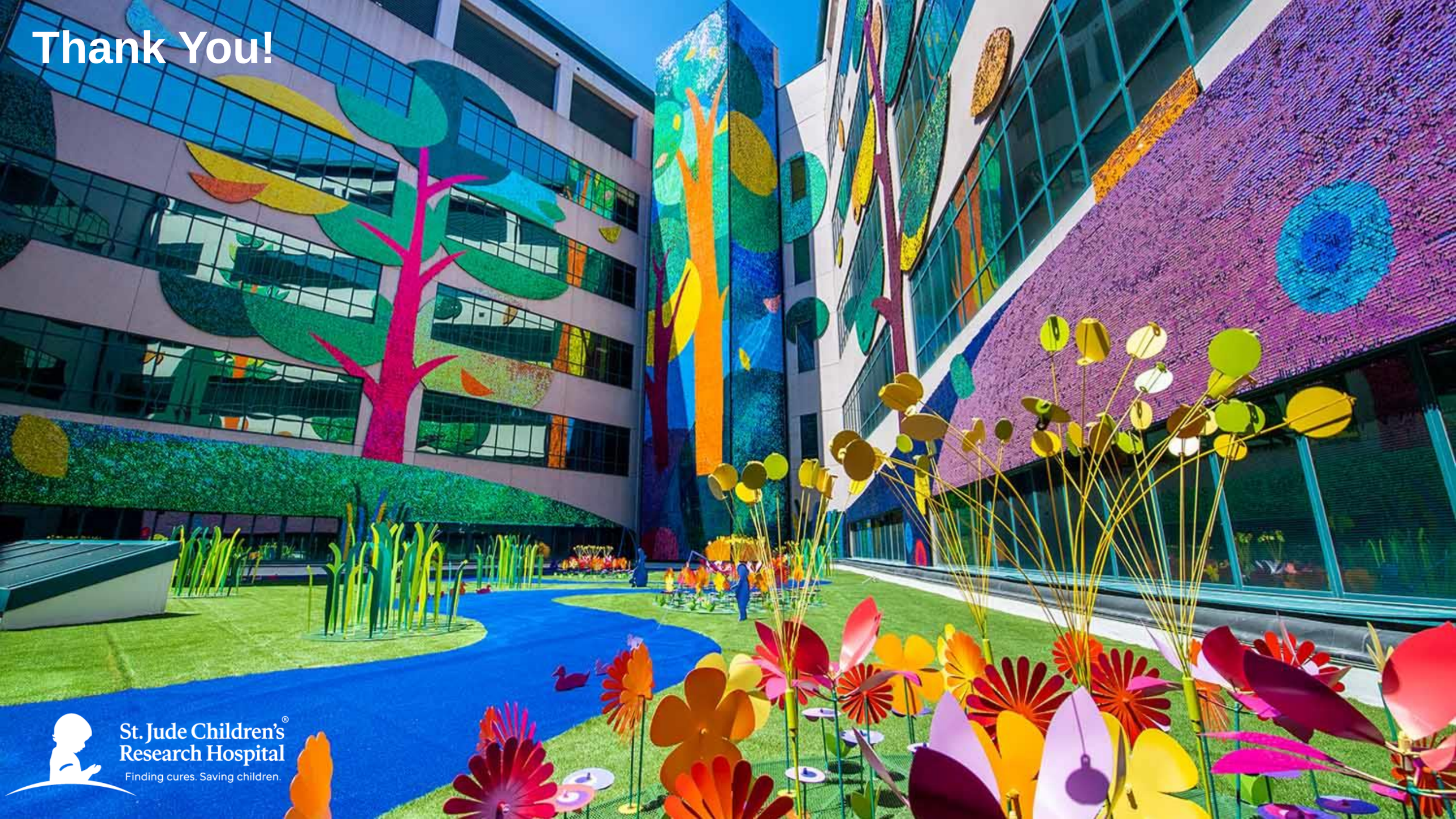
Robison & Bhatia, Cancer Epi Bio Prev 2008

Reducing the Cost of Cure through Research



Robison & Bhatia, Cancer Epi Bio Prev 2008

Thank You!



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Finding cures. Saving children.

Cancer Survivorship Fellowship

www.stjude.org

daniel.mulrooney@stjude.org