



**American Society of Breast Disease
30th Anniversary Symposium**

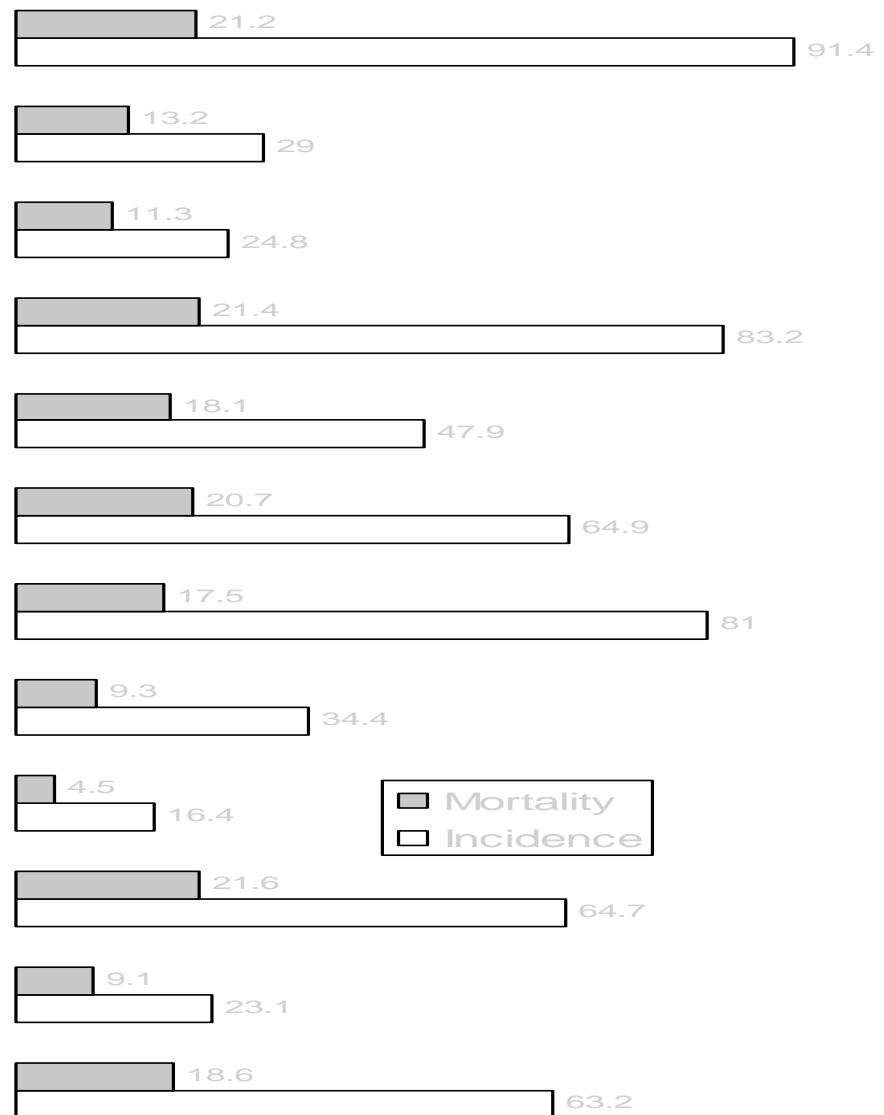


**BREAST CANCER IN SPECIAL
POPULATIONS:
AFRICAN AMERICAN
WOMEN**

**Lisa A. Newman, M.D., M.P.H., F.A.C.S.
Associate Professor of Surgery
Director, Breast Care Center
University of Michigan
Ann Arbor, MI**



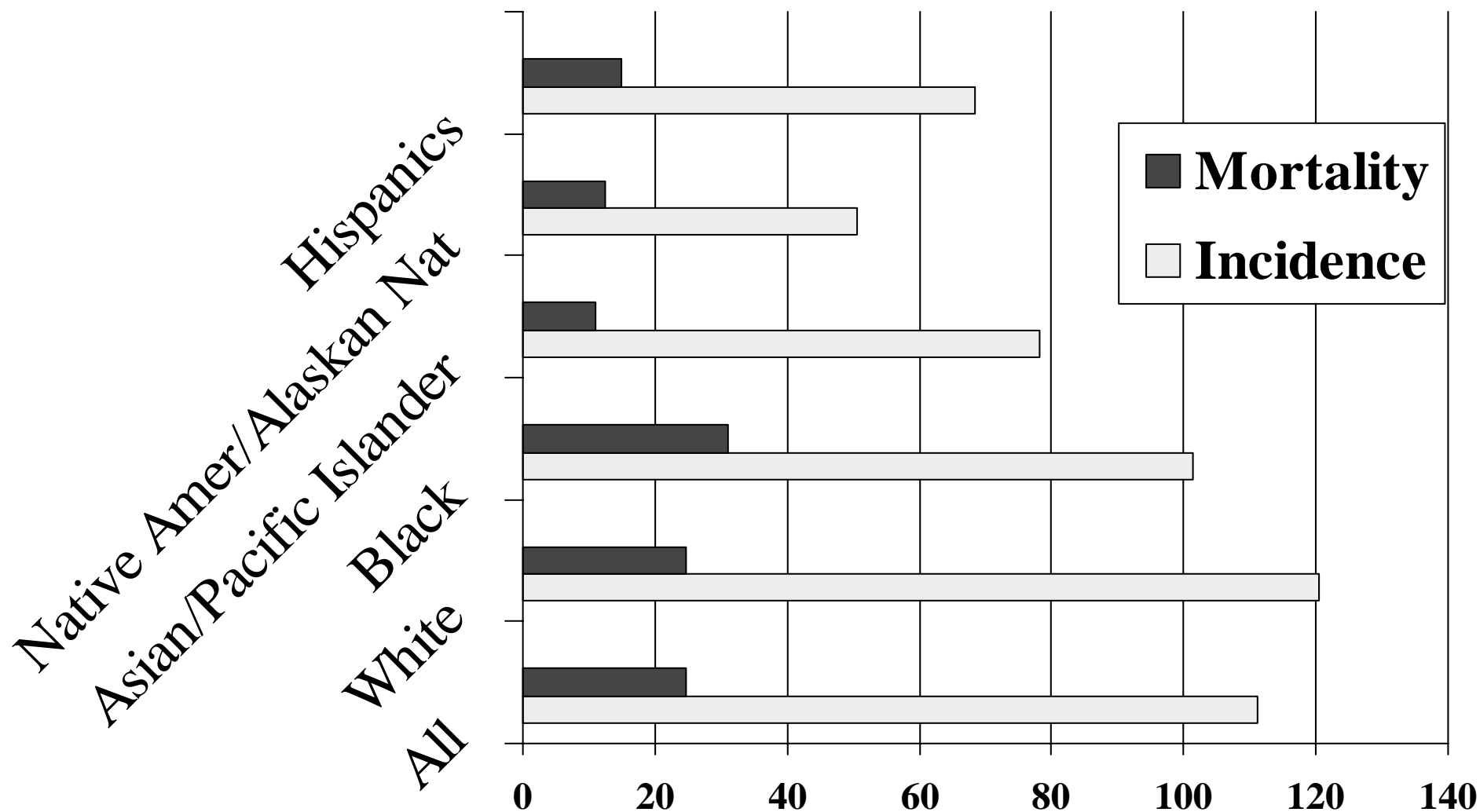
BREAST CANCER: A GLOBAL PERSPECTIVE





BREAST CA INCIDENCE & MORTALITY

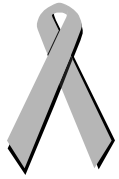
Age-Adjusted Rates (per 100,000 pop'n)





BREAST CA IN AFRICAN AMERICANS

- Overall lower incidence
- Higher mortality
- More advanced stage distribution
- Younger age distribution
- Increased prevalence of adverse prognostic tumor features

