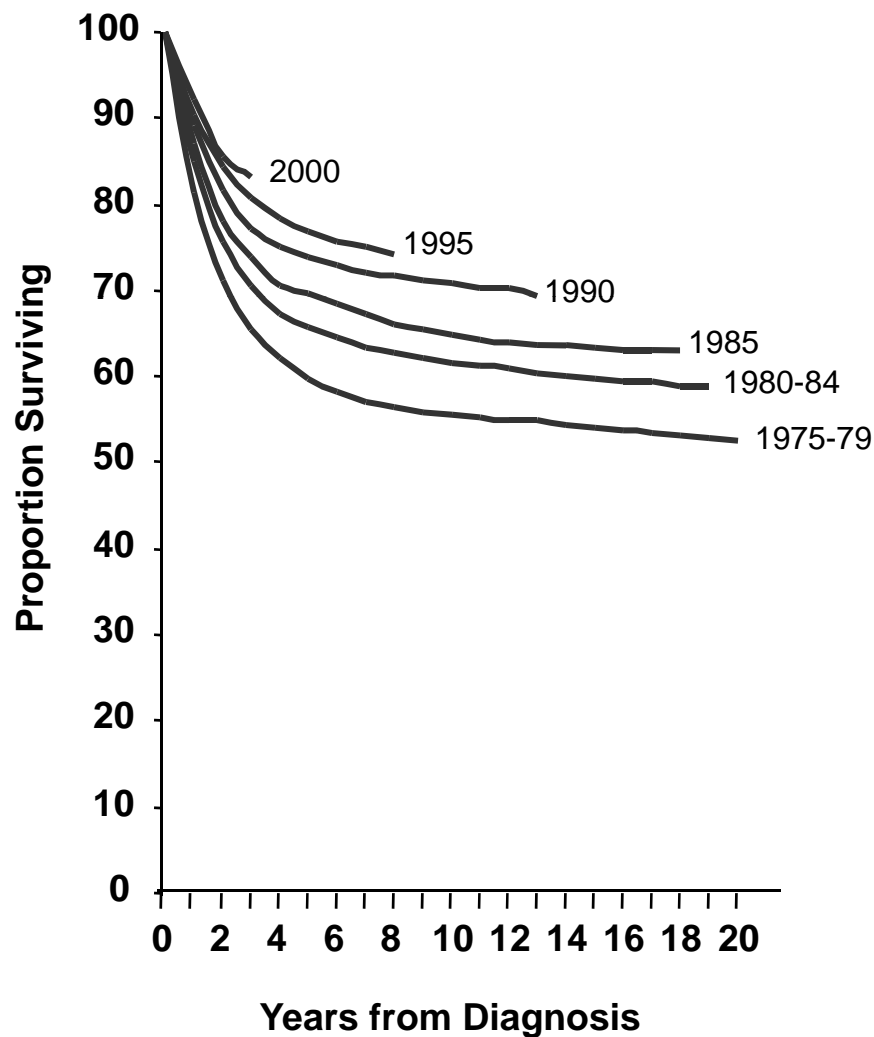


# Long-term Effects of Radiation Exposure Among Adult Survivors of Childhood Cancer

Leslie L. Robison, Ph.D.  
Department of Epidemiology and Cancer Control  
St. Jude Children's Research Hospital  
Memphis, TN



# Cancer Survival, 0-14 Years of Age SEER Program 1975-2005



## Survivorship Statistics\*

- In 2005, estimated 328,600 childhood cancer survivors in the U.S.
- 1 in 900 is a survivor of childhood cancer
- 1 in 680 is a childhood cancer survivor (ages 20 to 50 years)

\* Source: NCI Office of Cancer Survivorship, Mariotto et al, CEBP, 2009

# Childhood Cancer Survivors in US\*

Jan. 2005 for cases diagnosed 0-19 years of age

<b>Total</b>	<b>328,652</b>
ALL	49,271
AML	6,355
Hodgkin	31,598
NHL	18,668
CNS	51,650
Neuroblastoma	16,141
Renal	20,411
Osteosarcoma	8,145
Ewing sarcoma	3,947
Soft tissue sarcoma	27,544

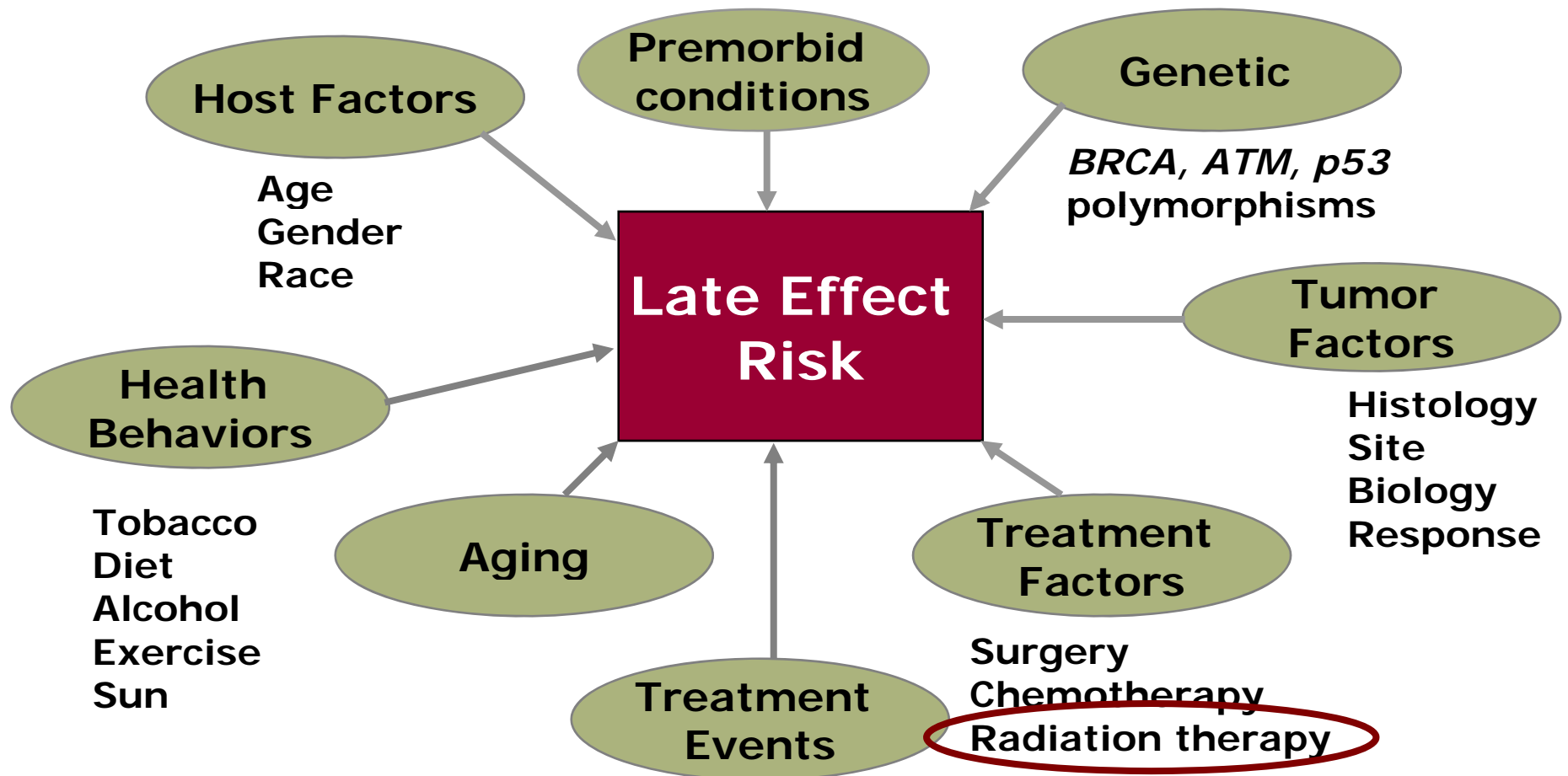
\* Source: NCI Office of Cancer Survivorship, Mariotto et al, CEBP, 2009

# Selected Health-Related Outcomes of Childhood Cancer Survivors

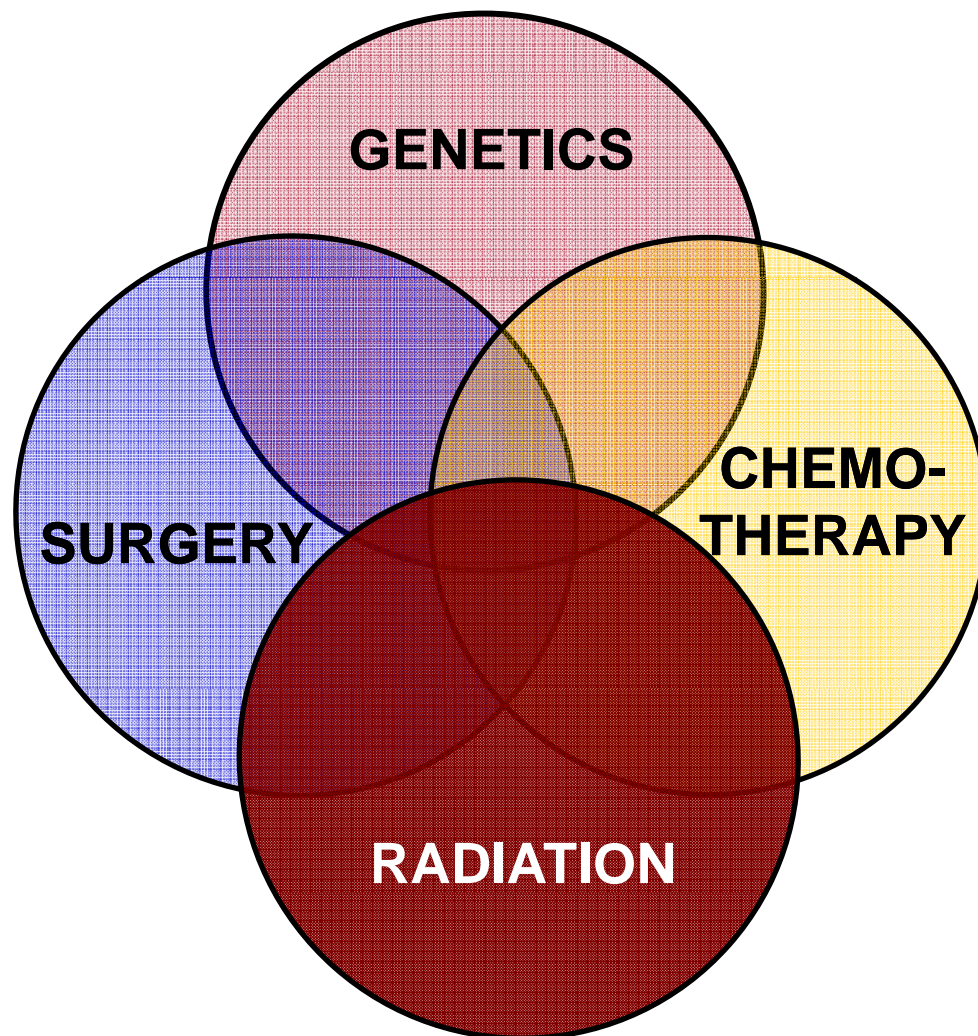
Cardiac/vascular  
Cytogenetic  
Dental  
Endocrinologic  
Educational  
Gastrointestinal  
Hearing  
Hepatic  
Neurologic

