THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

Prediction and Prevention of Treatment-related Complications

Smita Bhatia, MD, MPH

Gay and Bew White Endowed Chair in Pediatric Oncology

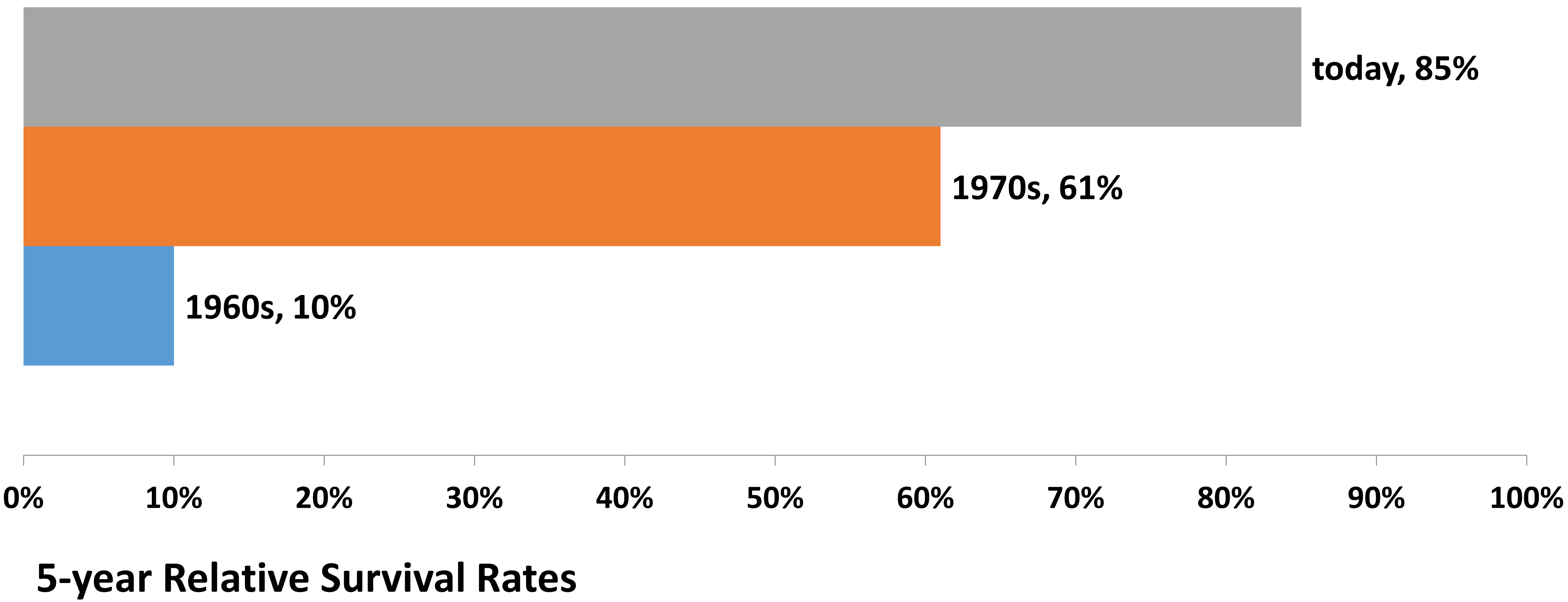
Distinguished Professor, Department of Pediatrics

Director, Institute for Cancer Outcomes and Survivorship

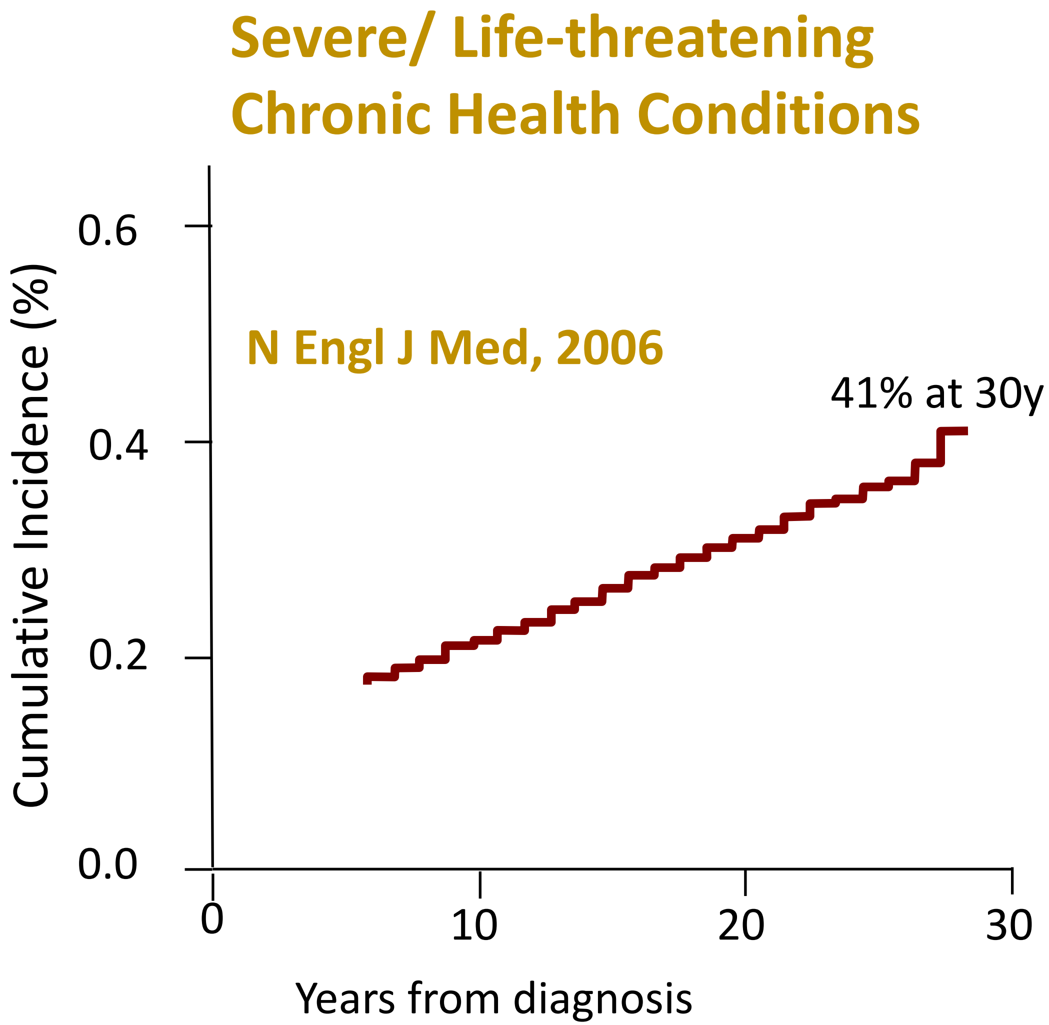
School of Medicine

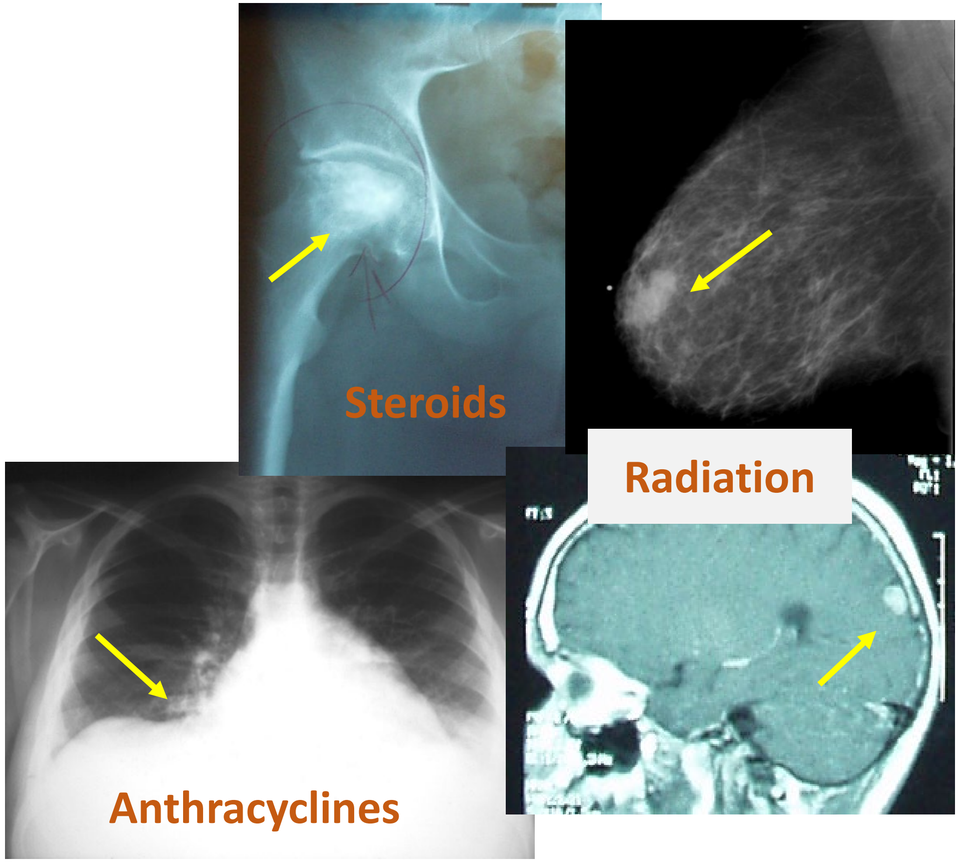
University of Alabama at Birmingham

Trends in Survival Rates after Childhood Cancer

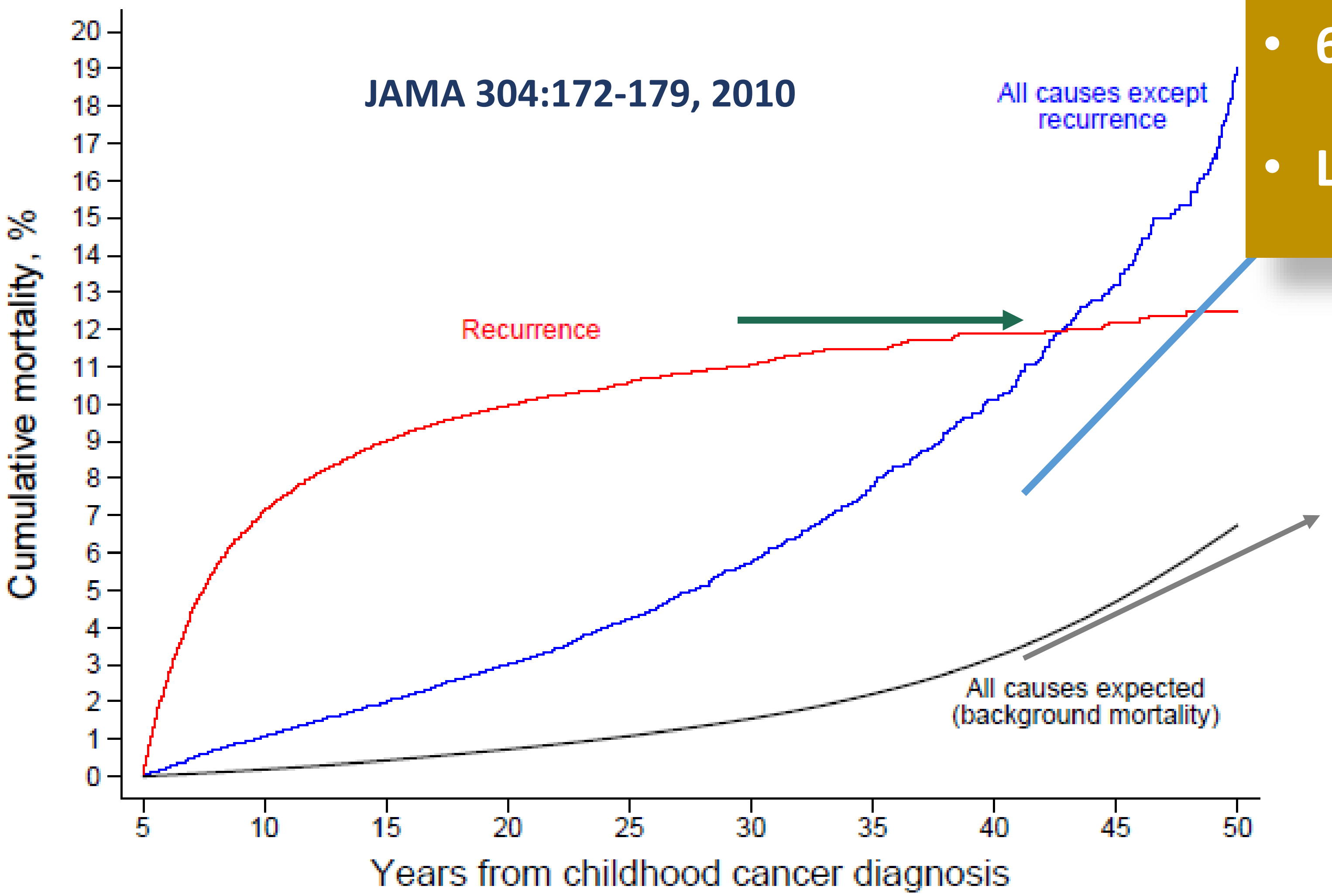


Burden of Morbidity in Childhood Cancer Survivors





Cumulative Cause-specific Mortality among 5-year Childhood Cancer Survivors



- **6-fold higher risk of dying**
- **Life shortened by 1-2 decades**

Clearly-defined association between therapeutic exposures and chronic health conditions

Steroids Radiation	→ Osteonecrosis
Anthracyclines Chest Radiation	→ Heart failure
Radiation Alkylating agents Topoisomerase II inhibitors Anthracyclines	→ Second cancers
Radiation	→ Stroke

Study Design

Eligibility - Cases

1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. Subsequent development of a key adverse event

Matching Criteria

Primary cancer diagnosis
Year of diagnosis (±5y)
Race/ethnicity
Time since primary cancer

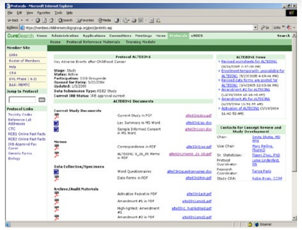
Eligibility - Controls

1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. No evidence of key adverse events

Collect DNA from **Cases and controls**

Self-report of **comorbidities**

Summarize therapeutic exposures for cases and controls



Source documentation (Cases only)

