

Radiation-Associated Subsequent Neoplasms: The Childhood Cancer Survivor Study

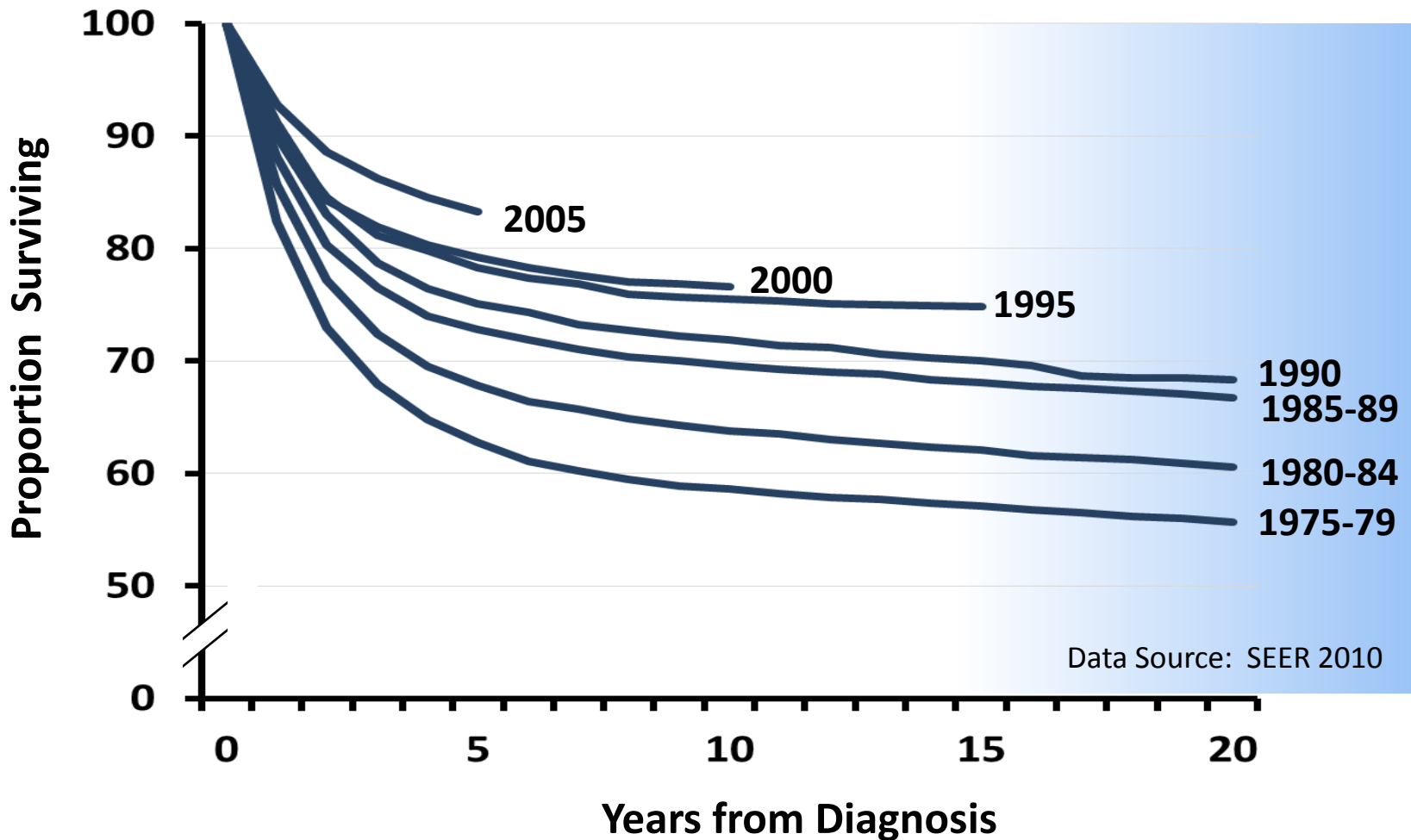
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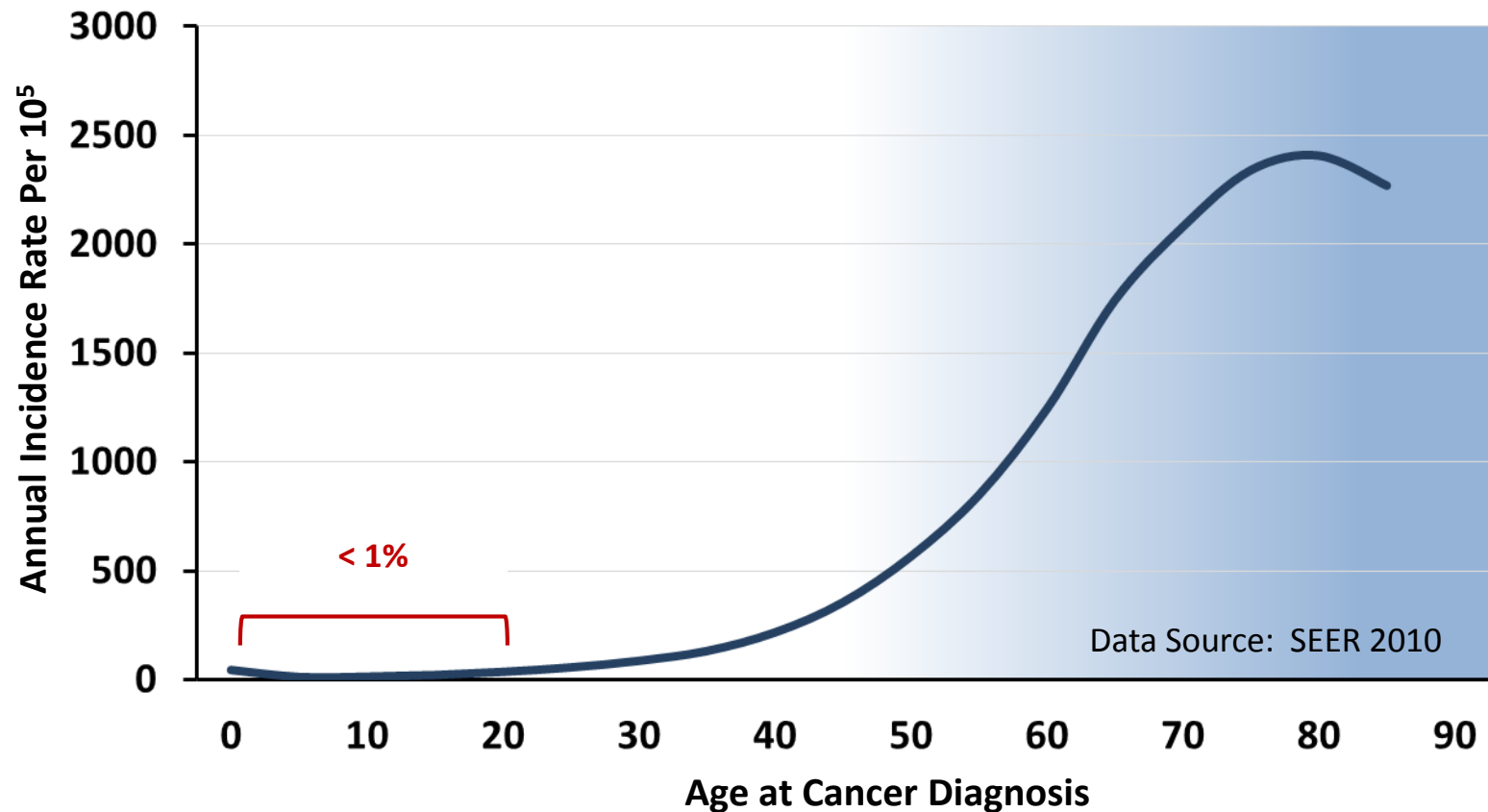
Childhood Cancers in the US: Survivorship Statistics

- Estimate 13,500 newly diagnosed cases annually
- End of 2013, estimated number surpass 420,000
- 1 in 750 in the US is a childhood cancer survivor
- Number of survivors will approach 500,000 by 2020

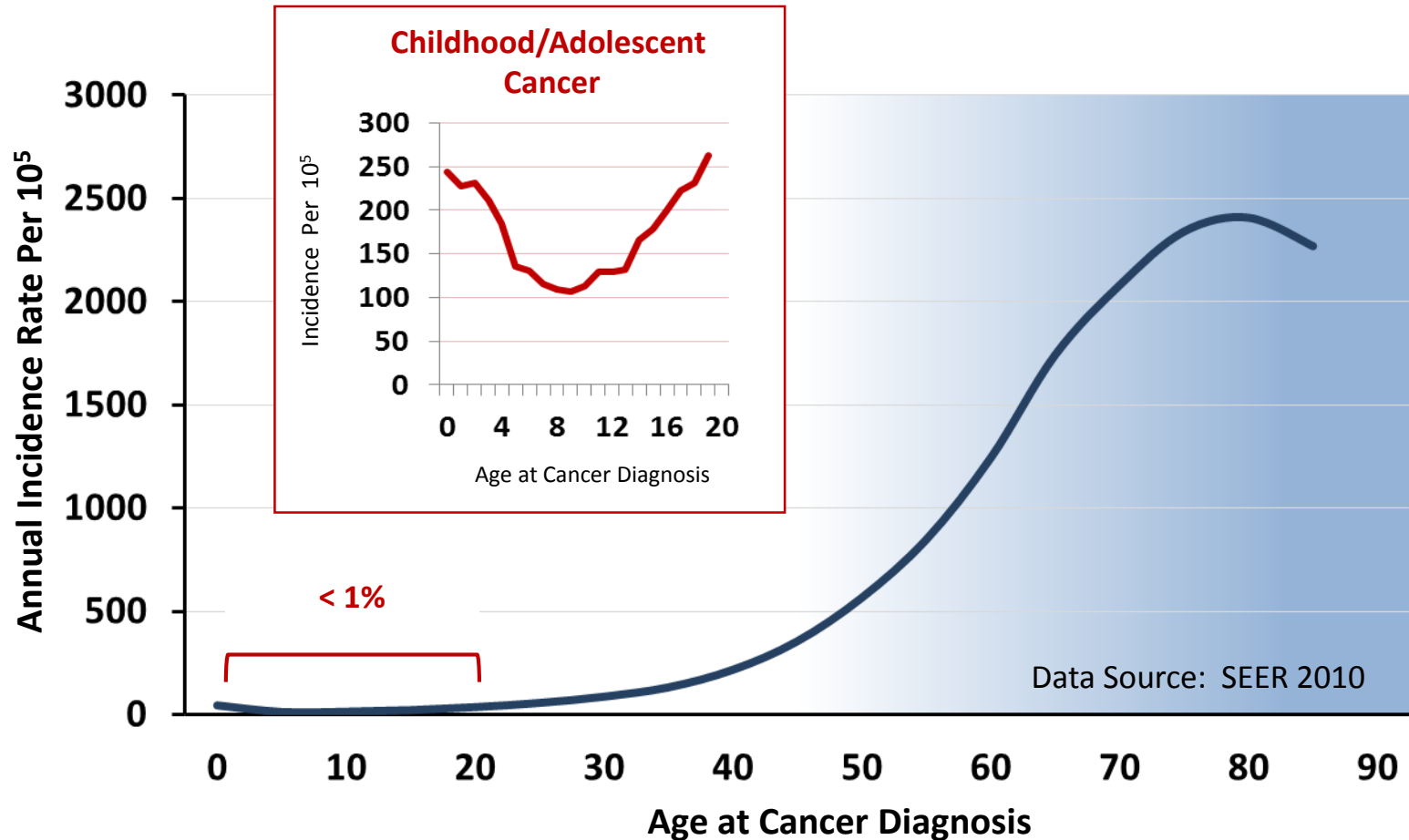
Survival of Childhood Cancers Ages 0-19 years



Age-specific Cancer Incidence

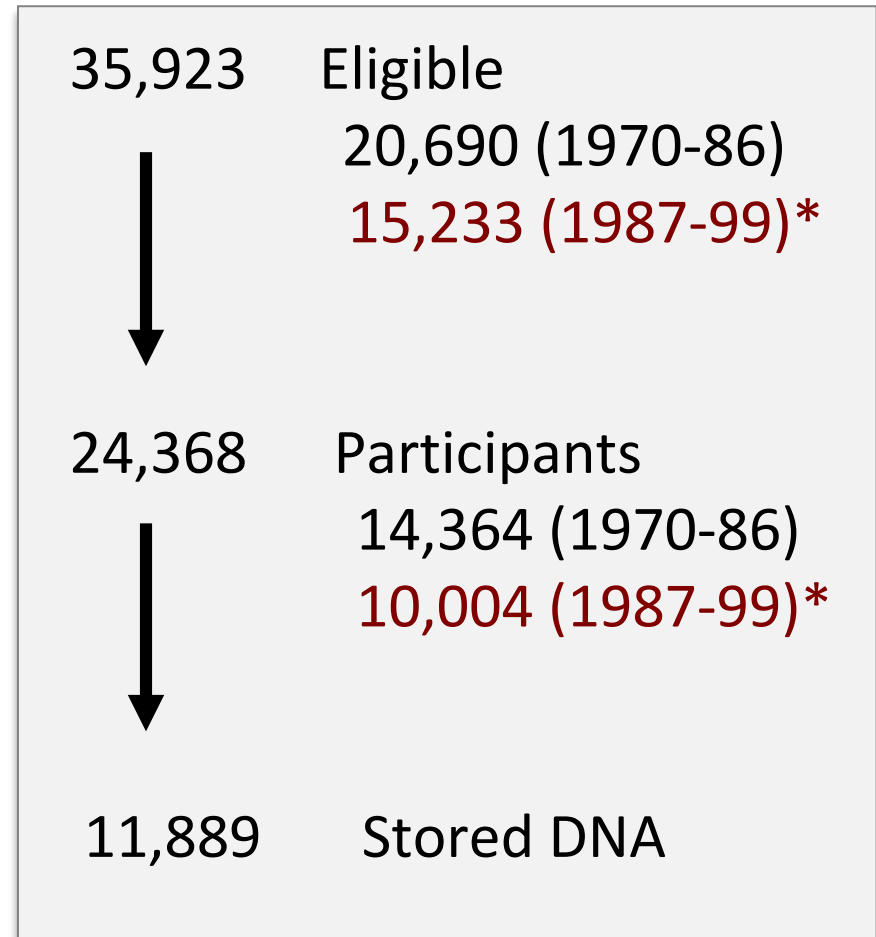


Age-specific Cancer Incidence

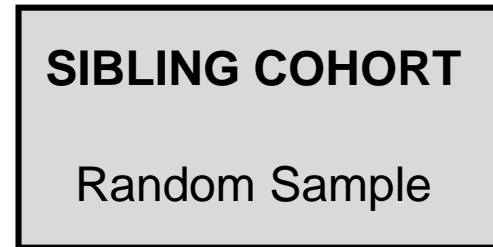
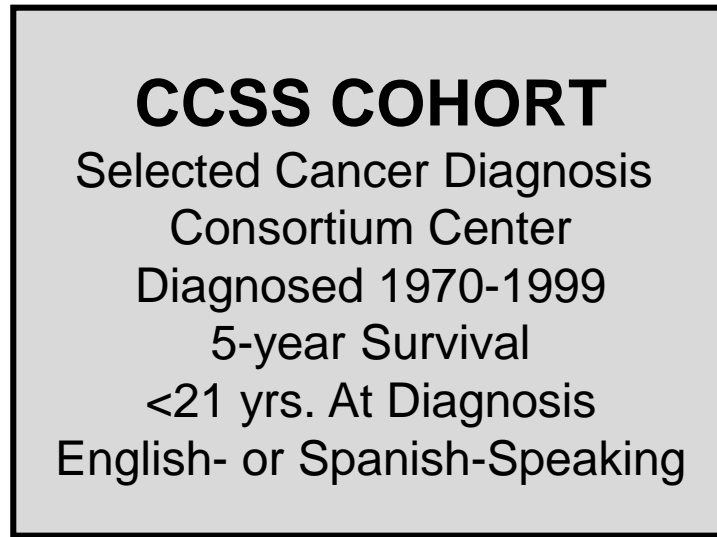


Childhood Cancer Survivor Study (U24 CA55727)

- Funded in 1994
- Retrospective cohort, recent **expansion** includes survivors diagnosed **1970-1999**
- 31 contributing centers
- 5-year survival
- Leukemia, lymphoma, CNS, bone, Wilms, NBL, soft-tissue sarcoma
- Detailed treatment data
- Wide range of outcomes