Neurocognitive  
Ophthalmologic  
Orthopedic  
Psychosocial  
Pulmonary  
Renal  
Reproduction  
Second Cancers  
Skeletal

# Issues in Survivorship Research

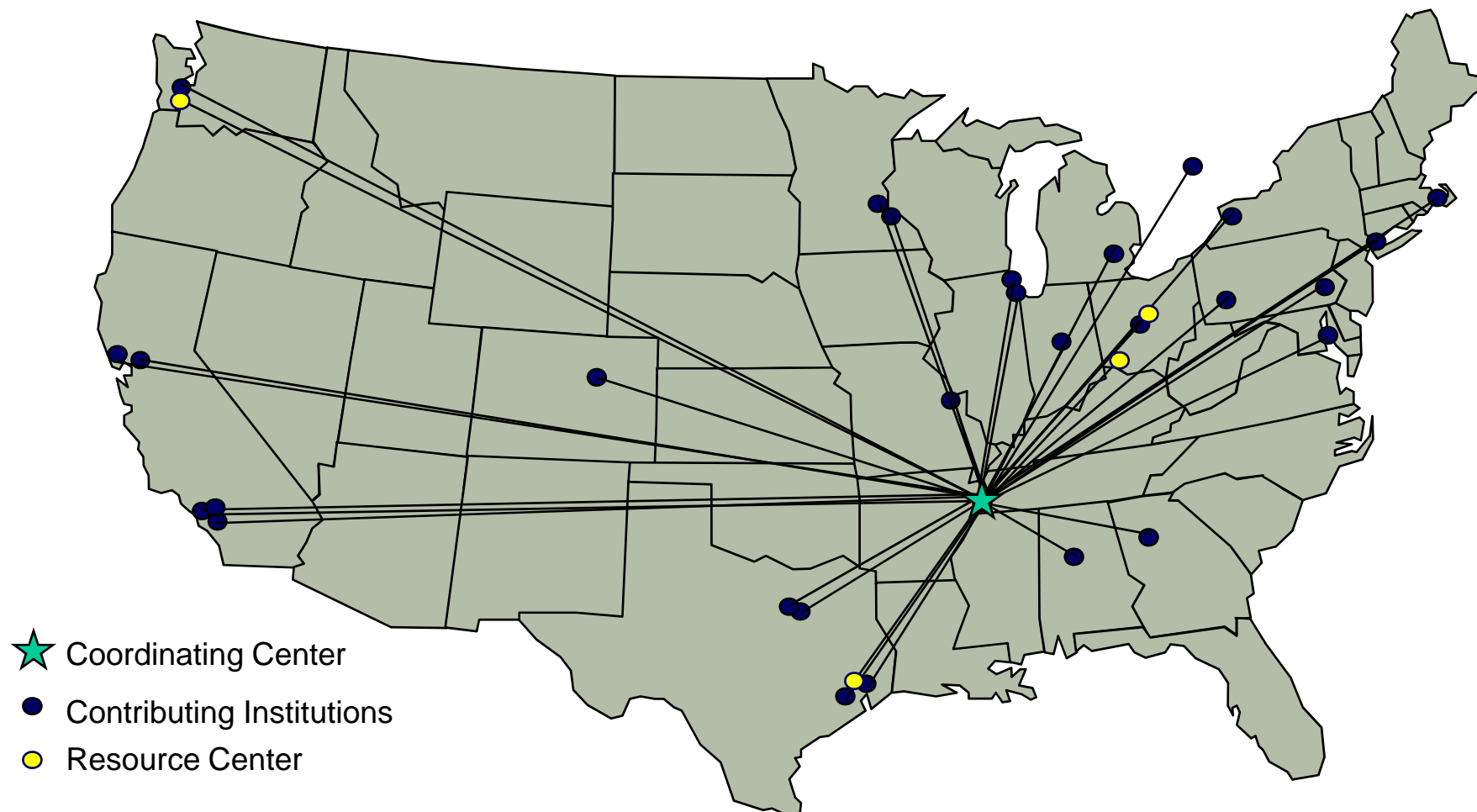


# Assessment of Risk for Late Effects



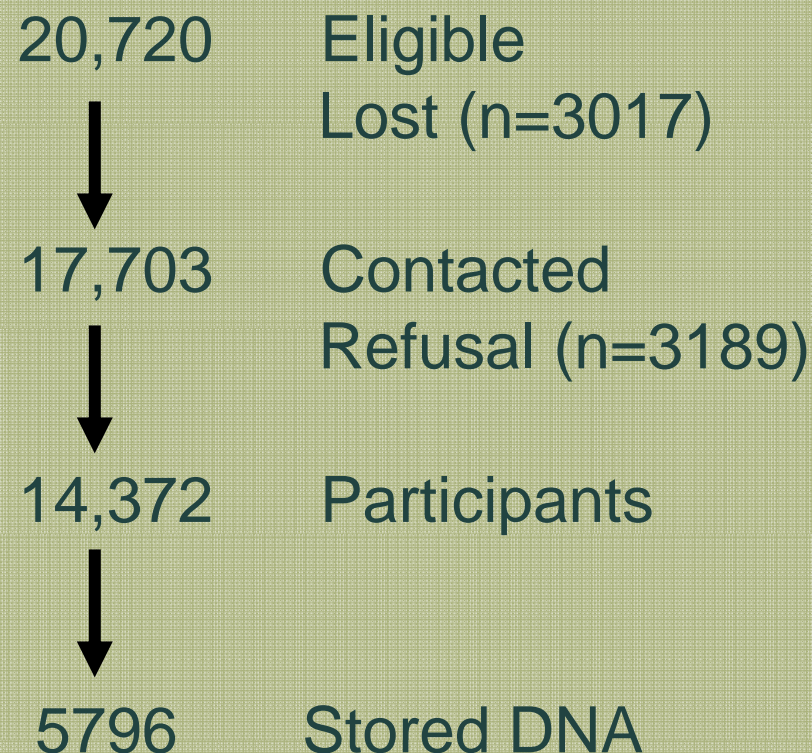
# Childhood Cancer Survivor Study (U24 CA 55727)

## Participating Centers



## Childhood Cancer Survivor Study (U24 CA55727)

- Funded in 1994
- Retrospective Cohort, diagnosed 1970-1986
- 26 Contributing Centers
- 5-Year Survival (median age=23yrs, range 5-45)
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Detailed Treatment Data, Wide Range of Outcomes
- 100+ Publications since 2001



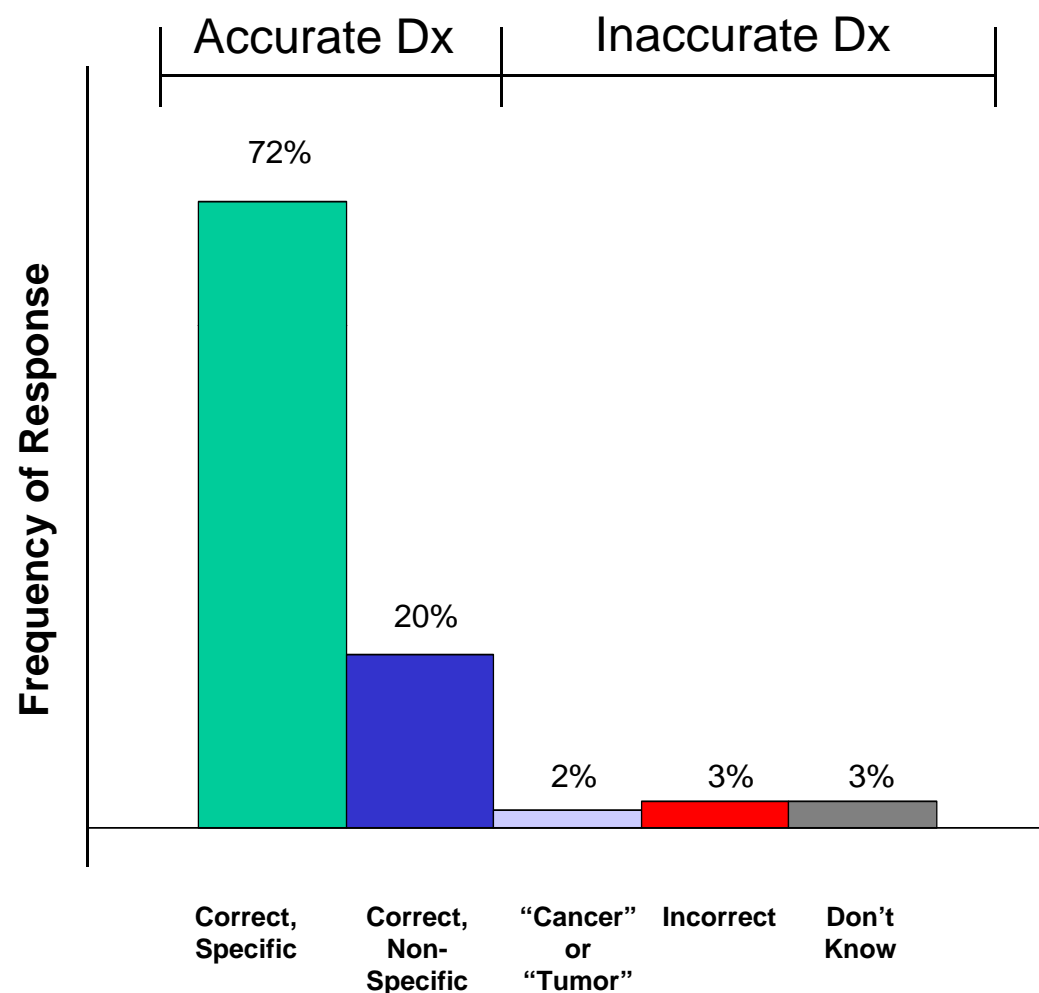
Cohort Expansion:  
1987-1999  
n=20,729



# Role of Radiation Exposure Among Selected Outcomes

- Knowledge of RT Exposure
  - Health Status
  - Late Mortality
  - Second Neoplasms
  - Obesity
  - Pulmonary Function
  - Thyroid Function
  - Chronic Health Conditions
-

# Adult Survivors' Knowledge of the Cancer Diagnosis and Radiation Therapy Exposure



- Survivors generally knew the type of cancer they had.
- 89% accurately recalled whether they were treated with RT
- 10% of those not exposed thought they were
- >10% of Wilms, ALL, and Neuroblastoma did not know if they had been treated with RT

## Health Status Among 5+ Year Survivors

Health Domain	Survivors
General health	10.6%
Functional status	11.8%
Activity limitation	13.4%
Mental health	12.6%
Pain	10.2%
Anxiety/fears	13.2%
Any health domain	41.3%

## Health Status Among 5+ Year Survivors

Health Domain	Survivors	RT-Exposed Survivors
General health	10.6%	11.4%
Functional status	11.8%	12.6%
Activity limitation	13.4%	11.9%
Mental health	12.6%	17.8%
Pain	10.2%	9.5%
Anxiety/fears	13.2%	13.9%
Any health domain	41.3%	44.0%