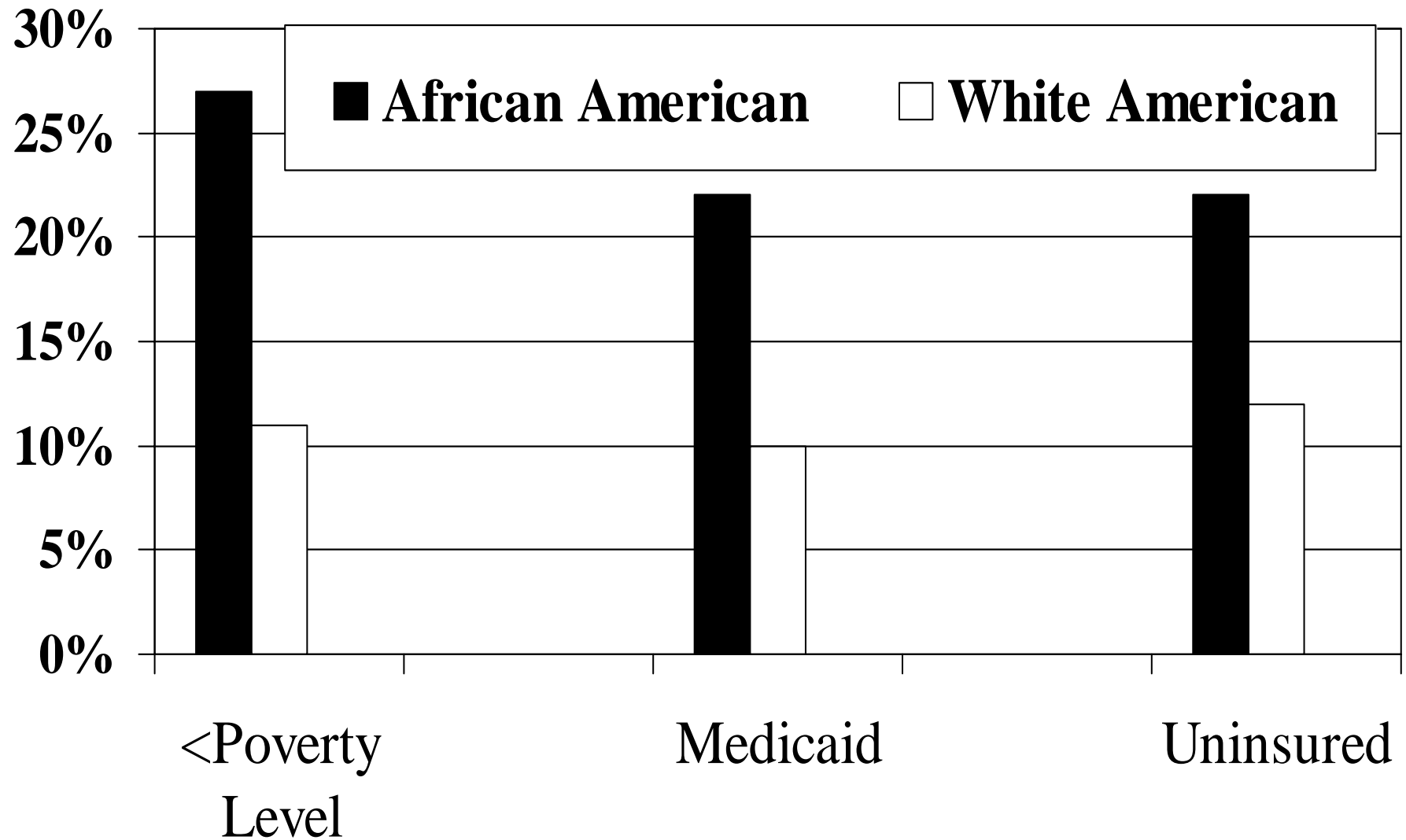


ETIOLOGY OF DISPARITIES IN BREAST CANCER OUTCOME

- *Socioeconomic Resources*
- *Socioeconomic Resources*
- *Socioeconomic Resources*
- Delivery of Care
- Tumor biology
- Genetics
- Lifestyle & Reproductive Experiences
- Environmental exposures
- Diet/Nutrition



Ethnicity and SES





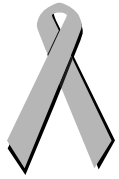
META-ANALYSIS OF STUDIES EVALUATING BREAST CANCER IN AFRICAN AMERICANS

- Medline Review:

– Breast CA and African Americans	398
– Breast CA and Ethnicity	843
– Breast CA and Race	907
– Breast CA and Black Women	432
– <u>Breast CA and SES</u>	<u>1,382</u>
TOTAL	3,962

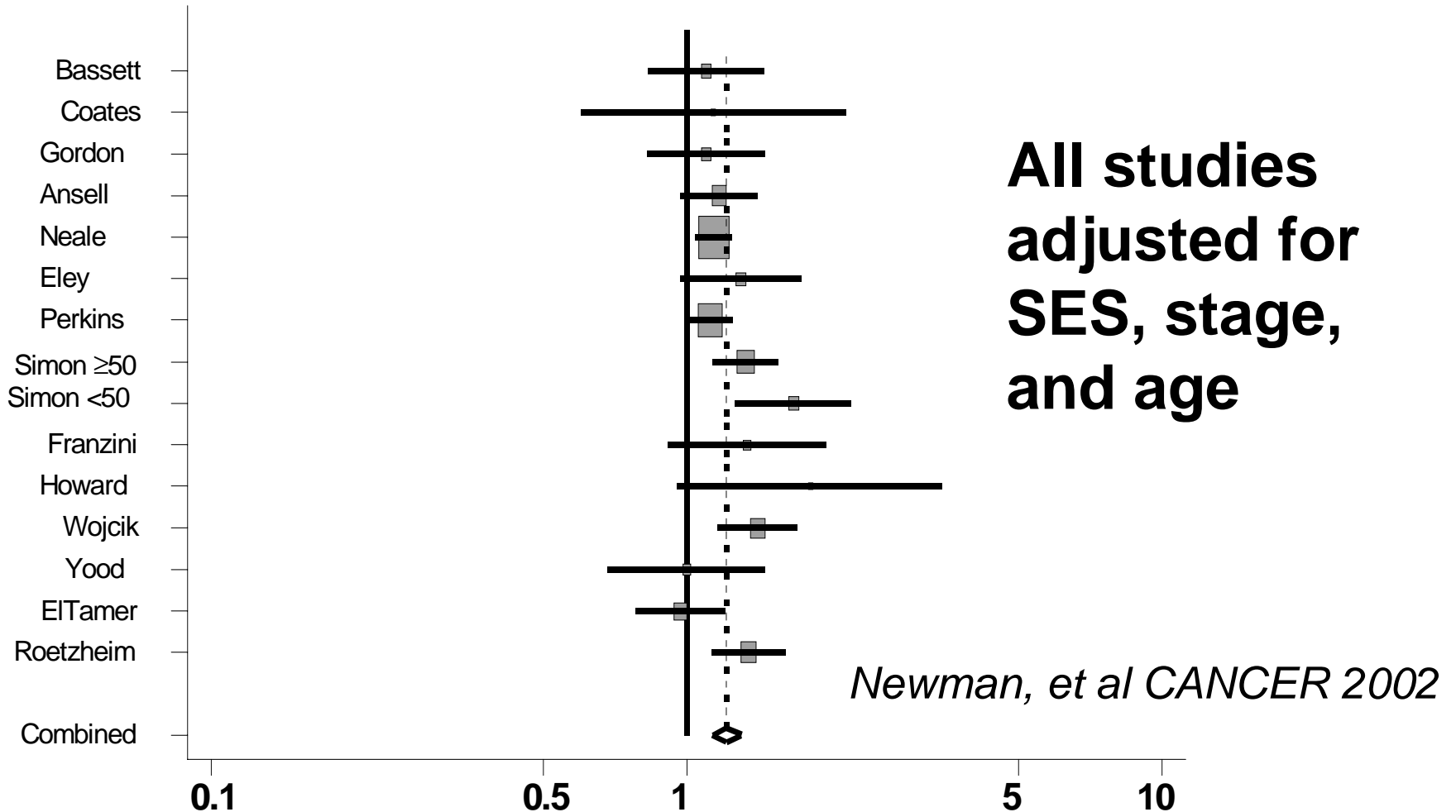
- **14** Studies included survival analysis stratified by ethnicity, with outcome adjusted for stage, age, and socioeconomic status

Newman et al, CANCER 2002



META-ANALYSIS: 14 STUDIES

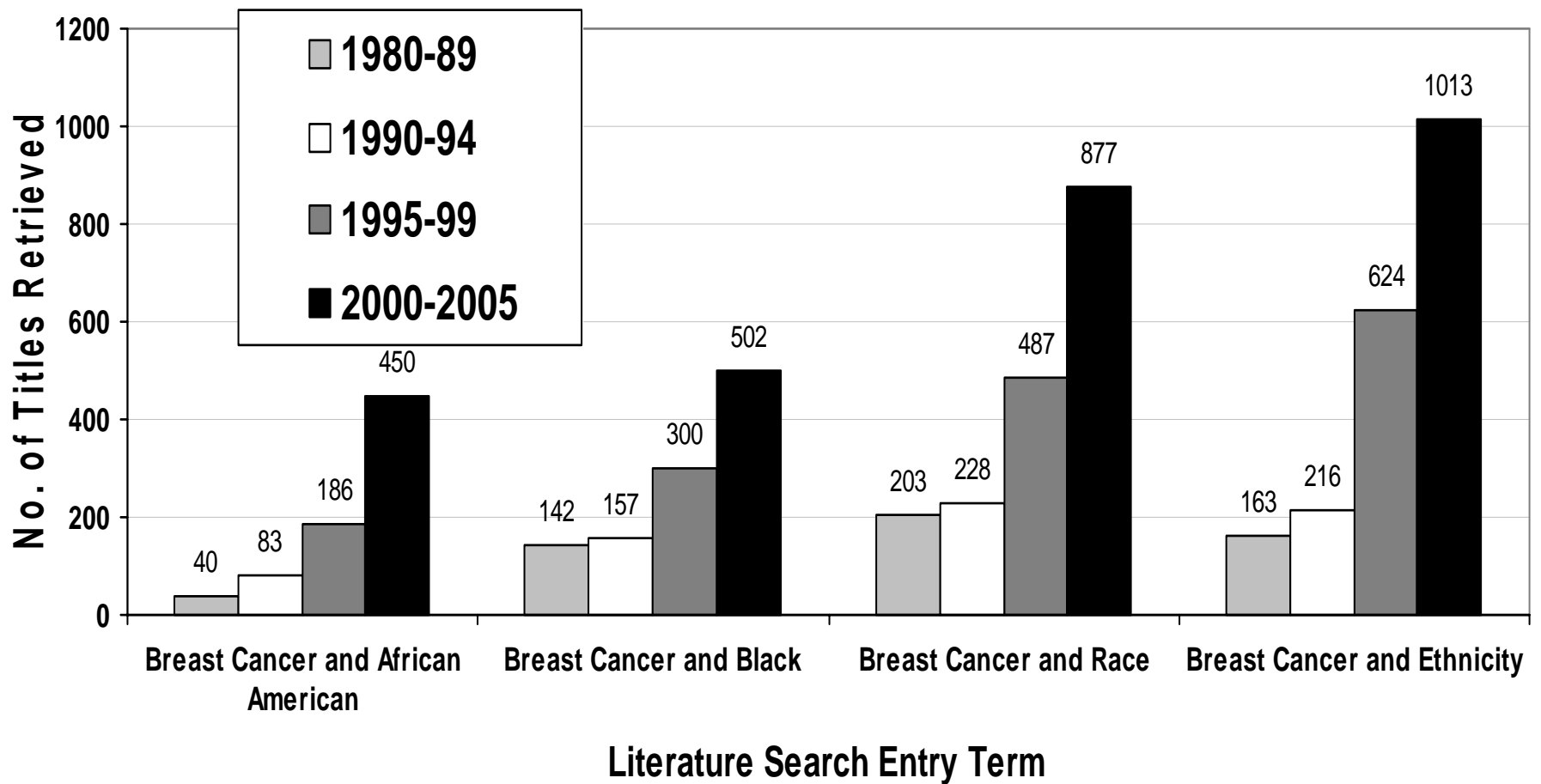
>10,000 AA AND 40,000 WA BREAST CA PTS

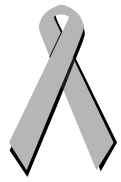


Mortality Risk for AA pts: 1.22
(95% Confidence Interval: 1.13-1.30)