* indicates expansion cohort population, now available to investigators



Questionnaire / Interview Data
Survivors
Parents

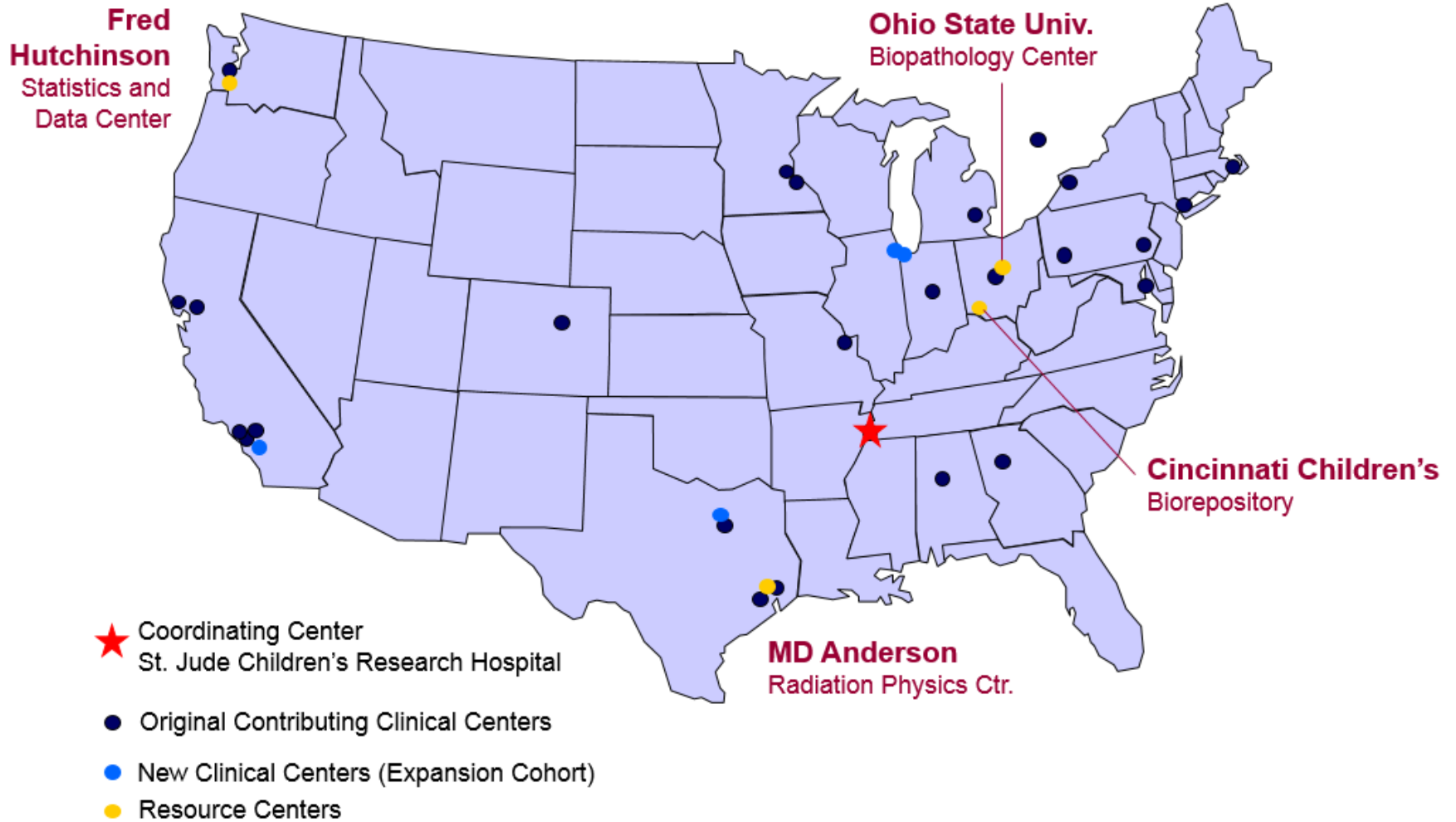
Repository - Buccal Cell DNA
LCL for SMN Cases

Treatment Information
Medical Record Abstraction
Radiation Therapy Records
(RT Physics Center)

Pathology Center
Confirm Subsequent Malignancies
Repository - Second Cancers

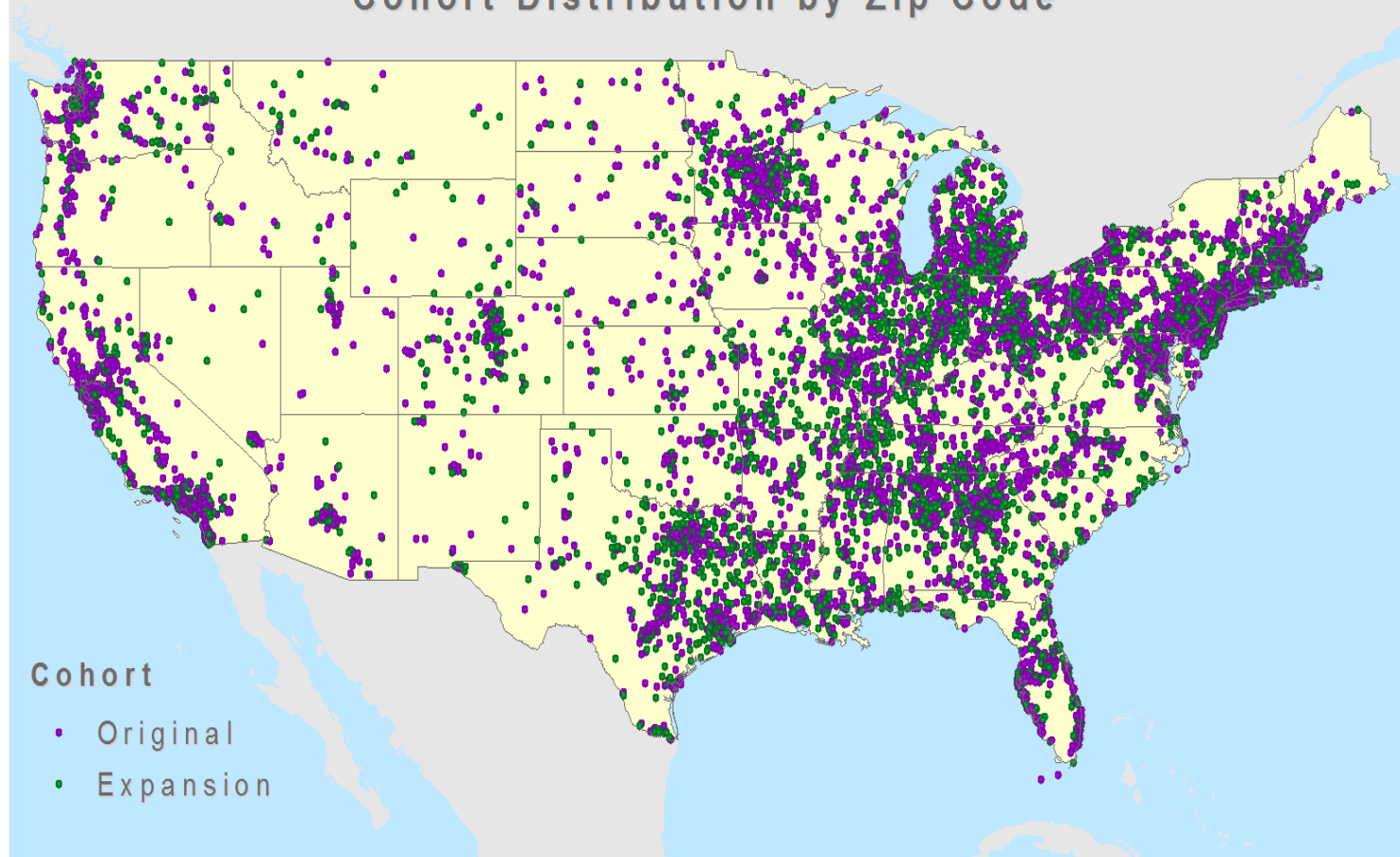
National Death Index

Participating Sites



Childhood Cancer Survivor Study (U24 CA55727) Study Participants

CCSS Original/Expansion Cohort Continental US Participants
Cohort Distribution by Zip Code



St. Jude Children's Research Hospital

University of Minnesota

Children's Hospital of Pittsburgh

Stanford University

Dana-Farber Cancer Institute

Children's National Medical Center

Roswell Park Cancer Center

Memorial Sloan-Kettering Cancer Center

Texas Children's Hospital

University of California, San Francisco

Seattle Children's Hospital

Toronto Hospital for Sick Children

Denver Children's Hospital

Nationwide Children's Hospital, Columbus

Emory University

Cook Children's Medical Center

U.T. - M.D. Anderson Cancer Center

Mayo Clinic

Children's Hospitals of Minnesota

Children's Hospital of Philadelphia

St. Louis Children's Hospital

Children's Hospital of Los Angeles

UCLA Medical Center/Miller Children's

Children's Hospital of Orange County

Riley Hospital for Children – Indiana Univ.

UAB/Children's Hospital of Alabama

University of Michigan – Mott Children's

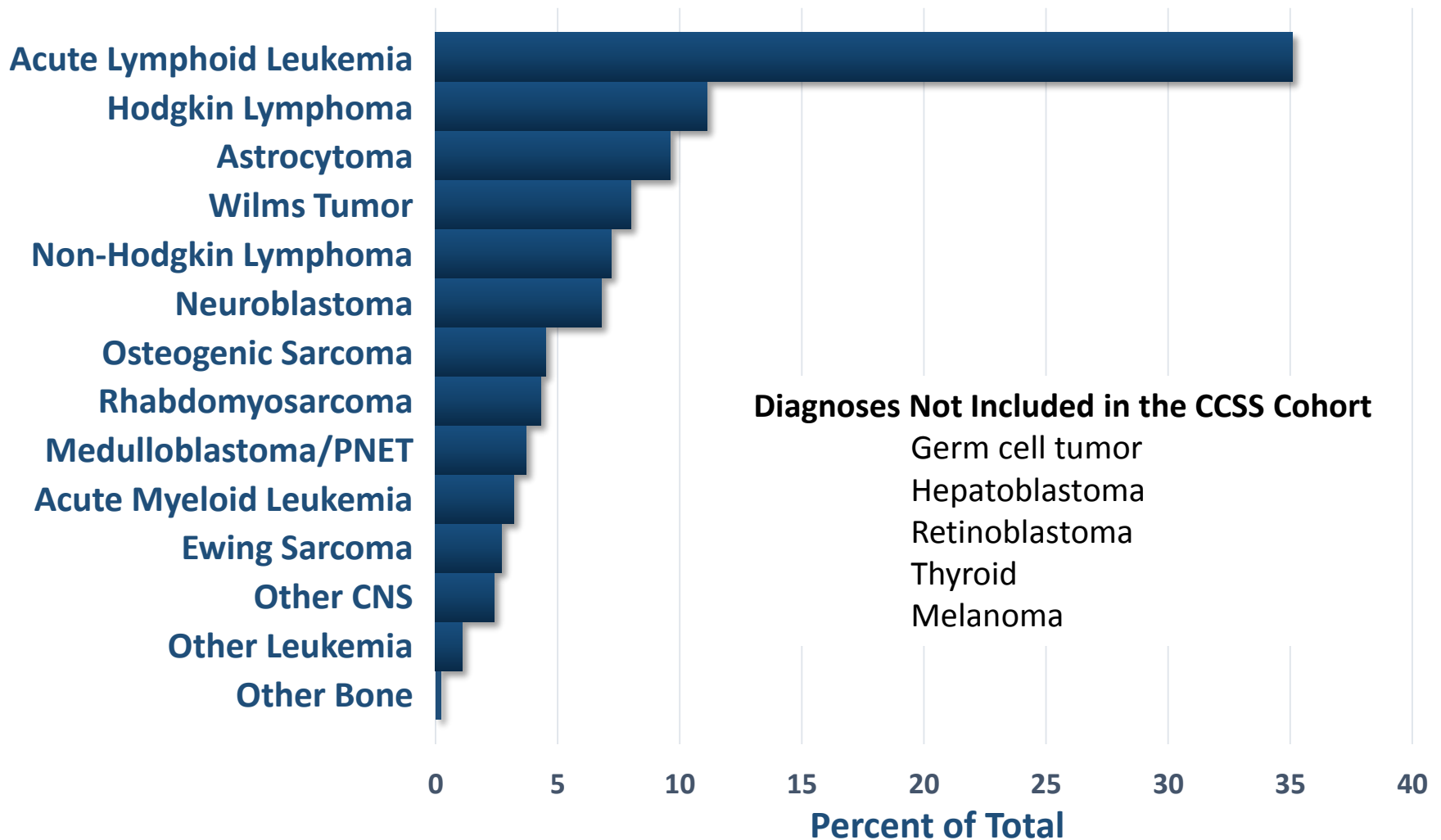
Children's Medical Center of Dallas

Fred Hutchinson Cancer Research Center

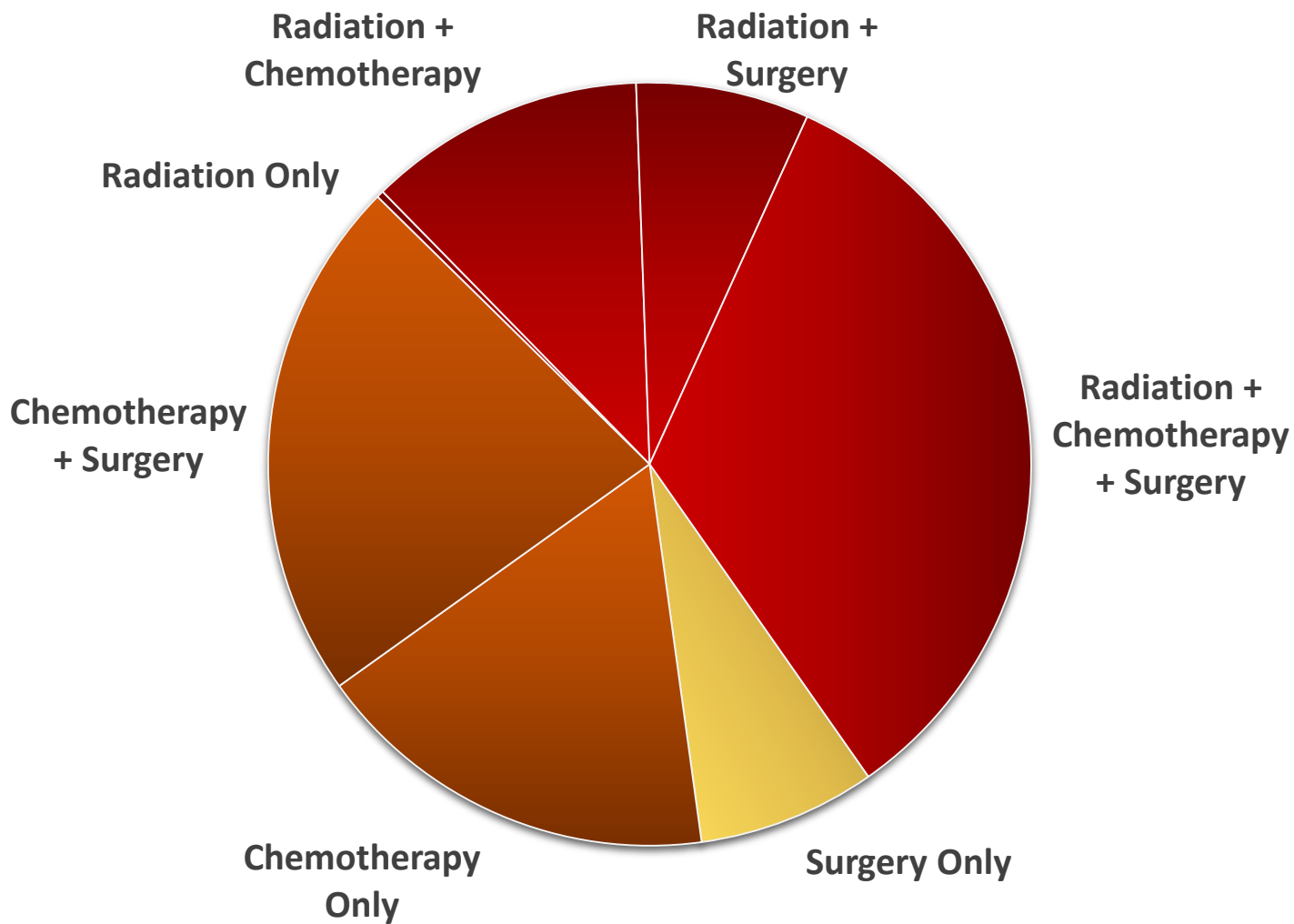
Northwestern University

University of Chicago

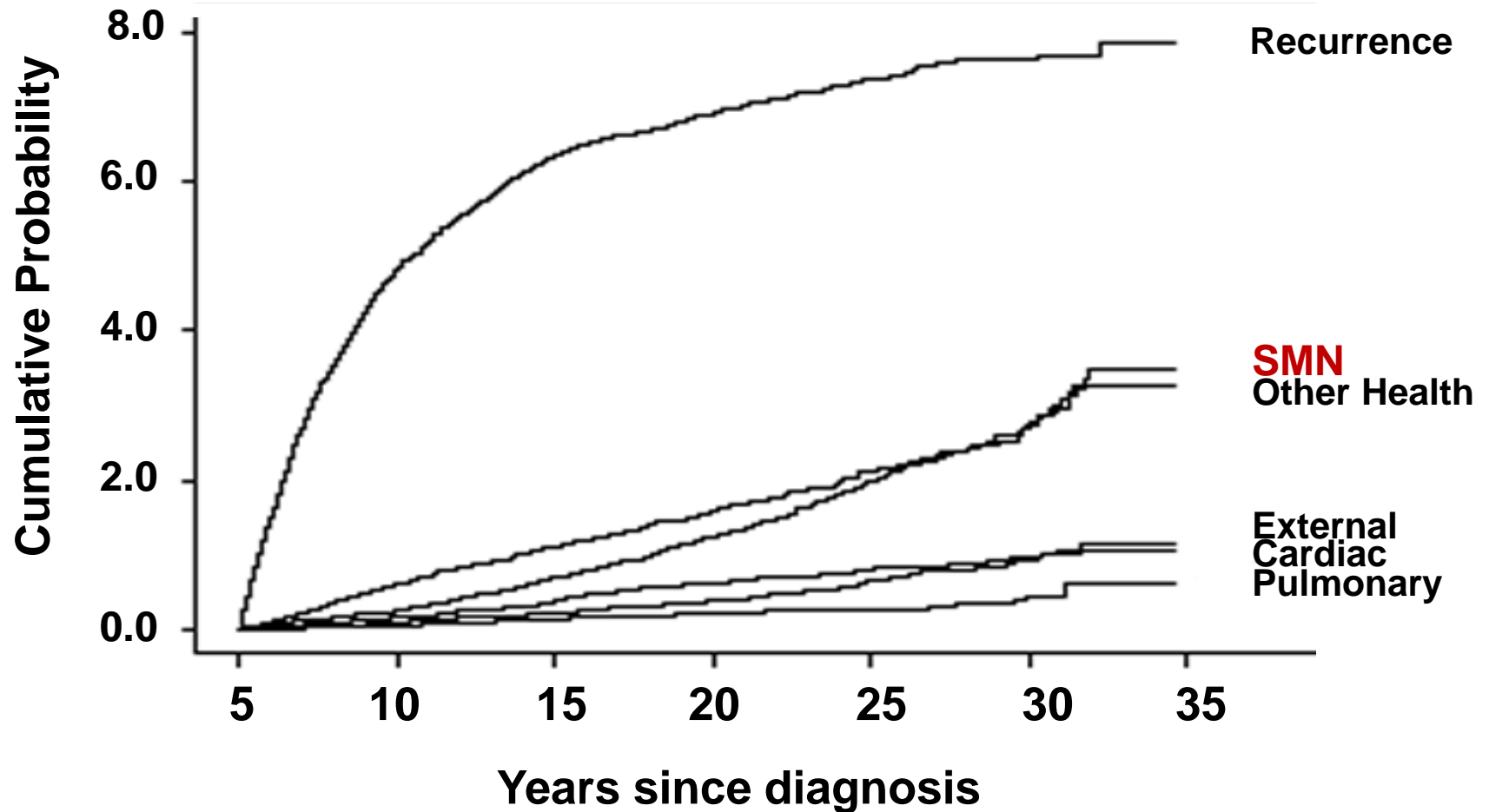
Initial Diagnosis (n=24,368)