Osteonecrosis *(diagnostic radiology)*

Congestive Heart Failure *(echocardiogram report)*

Subsequent neoplasms *(pathology report)*

Stroke *(diagnostic radiology)*

Cardiomyopathy in Cancer Survivors

Risk factors

Anthracycline chemotherapy

Risk modifiers

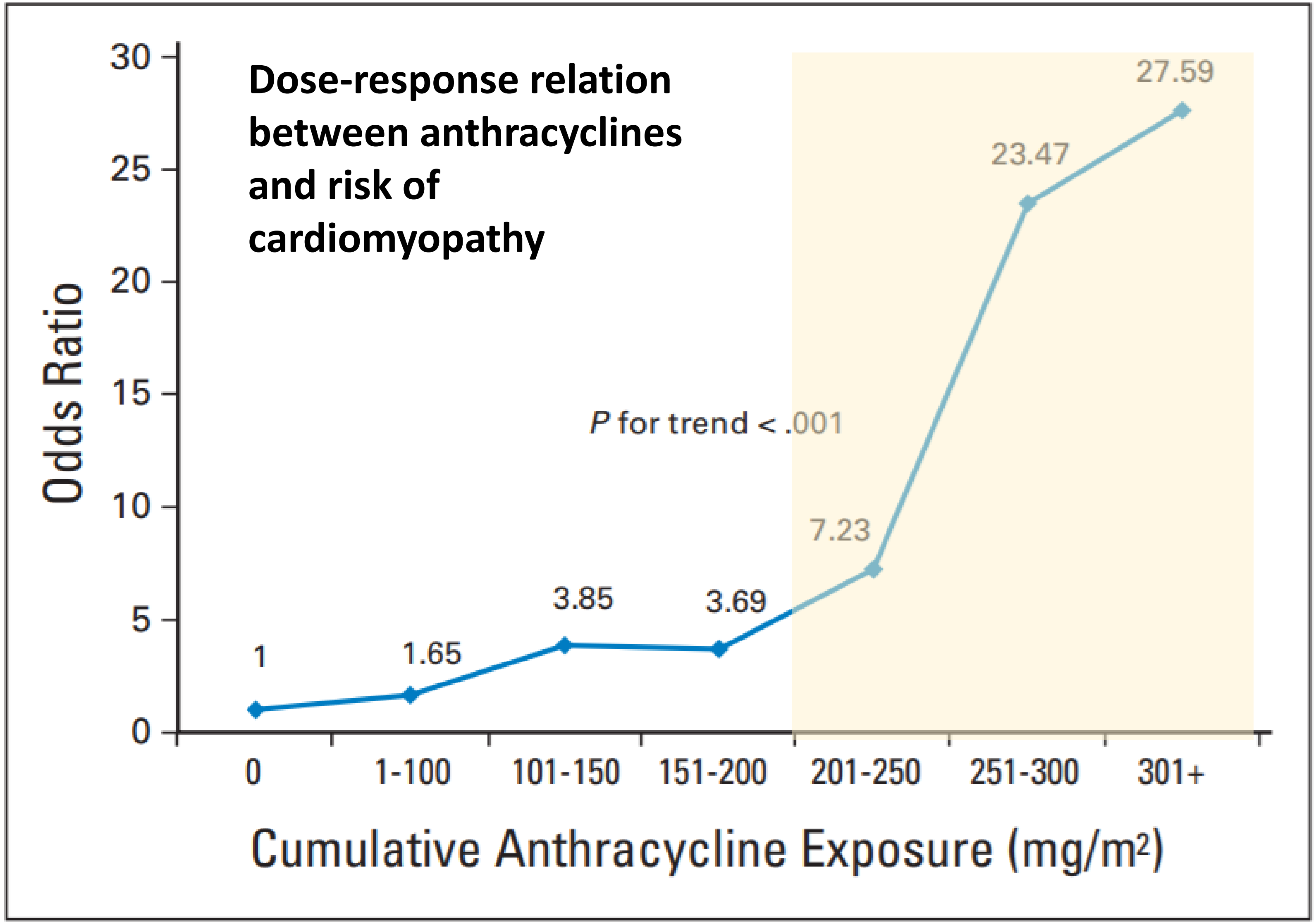
Chest radiation

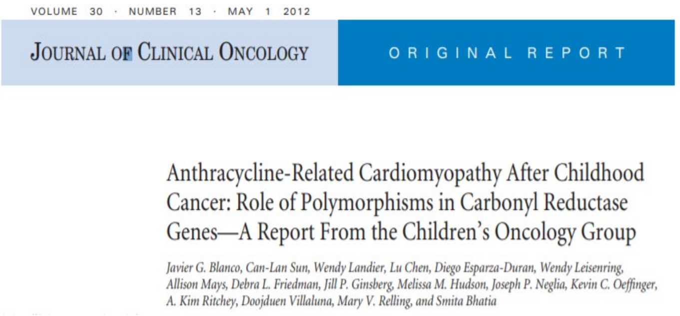
Young age at exposure

Female sex

Cardiovascular risk factors

Cardiomyopathy




VOLUME 30 · NUMBER 13 · MAY 1 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Anthracycline-Related Cardiomyopathy After Childhood Cancer: Role of Polymorphisms in Carbonyl Reductase Genes—A Report From the Children's Oncology Group

Javier G. Blanco, Can-Lan Sun, Wendy Landier, Lu Chen, Diego Esparza-Duran, Wendy Leisenring, Allison Mays, Debra L. Friedman, Jill P. Ginsberg, Melissa M. Hudson, Joseph P. Neglia, Kevin C. Oeffinger, A. Kim Ritchey, Doojduen Villaluna, Mary V. Relling, and Smita Bhatia

J Clin Oncol, 2012;30:1415-21

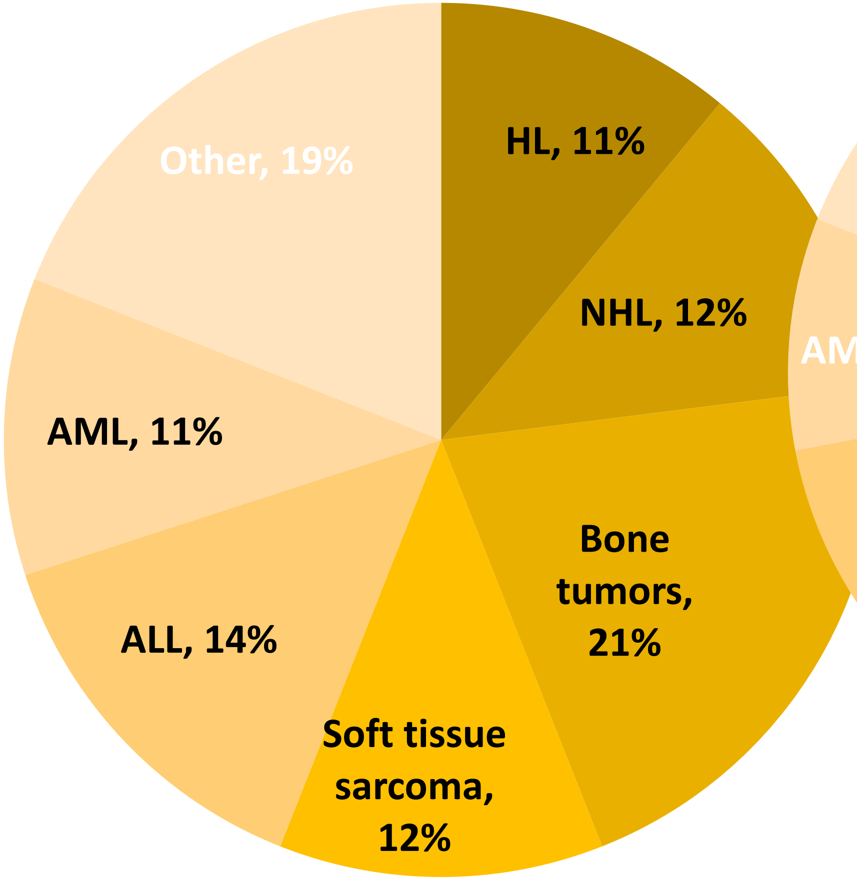
Inter-individual variability in risk of anthracycline-related cardiomyopathy

Role for genetic susceptibility?

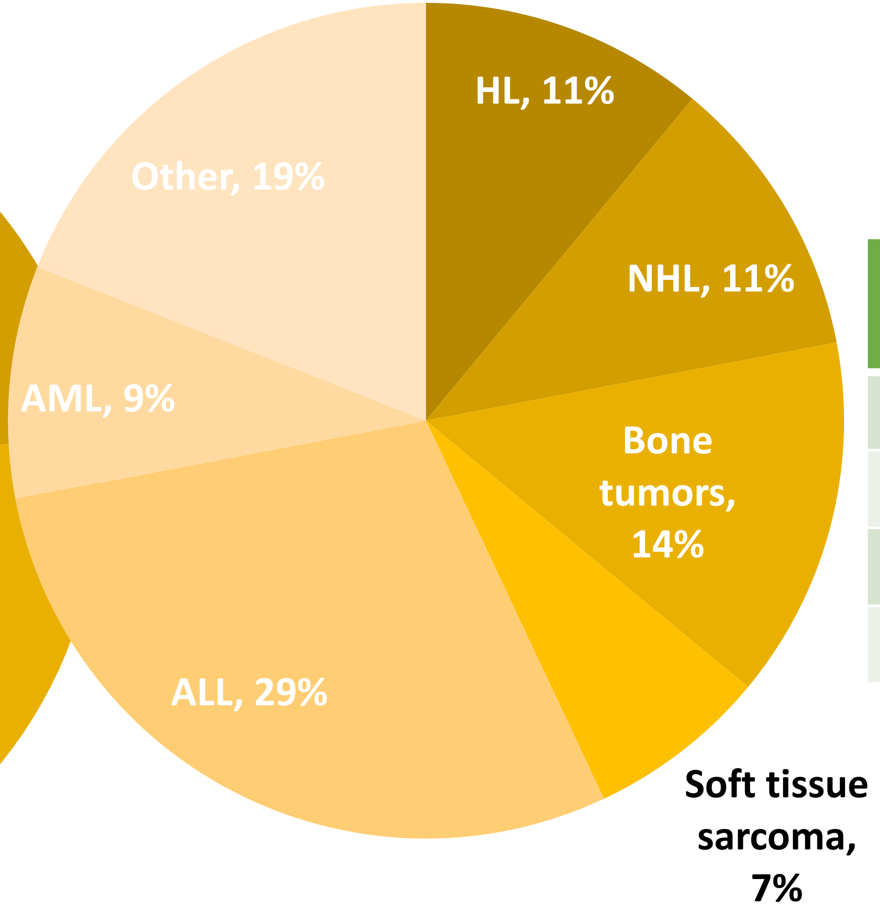
Demographic characteristics of case-control set

	Cases (n=170)	Controls (n=317)	P-value
Age at primary cancer diagnosis in years			
Median (range)	7.3 (0-20.7)	7.6 (0-21.1)	0.7
Age at study participation in years			
Median (range)	16.6 (0.4-41)	18.5 (2-49)	<0.001
Race/ethnicity, n (%)			
Non-Hispanic whites	124 (73%)	252 (79%)	Matched
Hispanics	16 (9%)	29 (9%)	
Blacks	12 (7%)	14 (5%)	
Other	18 (11%)	22 (7%)	

Clinical Characteristics of Case-control set



Cases (n=170)



Controls (n=317)

	Cases (n=170)	Controls (n=317)	P-value
Cumulative anthracyclines in mg/m^2			
Median	300	140	<0.001
Chest radiation, n (%)			
Yes	25%	14%	<0.001

Median EF (cases): 44%

Cardiac Dysfunction

VOLUME 30 · NUMBER 13 · MAY 1 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Anthracycline-Related Cardiomyopathy After Childhood Cancer: Role of Polymorphisms in Carbonyl Reductase Genes—A Report From the Children's Oncology Group

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J Clin Oncol, **2012;30:1415-21**

VOLUME 32 · NUMBER 7 · MARCH 1 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Hyaluronan Synthase 3 Variant and Anthracycline-Related Cardiomyopathy: A Report From the Children's Oncology Group

Xuexia Wang, Wei Liu, Can-Lan Sun, Saro H. Armenian, Hakon Hakonarson, Lindsey Hageman, Yan Ding, Wendy Landier, Javier G. Blanco, Lu Chen, Adolfo Quiñones, Daniel Ferguson, Naomi Winick, Jill P. Ginsberg, Frank Keller, Joseph P. Neglia, Sunil Desai, Charles A. Sklar, Sharon M. Castellino, Irene Cherrick, ZoAnn E. Dreyer, Melissa M. Hudson, Leslie L. Robison, Yutaka Yasui, Mary V. Relling, and Smita Bhatia

J Clin Oncol, **2014;32:647-53**

VOLUME 34 · NUMBER 8 · MARCH 10, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children's Oncology Group Genome-Wide Association Study

Xuexia Wang, Can-Lan Sun, Adolfo Quiñones-Lombraña, Purnima Singh, Wendy Landier, Lindsey Hageman, Molly Mather, Jerome I. Rotter, Kent D. Taylor, Yii-Der Ida Chen, Saro H. Armenian, Naomi Winick, Jill P. Ginsberg, Joseph P. Neglia, Kevin C. Oeffinger, Sharon M. Castellino, Zoann E. Dreyer, Melissa M. Hudson, Leslie L. Robison, Javier G. Blanco, and Smita Bhatia

J Clin Oncol **2016; 34:863-70**

Cancer
Original Article | Full Access

Association of *GSTM1* null variant with anthracycline-related cardiomyopathy after childhood cancer—A Children's Oncology Group ALTE03N1 report

Purnima Singh PhD, MSPH, Xuexia Wang PhD, Lindsey Hageman MPH, Yanjun Chen MS, Tarek Magdy PhD, Wendy Landier PhD, Jill P. Ginsberg MD, Joseph P. Neglia MD, MPH ... See all authors

Cancer. **2020;126:4051-4058**

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal
ORIGINAL REPORTS | Pediatric Oncology

Genome-Wide Association Study Identifies *ROBO2* as a Novel Susceptibility Gene for Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors

Check for updates

Xuexia Wang, PhD[1]; Purnima Singh, MSc, PhD, MSPH[2]; Liting Zhou, MS[2]; Noha Sharafeldin, MD, MSc, PhD[2]; Wendy Landier, PhD[2]; Lindsey Hageman, MPH[2]; Paul Burridge, PhD[3]; Yutaka Yasui, PhD[4]; Yadav Sapkota, PhD[4]; Javier G. Blanco, PhD[5]; Kevin C. Oeffinger, MD[6]; Melissa M. Hudson, MD[4]; Eric J. Chow, MD, MPH[7]; Saro H. Armenian, DO, MPH[8]; Joseph P. Neglia, MD, MPH[9]; A. Kim Ritchey, MD[10]; Douglas S. Hawkins, MD[7]; Jill P. Ginsberg, MD[11]; Leslie L. Robison, PhD[4]; Gregory T. Armstrong, MD, MSCE[4]; and Smita Bhatia, MD, MPH[2]

J Clin Oncol. **2023;41:1758-1769**

JAHA
Journal of the American Heart Association

Altered Peripheral Blood Gene Expression in Childhood Cancer Survivors With Anthracycline-Induced Cardiomyopathy – A COG-ALTE03N1 Report

Purnima Singh, Disheet A. Shah, Mariam Jouni, Romina B. Cejas, David K. Crossman, Tarek Magdy, Shaowei Qiu, Xuexia Wang, Liting Zhou, Noha Sharafeldin, Lindsey Hageman, Donald E. McKenna, Saro H. Armenian, Frank M. Balis, Douglas S. Hawkins, Frank G. Keller, Melissa M. Hudson, Joseph P. Neglia, A Kim Ritchey, Jill P. Ginsberg, Wendy Landier, Ravi Bhatia, ... See all authors

JAHA **2023;e029954**

ORIGINAL RESEARCH

Haptoglobin Gene Expression and Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors

A COG-ALTE03N1 Report

Purnima Singh, MS, PhD, MSPH,[a,b] David K. Crossman, PhD,[c] Liting Zhou, MS,[a] Xuexia Wang, PhD,[d] Noha Sharafeldin, PhD,[a] Lindsey Hageman, MPH,[a] Javier G. Blanco, PhD,[e] Paul W. Burridge, PhD,[f] Saro H. Armenian, DO, MPH,[g] Frank M. Balis, MD,[h] Douglas S. Hawkins, MD,[i] Frank G. Keller, MD,[j] Melissa M. Hudson, MD,[k] Joseph P. Neglia, MD, MPH,[l] A. Kim Ritchey, MD,[m] Jill P. Ginsberg, MD,[h] Wendy Landier, PhD,[a,b] Smita Bhatia, MD, MPH[a,b]

JACC CO **2023; 5:392-401**

scientific reports

OPEN Identification of novel hypermethylated or hypomethylated CpG sites and genes associated with anthracycline-induced cardiomyopathy

Check for updates

Purnima Singh[1,2,15], Liting Zhou[1,15], Disheet A. Shah[3,15], Romina B. Cejas[3], David K. Crossman[4], Mariam Jouni[3], Tarek Magdy[14,3], Xuexia Wang[5], Noha Sharafeldin[1], Lindsey Hageman[1], Donald E. McKenna[3], Steve Horvath[6], Saro H. Armenian[7], Frank M. Balis[8], Douglas S. Hawkins[9], Frank G. Keller[10], Melissa M. Hudson[11], Joseph P. Neglia[12], A. Kim Ritchey[13], Jill P. Ginsberg[8], Wendy Landier[1,2], Paul W
Smita Bhatia[1,2]

Sci Rep. **2023;13:12683**

ELSEVIER
JACC: CardioOncology
Available online 14 September 2023
In Press, Corrected Proof What's this?
JACC

Original Research

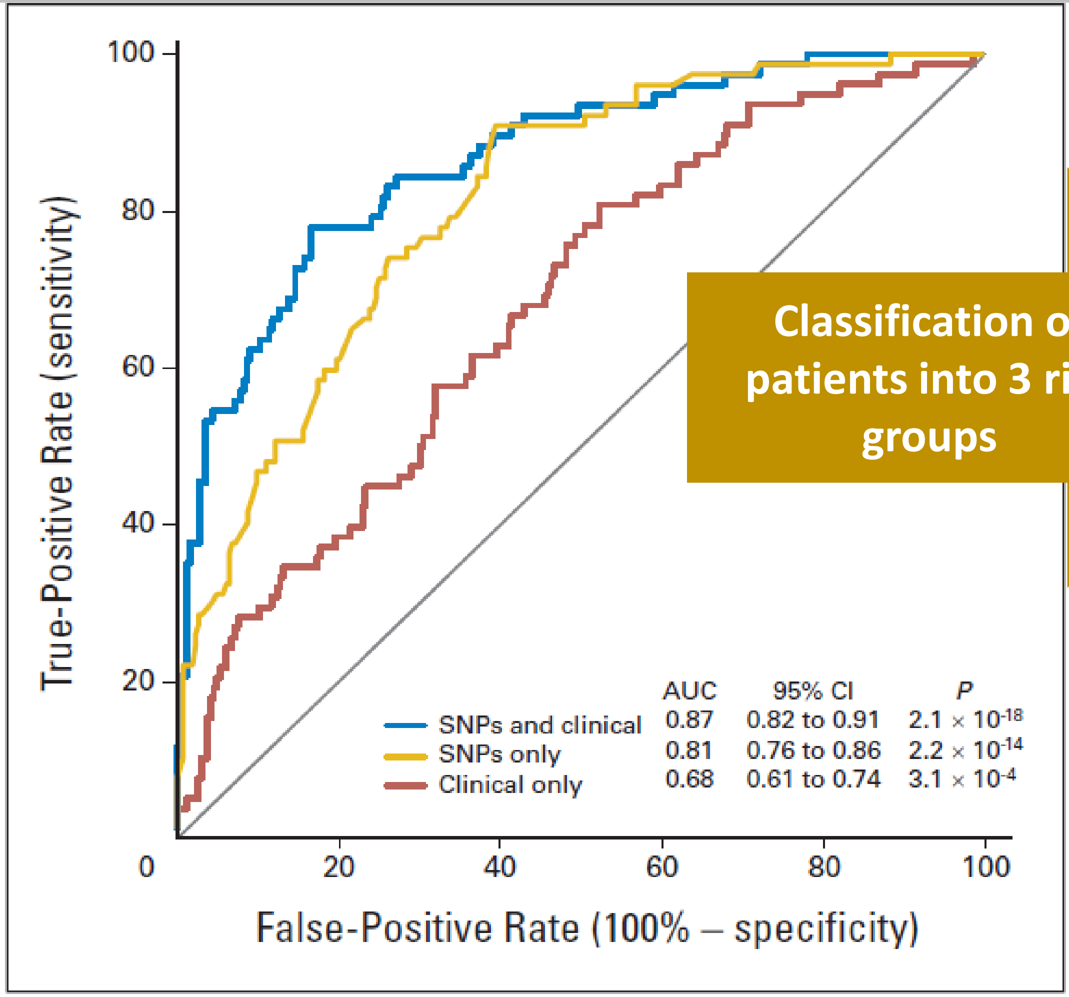
JACC CO **2023**

Gene-Level Analysis of Anthracycline-Induced Cardiomyopathy in Cancer Survivors: A Report From COG-ALTE03N1, BMTSS, and CCSS

Noha Sharafeldin MD, MSc, PhD[a], Liting Zhou MSc[a], Purnima Singh MSc, PhD, MSPH[a], David K. Crossman PhD[b], Xuexia Wang PhD[c], Lindsey Hageman MPH[a], Wendy Landier PhD[a], Javier G. Blanco PhD[d], Paul W. Burridge PhD[e], Yadav Sapkota PhD[f], Yutaka Yasui PhD[f], Gregory T. Armstrong MD, MSCE[f], Leslie L. Robison PhD[f], Melissa M. Hudson MD[f], Kevin Oeffinger MD[g], Eric J. Chow MD, MPH[h], Saro H. Armenian DO, MPH[i], Daniel J. Weisdorf MD[j], Smita Bhatia MD, MPH[a]

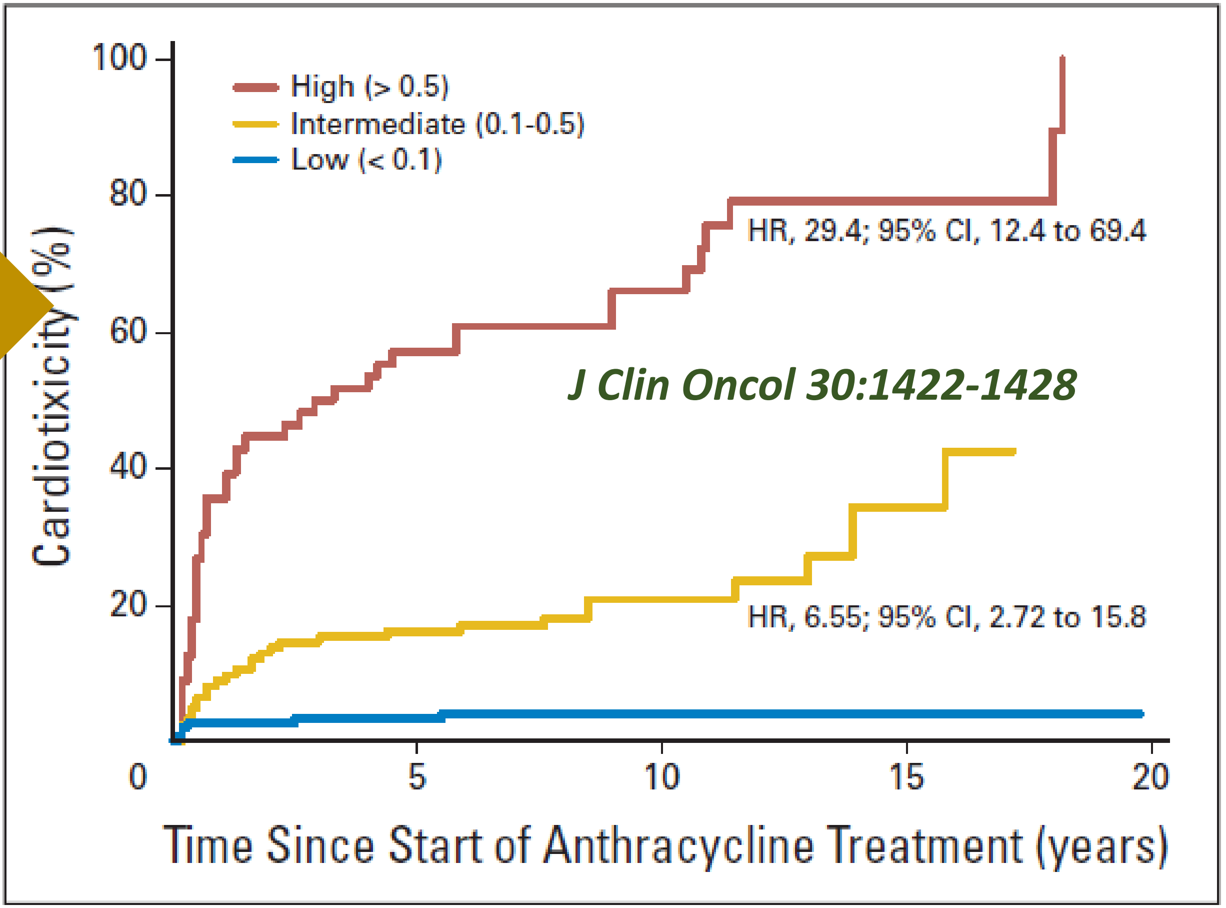
Pharmacogenomic Prediction of Anthracycline-Induced Cardiotoxicity

Multiple variants combined into single-prediction model that included clinical and genetic risk factors



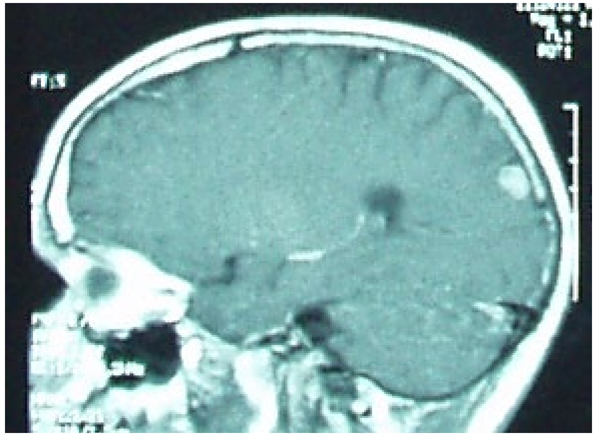
Classification of patients into 3 risk groups

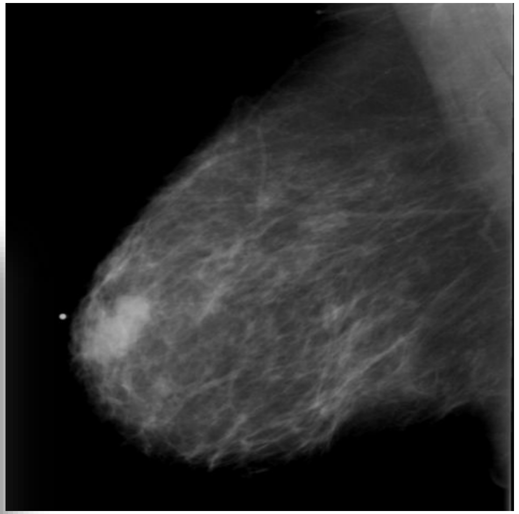
- **In high-risk group, 75% of patients accurately predicted to develop cardiomyopathy**
- **In low-risk group, 96% of patients accurately predicted not to develop cardiomyopathy.**

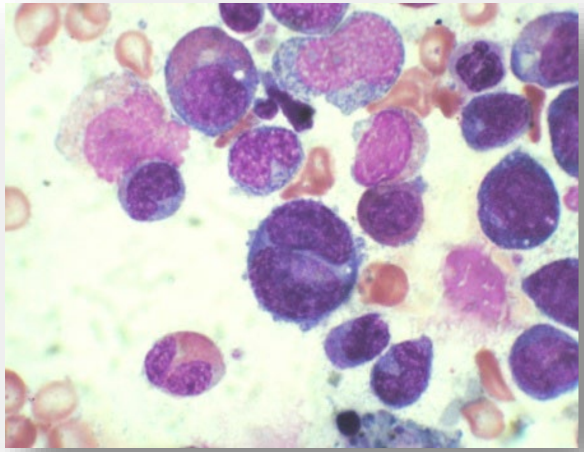


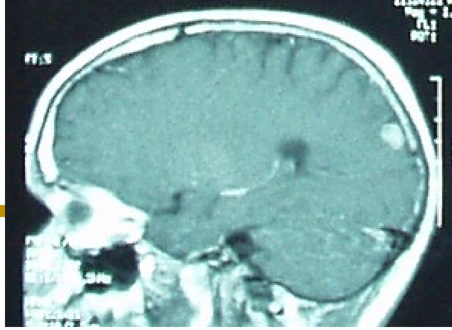
J Clin Oncol 30:1422-1428

Subsequent Neoplasms









Background

- Childhood cancer survivors are at a 10-fold increased risk for developing histologically distinct subsequent CNS tumors c/w general population

- High-grade gliomas and meningiomas are most common types of subsequent CNS tumors

- Subsequent CNS tumors are associated with significant morbidity and mortality
  - Five-year survival is <20% for gliomas
  - Meningiomas are often accompanied by significant morbidity

JNCI. 2010;102:1083-95
Lancet Oncol. 2013;14:e321-8

Risk factors

The risk for subsequent CNS tumors demonstrates a linear relation with radiation dose

- Exposure to cranial radiation is the major risk factor
- The risk is especially increased after exposure to radiation at a very young age