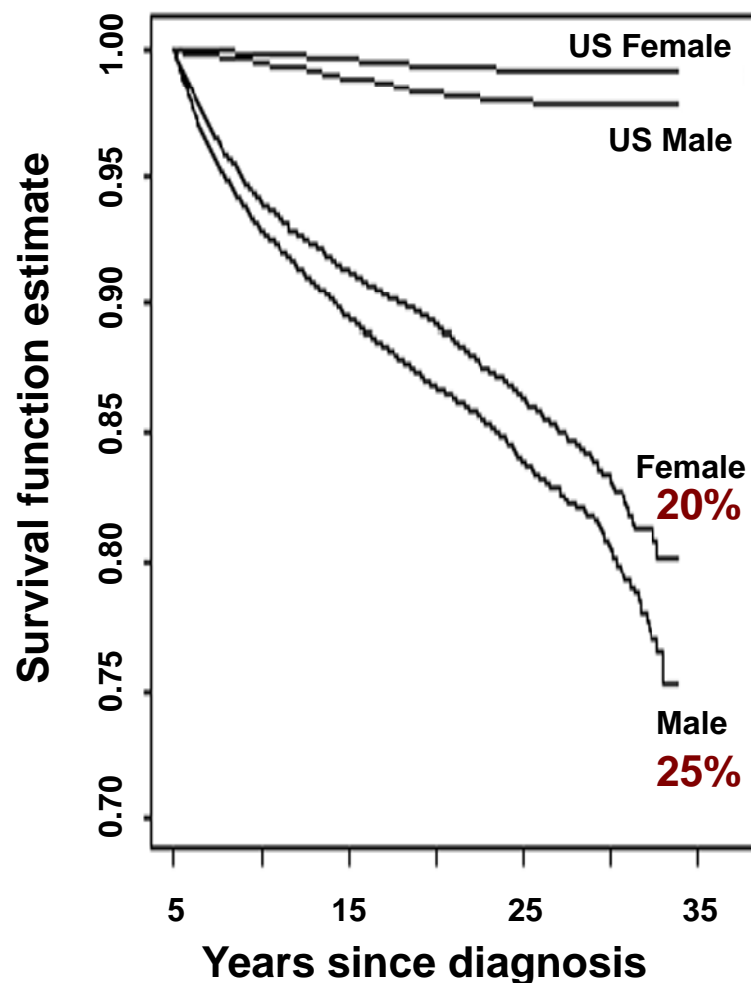
## Risk\* of Adverse Health Status by RT Exposure Among 5+ Year Survivors

Health Domain	Head Brain	Chest Mantle	Brain Chest	Other
General health	<b>1.5</b>	<b>1.4</b>	1.4	<b>1.4</b>
Functional status	<b>2.1</b>	1.1	<b>3.6</b>	<b>1.4</b>
Activity limitation	<b>1.3</b>	<b>1.3</b>	<b>2.0</b>	<b>1.2</b>
Mental health	1.0	1.1	1.1	1.1
Pain	<b>1.5</b>	<b>1.4</b>	<b>3.4</b>	<b>1.5</b>
Anxiety/fears	1.1	1.2	1.2	<b>1.2</b>
Any health domain	<b>1.4</b>	<b>1.2</b>	<b>2.1</b>	<b>1.2</b>

\* Odds Ratio Adjusted for Age, Sex, Race, Surgery, and Chemotherapy

# Late Mortality Among 5+ Year Survivors

## All-cause Mortality



## All Cause Mortality

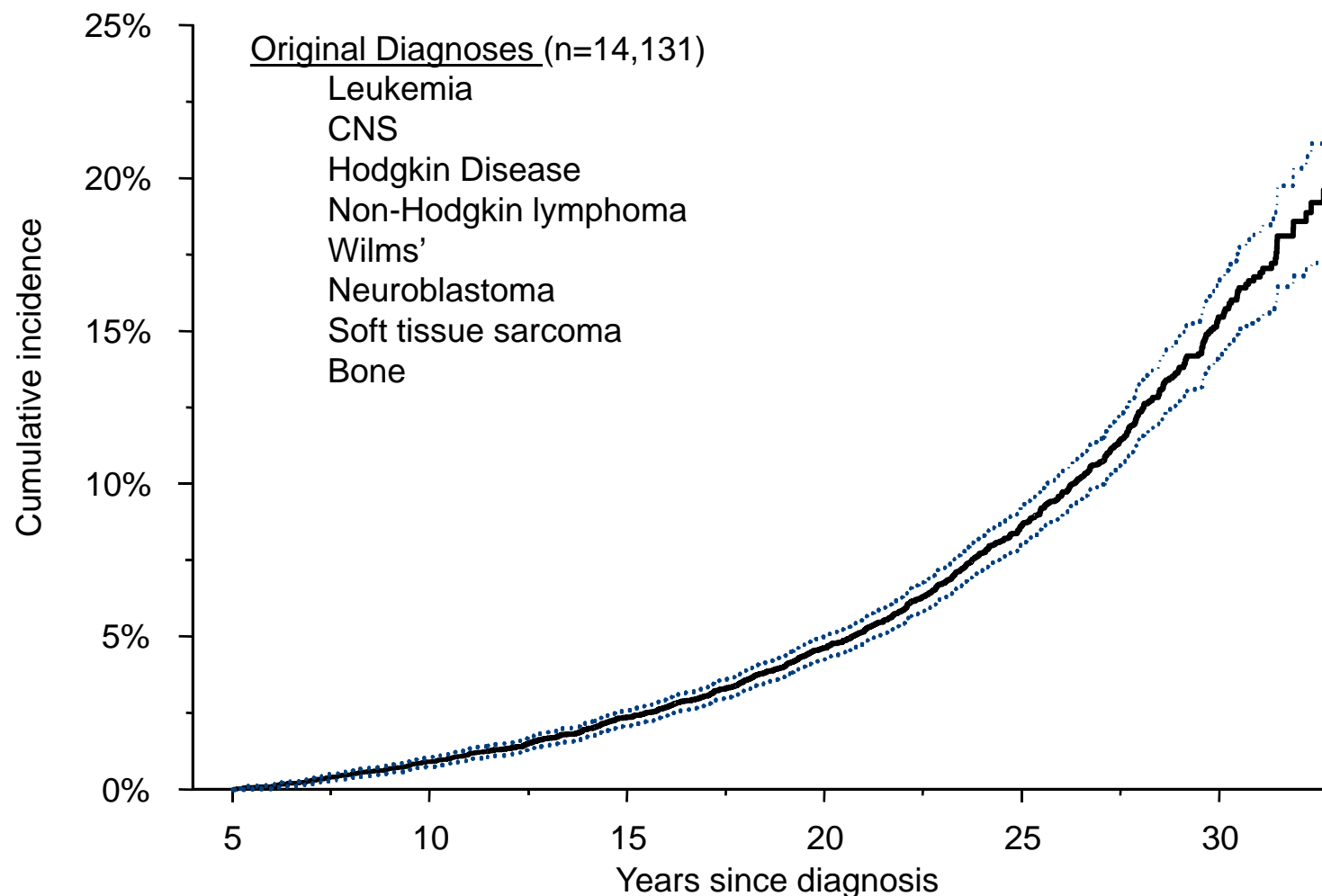
Cause of Death	SMR	95% CI
SMN	15.2	13.9 – 16.6
Cardiac	7.0	5.9 – 8.2
Pulmonary	8.8	6.8 – 11.2

## RT-Associated Risk of Death

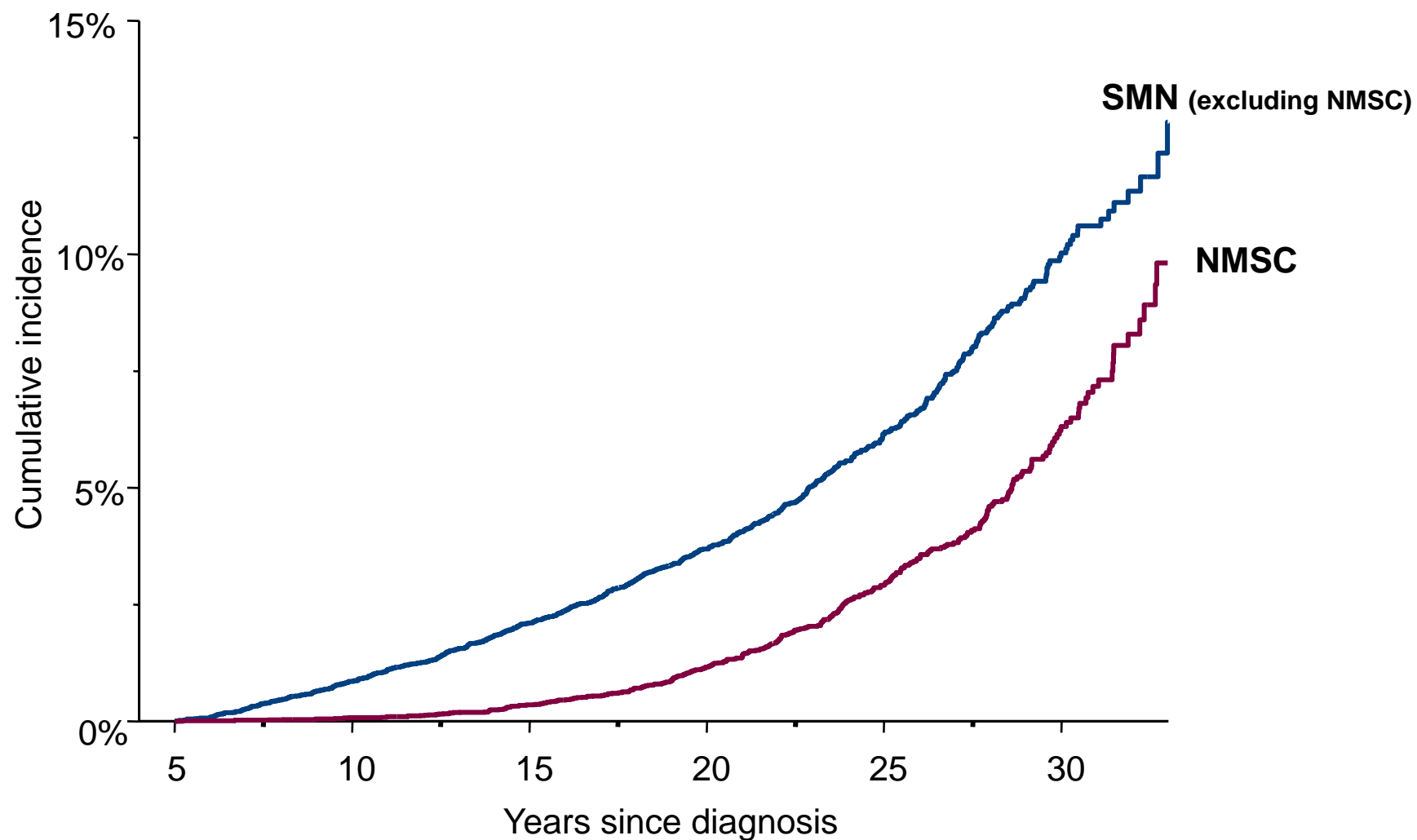
Cause of Death	RR*	95% CI
SMN	2.9	2.1 – 4.2
Cardiac	3.3	2.0 – 5.5
Pulmonary	1.4	0.7 – 2.9
Other causes	2.0	1.3 – 3.1