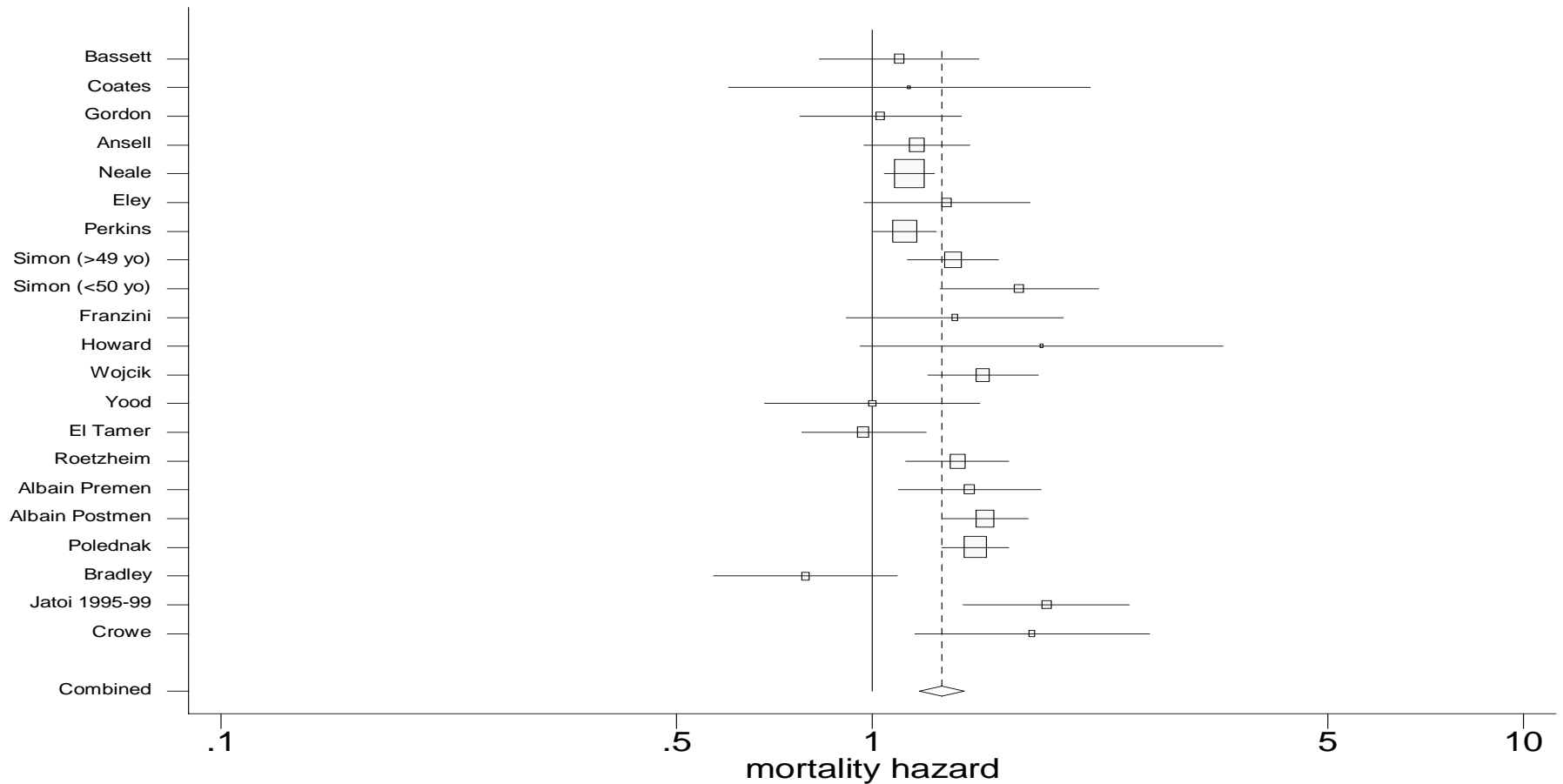
Expanding Interest in Disparities Research Literature Review, 1980-2005





SES-Adjusted Meta-Analysis, 2006

>13K AA & 75K WA Breast CA Pts; 19 Studies

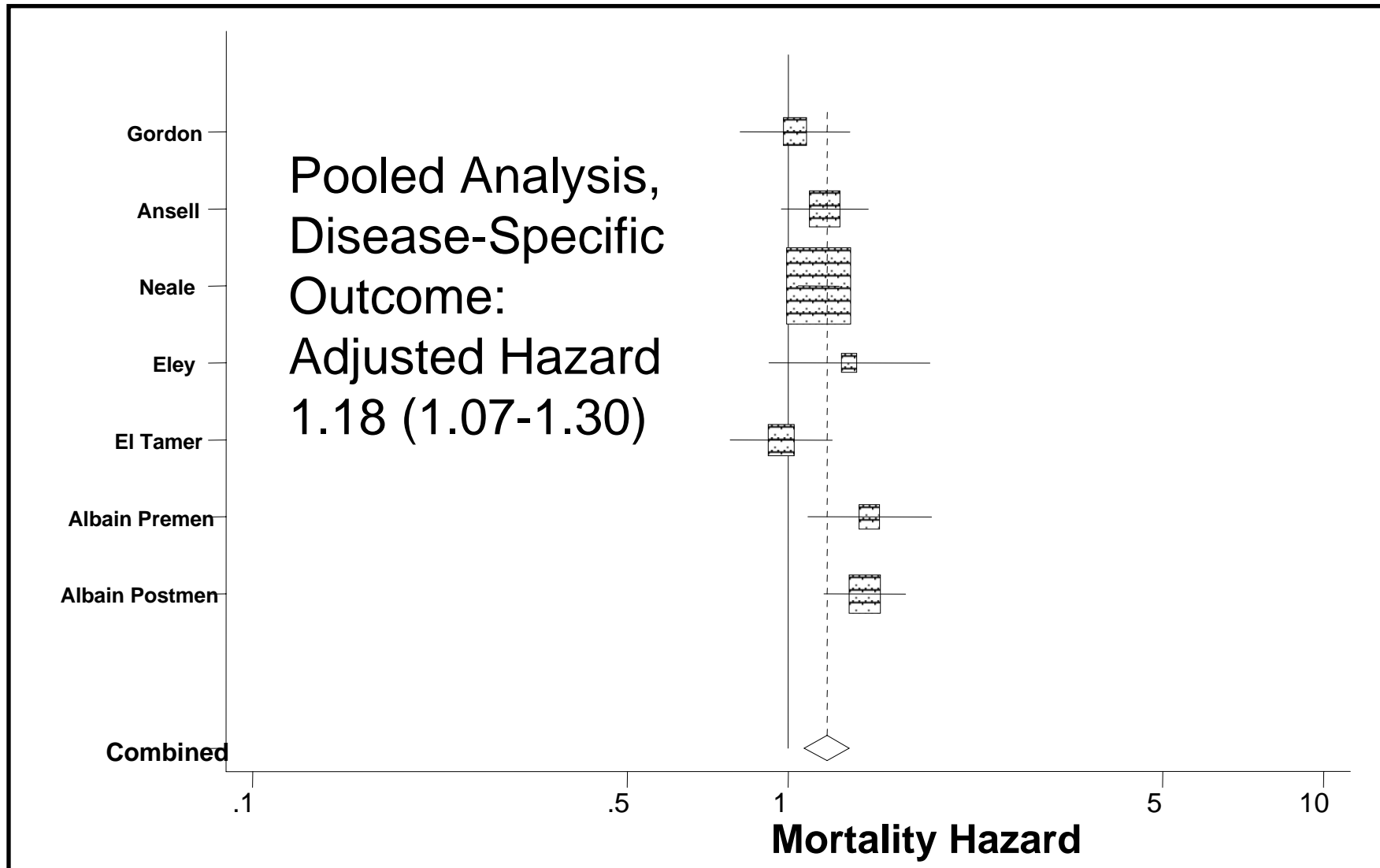


AA Mortality Risk: 1.28 (95% CI 1.18-1.38)

Newman et al, JCO 2006



SES-Adjusted Disease-Specific Survival





ETIOLOGY OF DISPARITIES IN BREAST CANCER OUTCOME

- Socioeconomic Resources
- *Delivery of Care*
- Tumor biology
- Genetics
- Lifestyle & Reproductive
Experiences
- Environmental exposures
- Diet/Nutrition



The Effect of Race and Sex on Physicians' Recommendations for Cardiac Catheterization

- **720 physicians viewed recorded interviews**
- **Reviewed data about a hypothetical patient**
- **The physicians then made recommendations about that patient's care**





DISPARITIES IN ACCESS TO BREAST CANCER TREATMENT

- Sentinel lymph node biopsy for breast cancer
 - SEER Data (1998-2000); comparison of SLN Bx rates
 - African American: 0.64 (95% CI, 0.58-0.69)
 - Hispanic American: 0.58 (95% CI, 0.53-0.64)
 - Asian American: 0.80 (95% CI, 0.73-0.89)
- Reconstruction for breast cancer
 - M. D. Anderson Cancer Center: evaluation of reconstruction referral and utilization patterns
 - African American breast cancer patients less likely to be referred for reconstruction consult; less likely to be recommended for reconstruction; and less likely to undergo reconstruction

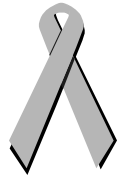
Maggard et al, Ann Surg Onc 2005

Tseng et al, Cancer 2005



Breast Cancer and African Americans: Impact of Comorbidities

- Tammemagi et al, JAMA 2005: Henry Ford Health System, Detroit, MI
 - 264 African American and 642 White American breast cancer patients; median follow-up 10 years
- Comorbidities caused substantial mortality risk in African Americans; but did not eliminate the breast cancer-specific survival disparity
 - HR; all-cause survival: 1.34 (95% CI 1.11-1.62)
 - HR; breast cancer-specific survival: 1.47 (95% CI 1.08-2.00)
 - HR; competing-causes survival: 1.27 (95% CI 1.00-1.63)



ETHNICITY AND EARLY-STAGE CANCER: Can We Eliminate Disparities with Better Screening?

