



CDC Advisory Committee on Breast Cancer in Young Women



Biology of Breast Cancer in Young Women

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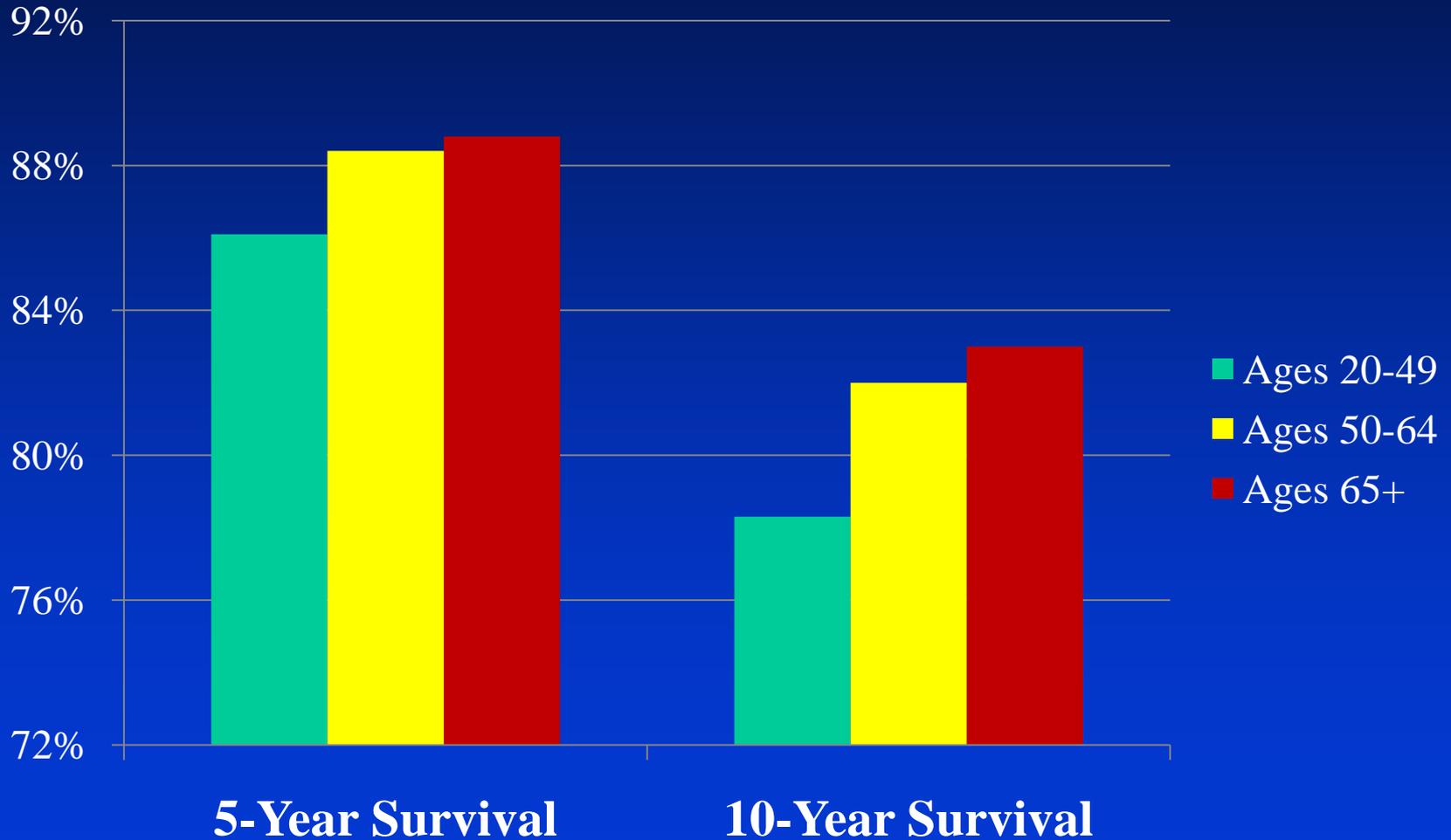


Age-Specific Probabilities of Developing Invasive Breast Cancer

If current age is....	The probability of developing breast cancer in the next 10 years is:	or 1 in:
20	0.06%	1,760
30	0.44%	229
40	1.44%	69
50	2.39%	42
60	3.40%	29
70	3.73%	27
Lifetime risk	12.08%	8