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

## Second Neoplasms Occurring 5+ years (n=1039) Including Nonmelanoma Skin Cancer

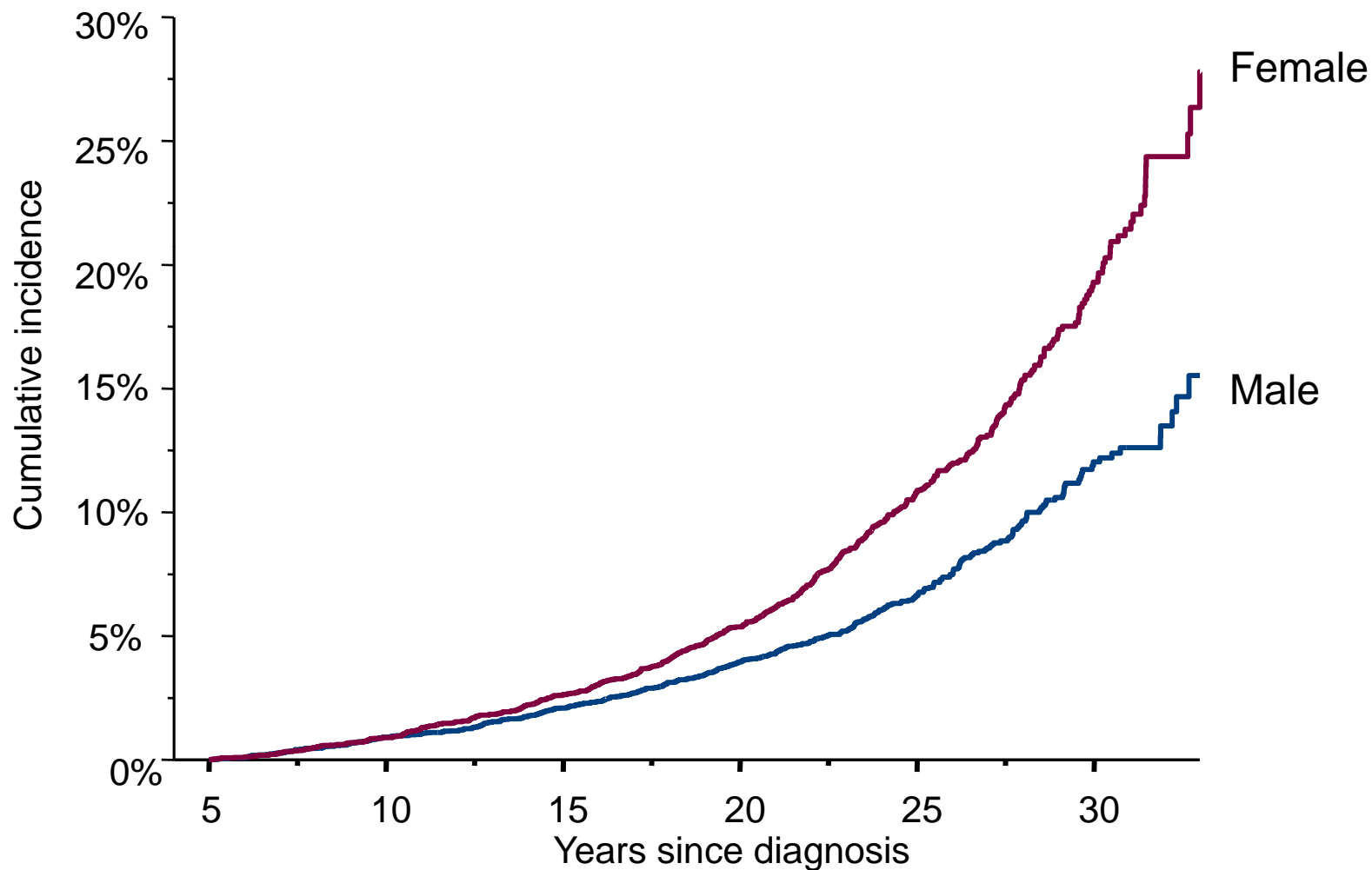


## Second Neoplasms Occurring 5+ years (n=1039)

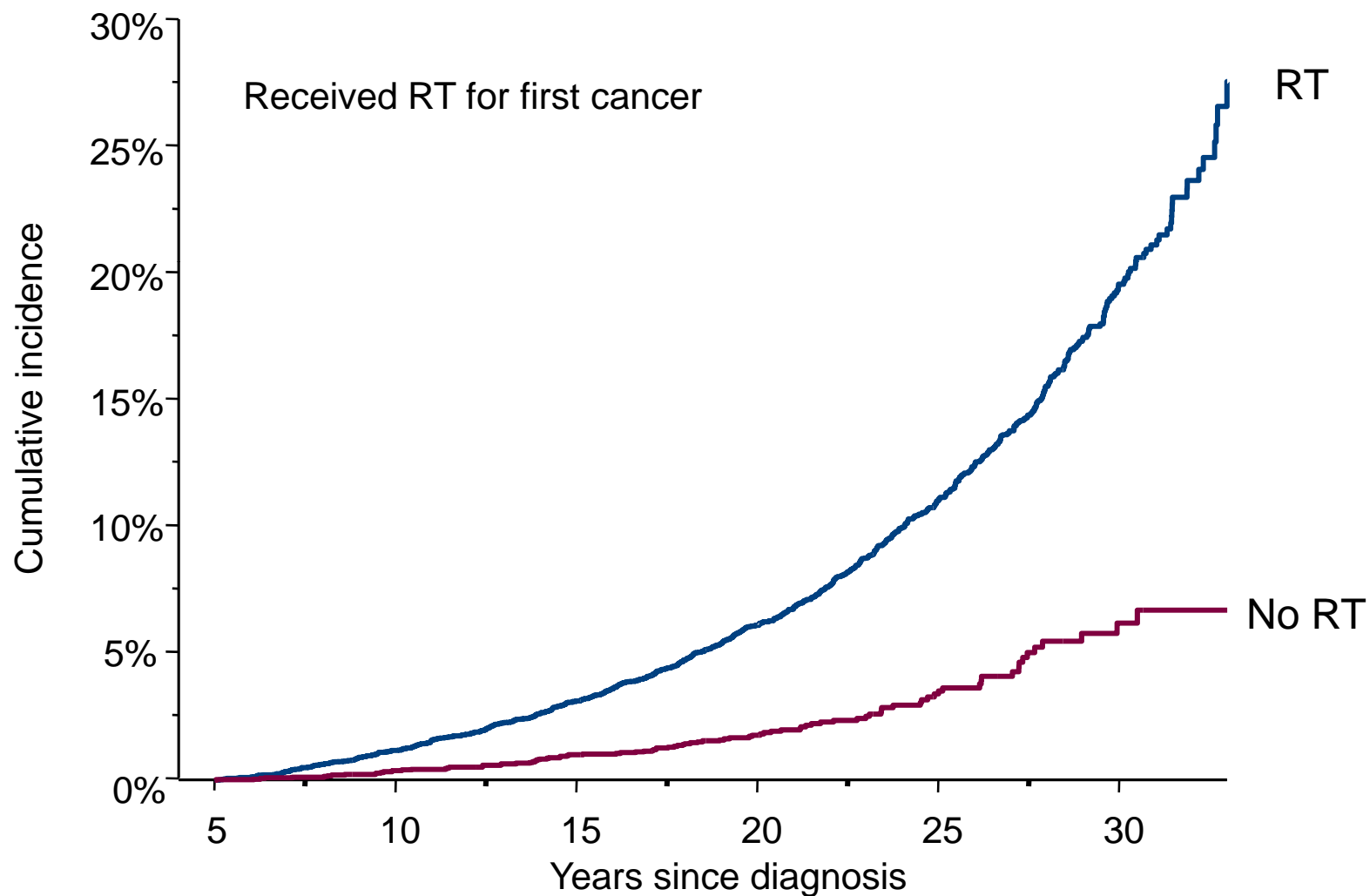




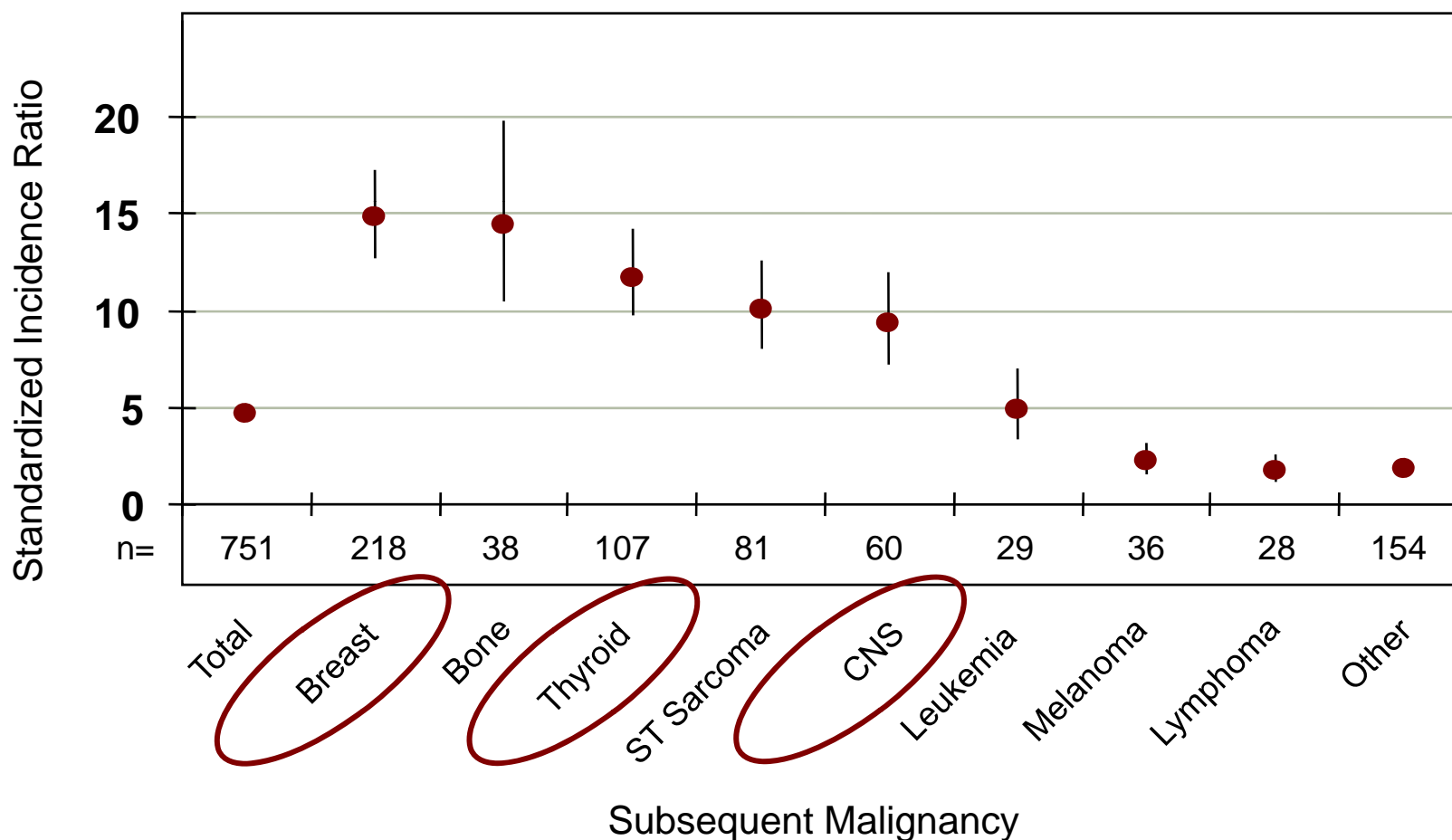
## Second Malignancies Occurring 5+ years (n=1039) Including Nonmelanoma Skin Cancer