Distribution of Therapy for Initial Cancer

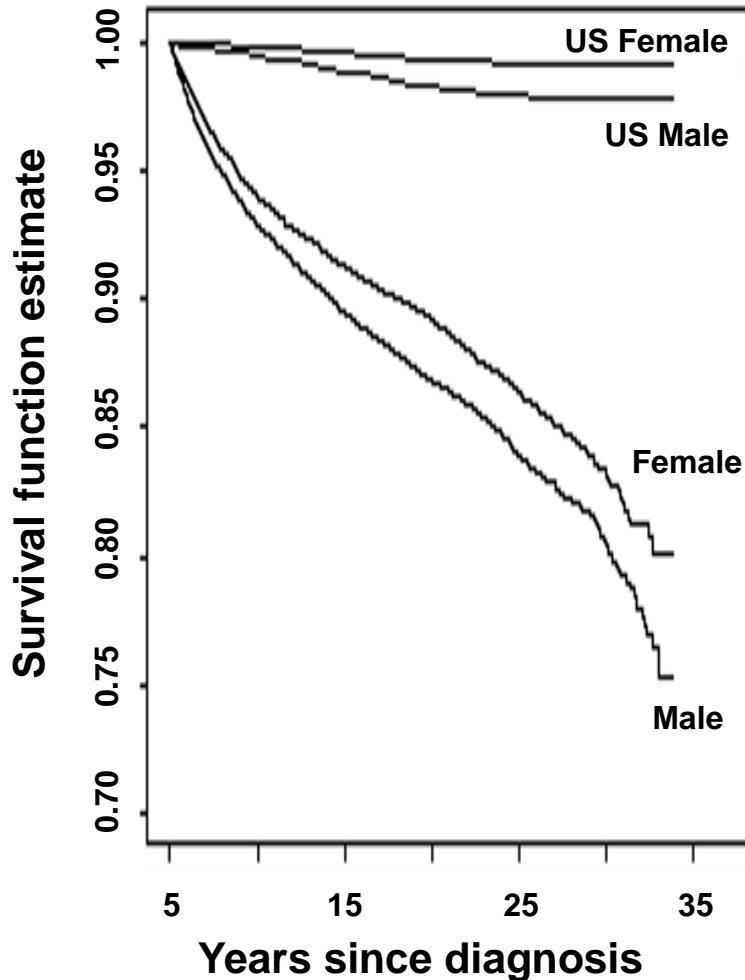


All Cause Mortality in 5+ Year Survivors



Late Mortality Among 5+ Year Survivors

All-cause Mortality



All Cause Mortality

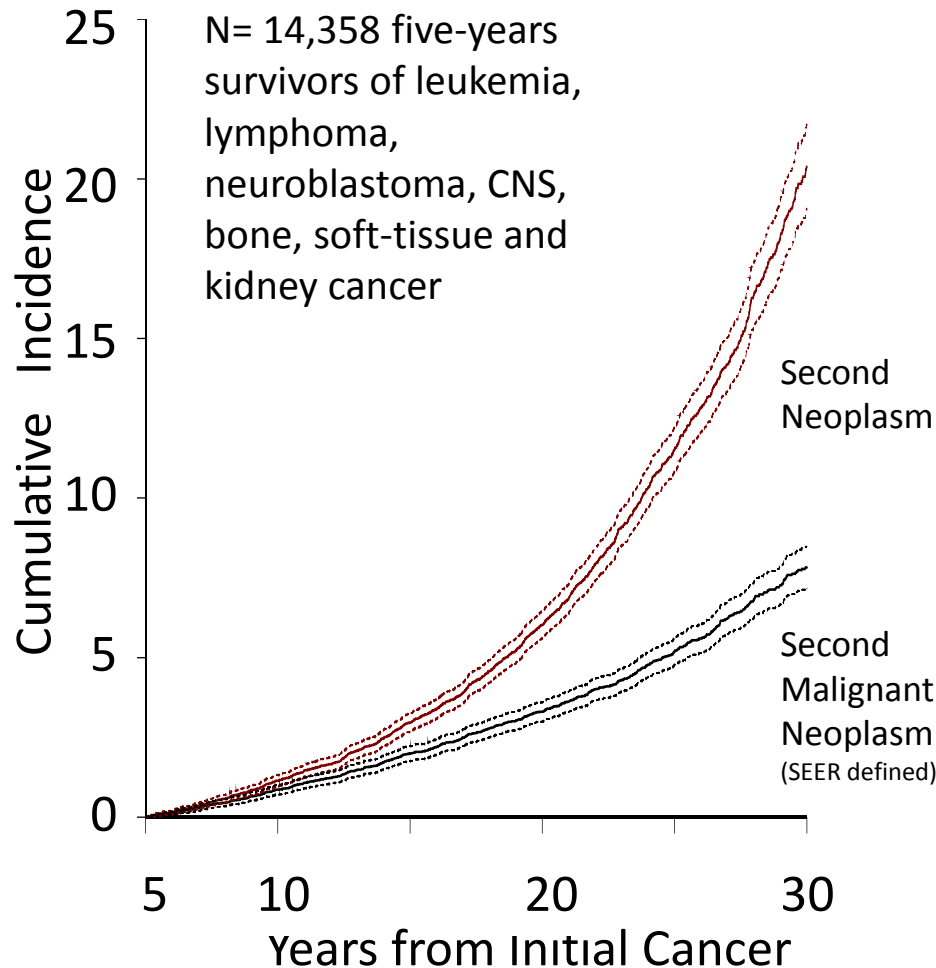
	SMR	95% CI
SMN	15.2	13.9 – 16.6
Cardiac	7.0	5.9 – 8.2
Pulmonary	8.8	6.8 – 11.2

RT-Associated Risk of Death

Cause of Death	RR*	95% CI
SMN	2.9	2.1 – 4.2
Cardiac	3.3	2.0 – 5.5
Pulmonary	1.4	0.7 – 2.9
Other causes	2.0	1.3 – 3.1

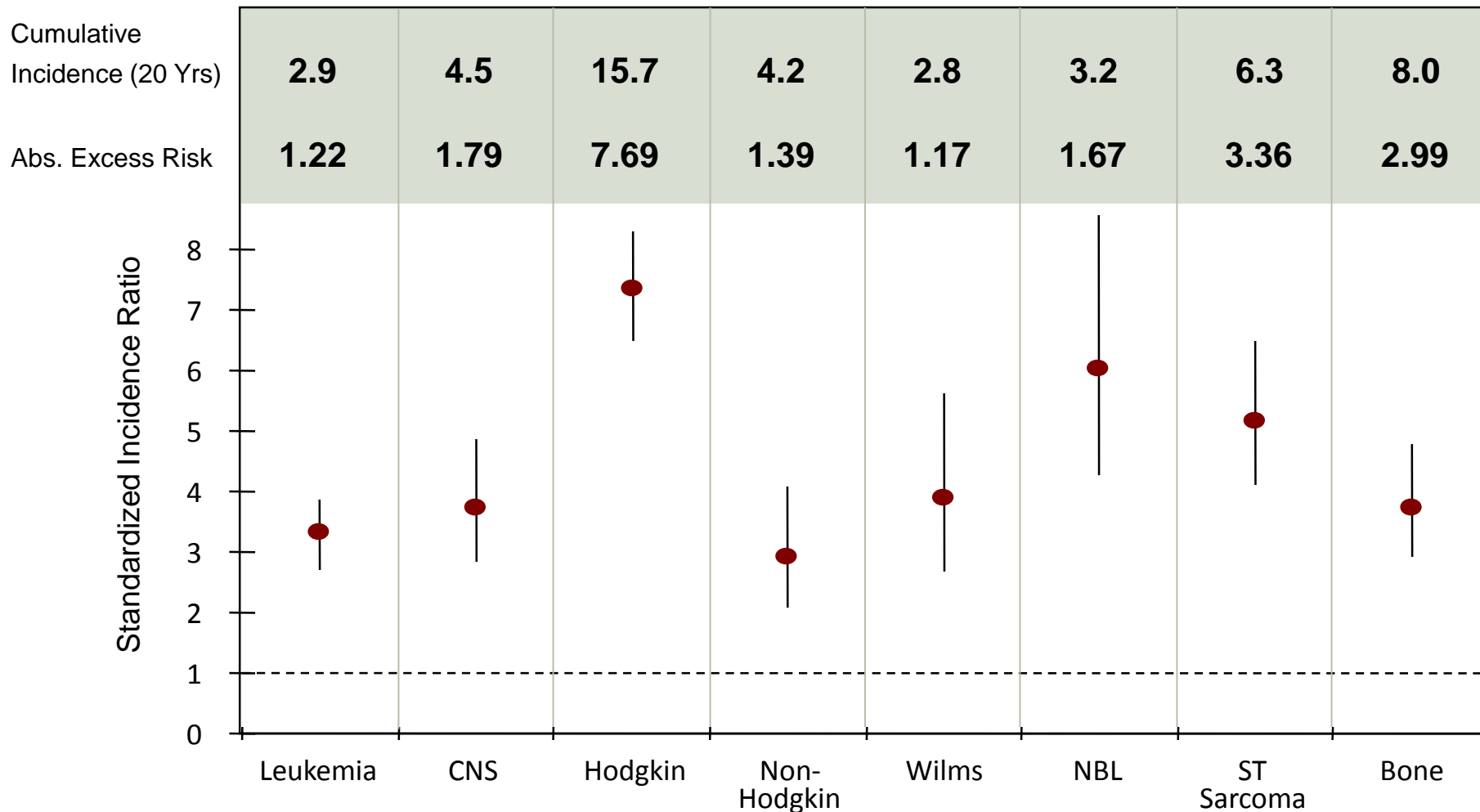
* Adjusted for age, sex, year of dx, follow-up, anthracycline dose, epidodophyllotoxin dose, Bleomycin dose

Second Neoplasms Among 5+ Year Survivors of Childhood Cancer

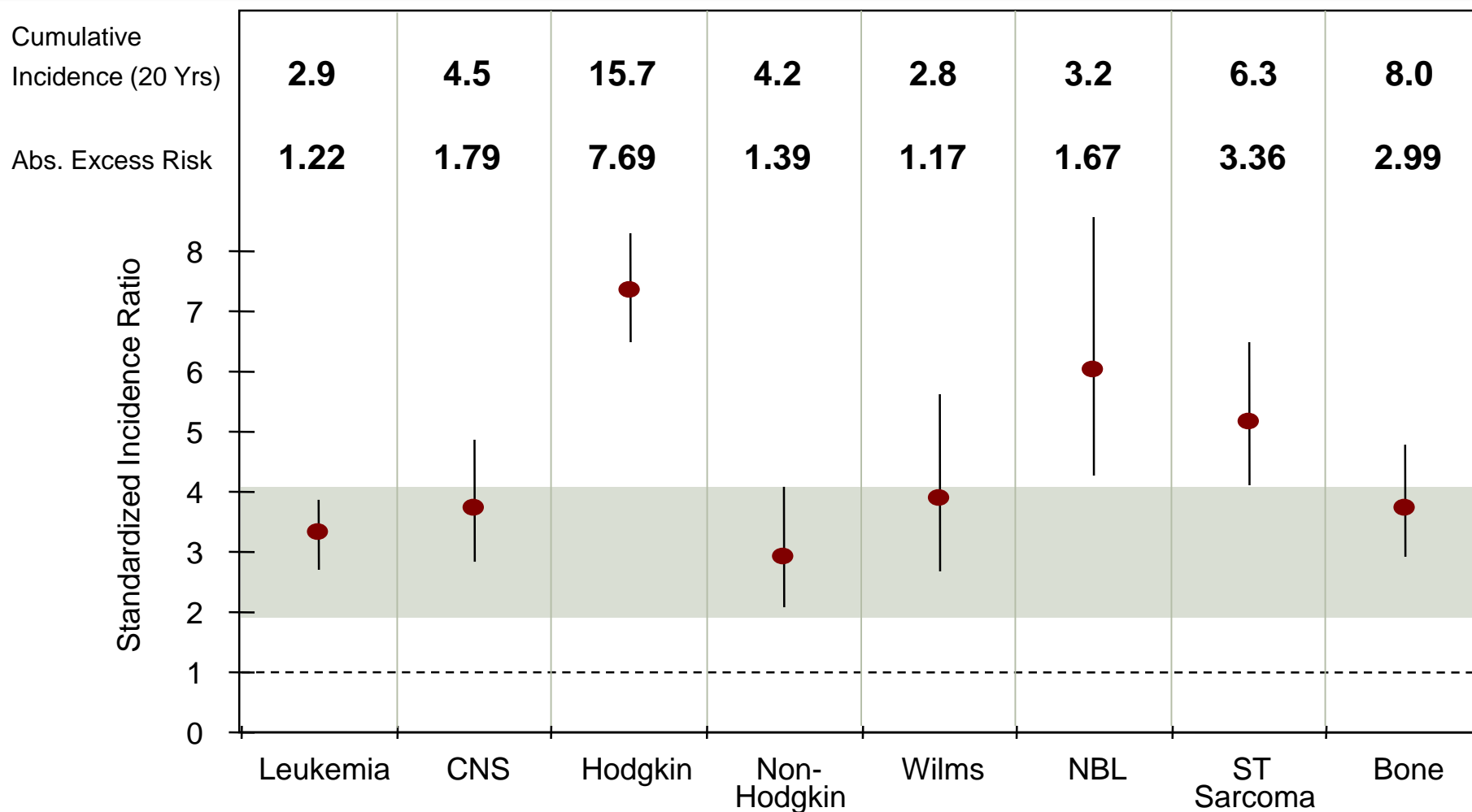


- 21% cumulative incidence of second neoplasm at 30 years
- 8% cumulative incidence of second malignancy at 30 years
- Highest risks associated with female sex, treatment with radiation therapy, older age at initial cancer diagnosis, earlier treatment era, diagnosis of Hodgkin lymphoma.

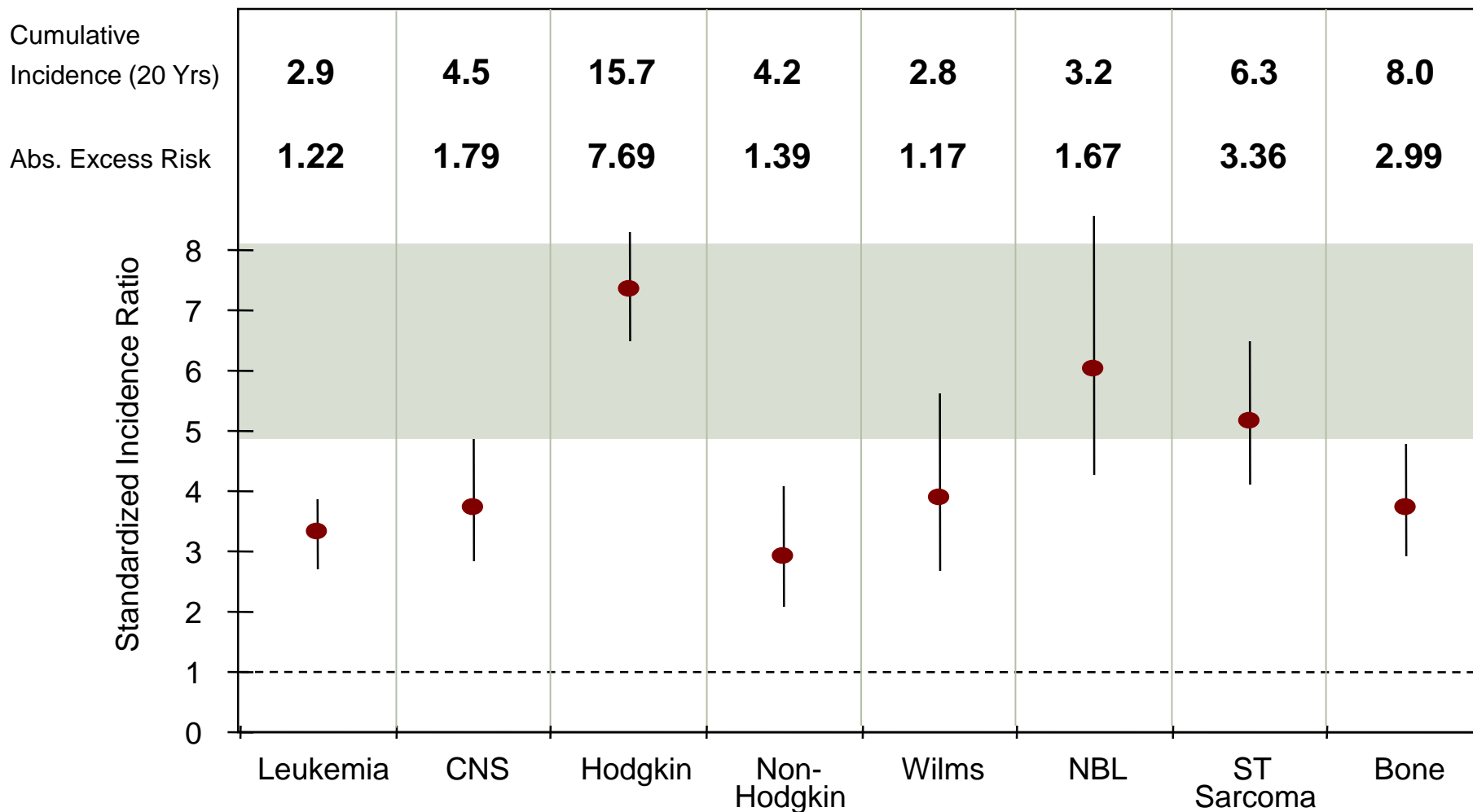
Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