SEER Registry, 1990-94

- T1 tumors: 1,860 AA and 27,429 WA

*Multivariate mortality hazard ratio
for AA pts: 1.29 (1.18-1.41)*

- Subset analysis of pts with 1 cm tumors
 - Node pos: 17.4% AA vs. 11.7% WA ($p < 0.0001$)
 - Mortality hazard ratio for AA pts 1.15 (0.95-1.39)

Blake et al, ASCO 2003



BREAST CANCER DISPARITIES & SCREENING

ASCO, 2005 DCIS Outcome, SEER Data

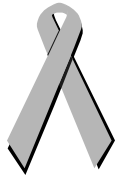
Distribution		Ipsilateral Breast Cancer Hazard Ratio	
Group	Lumpectomy	1.0	
	Lumpectomy+RT	0.43	p<0.0001
Age (5-yr groups)		0.93	p=0.003
<i>Race/</i>	<i>Non-African American</i>	<i>1.0</i>	
<i>Ethnicity</i>	<i>African American</i>	<i>1.70</i>	<i>p=0.0004</i>
Comedo Status	Absent	1.0	
	Present	1.25	p=0.06

Proportional Hazards Model; *Baxter et al ASCO, 2005*

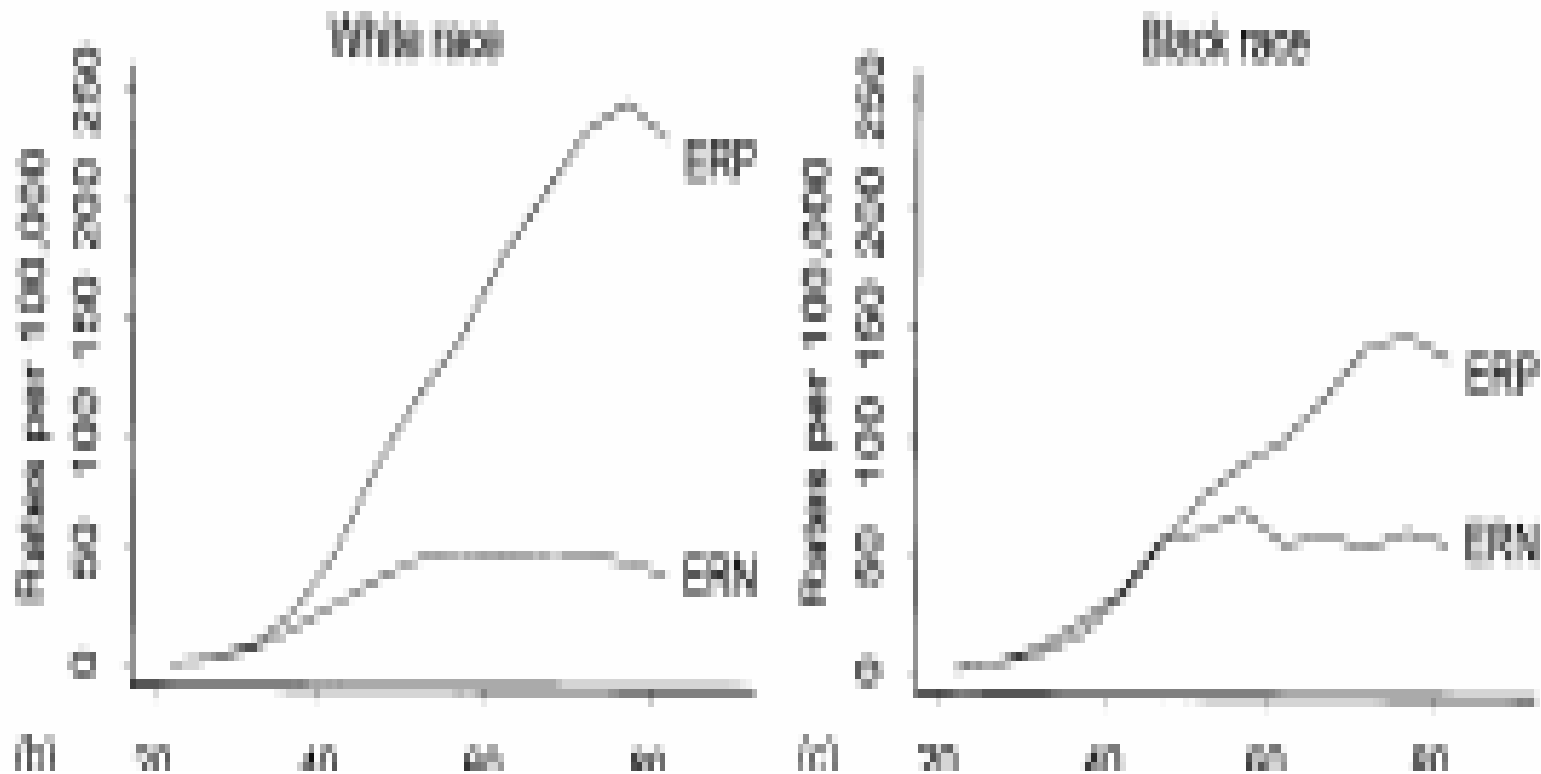


ETIOLOGY OF DISPARITIES IN BREAST CANCER OUTCOME

- Socioeconomic Resources
- Delivery of Care
- *Tumor biology*
- *Genetics*
- *Lifestyle & Reproductive*
Experiences
- Environmental exposures
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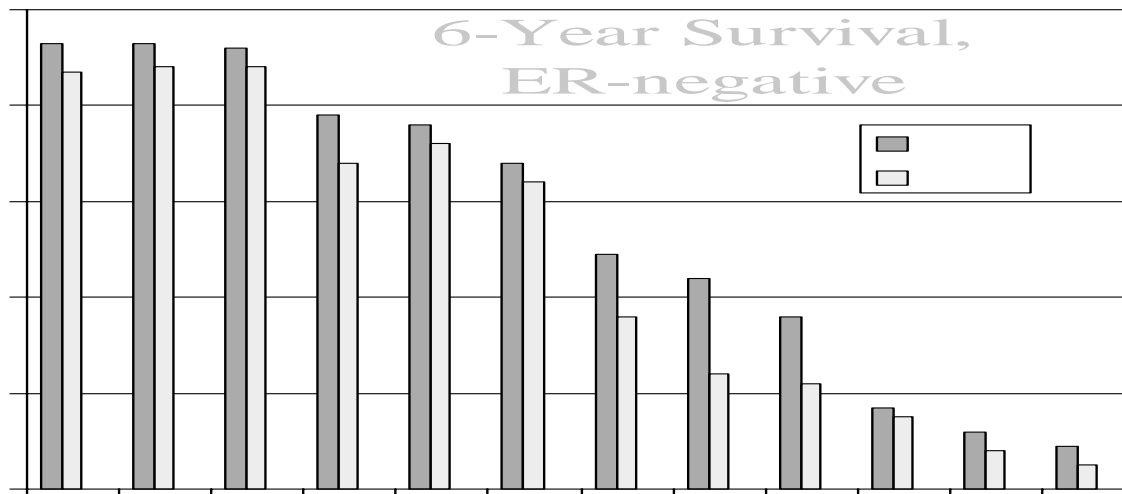
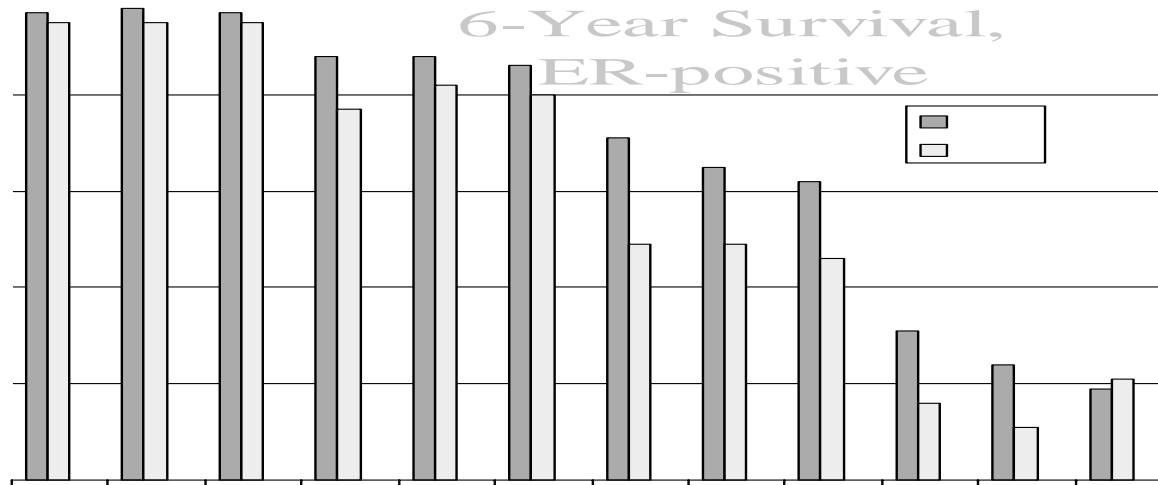
Breast Cancer Incidence by ER Status