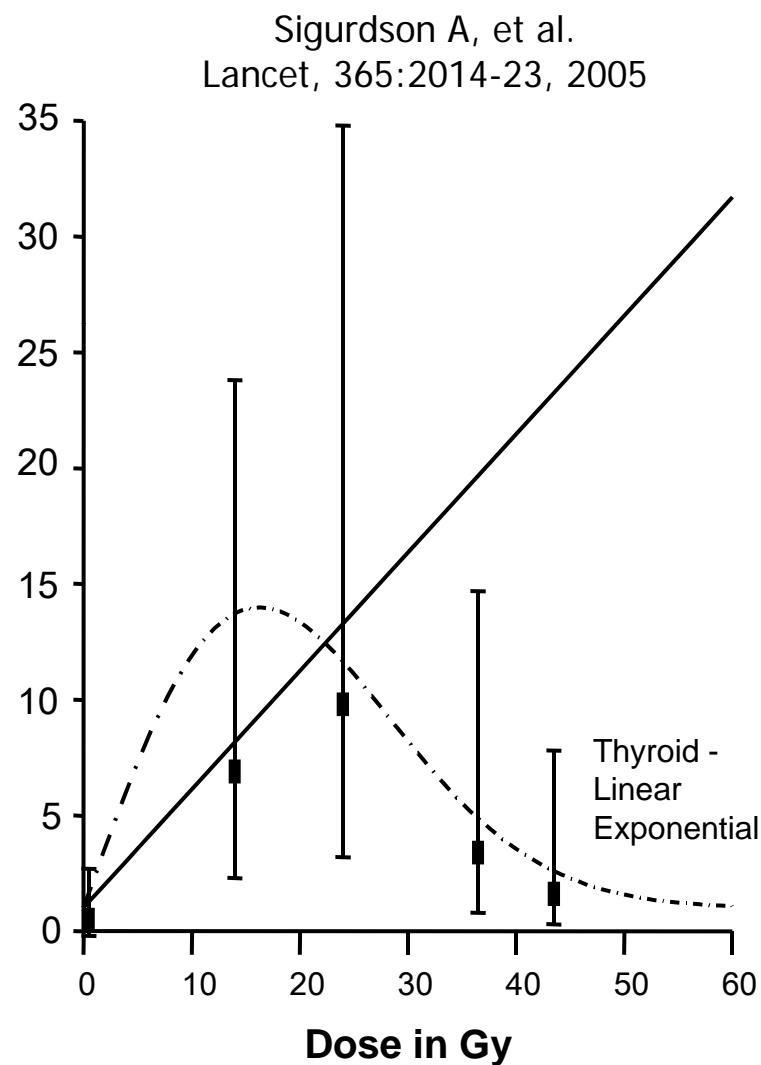
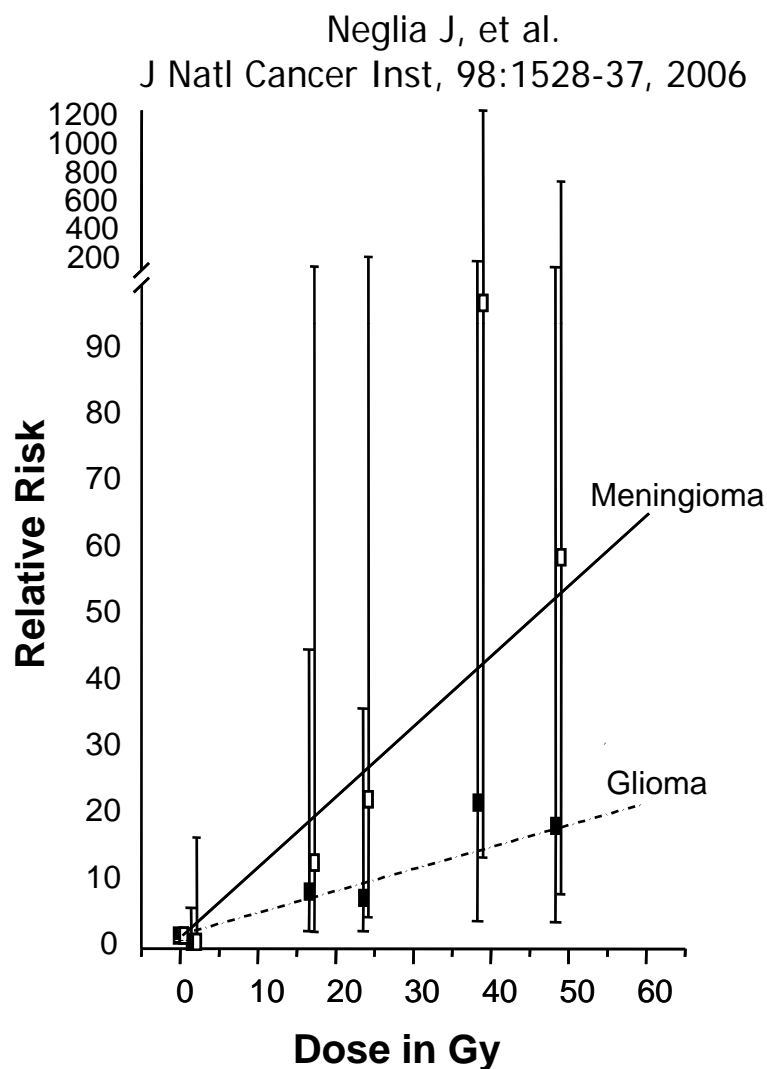
## Second Malignancies Occurring 5+ years (n=1039) Including Nonmelanoma Skin Cancer



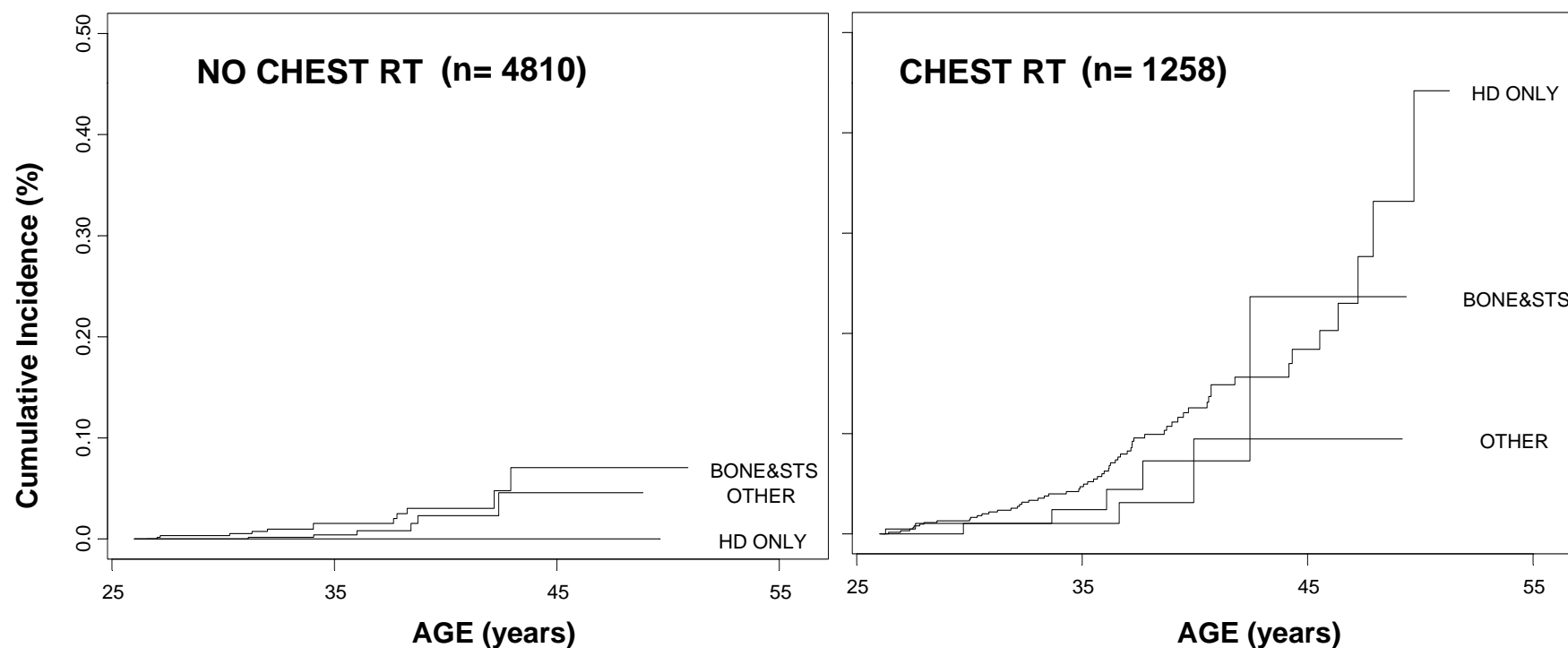
# Subsequent Neoplasm Among Long-term Survivors of Childhood Cancer