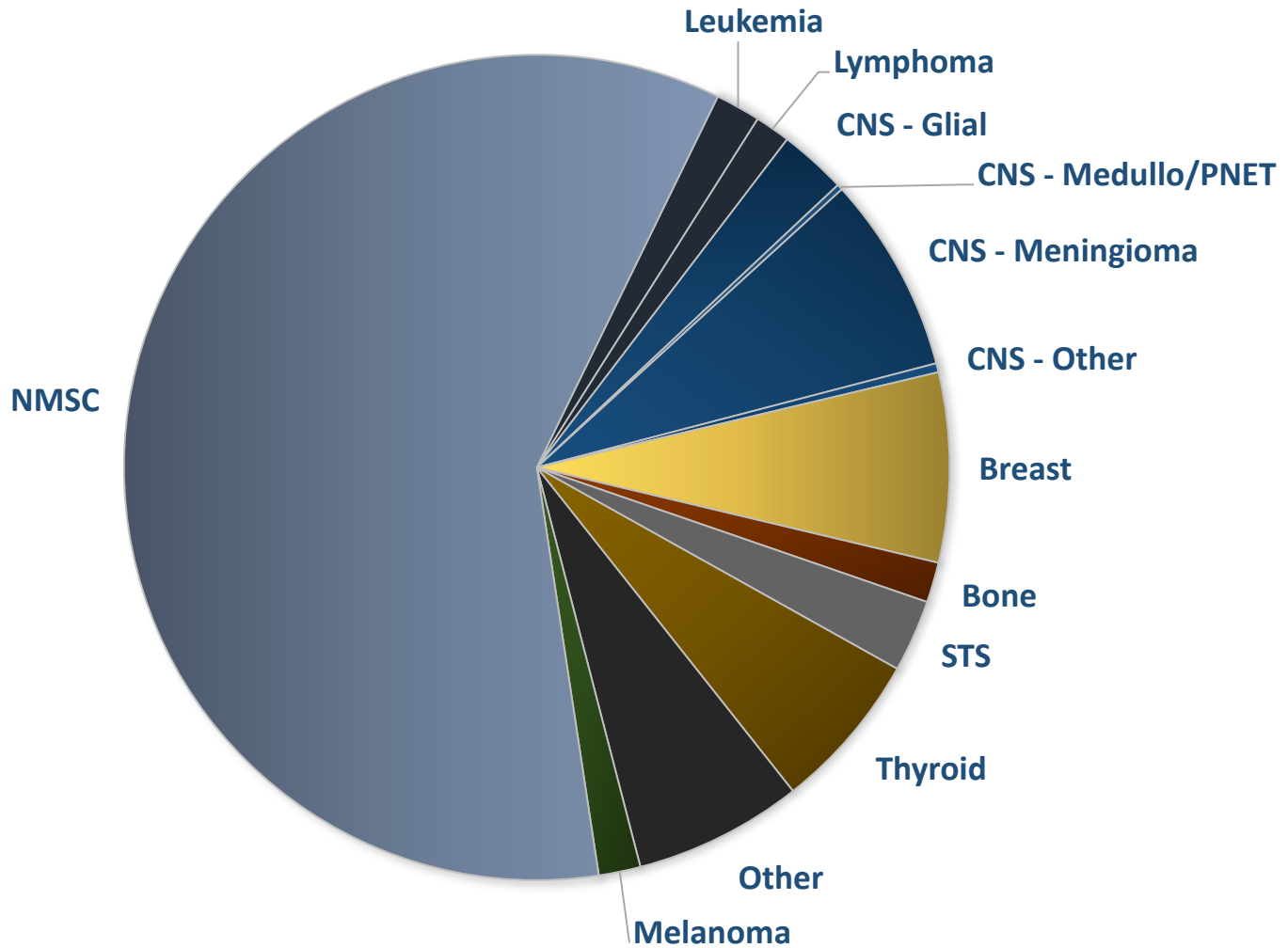
Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



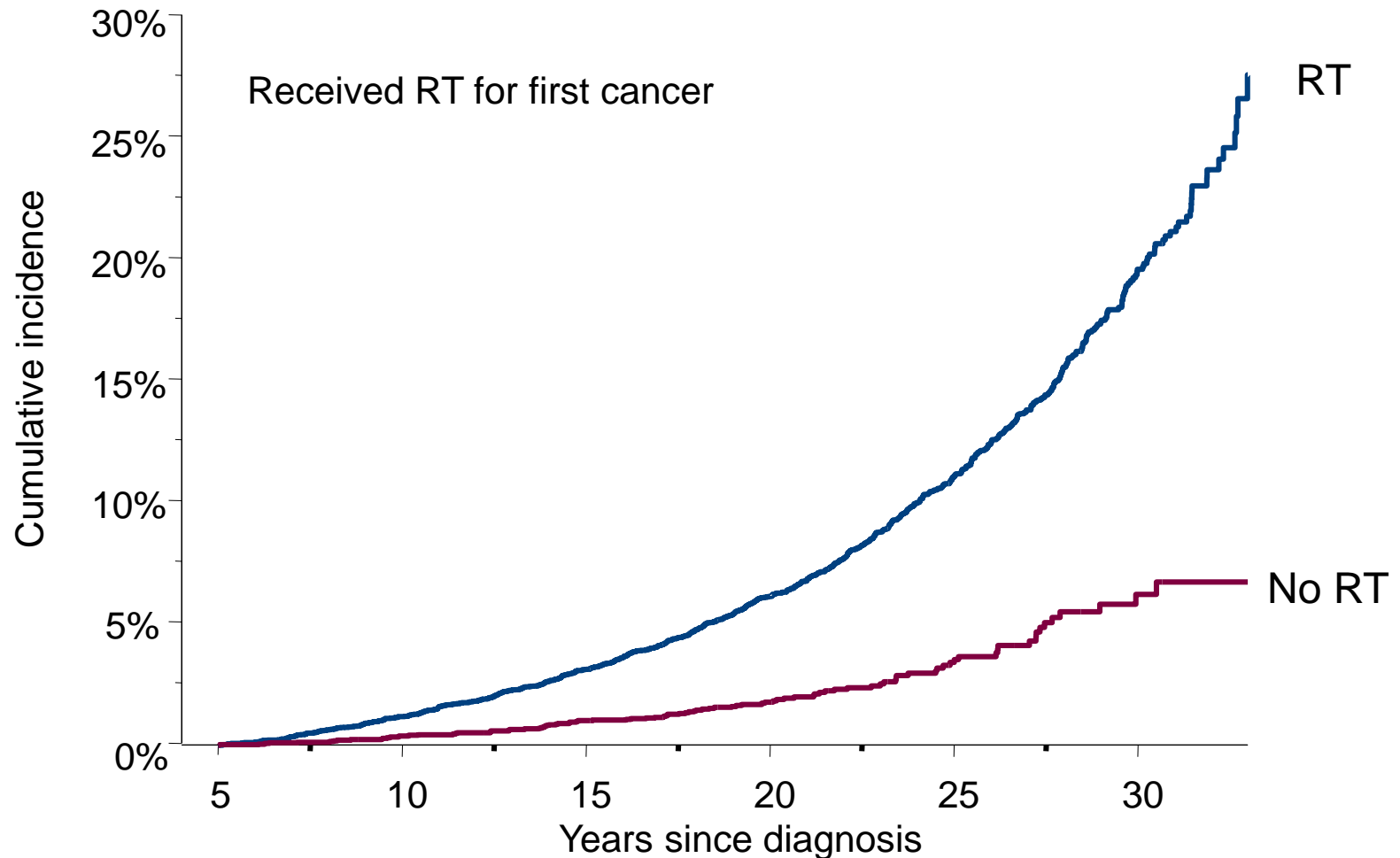
Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



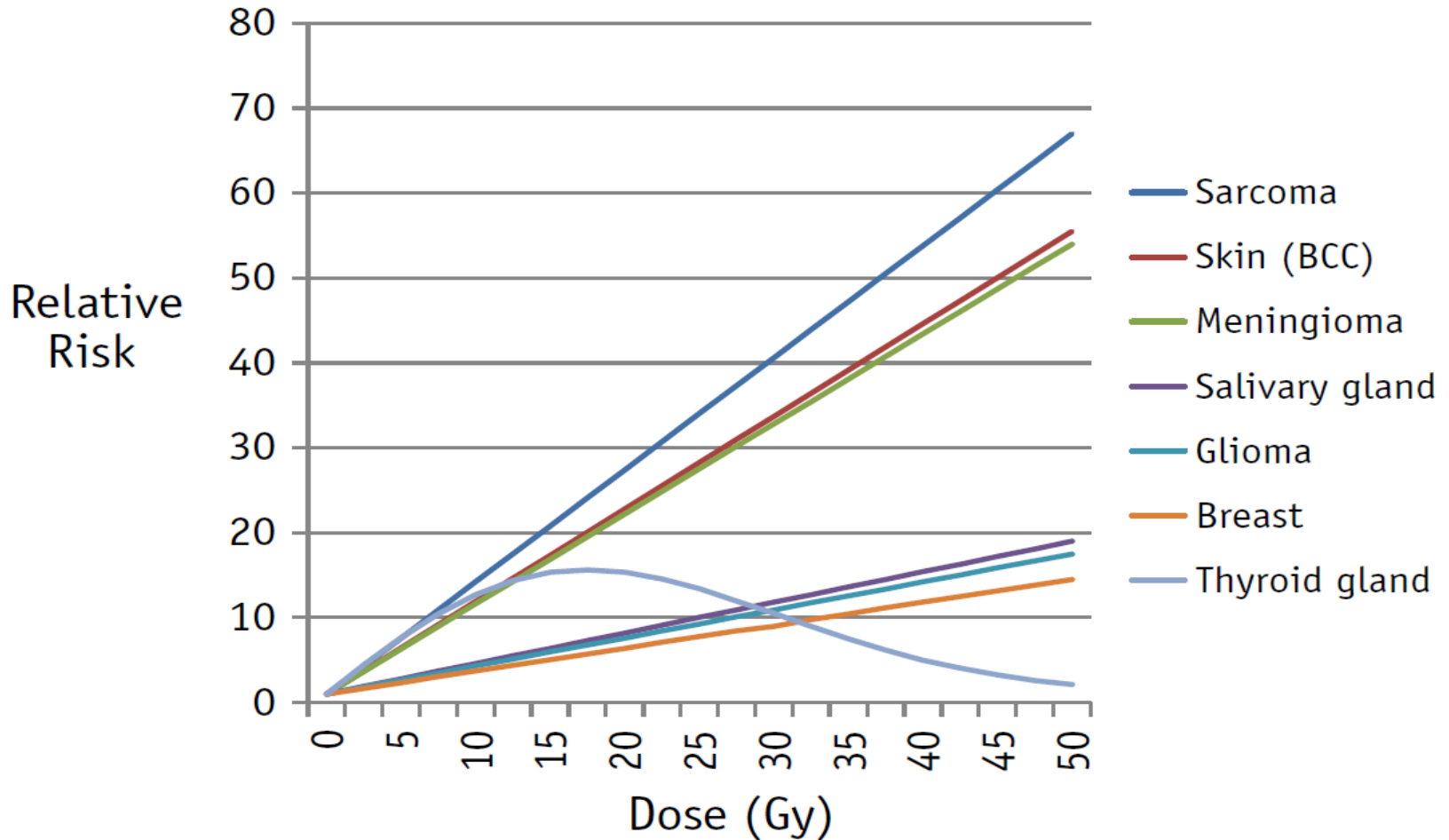
Distribution of Subsequent Neoplasms Original + Expanded Cohort (n=3115)



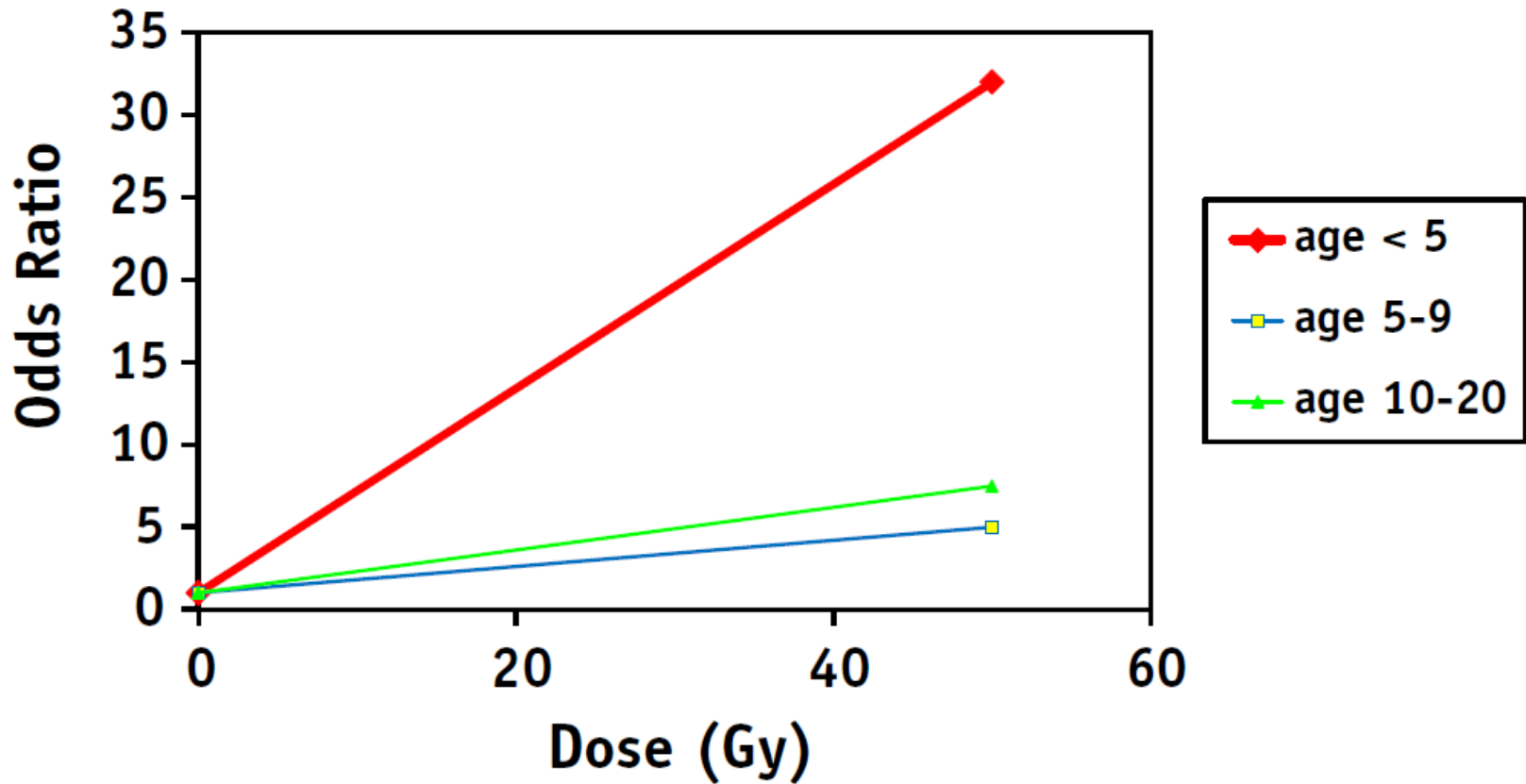
Second Neoplasms Occurring 5+ years Including Nonmelanoma Skin Cancer