Risk factors

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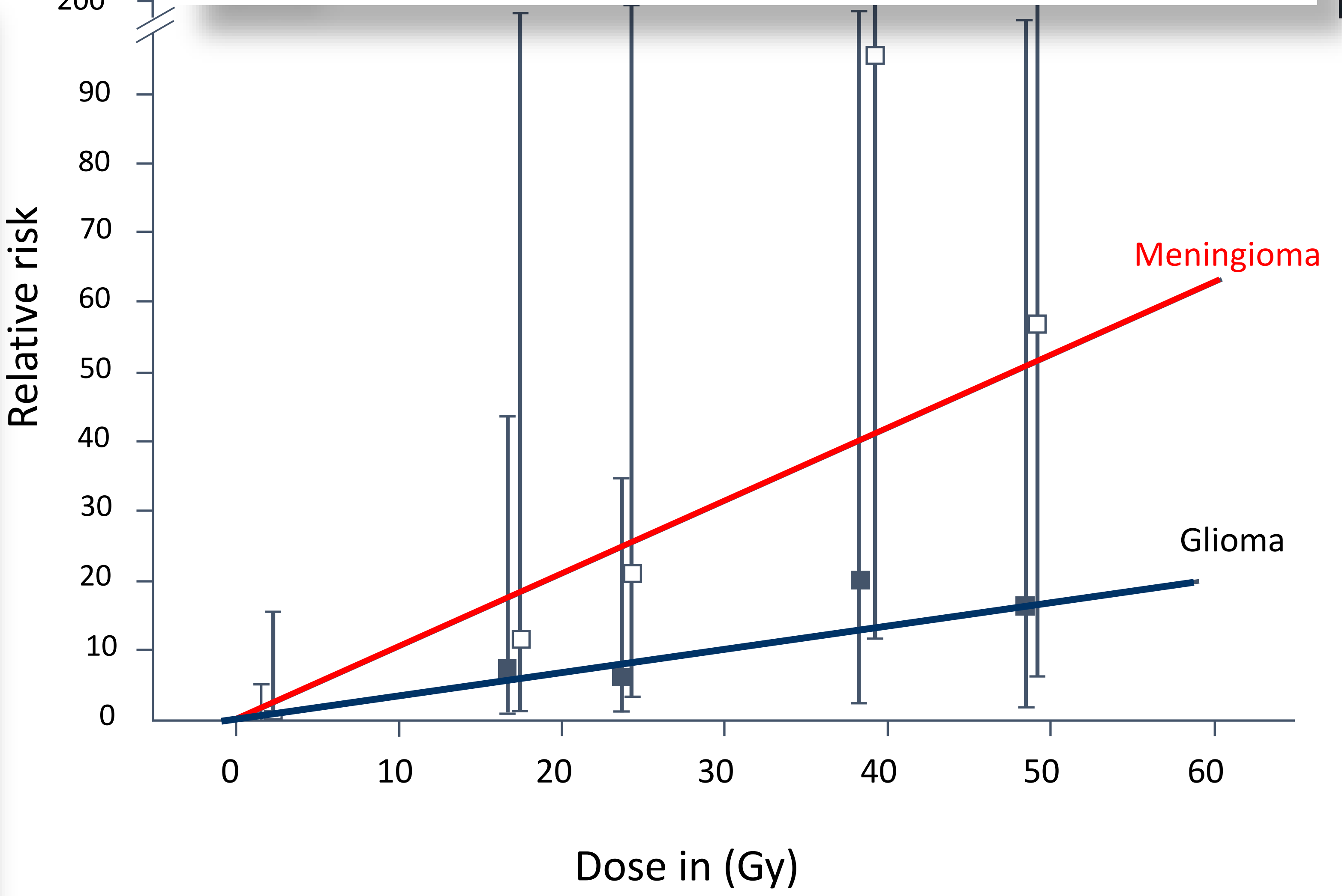
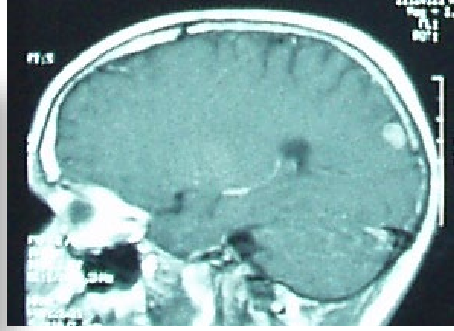
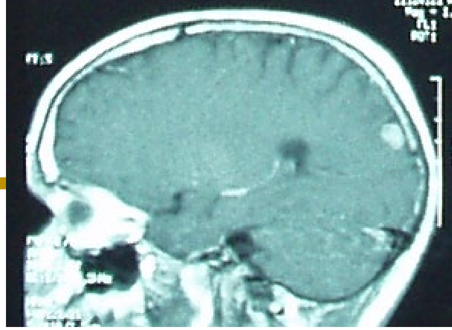
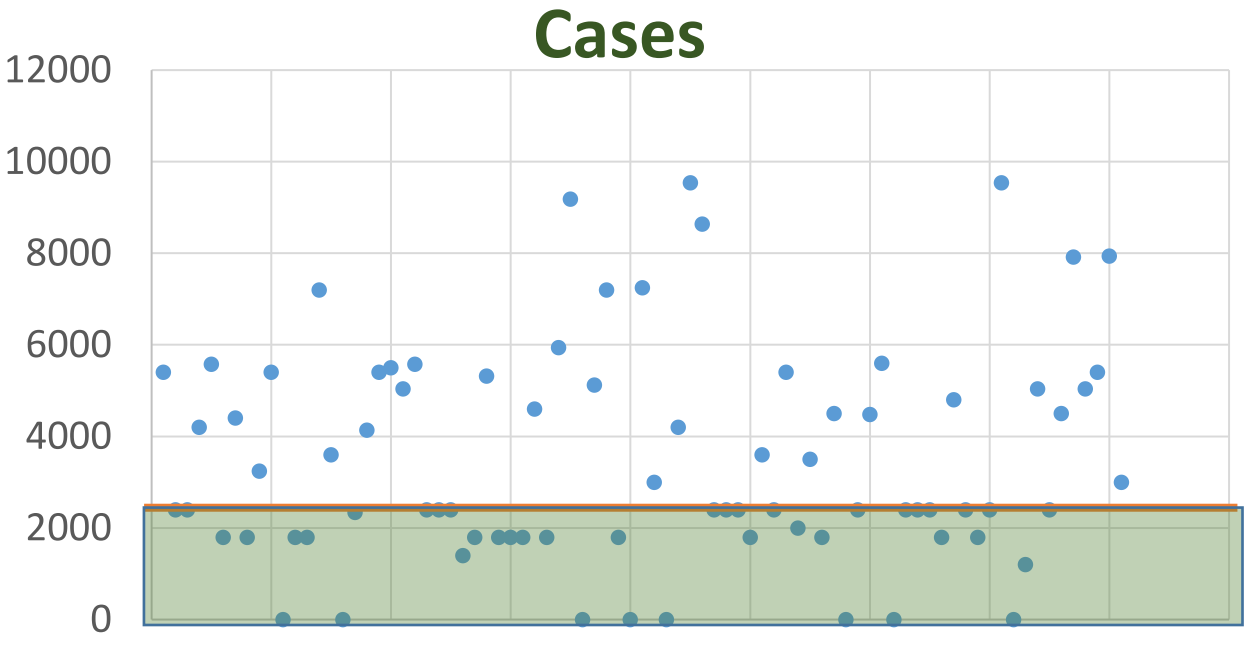


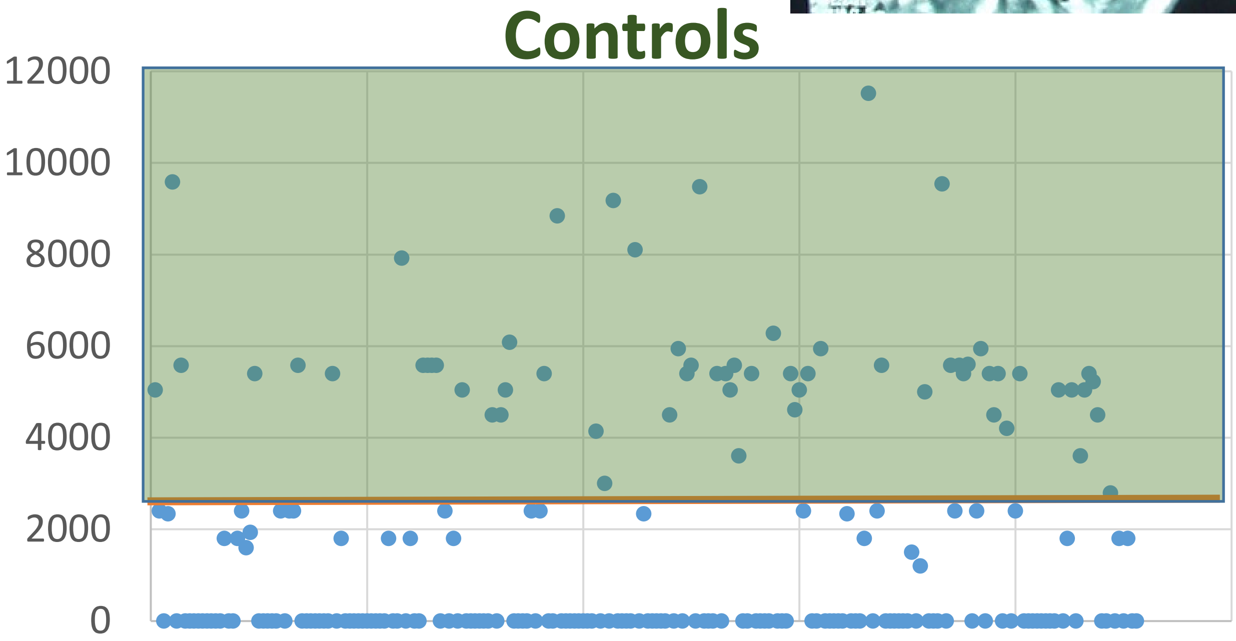


JNCI. 2010;102:1083-95

Cranial radiation dose and subsequent CNS tumors - inter-individual variability in risk







Role for Genetic Susceptibility?

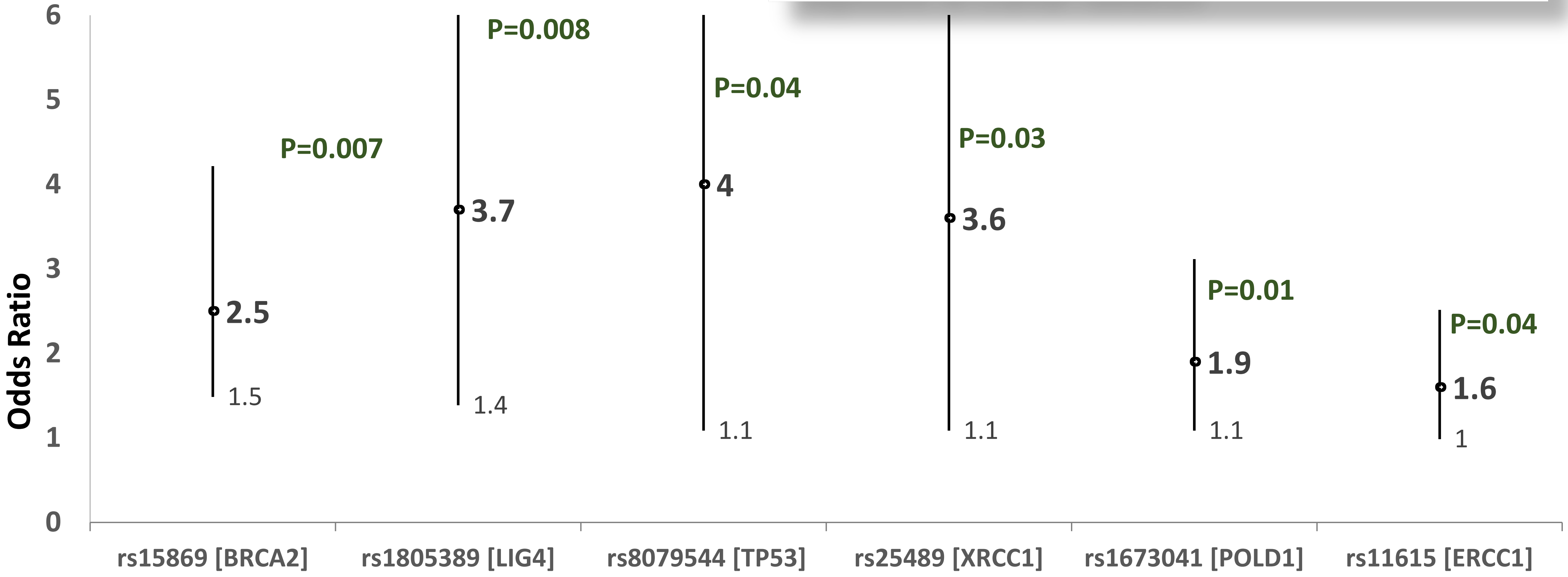
Candidate gene approach

- Examined genetic variants associated with *de novo* brain tumors

Results

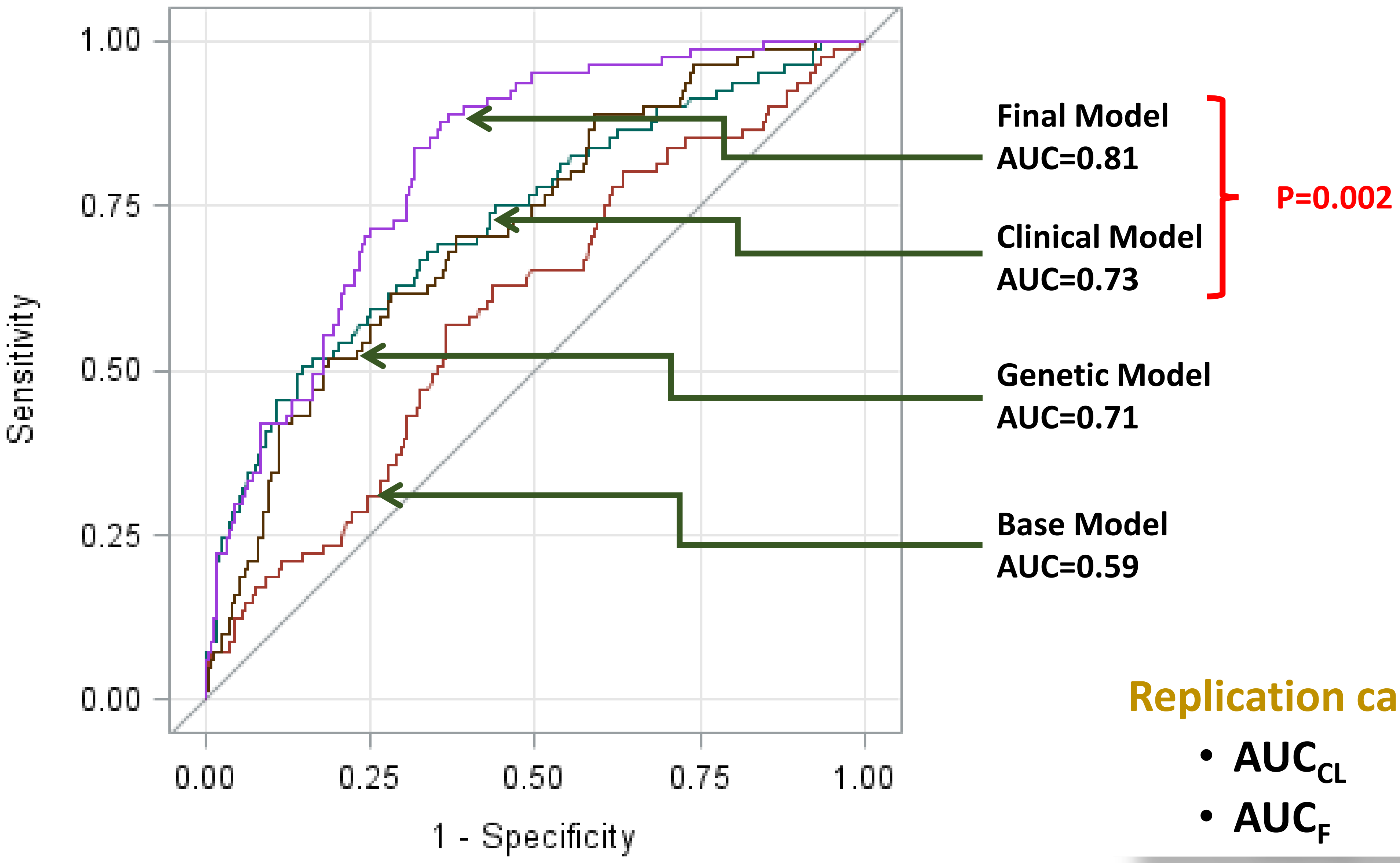
All Subsequent CNS tumors – Replication of Candidate SNPs