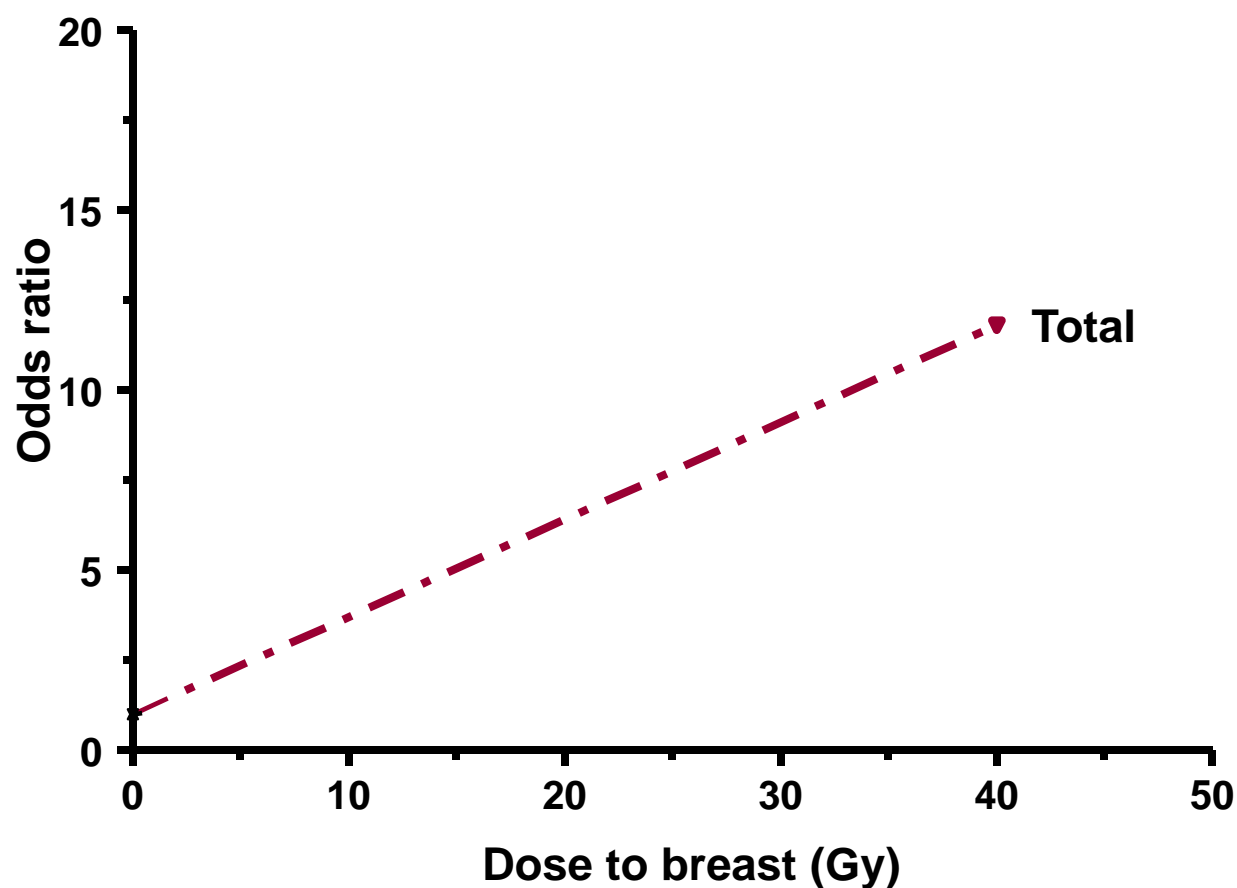
# Radiation-Associated Risk of Second Malignancies in Childhood Cancer Survivors



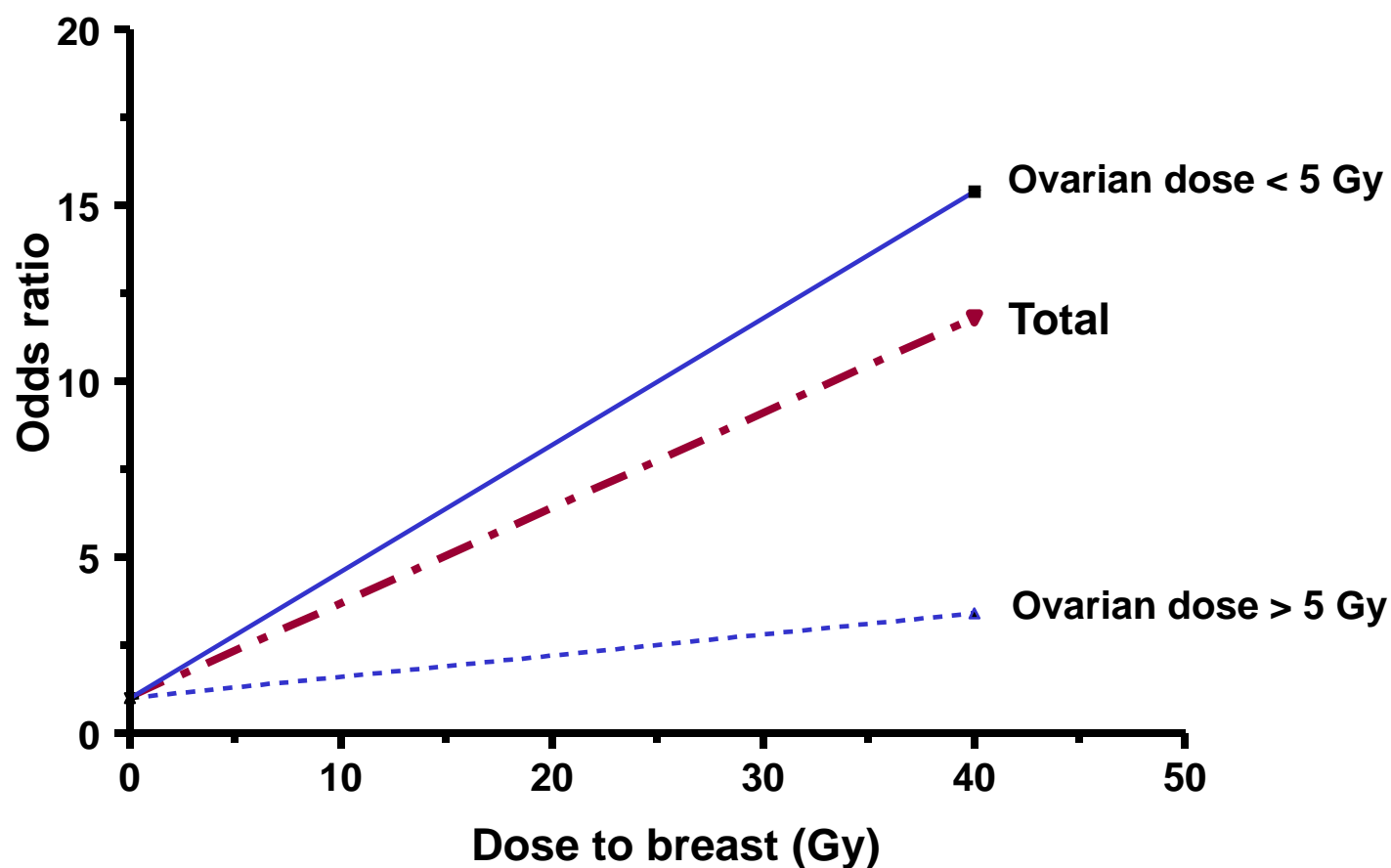
# Cumulative Incidence of Breast Cancer in Adult Female 5+ Year Survivors of Childhood Cancer



# Radiation-Associated Risk of Breast Cancer in Childhood Cancer Survivors



# Radiation-Associated Risk of Breast Cancer in Childhood Cancer Survivors



# Obesity During Childhood

- Obesity in childhood, adolescence, and young adulthood is an important predictor of Type 2 Diabetes, Hypertension, dyslipidemia, and ultimately CVD
  - Risk of death from all causes, CVD, and cancer increases throughout the ranges of being overweight and obese
-



## Risk of Obesity Among Adults Survivors of Childhood ALL Cranial RT $\geq 20$ Gy (n=841)

- Obesity in childhood, adolescence, and young adulthood is an important predictor of Type 2 Diabetes, Hypertension, dyslipidemia, and ultimately CVD
- Risk of death from all causes, CVD, and cancer increases throughout the ranges of being overweight and obese

	<u>Odds Ratio*</u>	<u>95% CI</u>
Females	2.59	1.88 - 3.55
Males	1.86	1.33 - 2.57

\* Age and Race Adjusted Compared to Sibling Cohort

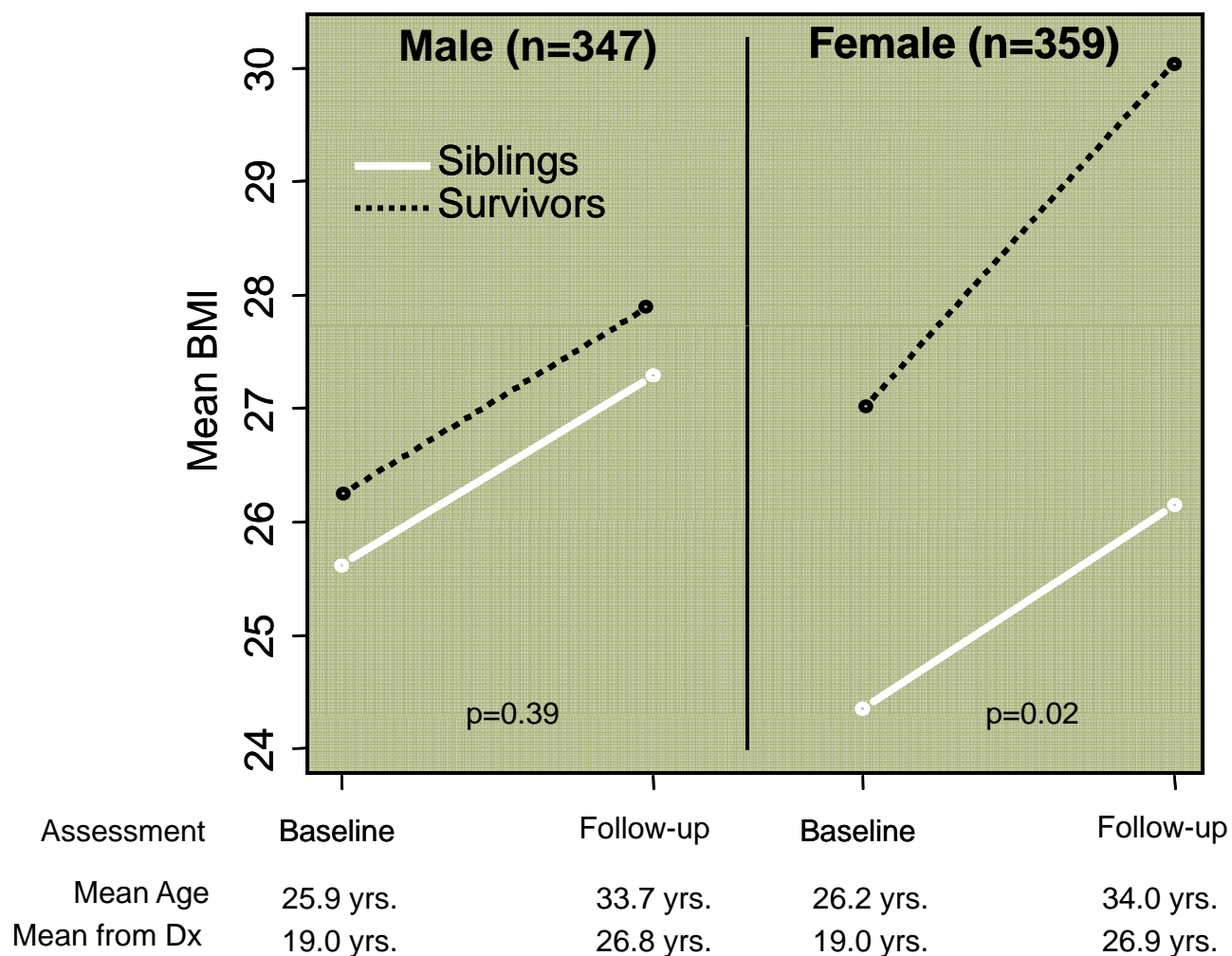
## Risk of Obesity Among Female Adults Survivors of Childhood ALL