RT Dose-Risk Relationship for Subsequent Neoplasms

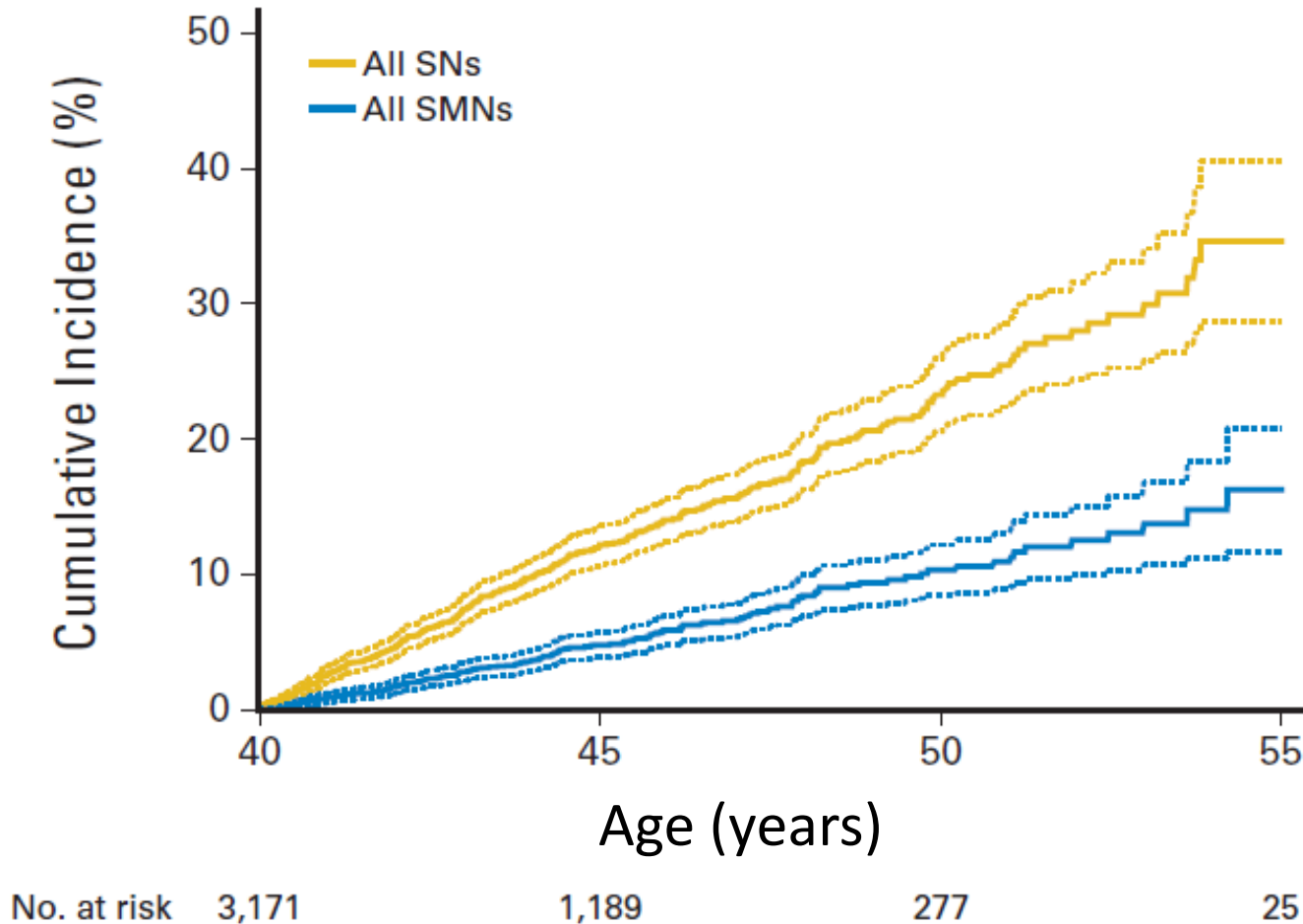


RT Dose-Risk Relationship for Subsequent Neoplasms



Late Occurring Subsequent Neoplasms

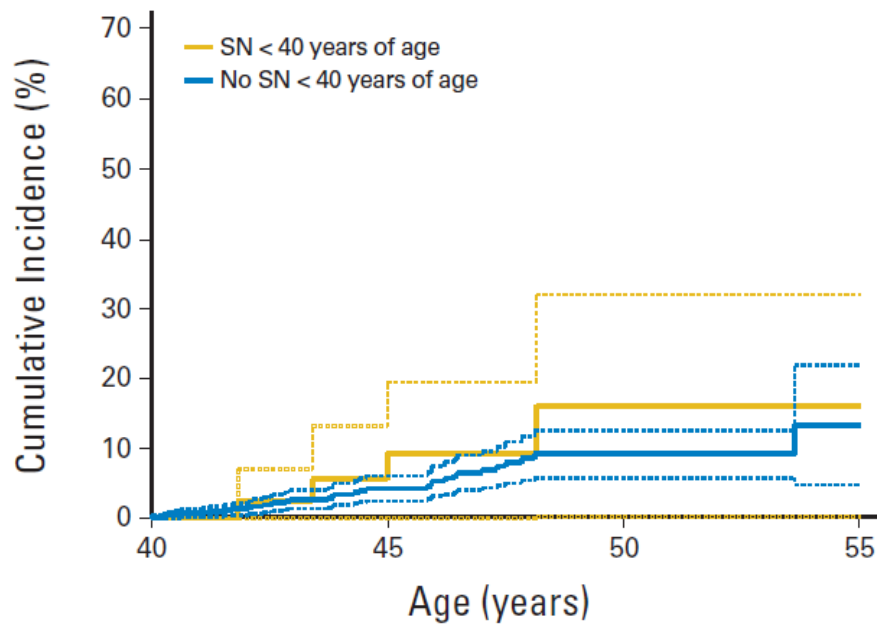
Subsequent Neoplasms after 40 years of age



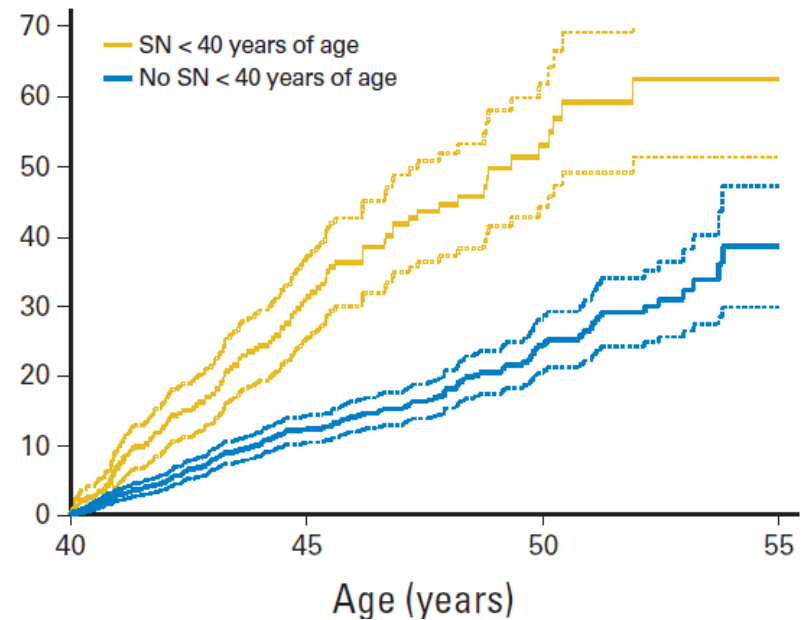
Late Occurring Subsequent Neoplasms

Subsequent Neoplasms after 40 years of age

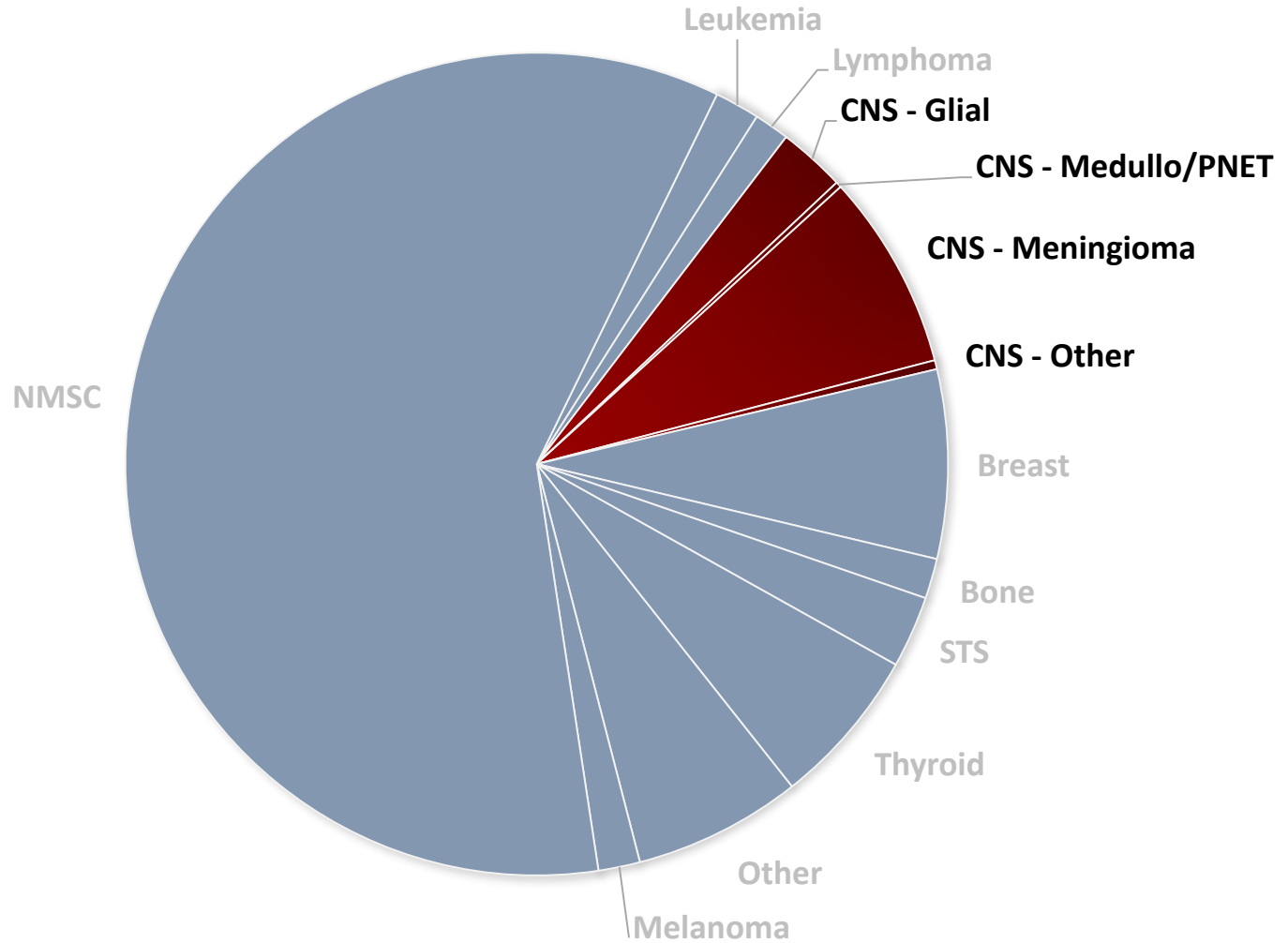
No Radiation Therapy



Radiation Therapy

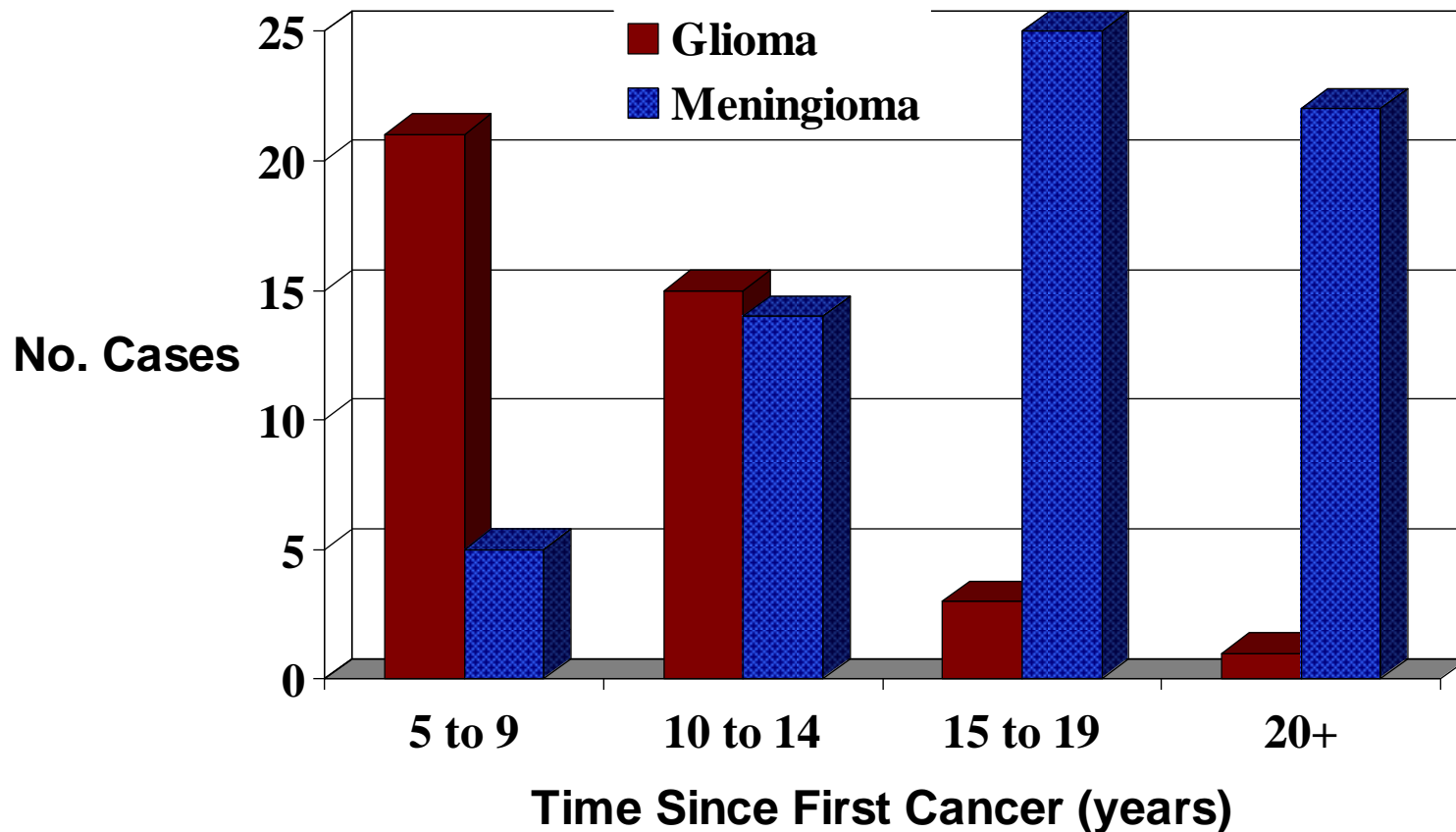


Distribution of Subsequent Neoplasms (n=3115)