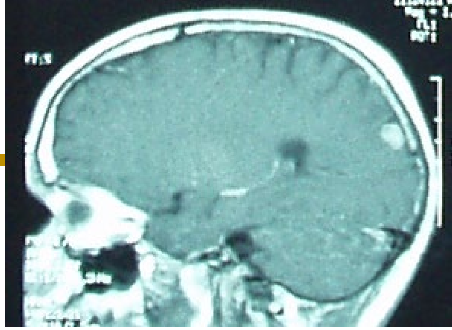
adjusted for age at diagnosis, sex, race/ethnicity and exposure to cranial radiation



DNA Damage Response or Repair Genes

Risk prediction models for subsequent CNS tumors



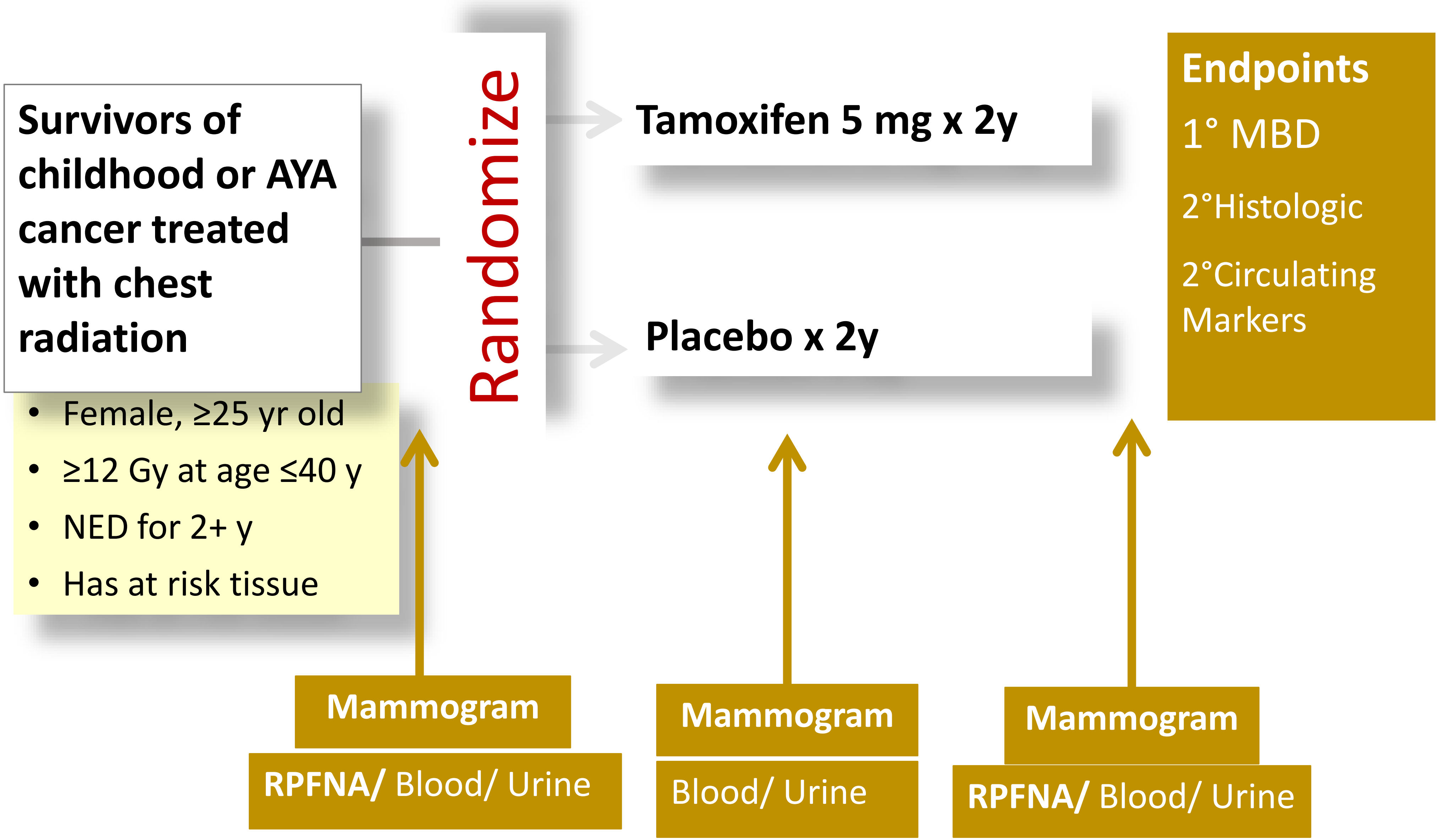


rs15869 [***BRCA2***]
rs8079544 [***TP53***]
rs498872 [***PHLB1***]
rs1673041 [***POLD1***]
rs25489 [***XRCC1***]
rs11615 [***ERCC1***]
rs828699 [***XRCC5***]

Replication case-control set

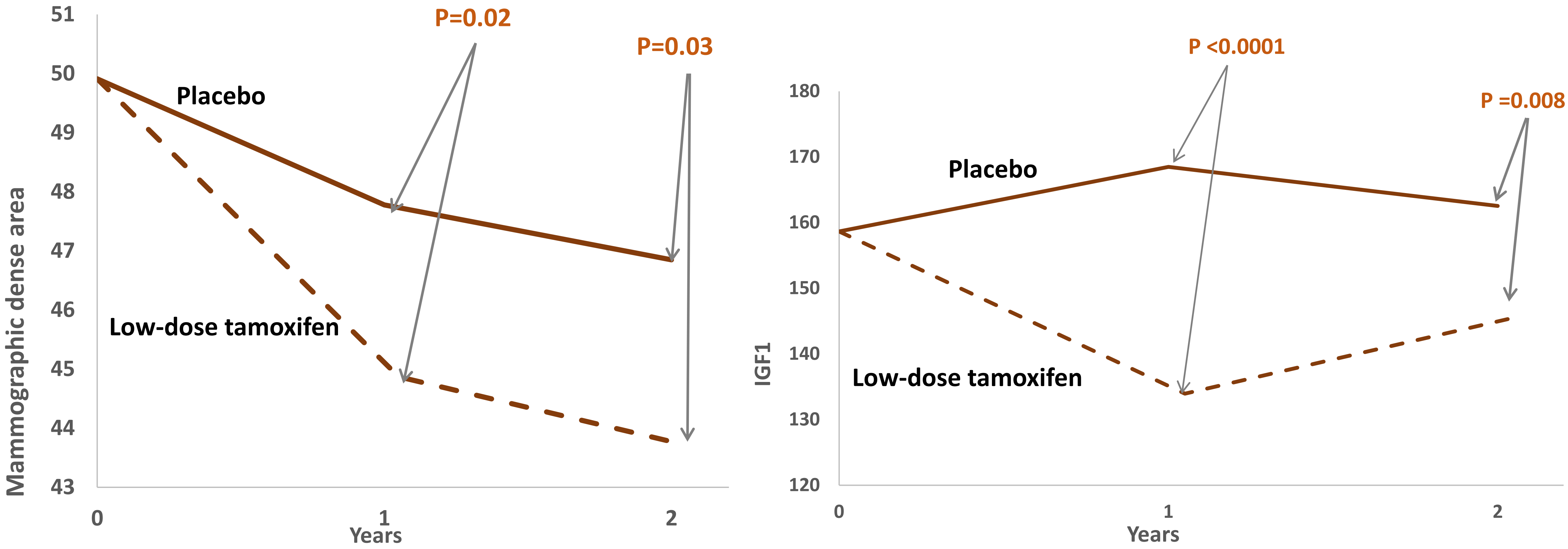
- **AUC_{CL} 73%**
- **AUC_{F} 89%**

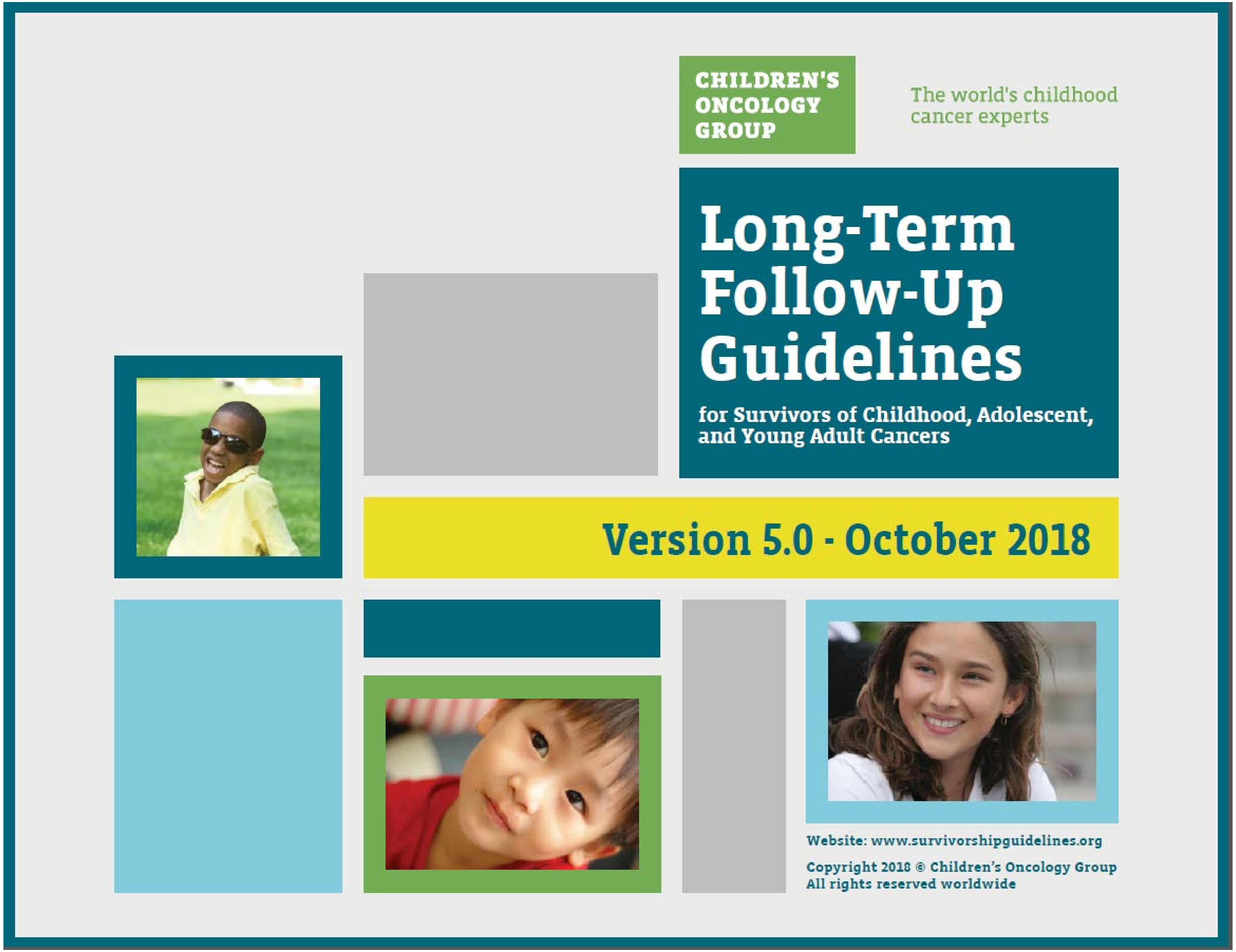
Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction



Low-dose tamoxifen and risk of radiation-related breast cancer

CLINICAL CANCER RESEARCH
Clin Cancer Res. 2021;27:967-974.





COG Long-term Follow-up Guidelines for survivors of Childhood, Adolescent, and Young Adult Cancers

www.survivirshipguidelines.org

Modification of Therapeutic Exposures

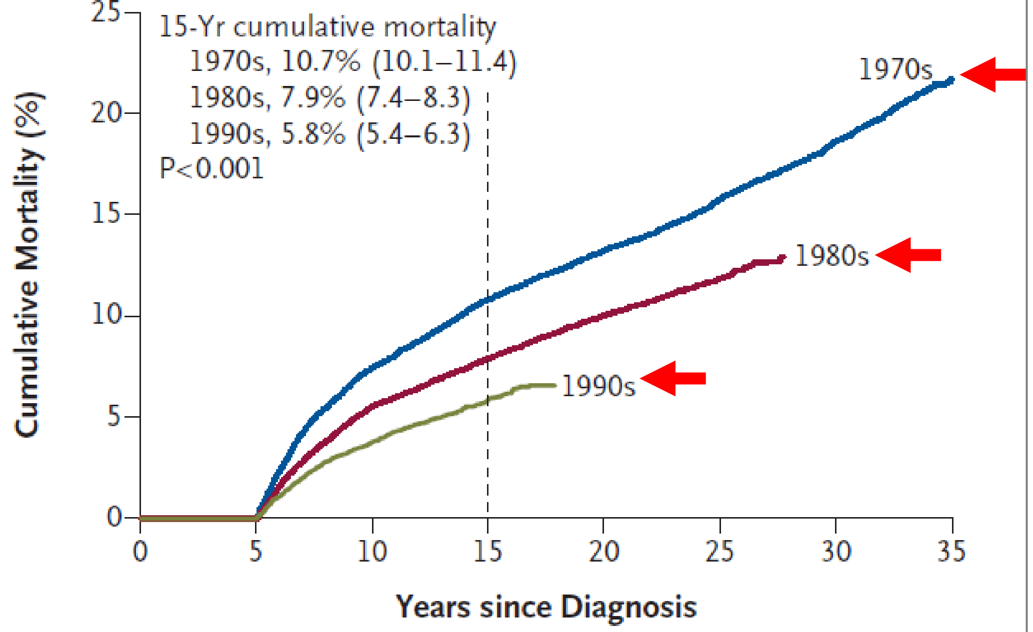
- Elimination of prophylactic **cranial radiation** therapy for children with standard/ low risk acute lymphoblastic leukemia
  - Reduction in risk of secondary brain tumors and cognitive impairment
- Reduction in dose and field of **chest radiation** for Hodgkin lymphoma
  - Reduction in risk of secondary breast cancer, pulmonary toxicity, coronary artery disease
- Reduction in **anthracycline dose**
  - Reduction in risk of cardiomyopathy
- Reduction of **dose and type of alkylators**
  - Reduction in risk of secondary leukemia