Females: Cranial RT  $\geq$  20 Gy

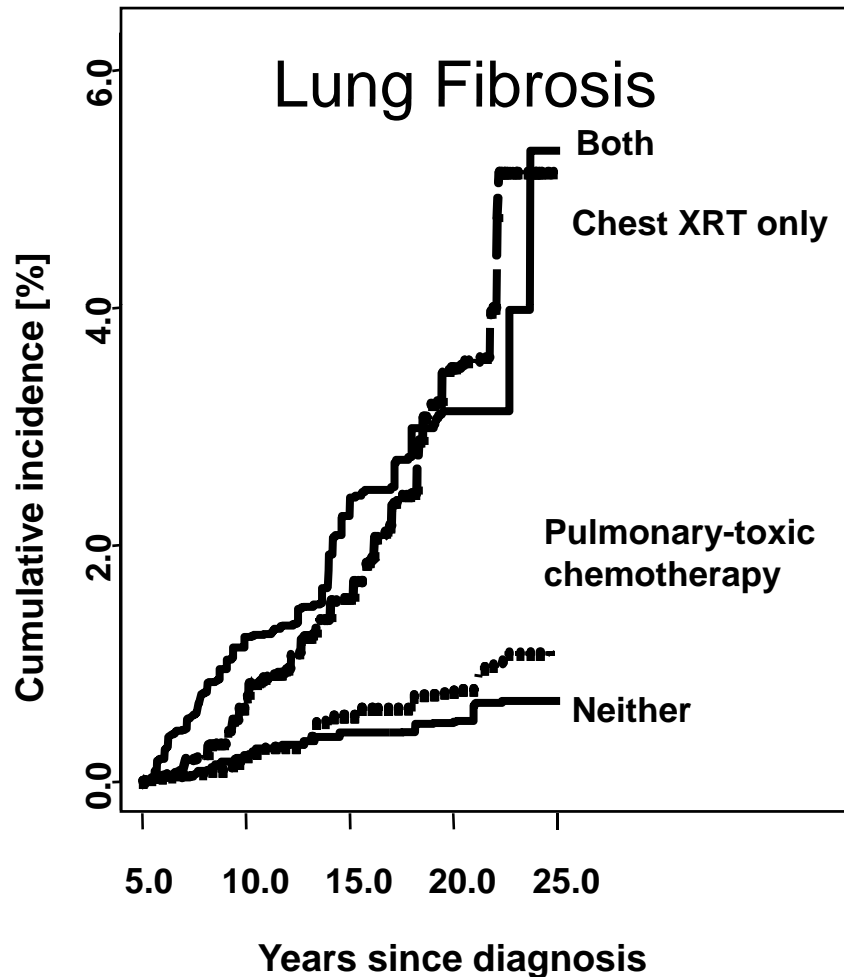
<u>Age at Dx</u>	<u>OR*</u>	<u>95% CI</u>
0-4	3.81	2.34 - 5.99
5-9	2.30	1.39 - 3.59
10-14	2.16	1.11 - 3.61
15-21	0.88	0.00 - 2.63

\* Age and Race Adjusted

# Mean Body Mass Index Among 706 Long-term Survivors of Childhood ALL with $\geq 20$ Gy Cranial RT

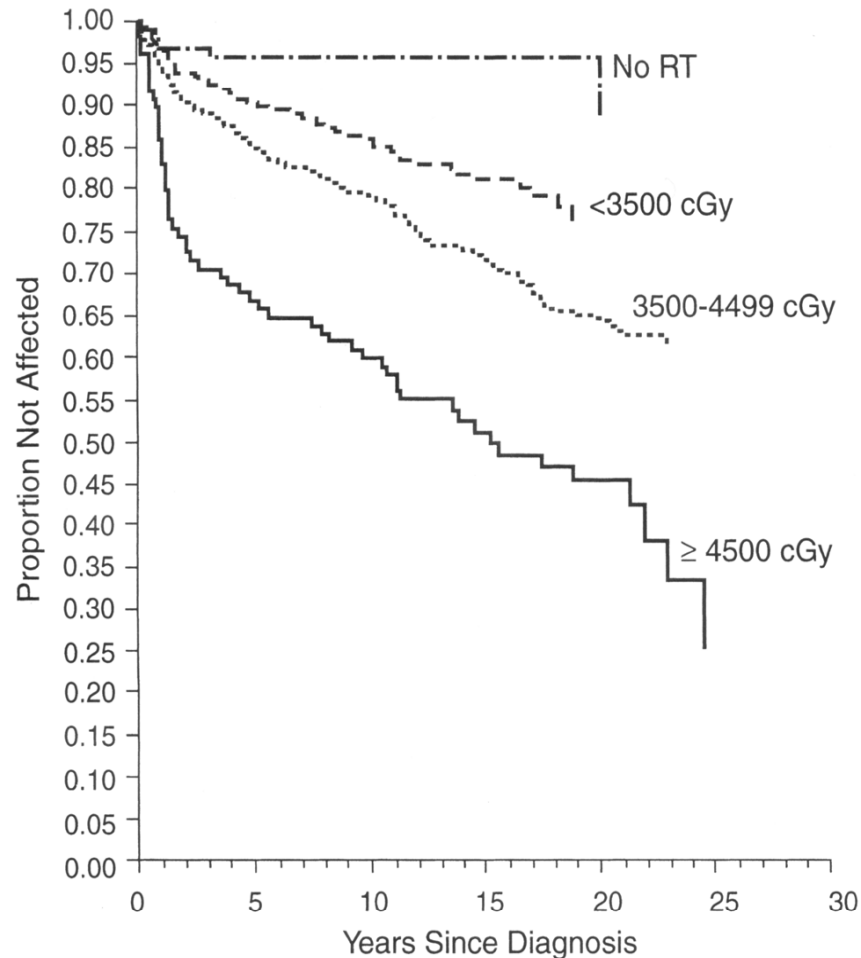


# Pulmonary Complications Among Childhood Cancer Survivors



- Five year survivors were 3.5-times more likely to be diagnosed with lung fibrosis, 5-times more likely to experience recurrent pneumonia, and 3-times more likely to require supplemental oxygen.
- Survivors treated with lung irradiation were 4.3-times more likely to have lung fibrosis.

# Thyroid Dysfunction Among Survivors of Hodgkin's Disease



- Among 1791 five year survivors of Hodgkin Disease, 34% were diagnosed with at least one thyroid abnormality.
- Hypothyroidism was the most common abnormality with a relative risk of 17.1 ( $p < 0.001$ ).
- Increasing dose of radiation to the thyroid, older age at diagnosis of Hodgkin disease, and female sex were all independently predictive of hypothyroidism.

## Chronic Health Conditions Among 5+ Year Survivors of Childhood Cancer

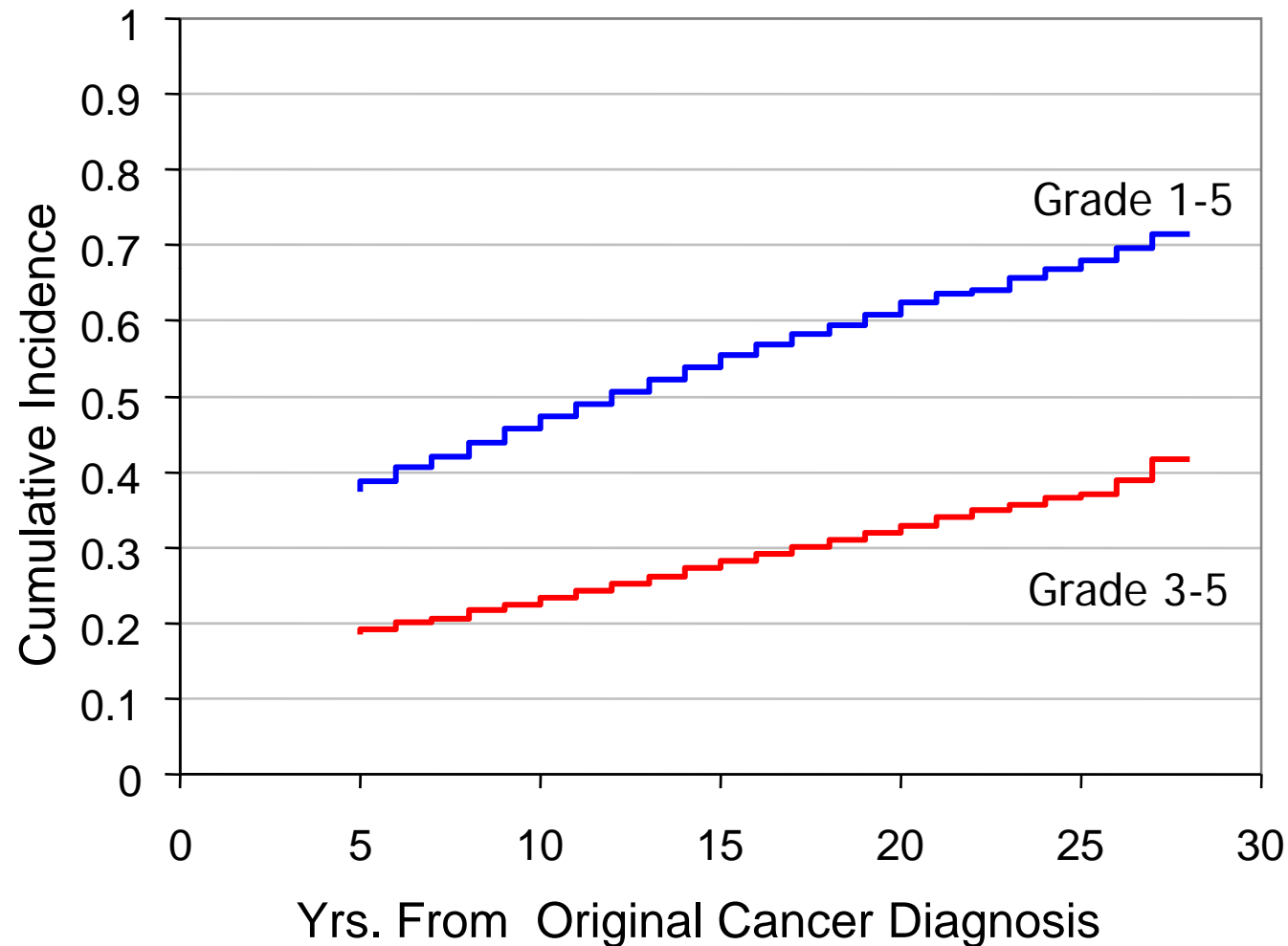
- 10,397 survivors, diagnosed 1970-1986
- 3,034 siblings