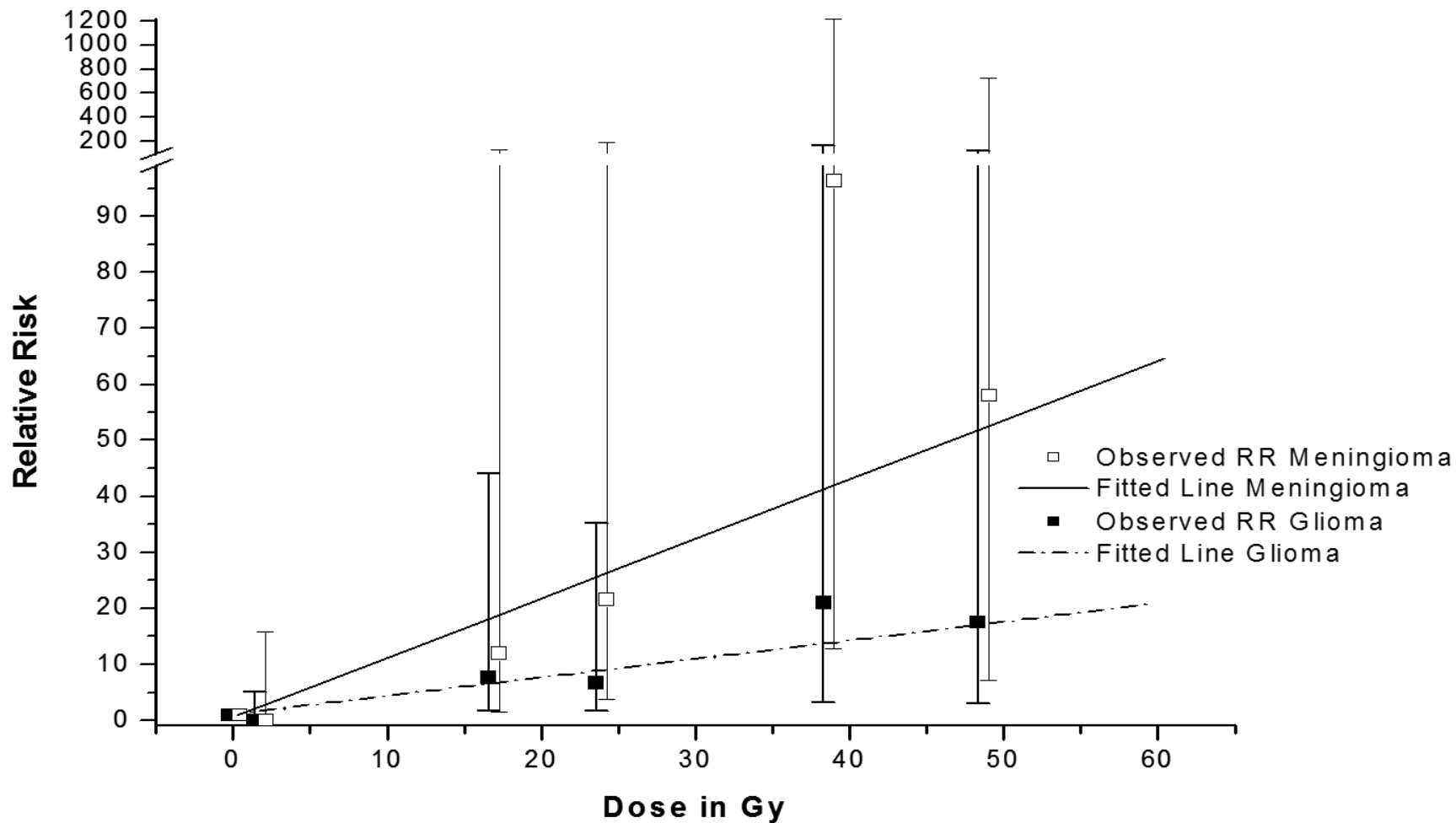


Brain Tumors Following Childhood Cancer

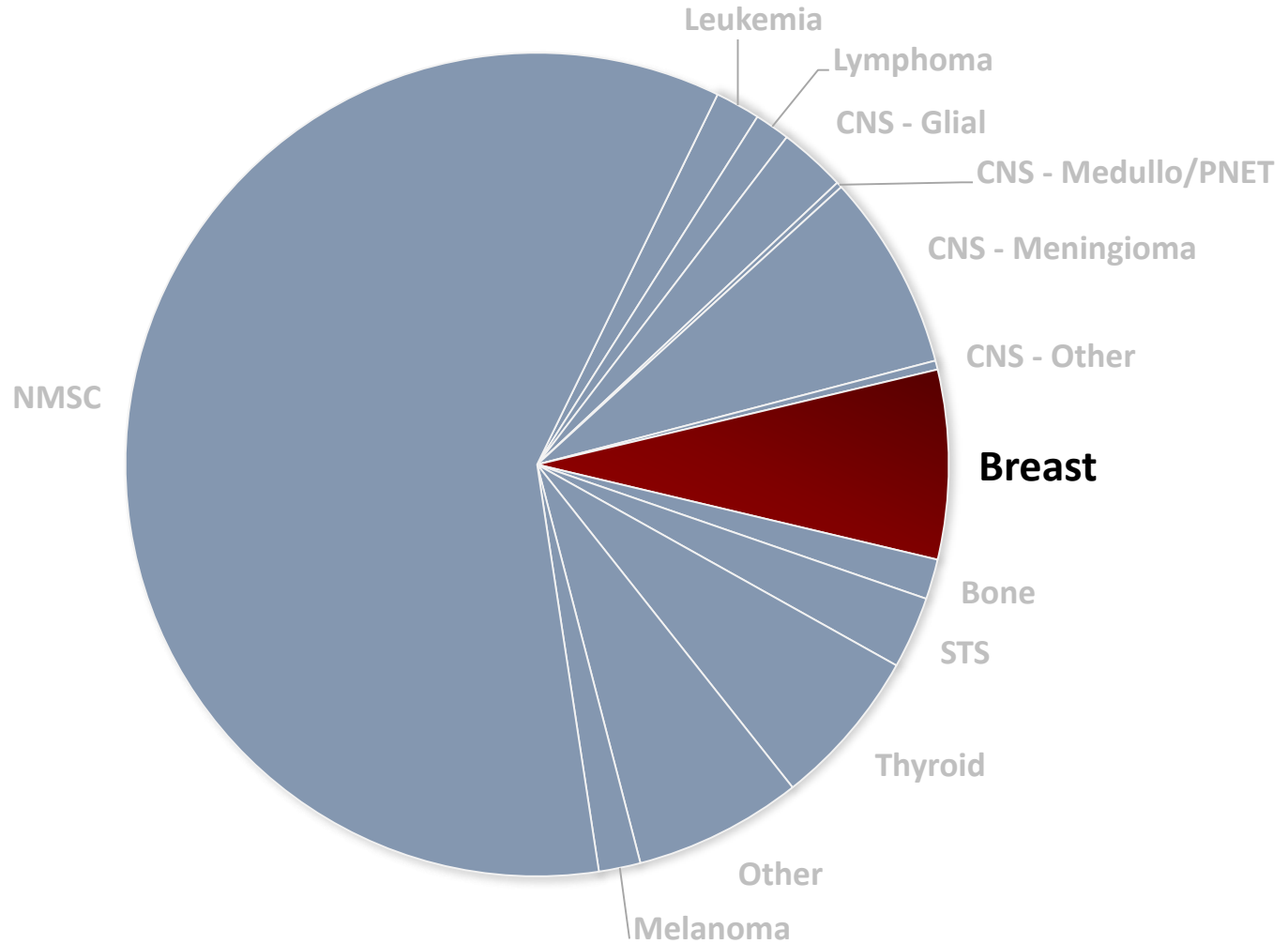
Glioma vs. Meningioma



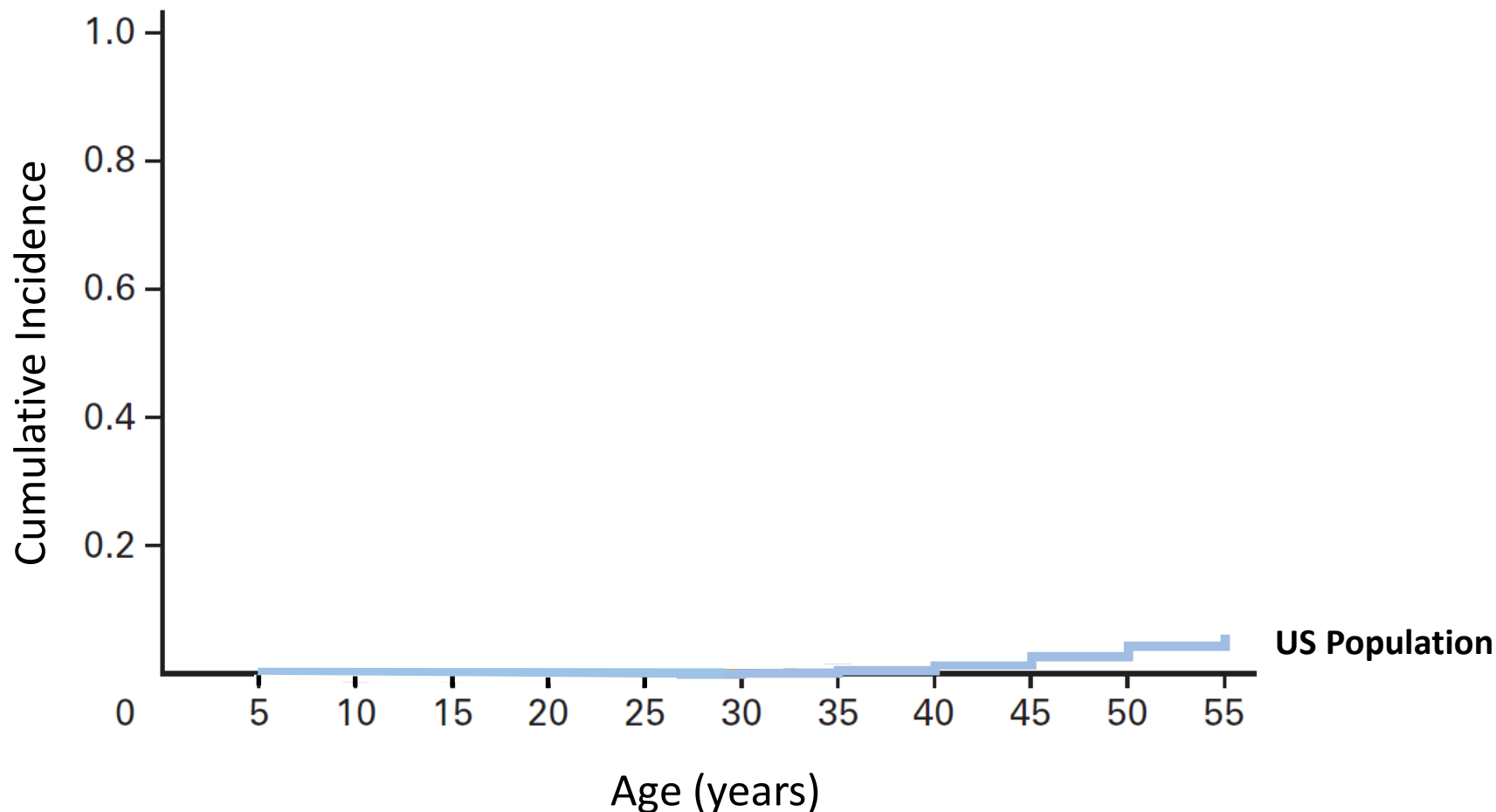
Brain Tumors Following Childhood Cancer Risk by Radiation Dose



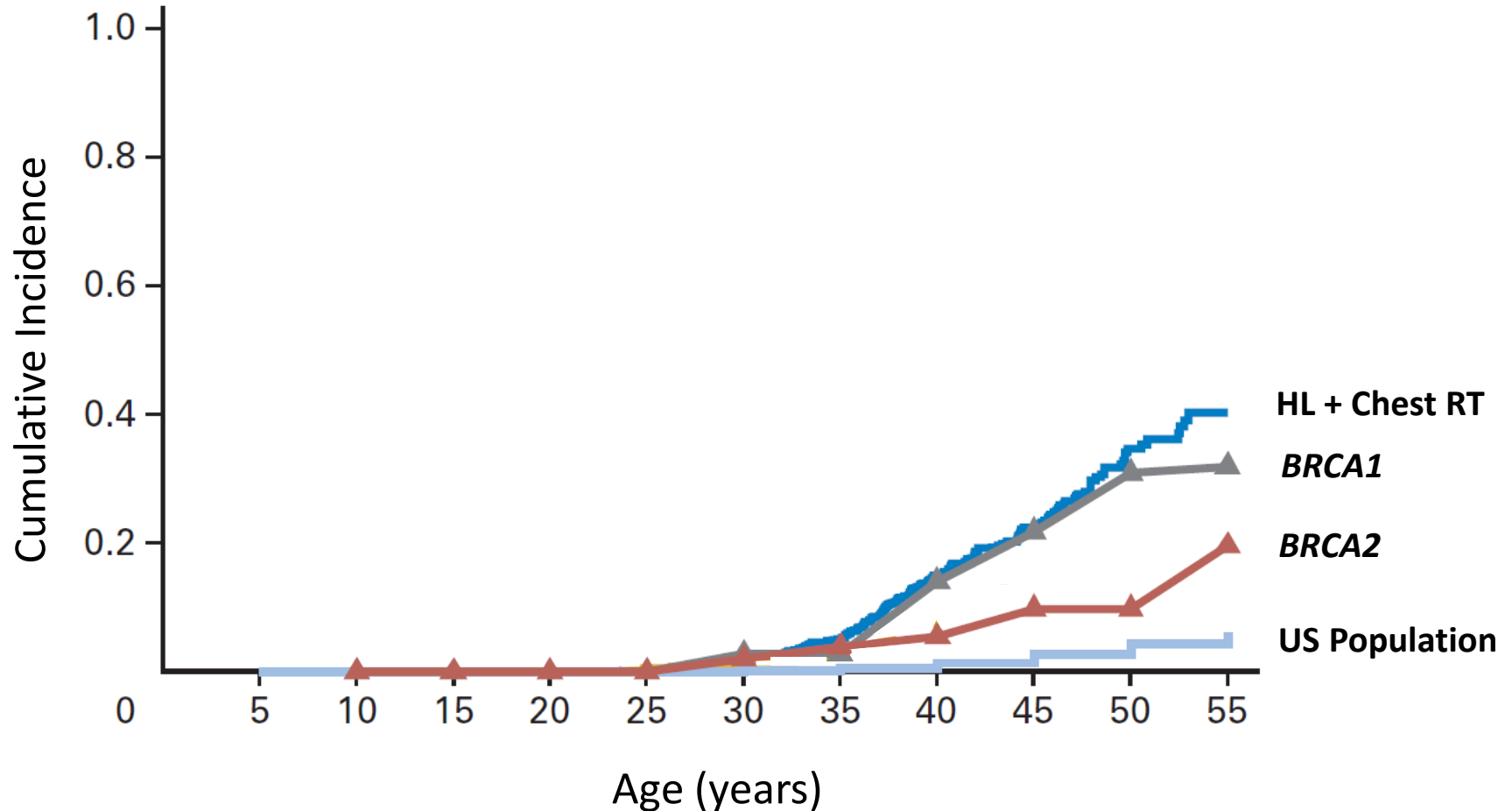
Distribution of Subsequent Neoplasms (n=3115)



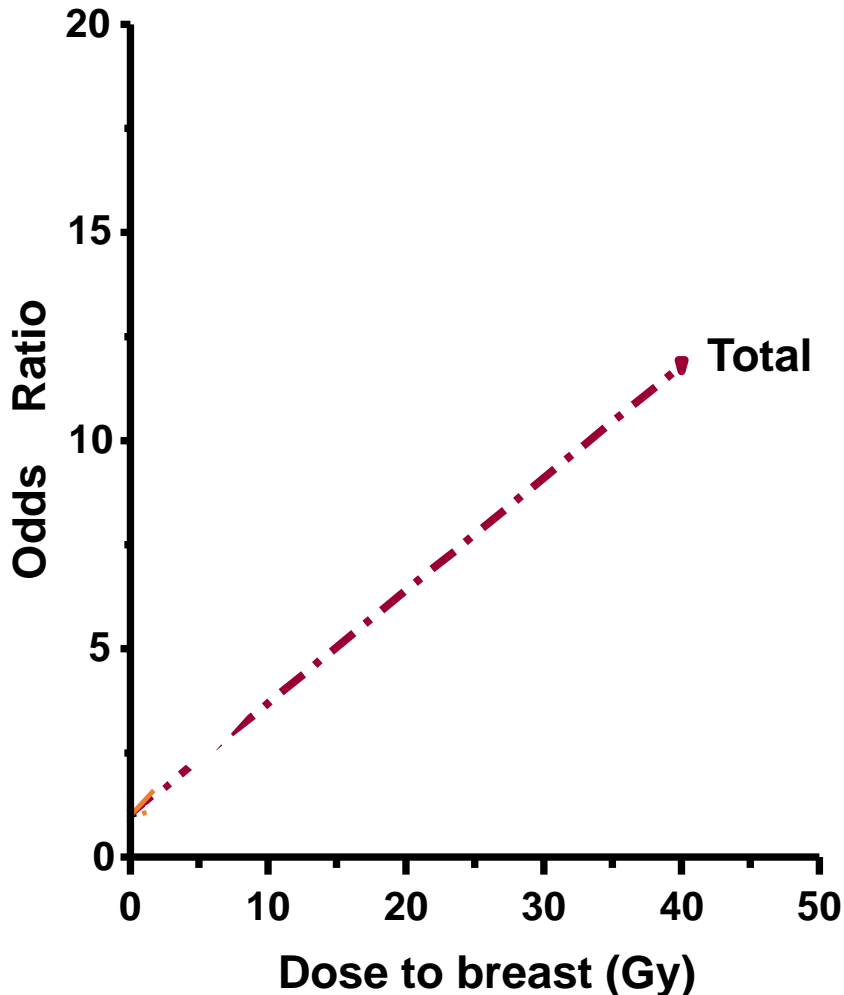
Cumulative Incidence of Breast Cancer Among Survivors of Pediatric Hodgkin Lymphoma



Cumulative Incidence of Breast Cancer Among Survivors of Pediatric Hodgkin Lymphoma

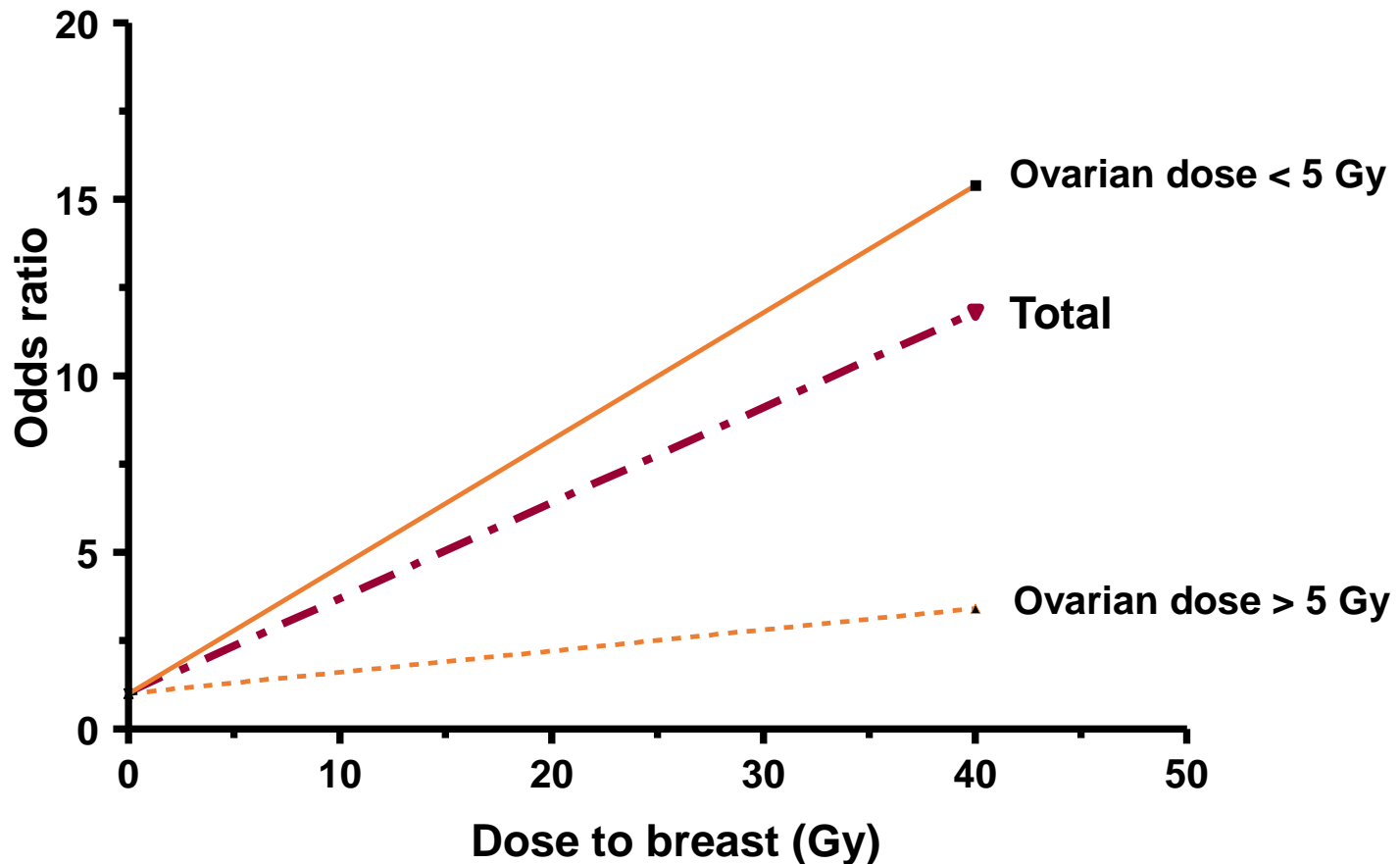


Dose-Risk Relationship for Tissue-Specific Radiation Exposure and Breast Cancer

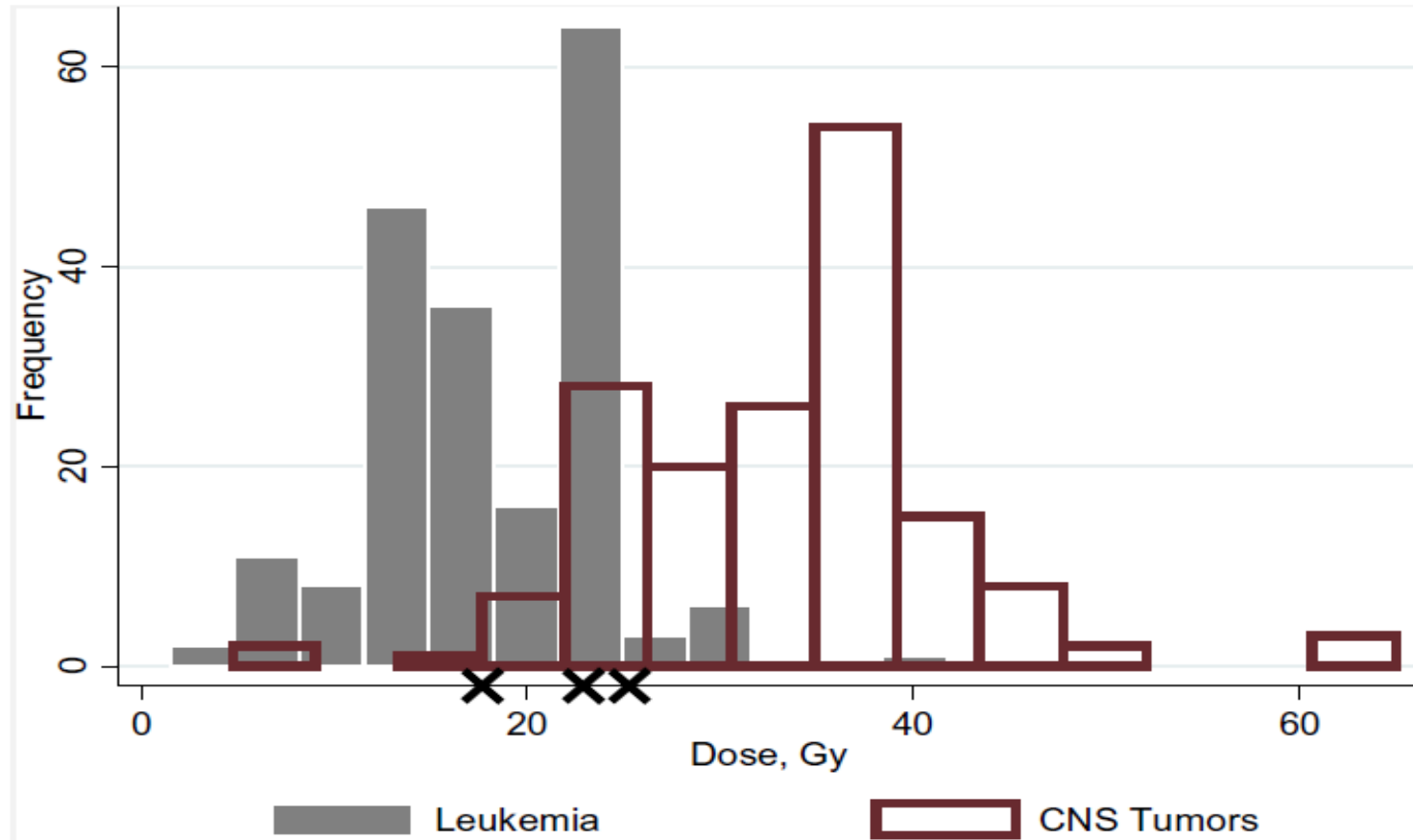


- Linear dose-response for secondary breast cancer
- 11-fold increased risk at 40 Gy (compared to no RT)
- Age at RT exposure not a risk factor for breast cancer
- Risk of breast cancer markedly reduced for women with ≥ 5 Gy ovarian RT