ORIGINAL ARTICLE

Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer

N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

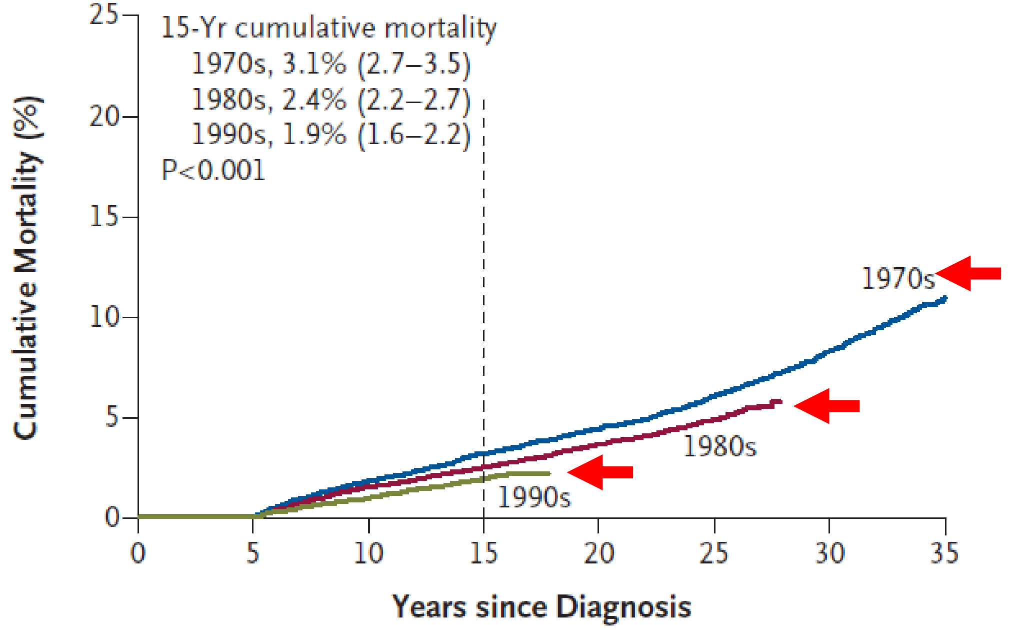
A Death from Any Cause



No. at Risk

1970s	9,416	8,722	8,406	8,182	7942	5556	1506
1980s	13,181	13,443	13,105	10,389	3583		
1990s	11,436	11,411	3,924				

C Death from Health-Related Cause



No. at Risk

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Acknowledgements

NIH NATIONAL CANCER INSTITUTE

R01 CA096670

R01 CA174683

R01 CA139633

R01 CA140245

RC4 CA156499

U10 CA098543

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Scholar Award for Clinical Research 2191-02

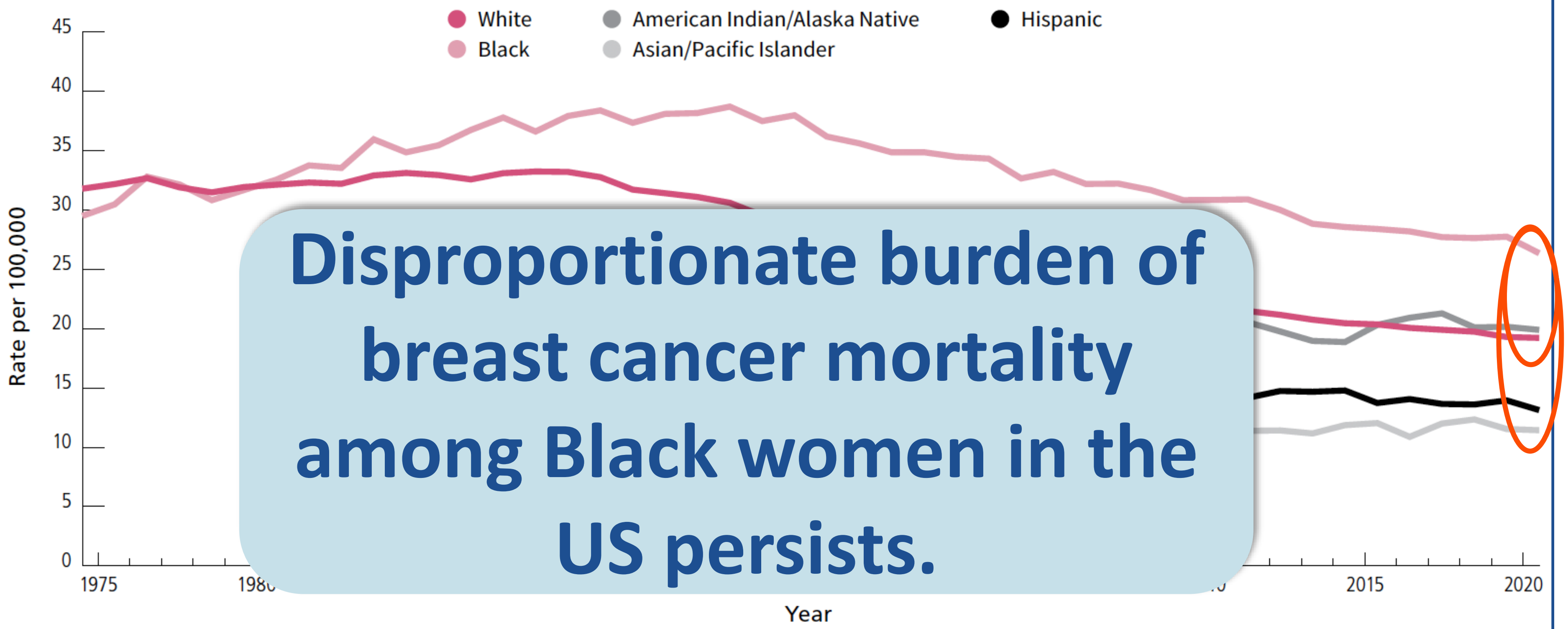
Translational Research Program 6093-08

EXPLORING SOCIAL/STRUCTURAL AND BIOLOGIC DETERMINANTS OF BREAST CANCER SURVIVAL INEQUITIES

Adana A.M. Llanos, PhD, MPH
Associate Professor of Epidemiology

Statement of the problem

Trends in female breast cancer death rates by race and ethnicity, US, 1975-2020



Disproportionate burden of breast cancer mortality among Black women in the US persists.

Note: Rates are per 100,000 and age adjusted to the 2000 US standard population. Race is exclusive of Hispanic origin, except for 1975-1989 for Black and White women. Rates for American Indian/Alaska Native are 3-year moving averages and are adjusted for racial misclassification (see Sources of Statistics, page 34).

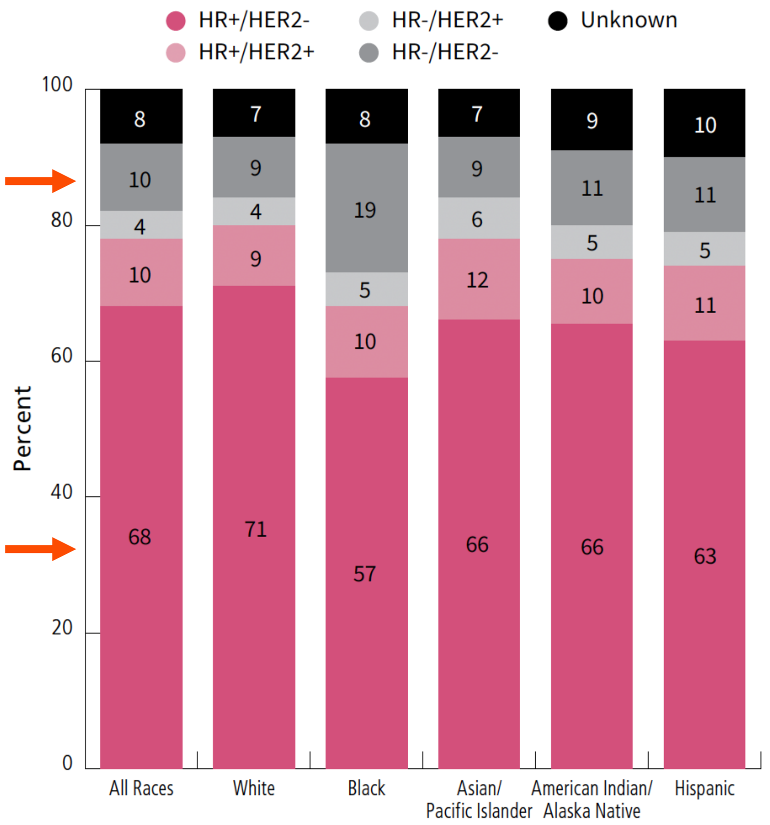
Source: NCHS, 2022.

Figure Source: Breast Cancer Facts & Figures 2022-2024, American Cancer Society

Aggressive tumor clinicopathology?

Distribution of tumor subtype by race and ethnicity

Distribution of breast cancer subtypes by race and ethnicity, ages 20 and older, US, 2015-2019



HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.
Note: Except for all races, race is exclusive of Hispanic origin. Data for American Indians/Alaska Natives are based on Purchased/Referred Care Delivery Area (PRCDA) counties.

Source: NAACCR, 2022.

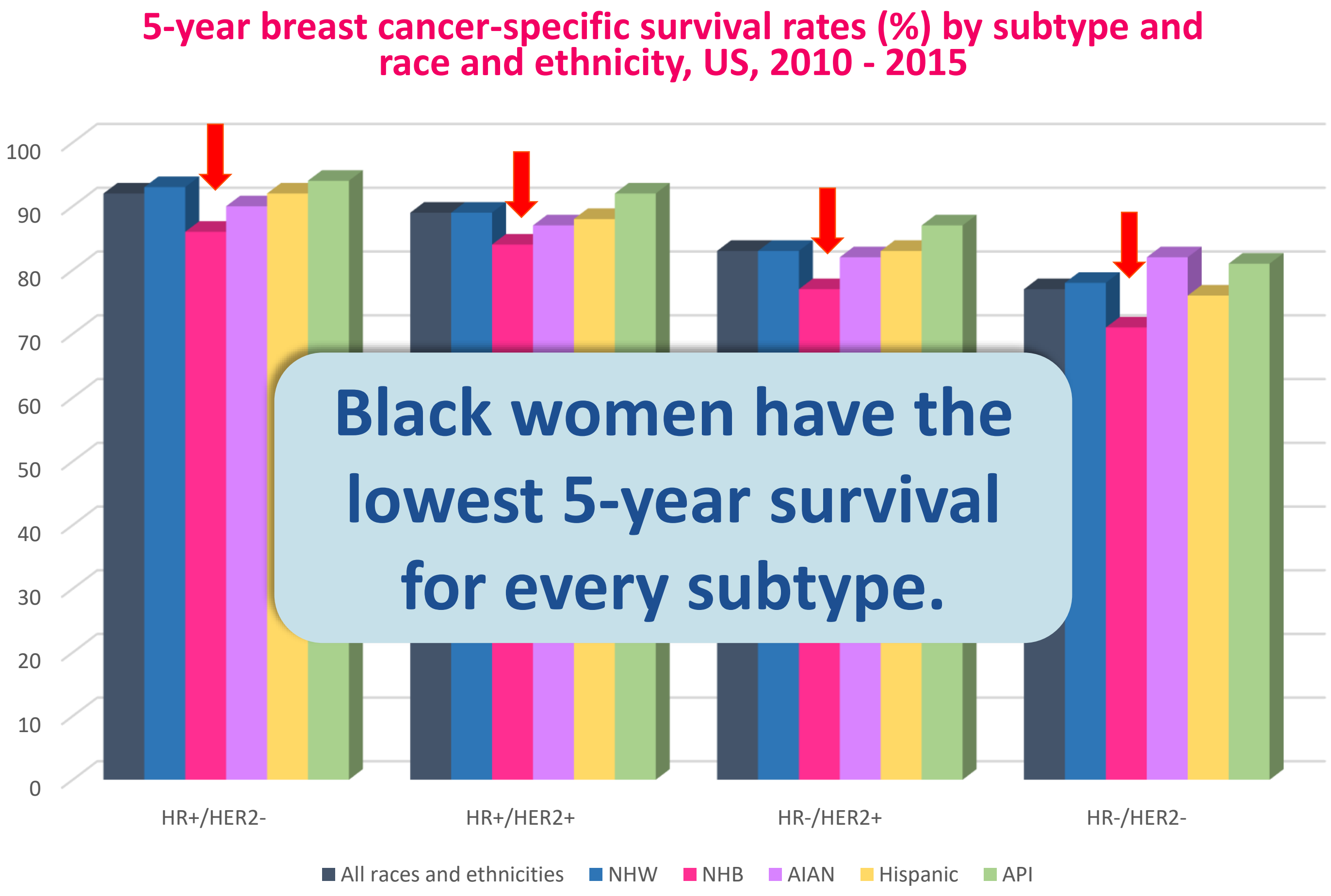
Figure Source: Breast Cancer Facts & Figures 2022-2024, American Cancer Society

- HR+/HER2- subtype is associated with the best survival rates
- HR-/HER2- subtype (triple-negative, TN) is associated with the worst survival rates
  - Incidence of the triple-negative (TN) subtype is highest among Black women and lowest among White and AAPI women

Sung H, *Cancer* 2019; Mavaddat N, *Cancer Epidemiol Biomarkers Prev* 2012

Aggressive tumor clinicopathology?

Breast cancer survival by subtype and race and ethnicity



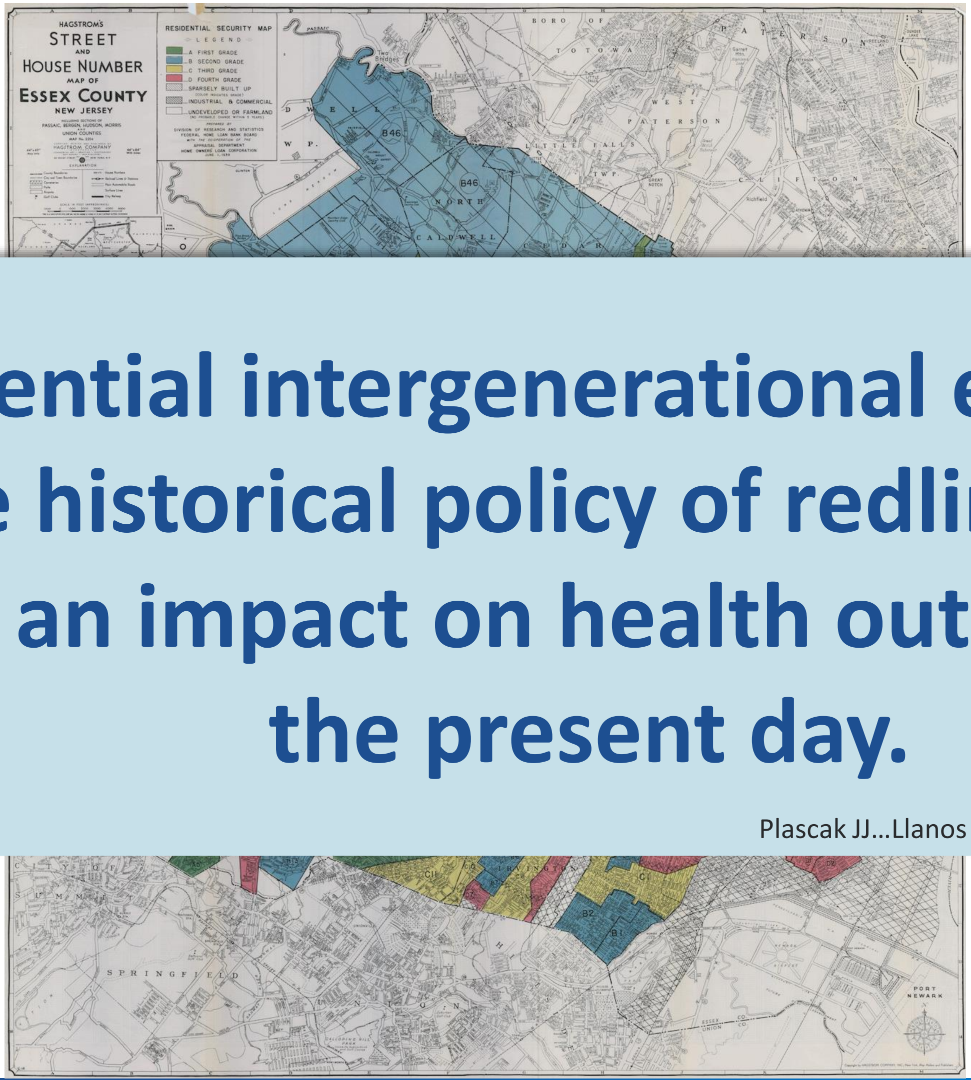
DeSantis CE, *CA Cancer J Clin* 2019

What factors might explain the incidence or more aggressive breast tumors and poorer survivorship outcomes among African American and Black women?