Grading of conditions: CTCAE v3.0

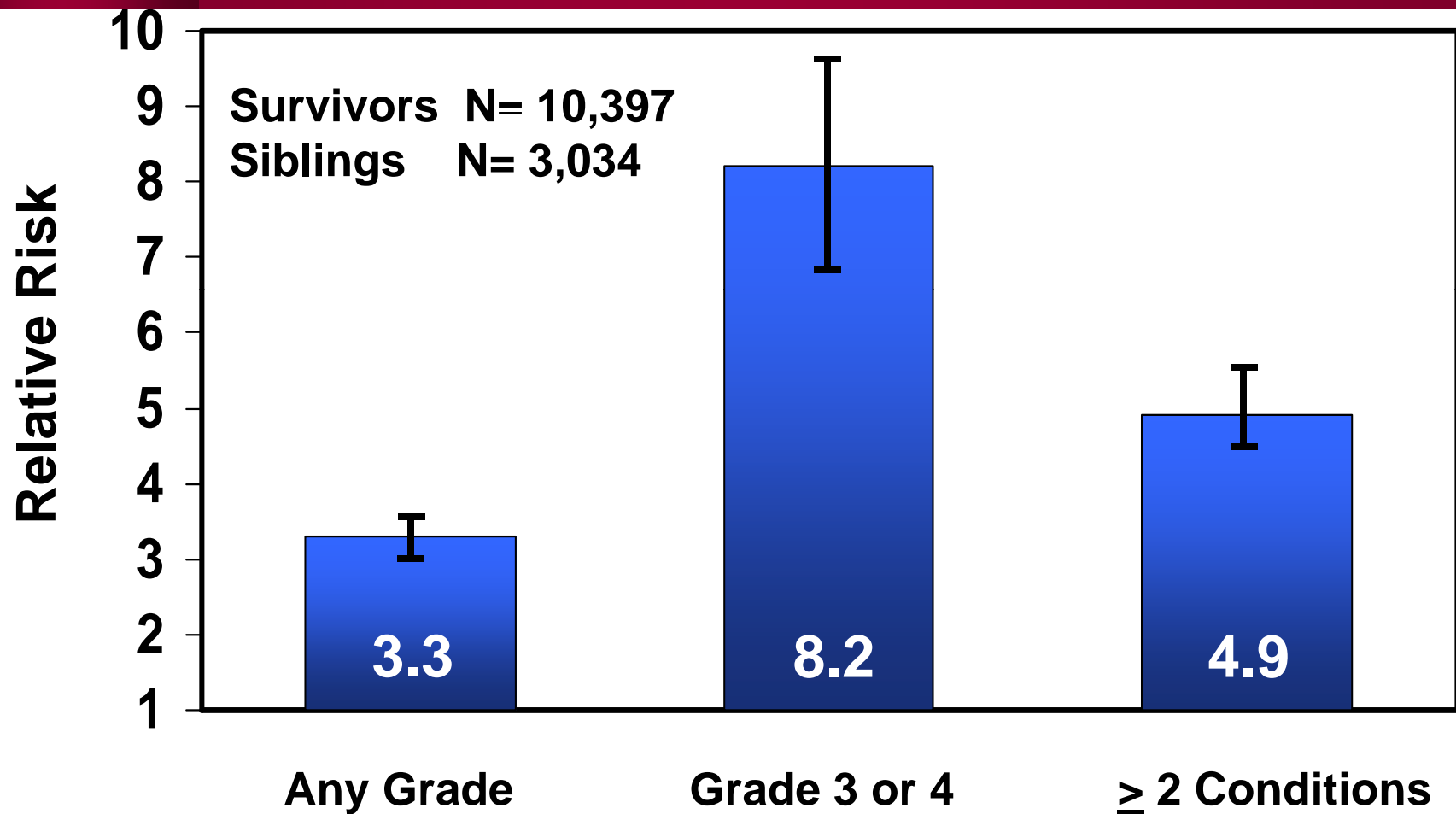
Common Terminology Criteria for Adverse Events

- |           |                               |
|-----------|-------------------------------|
| • Grade 1 | Mild                          |
| • Grade 2 | Moderate                      |
| • Grade 3 | Severe                        |
| • Grade 4 | Life-threatening or disabling |
| • Grade 5 | Death                         |

# Cumulative Incidence of Chronic Health Conditions in Survivors, by Grade



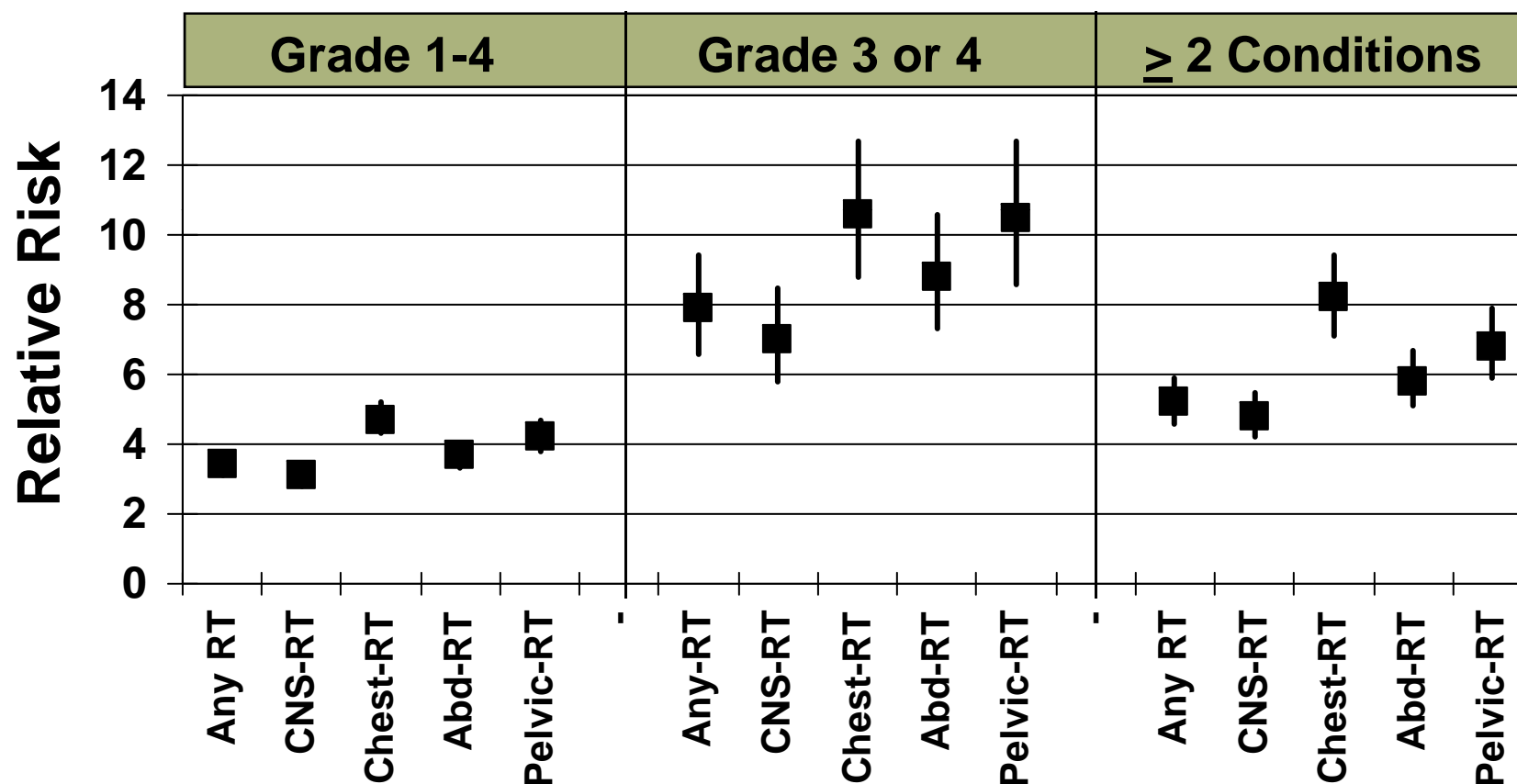
## Relative Risk\* of Chronic Health Conditions in Survivors Compared with Siblings



\* Adjusted for age, sex, and race



# Relative Risk\* of Chronic Health Conditions in Survivors Compared with Siblings



\* Adjusted for age, sex, and race

# OTHER OUTCOMES ASSOCIATED WITH RADIATION EXPOSURE

- Neurocognitive
- Fertility/Gonadal
- Cardiac/Stroke/Vascular
- Growth
- Dental
- Vision
- Auditory
- Metabolic Syndrome
- Quality of Life

Vol 27, No 14

May 10, 2009

## JOURNAL OF CLINICAL ONCOLOGY

### REVIEWS

**PEDIATRIC CANCER SURVIVORSHIP:  
THE CHILDHOOD CANCER SURVIVOR STUDY.**  
Editors: P.A. Ganz, L.L. Robison, M.M. Hudson, and C.A. Sklar

The Childhood Cancer Survivor Study: A National Cancer Institute-Supported Resource for Outcome and Intervention Research. *L.L. Robison et al*

High-Risk Populations Identified in Childhood Cancer Survivor Study Investigations: Implications for Risk-Based Surveillance. *M.M. Hudson et al*

Late Mortality Among Five-Year Survivors of Childhood Cancer: A Summary From The Childhood Cancer Survivor Study. *G.T. Armstrong et al*

Chronic Disease in the Childhood Cancer Survivor Study Cohort: A Review of Published Findings. *L. Diller et al*

Health Behaviors, Medical Care, and Interventions to Promote Healthy Living in the Childhood Cancer Survivor Study Cohort. *P. Nathan et al*

Second Neoplasms in Survivors of Childhood Cancer: Findings from the Childhood Cancer Survivor Study Cohort. *A.T. Meadows et al*

Psychological Status in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. *L.K. Zeltzer et al*

Official Journal of the American Society of Clinical Oncology

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**The Childhood Cancer Survivor Study**

**New Public Access Data Tables**

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The Childhood Cancer Survivor Study (CCSS) was created to take advantage of 1) the opportunity to gain new knowledge about the long-term effects of cancer and therapy, knowledge that can be used to help design treatment protocols and intervention strategies that will increase survival and minimize harmful health effects, and 2) the obligation to educate survivors about the potential impacts of cancer diagnosis and treatment on their health, and to provide follow-up care, for example, by creating and implementing programs for the prevention and early detection of late effects.

The CCSS is a component of the Long-Term Follow-Up Study. A collaborative, multi-institutional study funded by the National Cancer Institute, the CCSS is composed of individuals who survived five or more years after treatment for cancer, leukemia, tumor, or similar illness diagnosed during childhood or adolescence.

The CCSS, which includes all participants in the Long-Term Follow-Up Study with a confirmed diagnosis of cancer, is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed between 1970 and 1986. It also includes approximately 4,000 siblings of survivors who serve as the comparison group for the study.

The CCSS cohort has been assembled through the efforts of 27 participating centers in the United States and Canada. It is coordinated through St. Jude Children's Research Hospital in Memphis, Tennessee. Other core facilities include the Statistical Center, located at the Fred Hutchinson Cancer Research Center (Seattle); the Biopathology Center (Columbus); and the Radiation Physics Center at MD Anderson Cancer Center (Houston). Initiated in 1993, the study is funded by a grant from the National Cancer Institute.

[www.stjude.org/ccss](http://www.stjude.org/ccss)