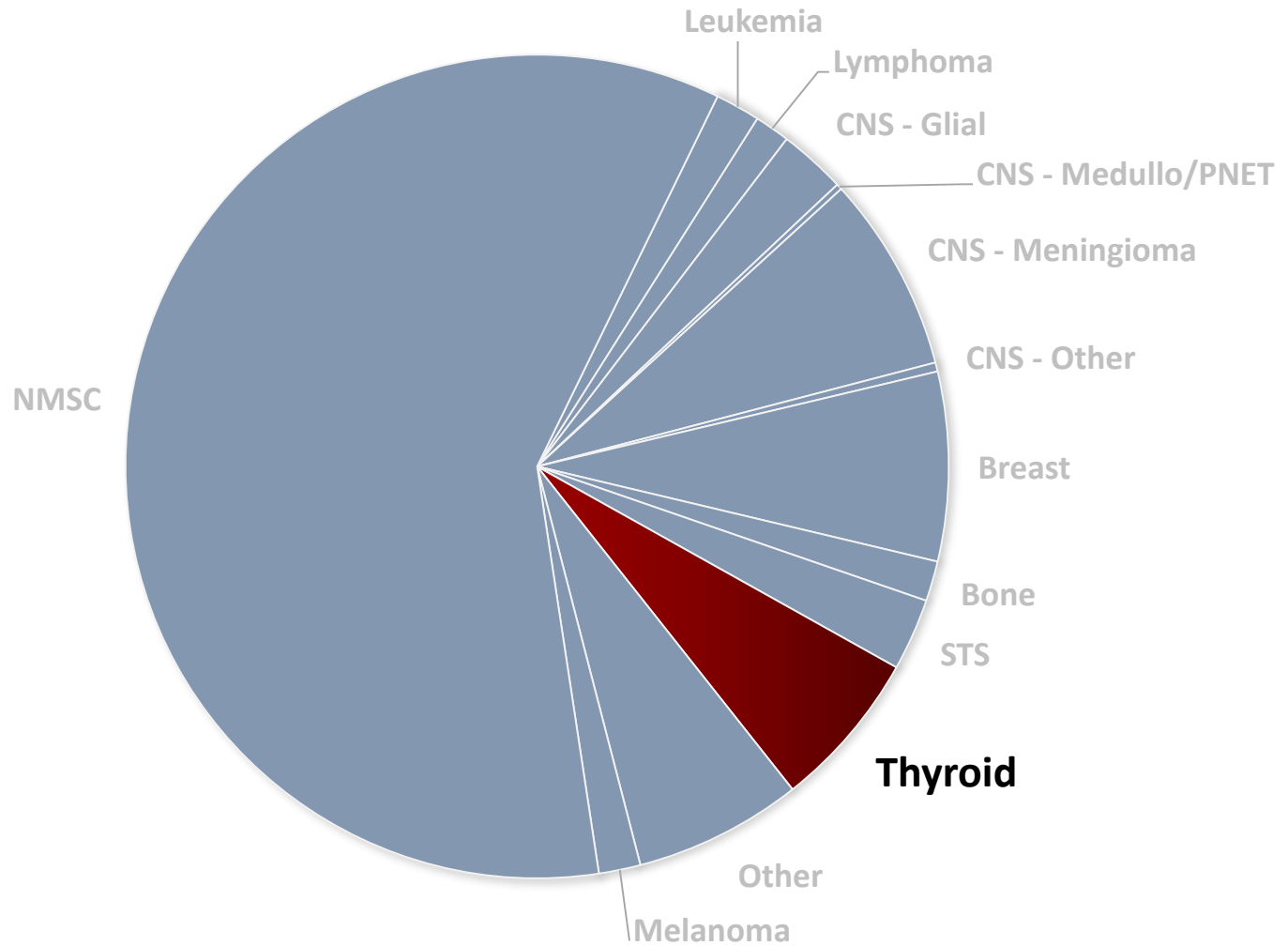
Radiation-Associated Risk of Breast Cancer in Childhood Cancer Survivors



Risk of Secondary Breast Cancer Following Spinal Field Radiation



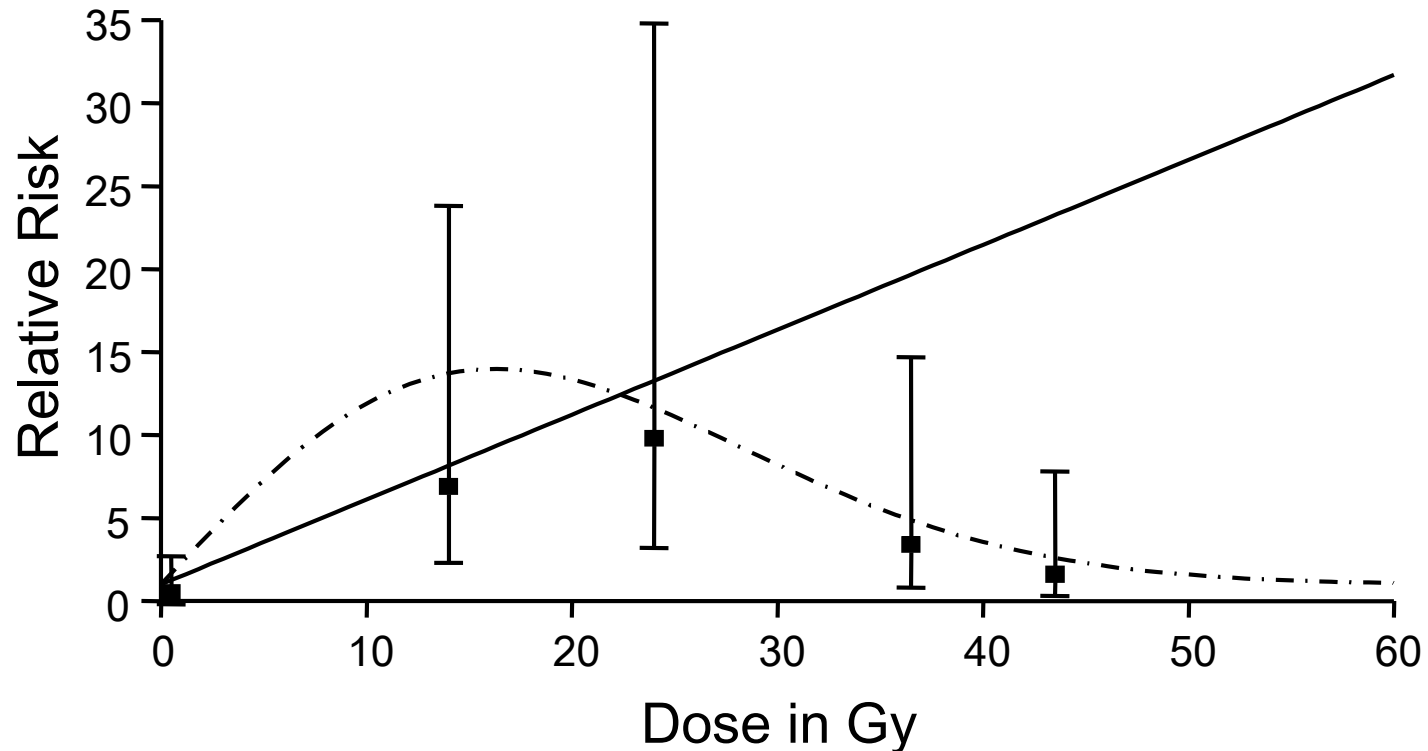
Distribution of Subsequent Neoplasms (n=3115)



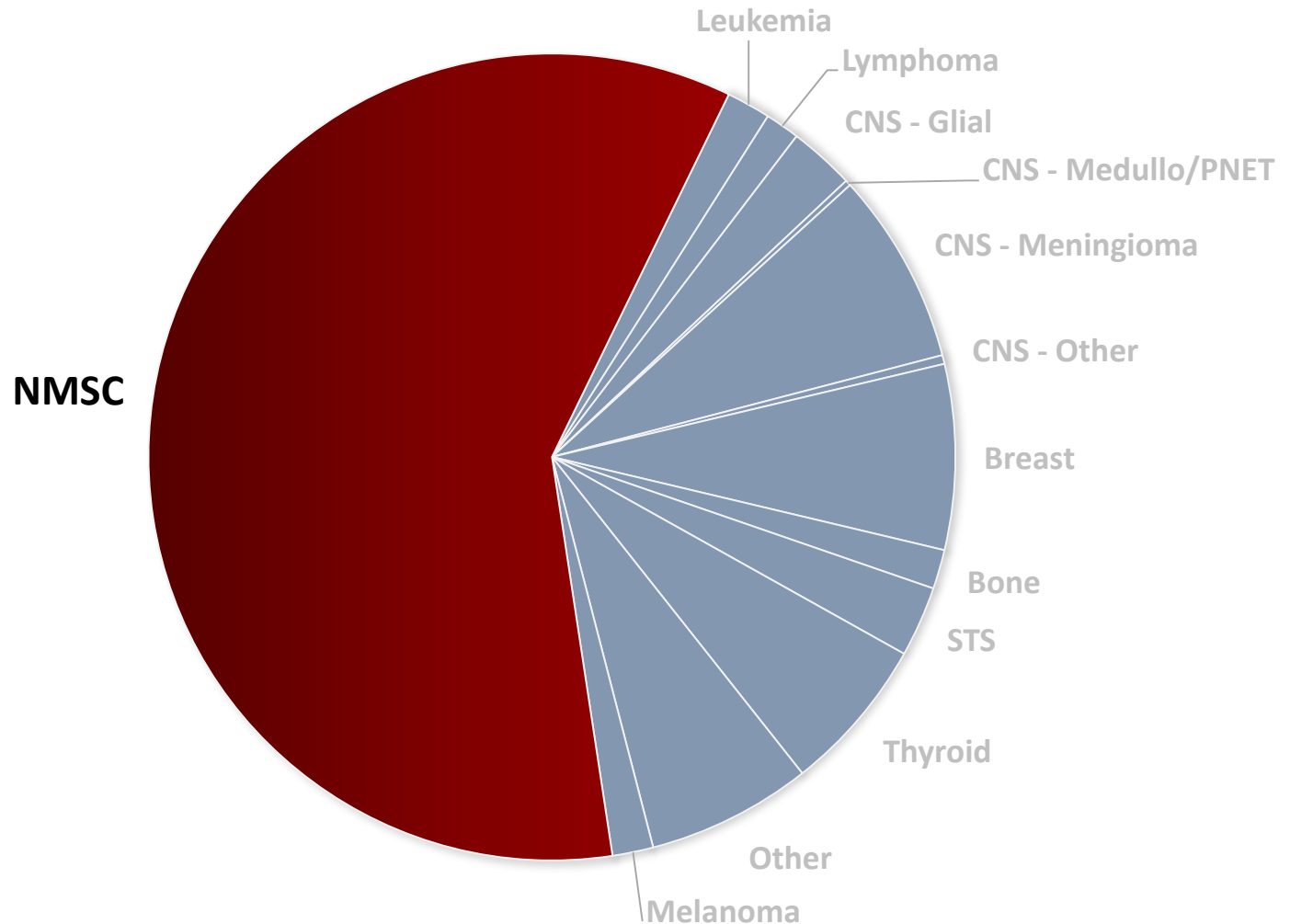
Thyroid Malignancy Among Long-term Survivors of Childhood Cancer

Dose Response Models of Relative Risk

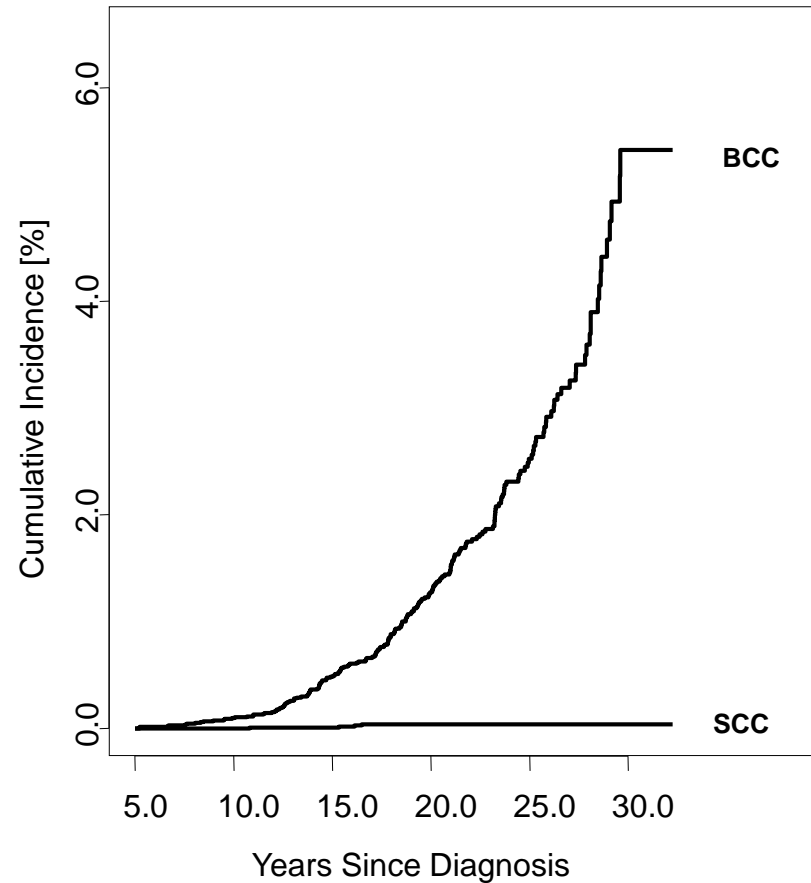
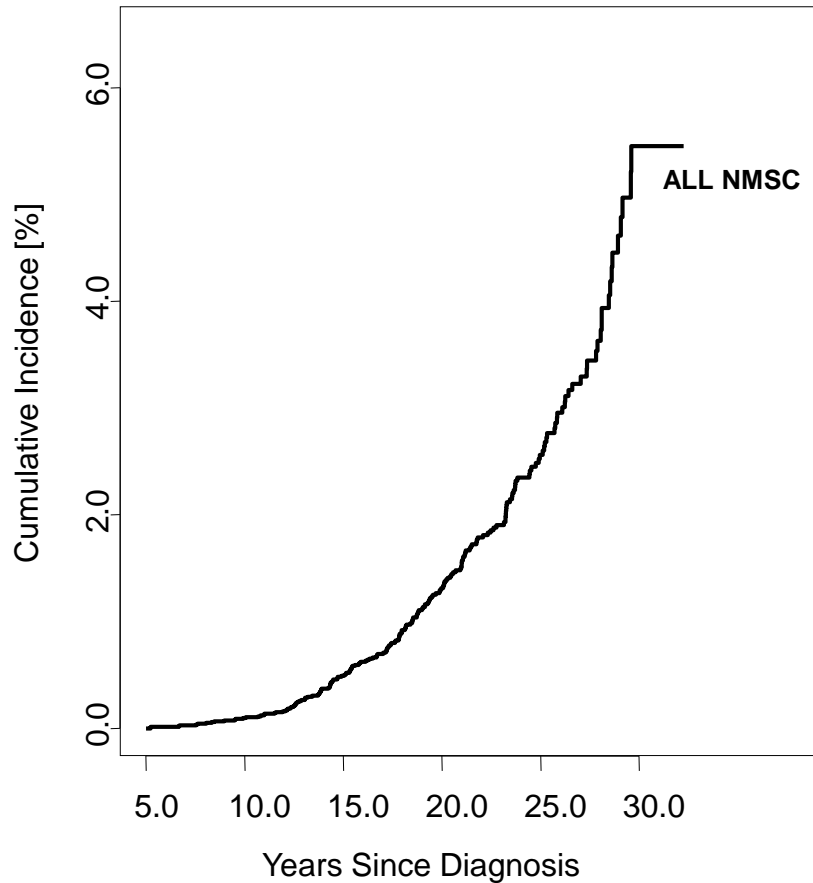
- Linear $1 + 0.5117(\text{dose})$
- · - · - Linear Exponential $1 + [1.316(\text{dose})]e^{-0.00189(\text{dose} \times \text{dose})}$