Neighborhood disinvestment vs. Neighborhood investment

Plascak JJ…Llanos AAM, *Cancer* 2022

1930s Home Owners’ Loan Corporation (HOLC) Mortgage Security Redlining Map of Essex County, NJ



Most desirable (Best)

Potential intergenerational effects of the historical policy of redlining still has an impact on health outcomes in the present day.

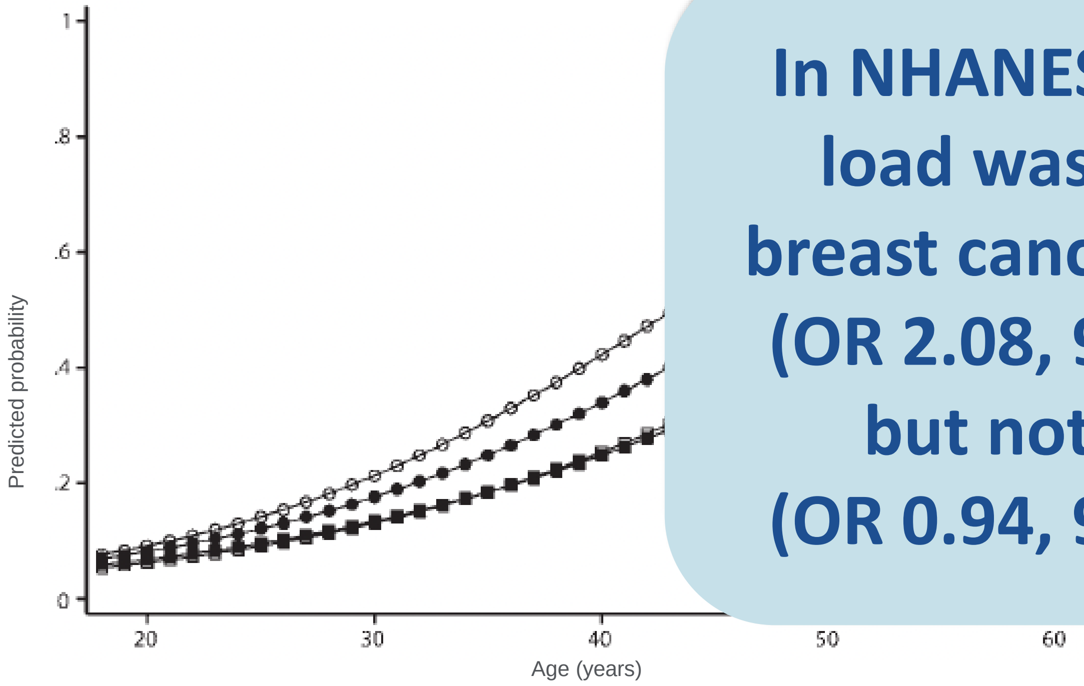
Plascak JJ…Llanos AAM, *JAMA Netw Open* 2022

Hazardous (Worst)

Image Source:
https://dsl.richmond.edu/panorama/redlining/#loc=11/40.801/-74.486&city=essex-co.-nj

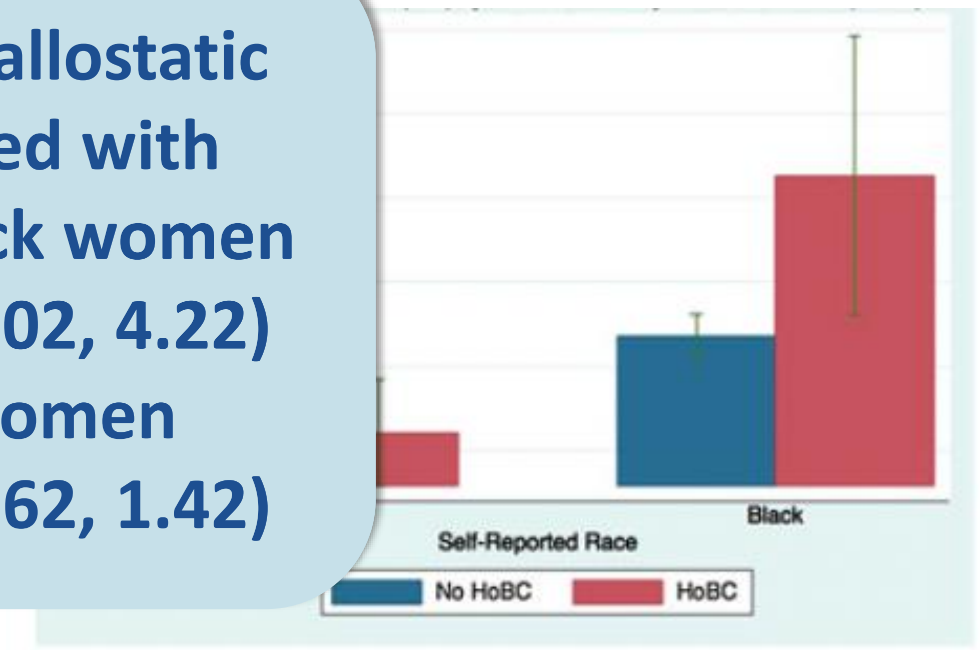
Allostatic load scores are higher in Black women (and men) and associated with breast cancer

Probability of having an allostatic load score ≥4, as predicted by race and gender



Source: Geronimus AT, *Am J Public Health* 2006

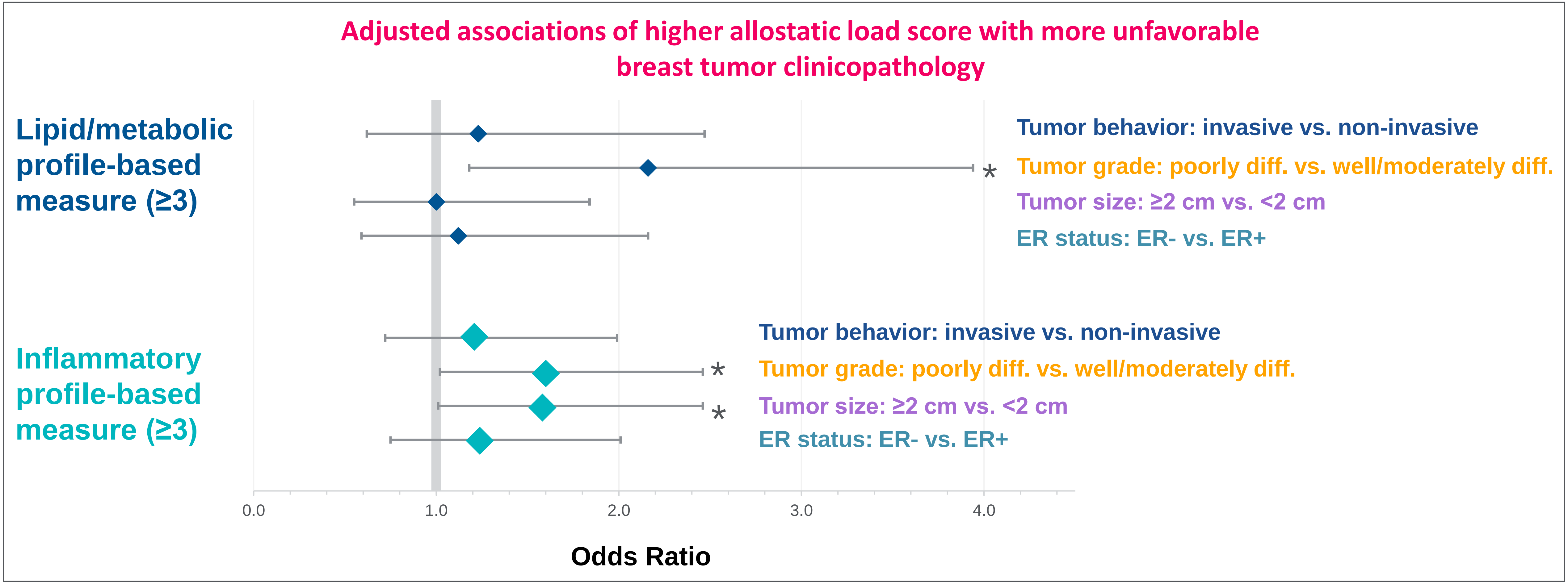
Elevated allostatic load (≥3) by race and history of breast cancer (HoBC)



Source: Parente V, *Psycho-Oncol* 2013

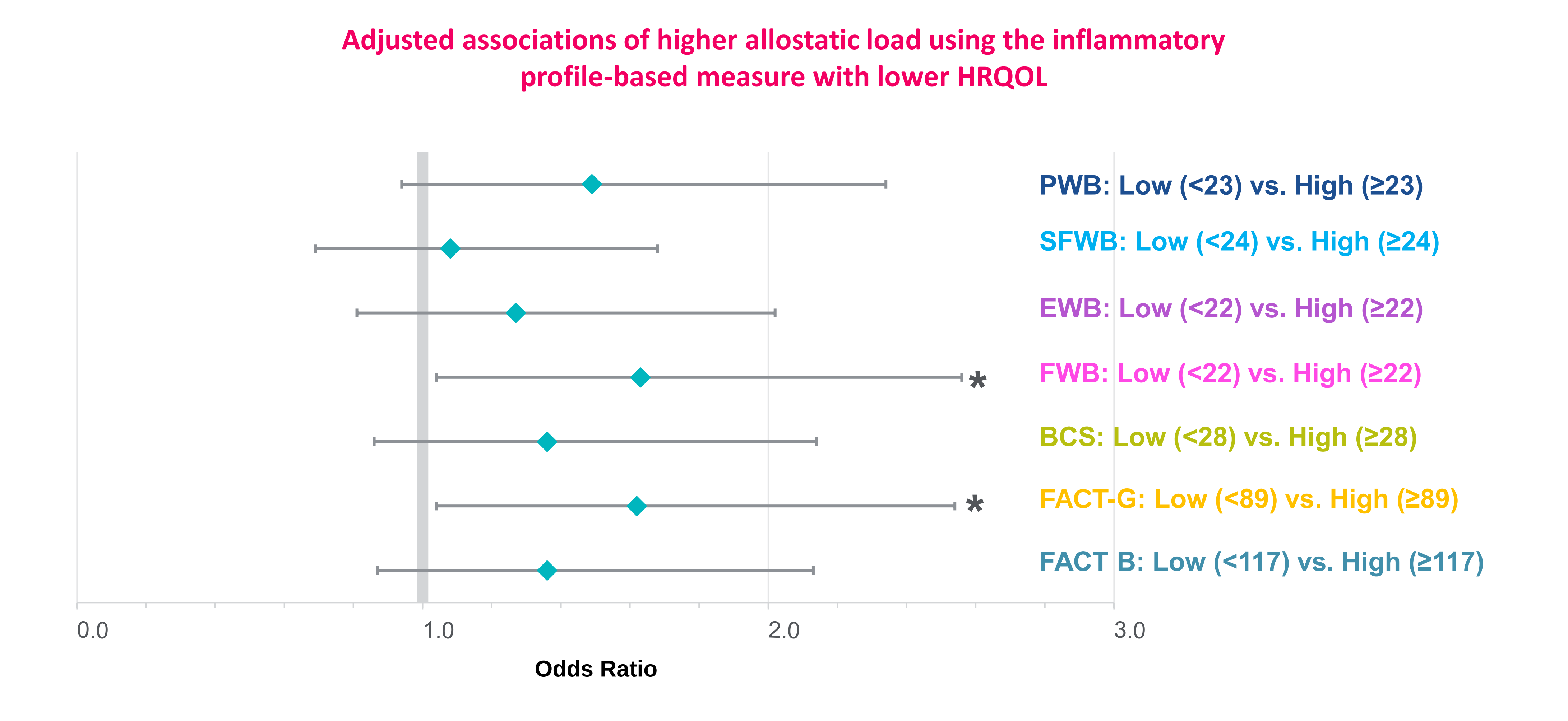
In NHANES, higher allostatic load was associated with breast cancer in Black women (OR 2.08, 95% CI: 1.02, 4.22) but not White women (OR 0.94, 95% CI: 0.62, 1.42)

Associations between pre-diagnostic allostatic load scores and breast tumor features



Xing CY…Llanos AAM, *Cancer Epidemiol Biomarkers Prev* 2020

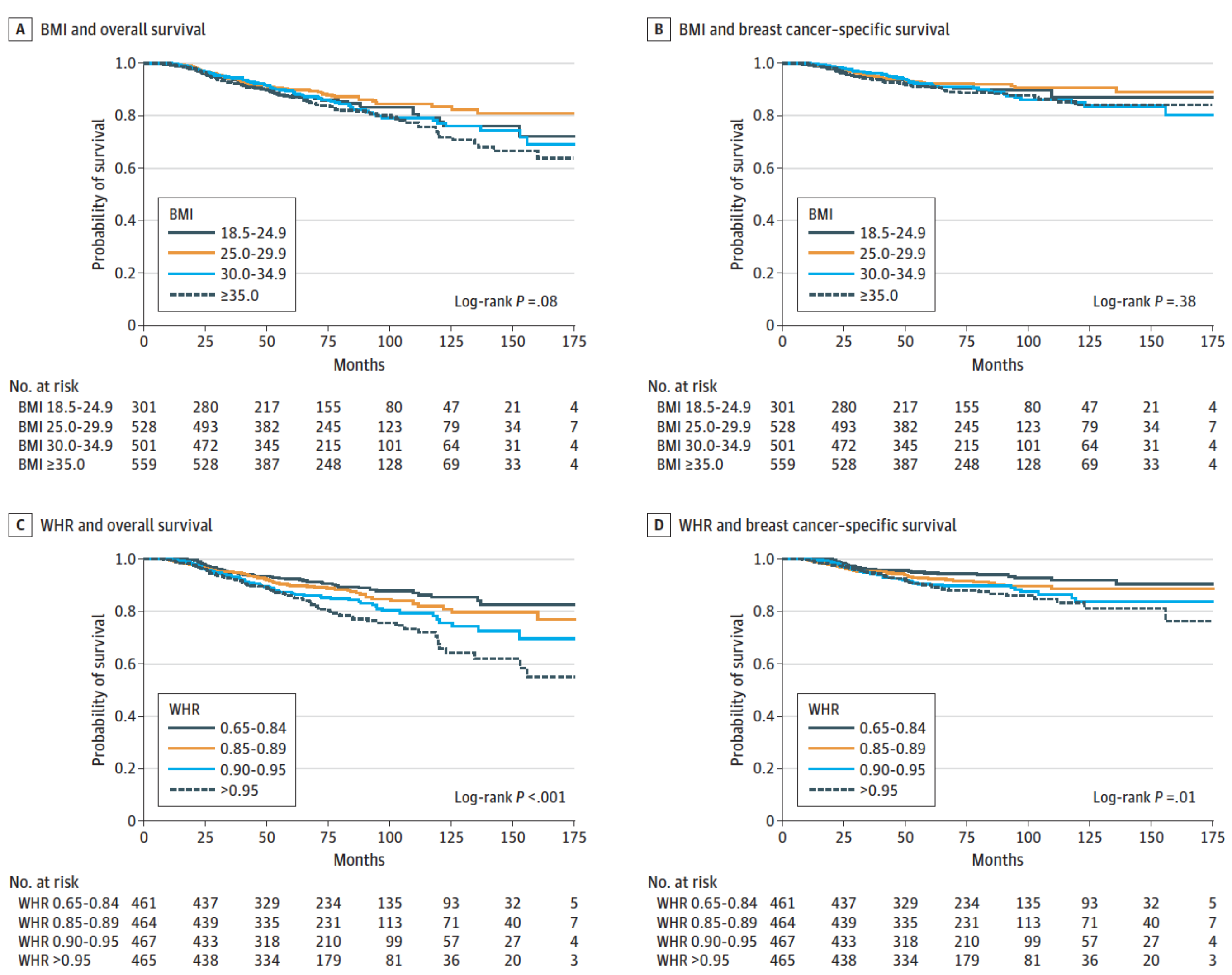
Associations between pre-diagnostic allostatic load scores and HRQOL 2-years post-diagnosis