From Anderson et al, Breast Cancer Res and Treat, 2002

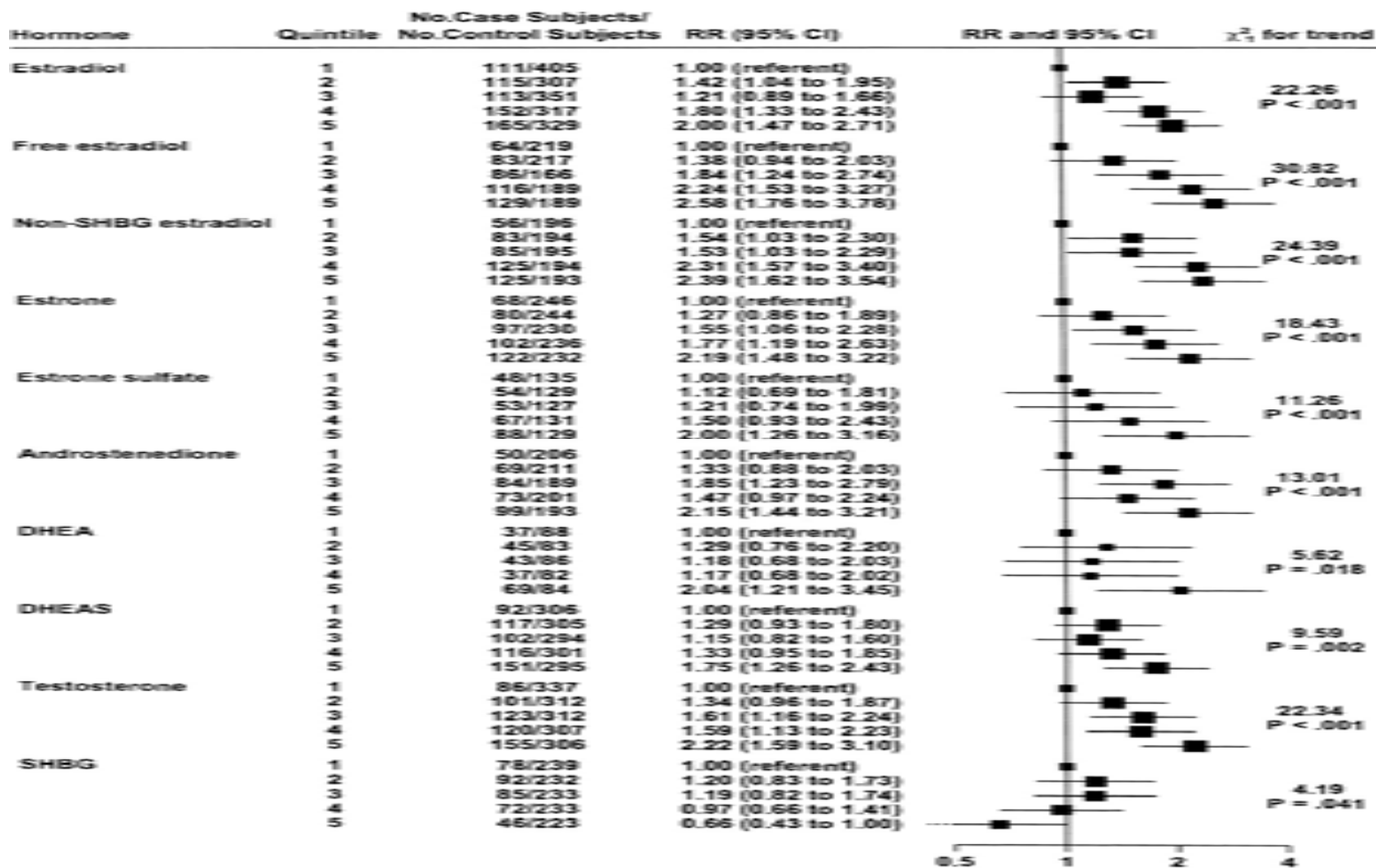


Chu et al, SEER Data (Cancer, 2003)





Meta-Analysis of Hormones and Breast Cancer Risk; JNCI 2002





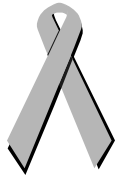
Hormones, ER and Breast Cancer in African American Women

- Documented Correlations:
 - Endogenous hormone levels (and surrogate markers, eg BMD) are risk factors for breast cancer
 - Association strongest for postmenopausal, ER-positive disease
 - AA women have increased BMD and may have increased hormone levels as well
- Paradoxical Observations:
 - Incidence rates of ER-positive, postmenopausal breast cancer are relatively low for AA compared to WA women
 - AA women with ER-positive, postmenopausal breast cancer have lower survival rates compared to WA women
- Does ethnicity-specific variation exist in the oncogenic effects of hormones on mammary tissue?



AGE DISTRIBUTION DISPARITIES: REPRODUCTIVE FACTORS?

- Does early child-bearing history account for the younger age distribution of AA breast CA pts?
 - Short-term increase in breast CA risk post-partum
 - Lifetime reduction in breast CA risk with multiple pregnancies
- Palmer et al, JNCI 2003
 - Black Women's Health Study
 - Consistent with a dual effect of pregnancy on early-onset versus post-menopausal breast cancer risk
- Ursin, et al, Cancer 2004
 - Women's CARE Study
 - Early childbearing not related to early-onset breast cancer

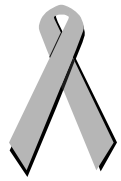


BREAST CANCER IN YOUNG WOMEN

- More difficult to detect
- More advanced stage distribution
- Increased prevalence of hormone-receptor negative tumors
- Increased prevalence of high-grade tumors
- Increased local recurrence rates following breast conserving therapy
- Increased treatment failure rates



To what extent does the increased prevalence of early-onset breast cancer contribute to the overall increased mortality rates seen in African American women?



BREAST CANCER IN YOUNG WOMEN: DETROIT SEER DATA, 1990-1999

507 AA and 1,378 W breast cancer pts <40 yrs

<i>Feature</i>		<i>African American</i>	<i>Caucasian</i>	<i>P</i>
Stage	local	42.4%	52.1%	0.001
	regional	45.7%	41.1%	
	distant	7.8%	4.4%	
Medullary Histology		5.8%	3.3%	0.021
ER Negative		61.9%	44.4%	0.001
PR Negative		59.7%	48.8%	0.001

Newman et al, *CANCER*, 2002



BREAST CANCER IN YOUNG WOMEN: DETROIT SEER DATA, 1990-1999

Proportional Hazard of Death*,
AA compared to W pts

<i>Stage</i>	<i>Risk Ratio</i>	<i>95% Confidence Interval</i>
Local	1.94	1.23-3.05
Regional	1.58	1.18-2.11
Distant	2.32	1.15-4.69

*adjusted for age, tumor size, nodal status, ER/PR & histology



Breast Cancer in African American *Clinical Trials Data*

- Can we correct for confounding effects related to disparate SES and delivery of care?
- Unger et al: ASCO 2004- Pooled analyses of SWOG adjuvant therapy trials
 - Outcome comparable for all ethnic groups with all cancers except African Americans with hormonally-driven cancers (breast & prostate)
- Albain et al: SABCS 2004- Five SWOG Phase III trials in node-pos cancer; outcome adjusted for stage, age, and SES

	Disease-free Outcome	Overall
Premenopausal	1.39 (1.12-1.73)	1.41 (1.10-1.82)
Postmenopausal	1.45 (1.27-1.66)	1.49 (1.28-1.73)

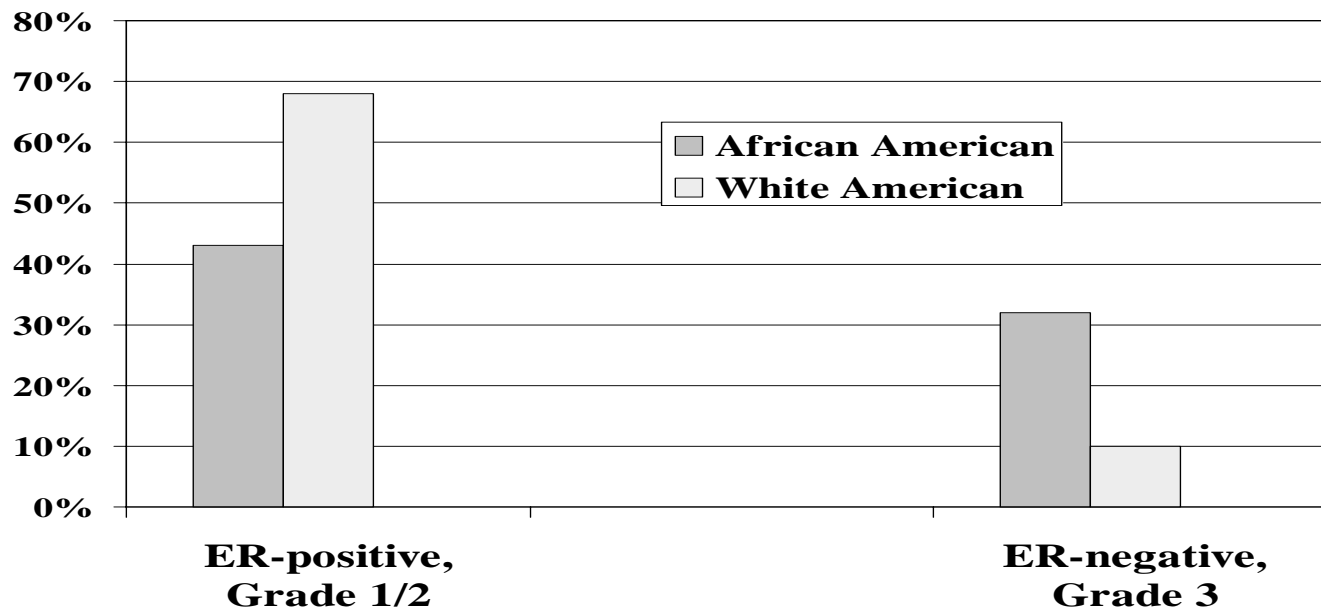


Breast Cancer in African Americans

Clinical Trials Data

Women's Health Initiative (WHI): "Ethnicity and Breast Cancer"-Chlebowski et al JNCI 2005

- Subset analysis: African American vs. White American participants that developed cancer
 - ER-neg tumors 4x more common in AA participants
 - Mortality for AA HR = 1.79, 95% CI = 1.05 to 3.05 (adjusted for breast cancer prognostic features)





CHEMOPREVENTION IN AFRICAN AMERICANS

- ↑ incidence of breast CA in young AA women
Improved safety profile of tamoxifen in young pts
- ↑ risk of thromboembolic events in AA pts
Tamoxifen associated with DVT, PE
- ↑ risk of ER-negative tumors in AA pts
Tamoxifen effective at preventing ER+ tumors only
- NSABP Chemoprevention Trials (P-1 and STAR)
<4% of study participants were African American



GAIL MODEL RISK CALCULATIONS

$$\text{5-Year Risk (\%)} = A \times B \times C \times D \times \text{Baseline 5-yr Risk Estimate}$$

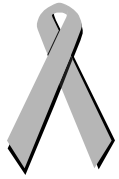
- A = RR, Age at Menarche
- B = RR, # Breast Biopsies
(stratified by age)
- C = RR, Age at First Live Birth
(stratified by FH)
- D = RR, Atypical Hyperplasia on Past Bx
- Baseline 5-yr Risk Estimate: Based on SEER age-specific breast cancer incidence, stratified by ethnicity