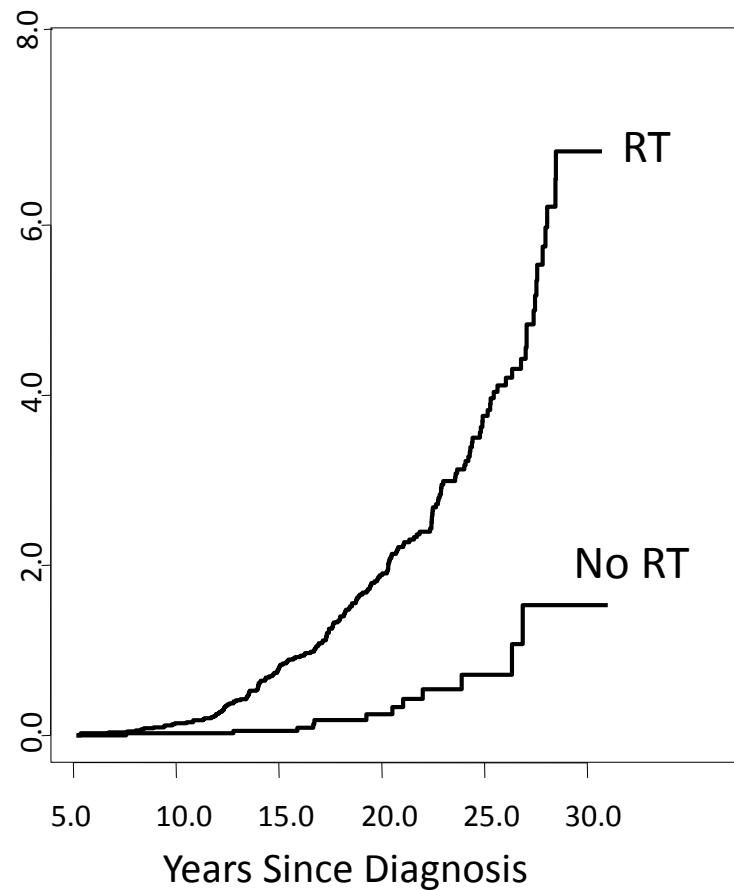
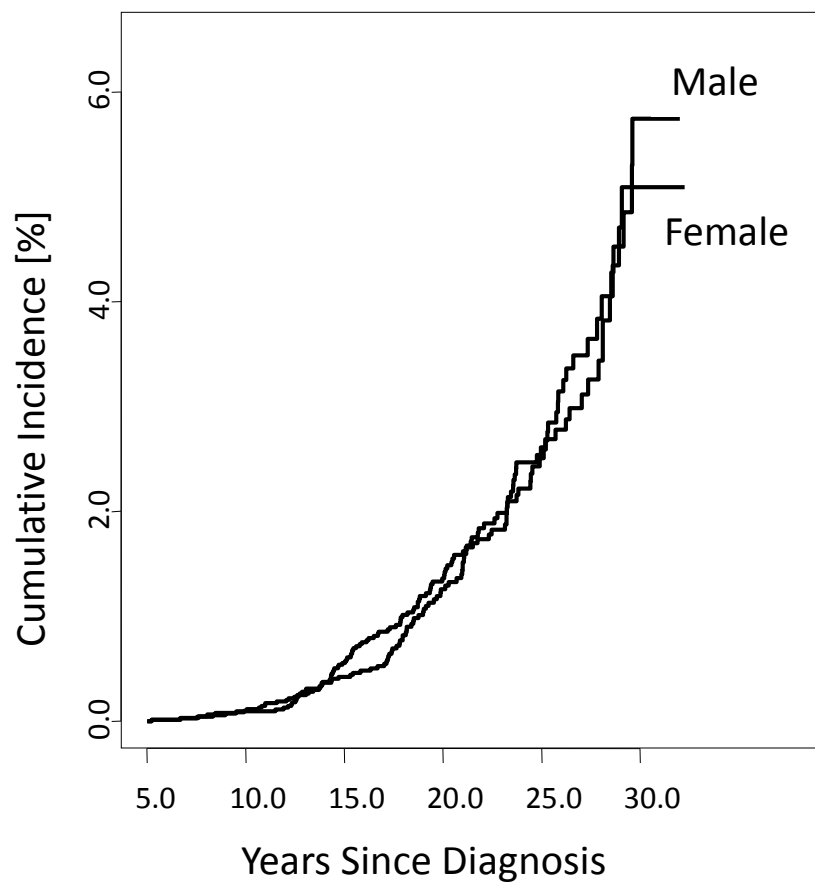
Distribution of Subsequent Neoplasms (n=3115)



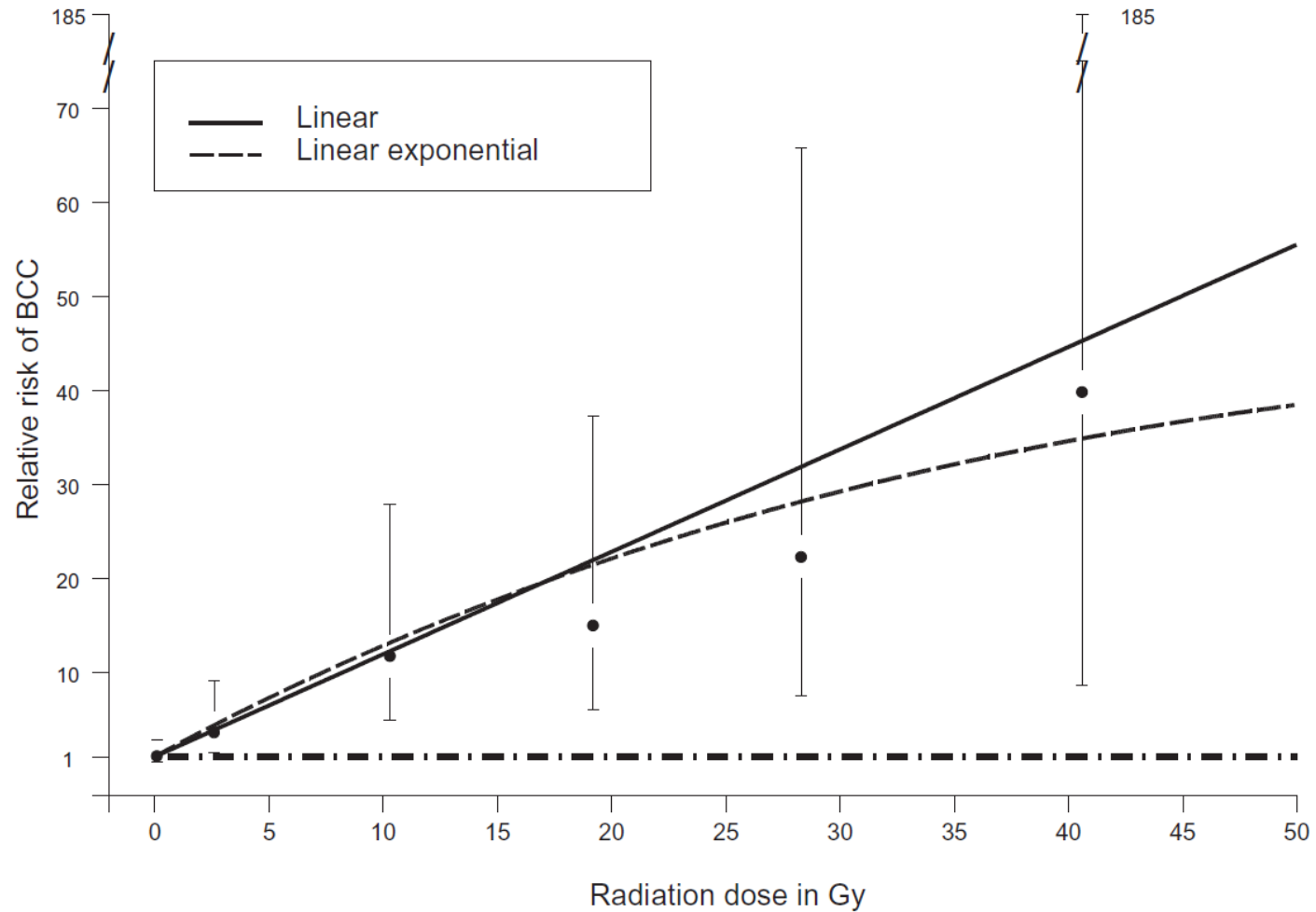
Childhood Cancer Survivor Study Subsequent Neoplasms



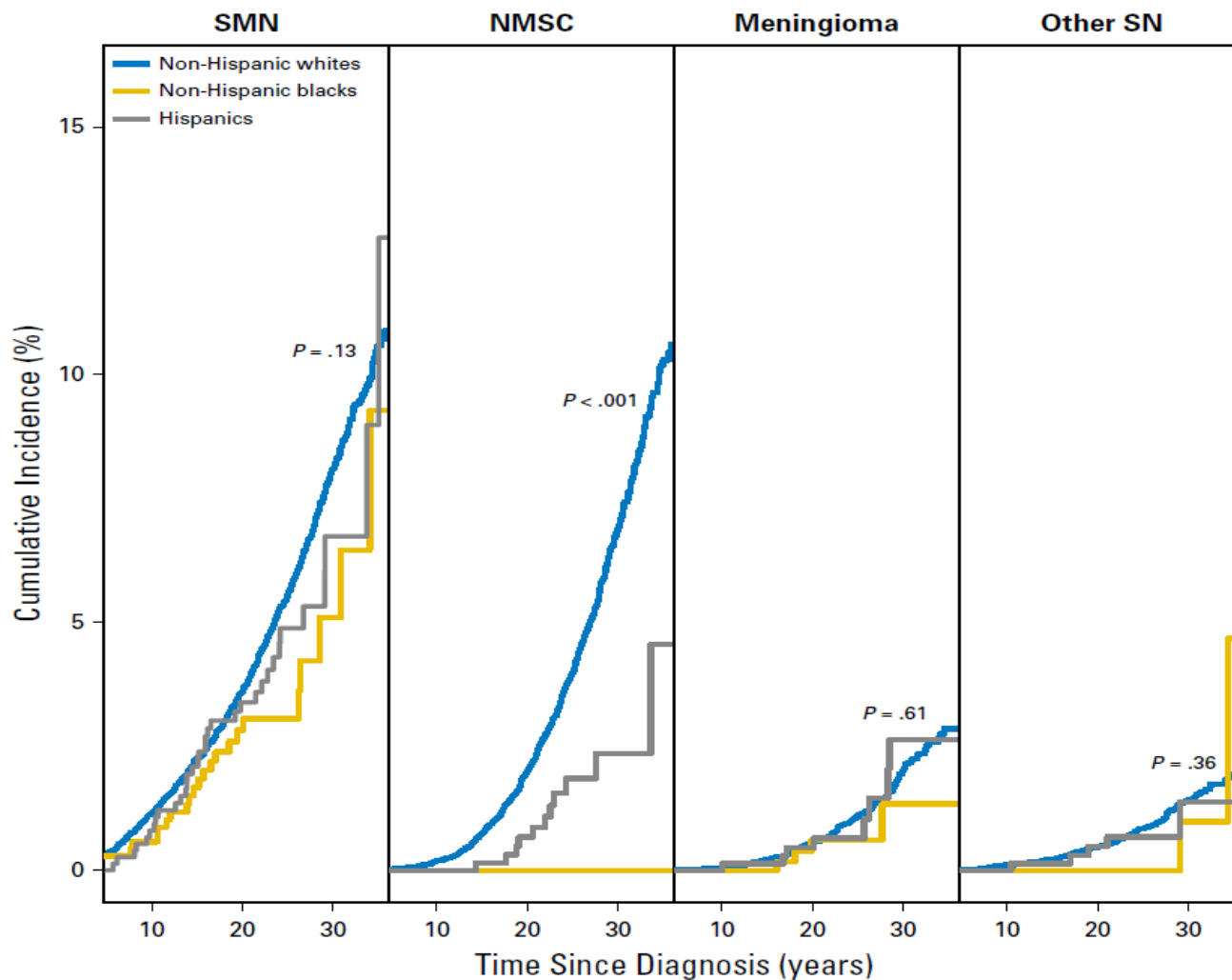
Cumulative Incidence of Nonmelanoma Skin Cancer



Radiation-related Risk of Basal Cell Carcinoma



Race Specific Radiation-Associated Second Neoplasms



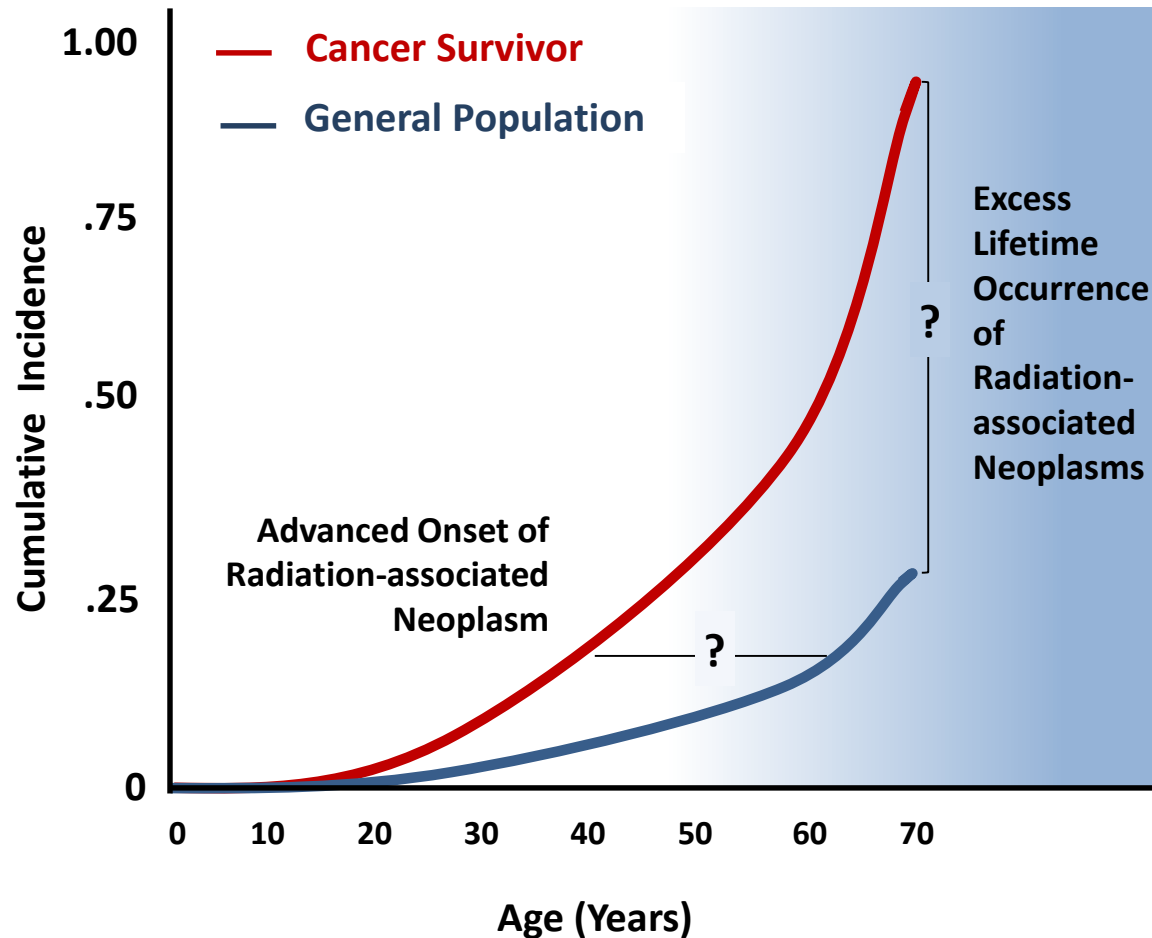
Race Specific Radiation-Associated Second Neoplasms

St. Jude Lifetime Cohort Study

SNs	Irradiated white survivors N = 1,509			Irradiated black survivors N = 237					
	No. of pts. with SNs	No. of SNs	Rate ^a	No. of pts. with SNs	No. of SNs (O)	Rate ^a	Expected (E)	O/E	95% CI
BCC	150	560	19.17	0	0	0.00	56.07	0.00	(0.00–0.07)
Nonradiation associated									
SCC	33	41	1.40	2	2	0.51	5.14	0.39	(0.04–1.41)
Non-BCC radiation associated ^b	160	320	10.95	14	30	7.61	34.22	0.88	(0.59–1.25)
Brain	98	232	7.94	9	25	6.34	21.60	1.16	(0.75–1.71)
Thyroid	53	63	2.16	4	4	1.01	8.53	0.47	(0.13–1.20)
Breast ^c	18	22	1.59	1	1	0.52	3.89	0.26	(0.00–1.43)
Melanoma	3	3	0.10	0	0	0.00	—	—	—

Author, year	Description	Median (range) follow-up duration (years)	White BCC/total irradiated	Black BCC/total irradiated
Walther and colleagues, 1981 (22)	Case report of child irradiated for tinea capitis	36	NA	1/1
Shore and colleagues, 2002 ^b (21)	U.S. children with tinea capitis	39.3 (16.1–46.9)	124/1,699	3/525
Schwartz and colleagues, 2009 ^c (17)	Fred Hutchinson Cancer Center hematopoietic stem cell transplant survivors	6.6 (0.3–36.2)	197/3,512	0/60
Liu and colleagues, 2016 (25)	CCSS participants	25.1 (6.5–38.9)	1,116/7,527	0/313 ^d

Gaps in Knowledge Regarding Long-term Radiation-Associated Cancer Risks



- Newer treatment techniques (IMRT, Proton)
- Genetic contributions to risk
- Radiation and Chemotherapy interactions
- Role of lifestyle factors

Childhood Cancer Survivor Study

A RESOURCE FOR RESEARCH

- The Childhood Cancer Survivor Study is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit:

www.stjude.org/ccss