Xing CY…Llanos AAM, *Breast Cancer Res Treat* 2020

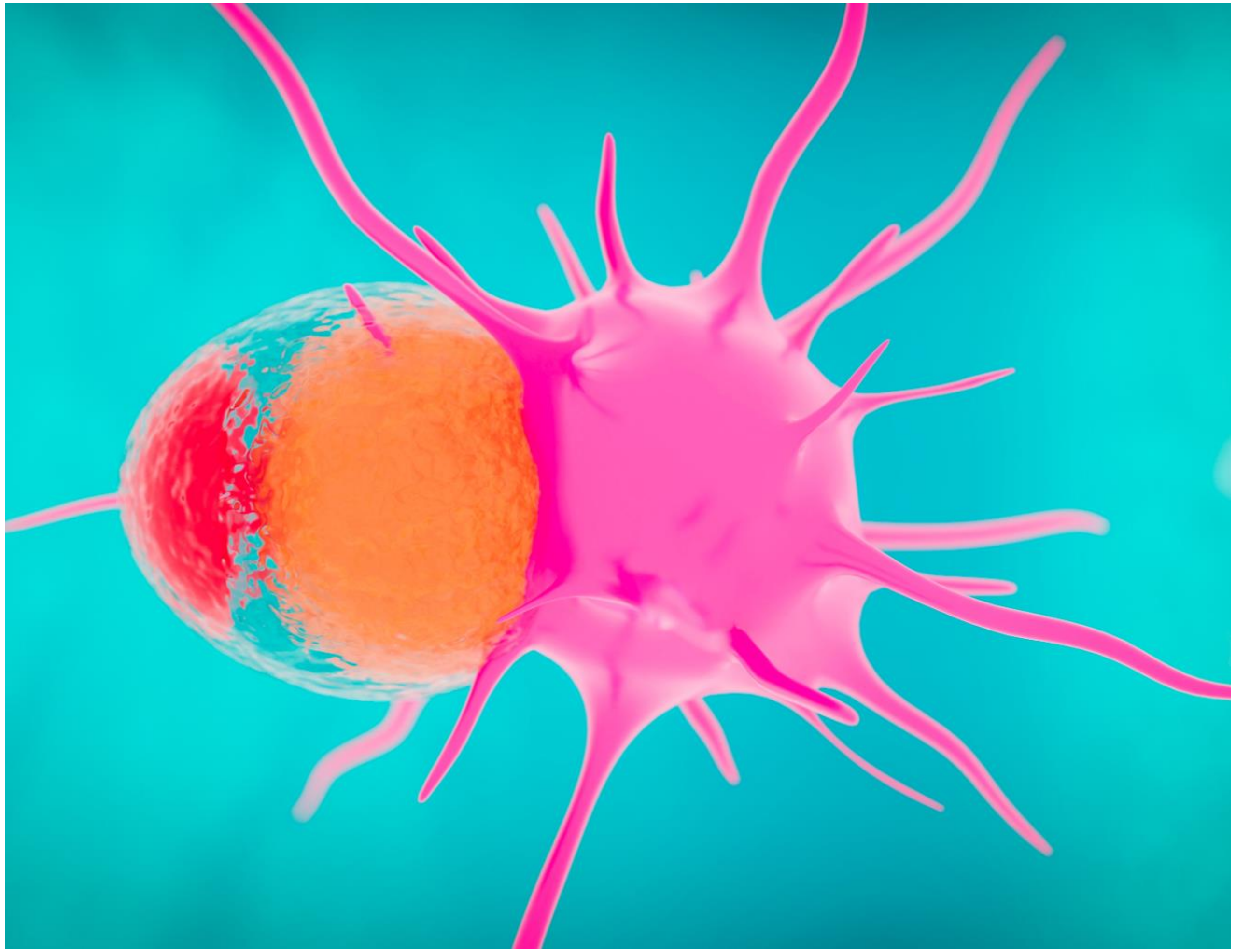
Associations between adiposity and breast cancer mortality

Figure. Kaplan-Meier Curves for All-Cause and Breast Cancer–Specific Survival by Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR)



Greater adiposity – especially central adiposity – is associated with higher all-cause and breast cancer-specific mortality among Black breast cancer survivors

Bandera EV, *JAMA Oncol* 2021



Adipokine pathway biomarkers – link between adiposity and breast cancer survival inequities?

Expression of adipokine receptors in the breast tumor microenvironment

More aggressive tumor clinicopathologic features associated with lower adipokine and adipokine receptor protein expression in the breast tumor microenvironment	
Higher tumor grade	✗
Larger tumor size	✗
Positive lymph nodes	✗
Ki67+ status	✗
ER- status	✓
HER2+ status	✗
Triple-negative subtype	✓

More aggressive tumor clinicopathologic features associated with lower adipokine and adipokine receptor gene expression in the breast tumor microenvironment	
Higher tumor grade	✓
Larger tumor size	✓
Positive lymph nodes	✗
Ki67+ status	✗
ER- status	✓
HER2+ status	✗
Triple-negative subtype	✓

Llanos AAM, *Breast Cancer Res*, 2020
Llanos AAM, *Breast Cancer Res Treat, 2020*

EDCs in hair products and possible mechanisms associated with breast cancer and other outcomes

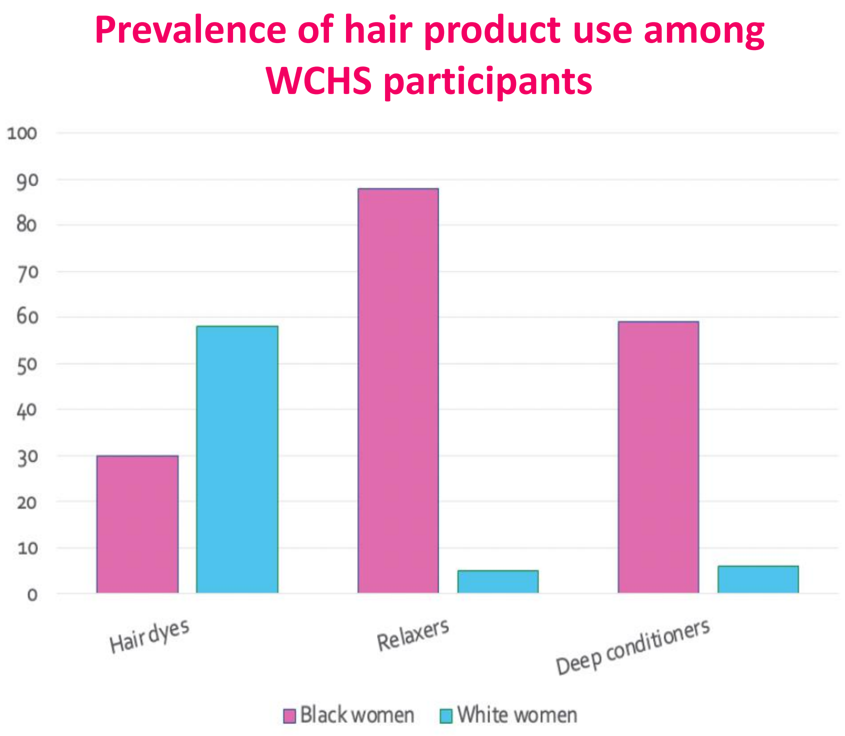
EDC Group	Use in HPCs	Possible Mechanisms
Estrogens	Promote hair growth	Epigenetic changes leading to predisposition to tumorigenesis, altered mammary gland development, and cell proliferation
Phthalates	Carry fragances	Alter mammary gland development through epigenetic changes, promote cell growth, and increase migratory and invasive properties in breast cancer cells
Parabens	Preservative	Induce growth of breast epithelial cells, increase migratory and invasive properties of breast cancer cells

Adapted from Stiel et al., Cancer Med 2016

- Greater breast cancer risk[1]
- Breast tumor features[4]
- Earlier age at puberty[2]
- Metabolic disease[5]
- Greater risk of fibroids[3]
- Lower sex steroid hormone levels[6]

[1] Heikkinen et al. 2015, Llanos et al. 2017, Taylor et al. 2018, Brinton et al. 2018, Eberle et al. 2019, Parada et al. 2019; [2] James-Todd et al. 2011, McDonald et al. 2018; Cathey et al. 2020; [3] Shen et al. 2013; [4] Rao et al. 2022; [5] Papalou et al. 2019; 6 Rivera-Núñez et al. 2022

Associations between hair dye and relaxer use and breast cancer



- Use of dark hair dye shades was associated with increased breast cancer risk
- Combination application (home kit + salon application) of permanent hair dye was associated with increased risk of more aggressive breast tumor characteristics including:
  - Larger tumor size
  - Higher tumor grade
- Longer duration (>10 years) and earlier use (before age 12) of relaxers were associated with larger tumor size

Llanos AAM et al., *Carcinogenesis* 2017
Rao R…Llanos AAM, *Environ Res* 2022

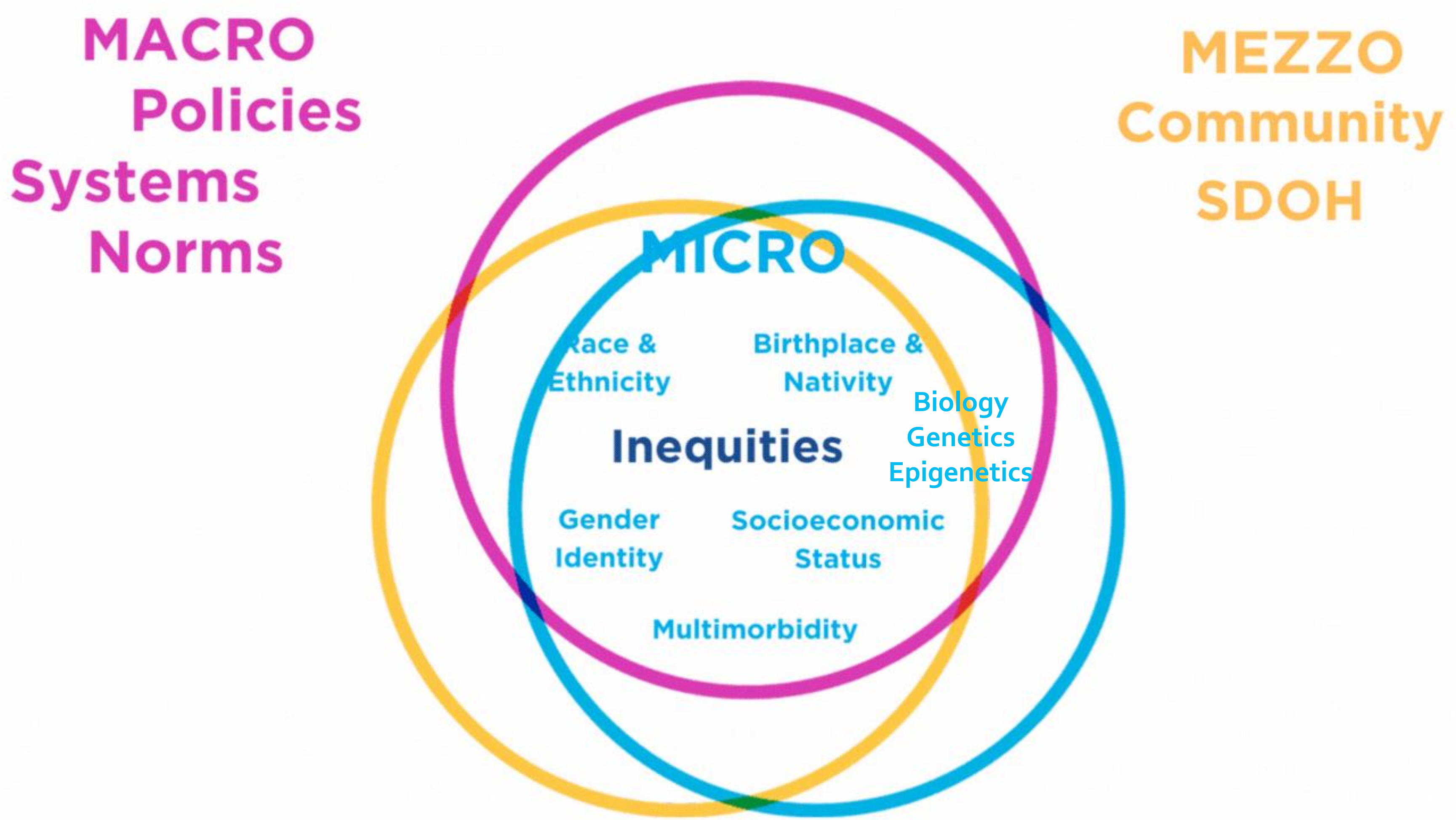
Summary

Neighborhood context in breast cancer inequities – considering "place," not just race

Allostatic load, adiposity-related biomarkers, and endocrine-disrupting chemical exposures from hair product use are important biologic/molecular contributors to breast cancer inequities

Interrelationships between social and structural factors and biological factors → sociobiologic mechanisms

The factors and mechanisms that cause cancer inequities act at multiple, intersecting levels of influence…



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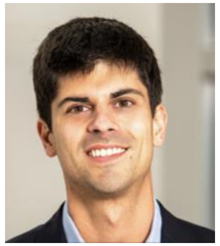
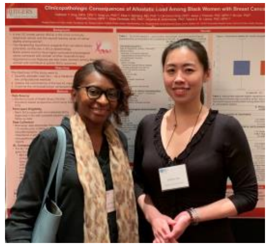
Women's Circle of Health Study





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