Gail Model Breast Cancer Risk Estimates

40 yo F, seeks counseling regarding breast cancer risk and options for risk reduction;

FH significant for breast CA in mother, sister

• Age of patient:	40 yo	40 yo
• Age at menarche:	12 yo	12 yo
• Age at first live birth:	30 yo	30 yo
• No. relatives with breast CA	2	2
• No. past breast biopsies	0	0
• Ethnicity	<i>Black</i>	<i>White</i>
<i>5-year breast CA risk estimate:</i>	<i>1.5%</i>	<i>2.3%</i>



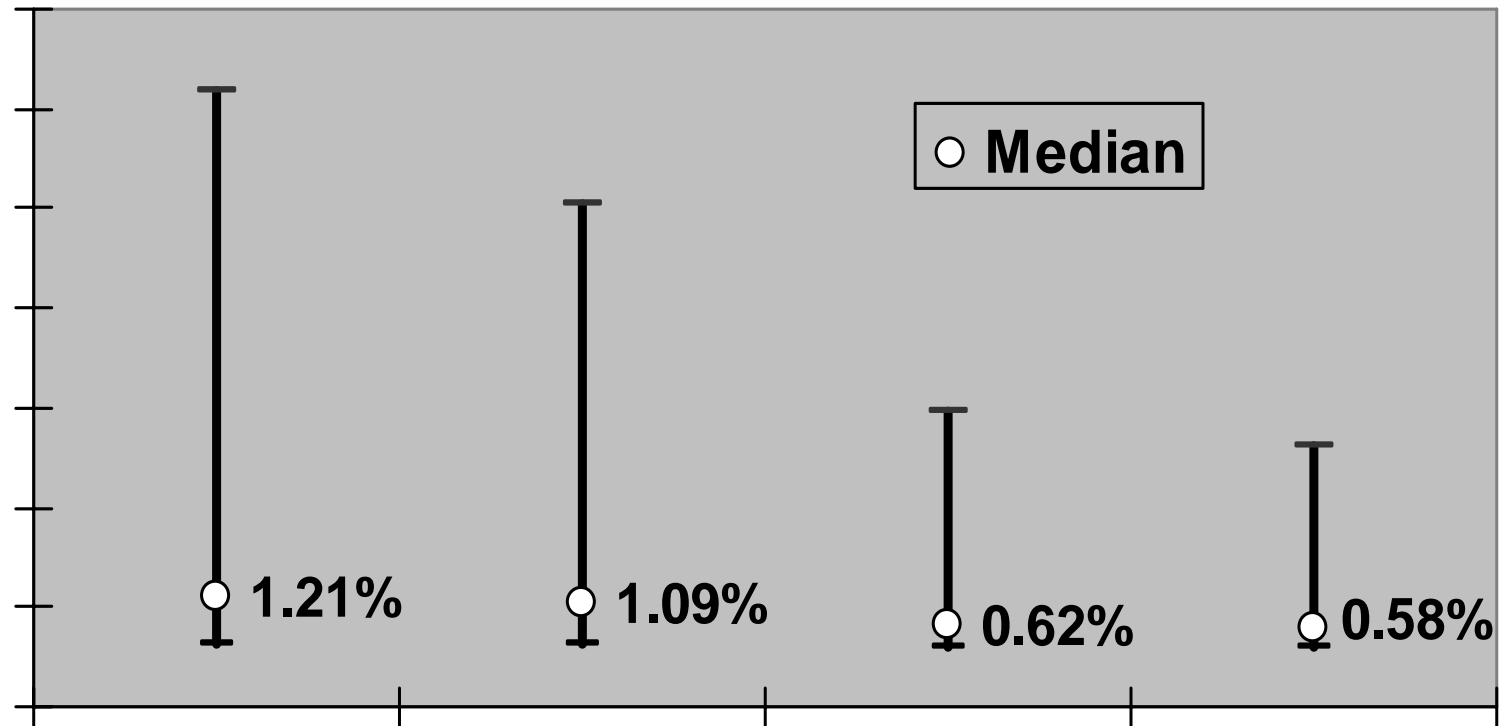
GAIL MODEL EVALUATION IN AFRICAN AMERICAN WOMEN

- **Women's Contraceptive and Reproductive Experiences (CARE) Study**
- **Case-control study designed to evaluate association between exogenous hormones and breast cancer**
- **African Americans oversampled**
- **Participating Centers:**
 - **Emory University, Atlanta, GA**
 - **Hutchinson Cancer Center, Seattle, WA**
 - **Karmanos Cancer Institute, Detroit, MI**
 - **University of Pennsylvania, Philadelphia, PA**
 - **University of Southern California, Los Angeles, CA**

Newman et al, ASCO, 2002 & 2003



RESULTS: GAIL MODEL RISK ESTIMATES



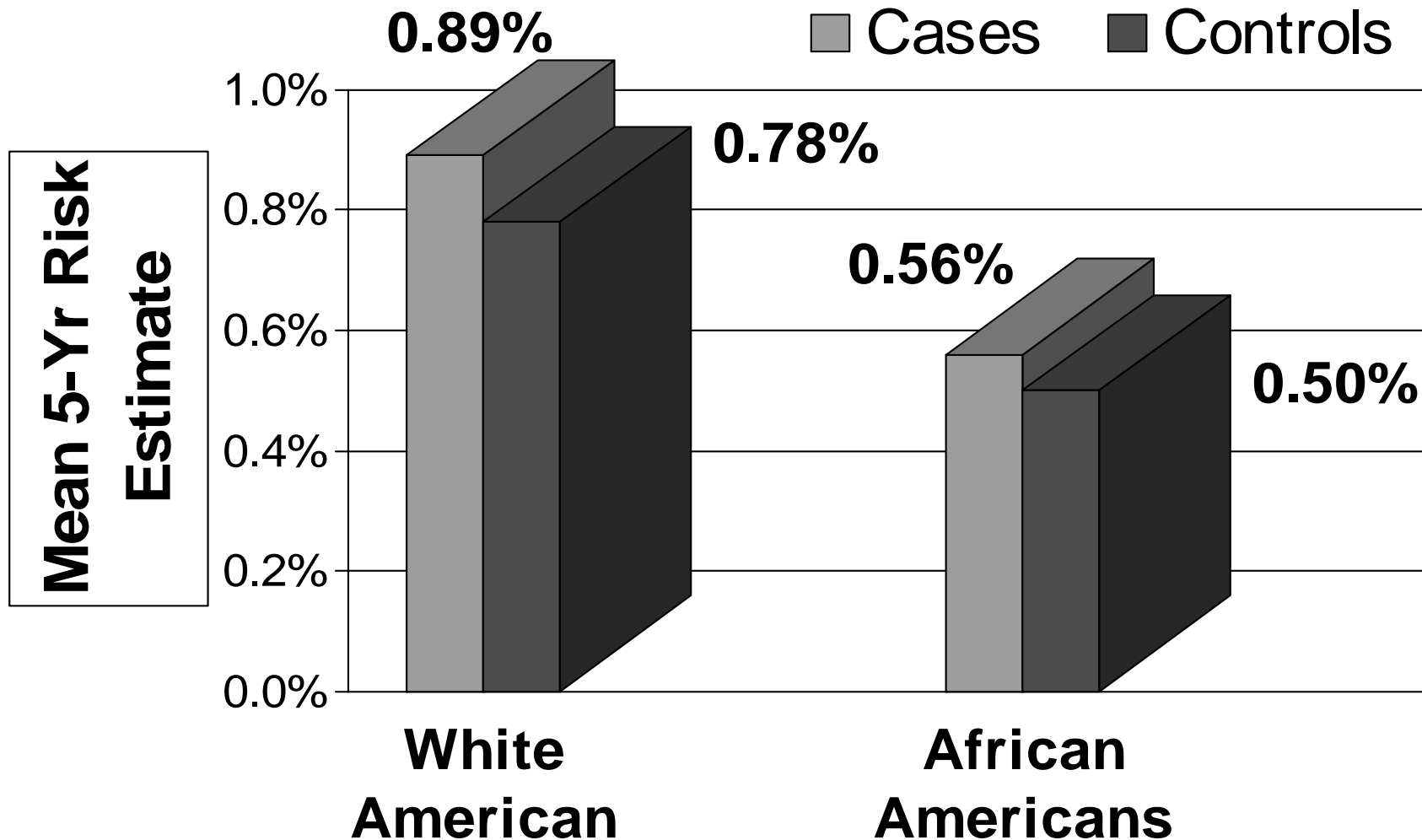
Discriminatory Accuracy:

Concordance Statistic 0.54-0.56 for AA and WA



GAIL MODEL SUBSET ANALYSIS

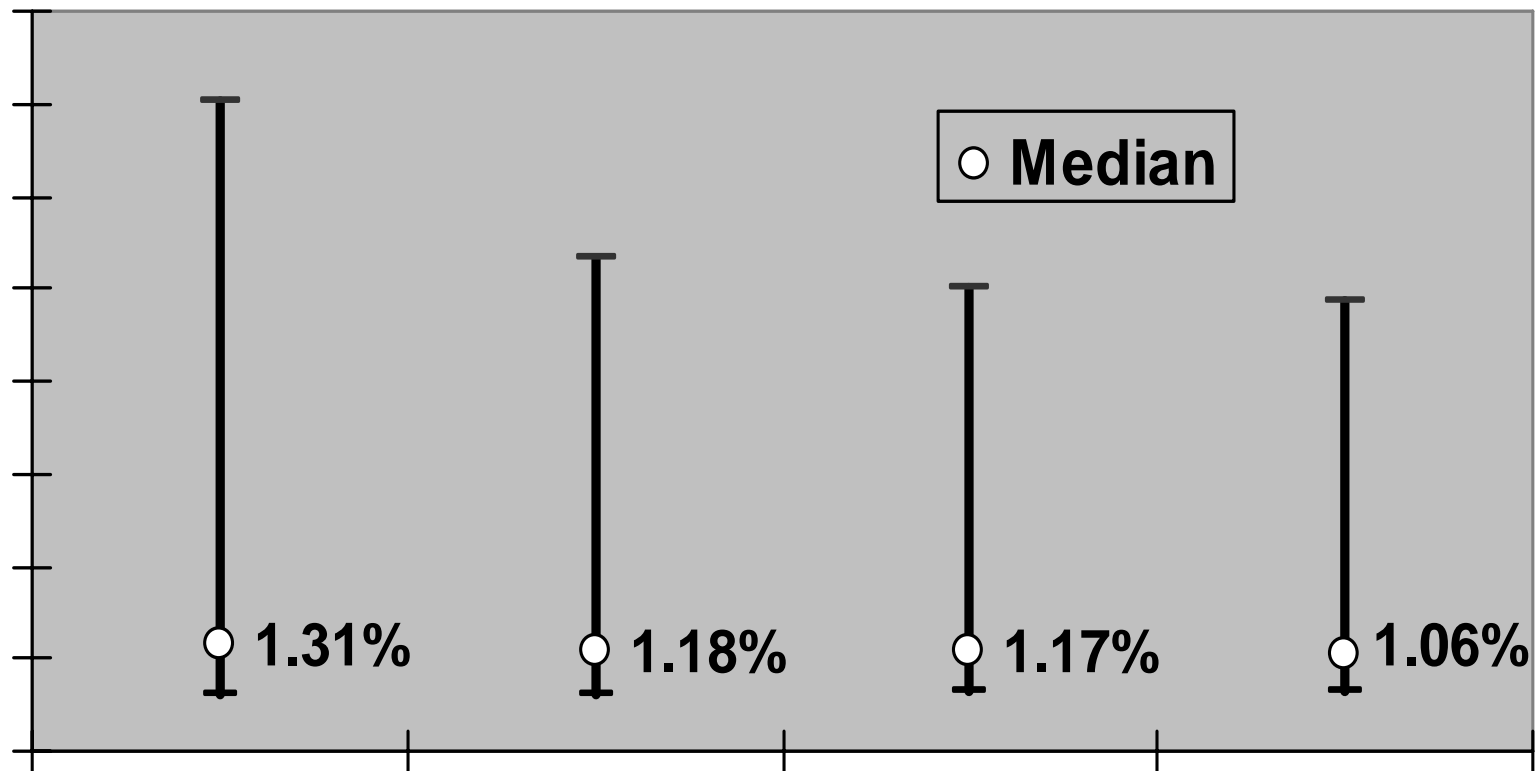
CARE Study Participants <45 yo





RESULTS: GAIL MODEL RISK ESTIMATES

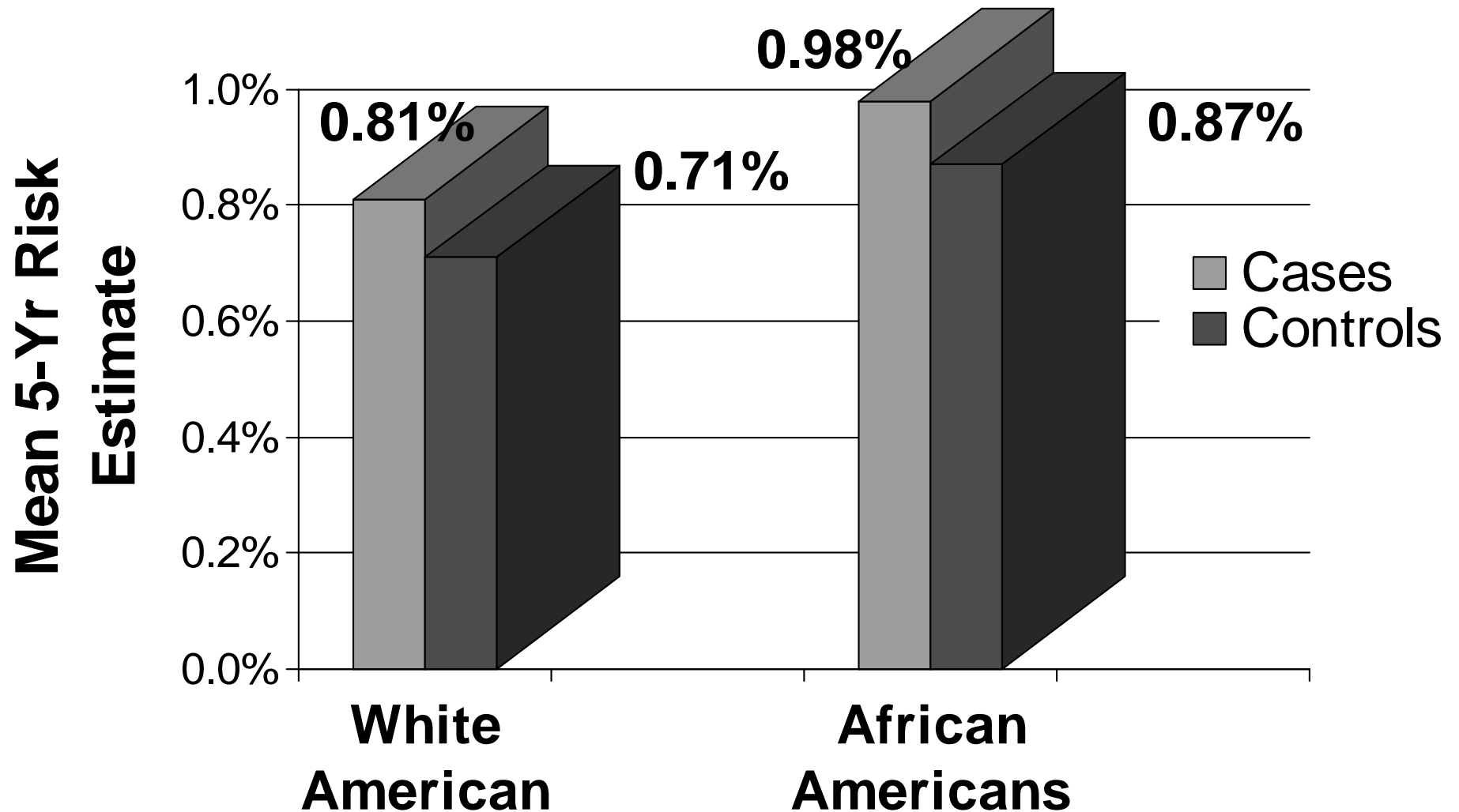
(with Revised Baseline Risk Estimates)





GAIL MODEL SUBSET ANALYSIS

CARE Study Participants <45 yo





Gail Model Breast Cancer Risk Estimates Revised

40 yo F, seeks counseling regarding breast cancer risk and options for risk reduction;

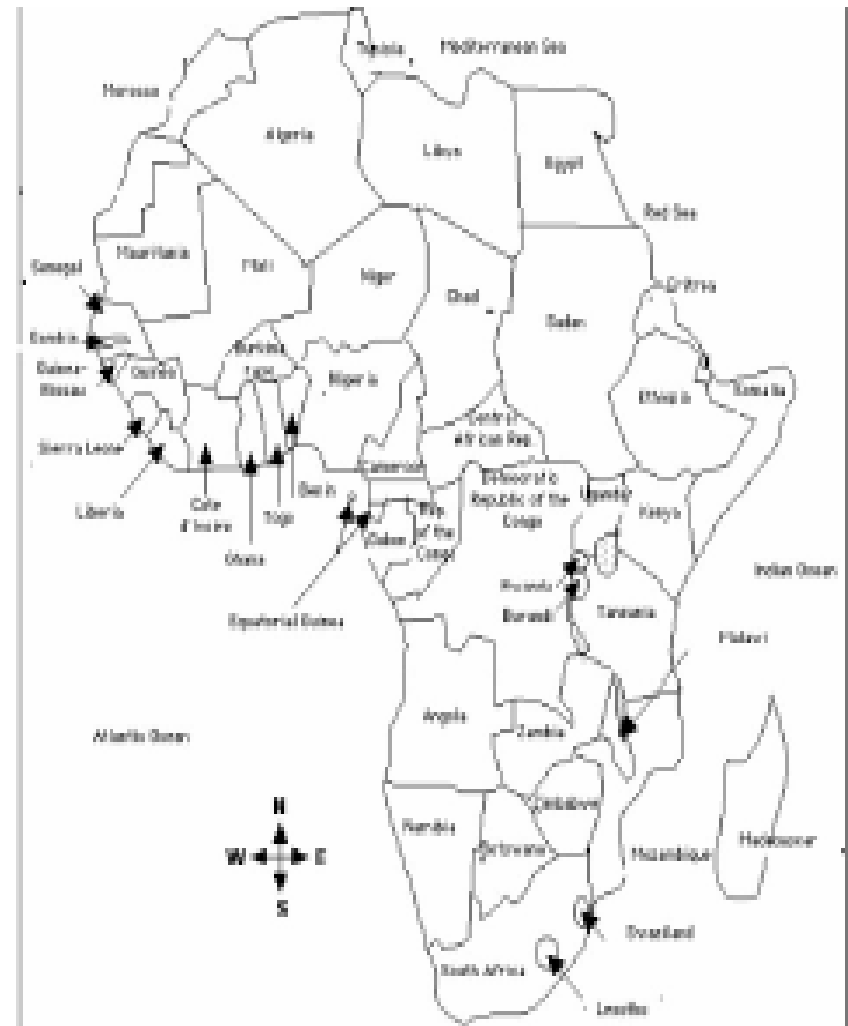
FH significant for breast CA in mother, sister

• Age of patient:	40 yo	40 yo
• Age at menarche:	12 yo	12 yo
• Age at first live birth:	30 yo	30 yo
• No. relatives with breast CA	2	2
• No. past breast biopsies	0	0
• Ethnicity	<i>Black</i>	<i>White</i>
<i>5-year breast CA risk estimate:</i>	<i>2.9%</i>	<i>2.3%</i>



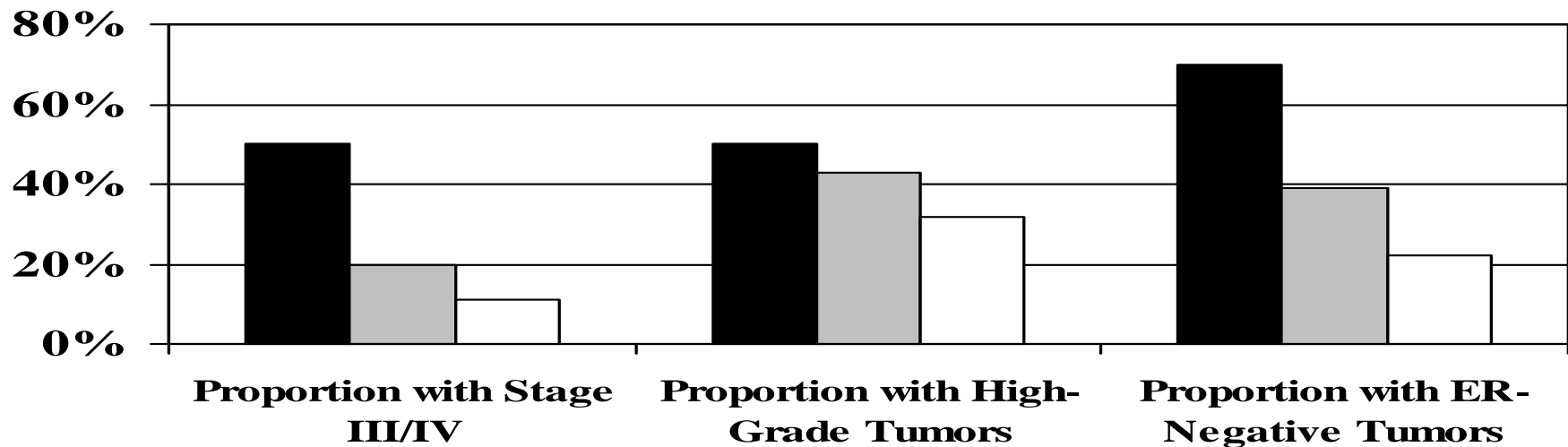
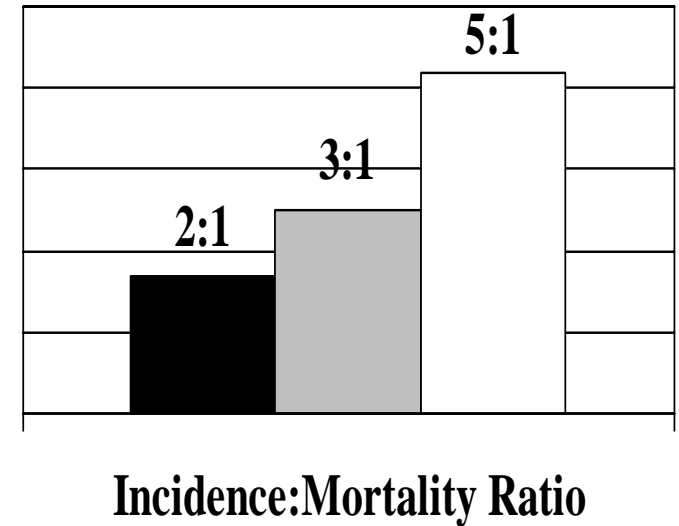
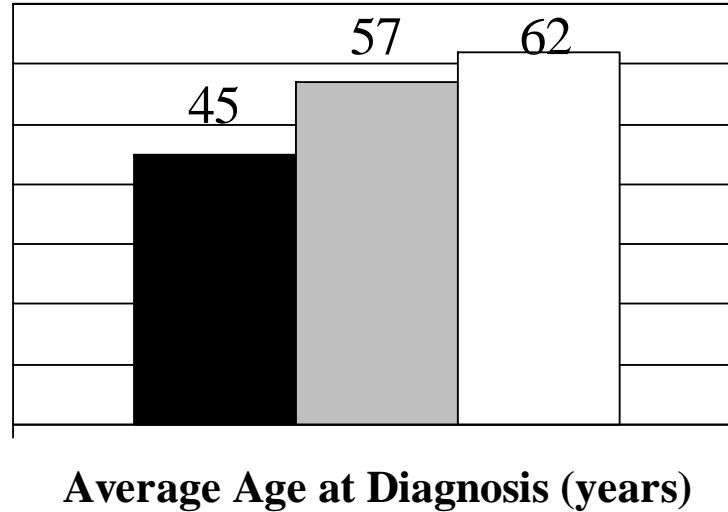
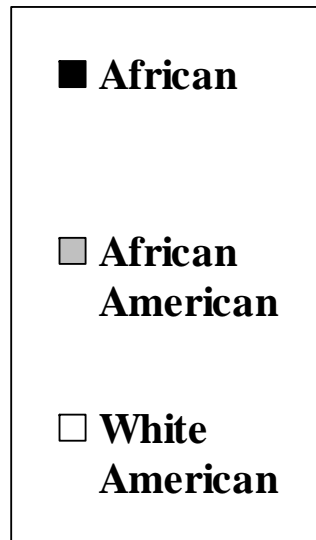
ETIOLOGY OF DISPARITIES: HEREDITARY FACTORS?

- Parallels between hereditary breast cancer and breast cancer in African Americans
 - younger age distribution
 - increased prevalence of medullary tumors
 - increased prevalence of ER-neg, aneuploid tumors
- *Is African ancestry associated with hereditary breast cancer susceptibility?*





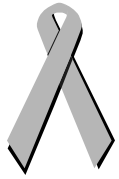
Breast Cancer in African American, Sub-Saharan African, and White American Women





Breast Cancer Risk and Estrogen Receptor Genotyping

<u>Study</u>	<u>Study Size</u>		<u>Findings</u>
	<u>Overall</u>	<u>African Ancestry</u>	
Zuppan 1991	11 families	None	Linkage in one family
Hill 1989	188 tumors	NR	C allele associated with risk of ER-neg disease
Parl 1989	59	<u>YES</u>	Younger age for cases with TT genotype
Yaich 1992	257	NR	Younger age for cases with TT genotype
Andersen 1994	360/672	None	Increased risk associated with c.454-351 A>G G allele
Roodi 1995	188	NR	c. 975 C>G: G associated with FH of breast cancer
Iwase 1996	57/30	None	c. 975 C>G: G associated with increased risk of breast CA
Southey 1998	388/294	None	c. 975 C>G: GG vs CC associated with increased risk of early-onset breast CA
Schubert 1999	105/151	<u>YES</u>	c. 975 C>G: No association with familial breast CA
Curran 2001	125/125	None	c. 975 C>G: trend for allele C associated with breast CA risk
Vasconcelos 2002	70/69	None	c. 975 C>G: G or GG associated with increased breast CA risk
Kang 2002	110/45	None	c. 975 C>G: trend for G allele associated with ER+/PR+ tumors
Comings 2003	67/145	<u>YES</u>	No Association
Shin 2003	205/205	None	c.454-351 A>G: A allele associated with decreased risk of breast CA
Cai 2003	1069/1166	None	c.454-397 C>T: TC and CC genotypes associated with increased breast CA risk
Kang 2002	110/45	None	975 G>C associated with PR/ER expression
Han 2003	100/100	None	975 G>C: GG and 1782 G>A: AA associated with decreased breast CA risk
Cai 2003	947/993	None	GT17 or GT18 allele carriers had reduced risk of breast CA compared to GT16 homozygotes
Wedren 2004	1500/1500	None	No association with SNPs; haplotype c.454-351 A>G or c.454-397 C>T and c975 C>G associated with increased breast CA risk, esp in high-BMI women
Boyapati 2005	1069	None	PvuII PP vs pp associated with increased mortality in women with ER-negative tumors
Gold 2004	1011/615	<u>YES</u>	3 ESR1 haplotypes associated with decreased breast CA risk



Research Opportunity I

To evaluate African ancestry as a risk factor for estrogen receptor-negative, early onset breast cancer

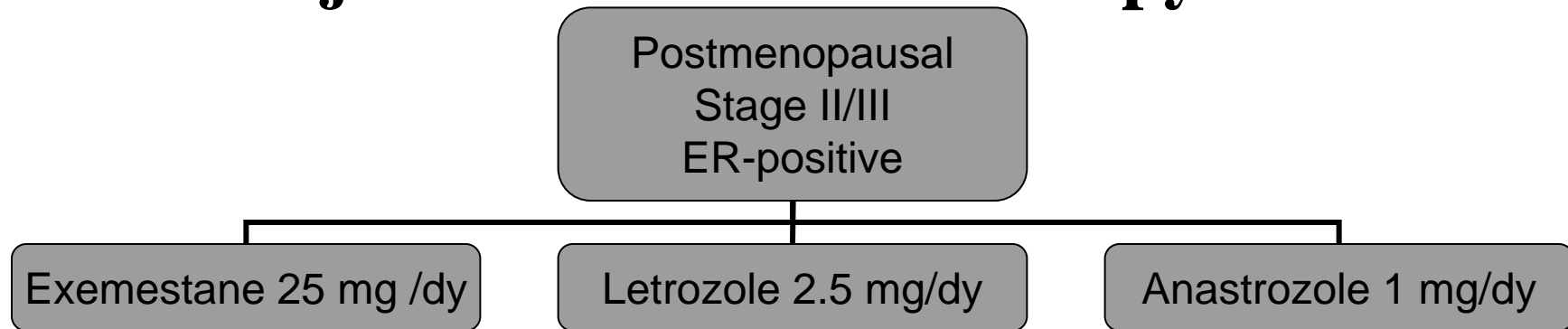
- Case-control, multicenter/international study
 - African Americans
 - White Americans
 - Ghanaians
- Comparison of clinical risk factors
- Comparison of breast tumor phenotypes
 - histology/grade/ER/PR
- Comparison of DNA/genotyping analyses
 - ER α ; ER β ; PR genotypes



Research Opportunity II

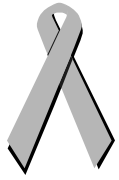
American College of Surgeons Oncology Group (ACOSOG) Z0031

Neoadjuvant Endocrine Therapy Protocol



- Preoperative aromatase inhibitor for four months
- Research Questions: Do circulating hormone levels differ between AA and WA women with endocrine-responsive postmenopausal breast cancer?

www.acosog.org



SURVIVAL RATES

- **60%**

- **43%**

- **20%**



R.M.S. TITANIC

Passenger Status	Survival Rate
1st Class	60%
2nd Class	43%
3rd Class	20%

Outcome is dependent on *access* to care