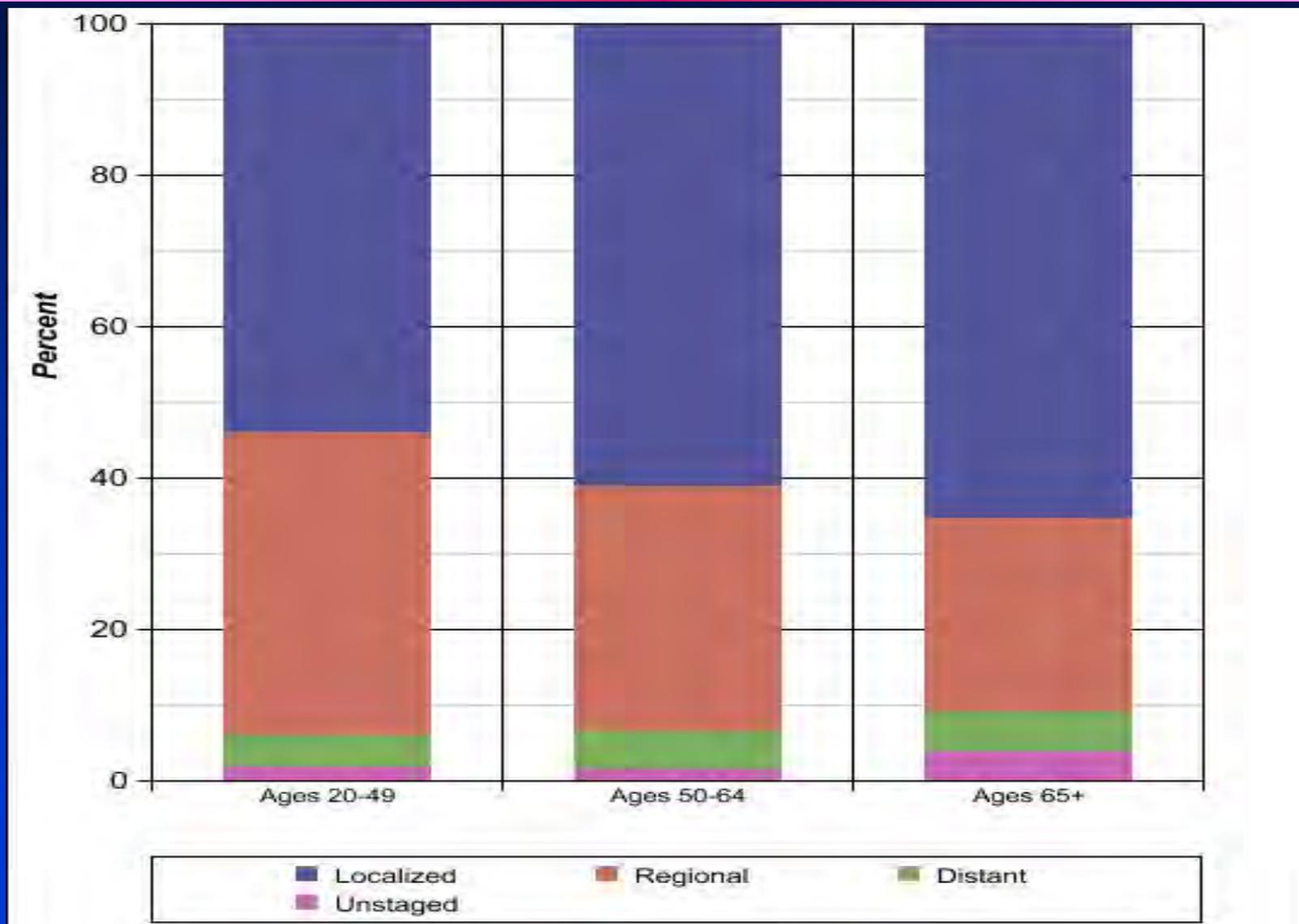
Breast Cancer Survival, by Age at Diagnosis



BIOLOGY OF BREAST CANCER

- Defining Breast Cancer Biology
 - Stage at Diagnosis
 - *T*umor size *N*odal status *M*etastastic burden
 - *L*ocal *R*egional *D*istant
 - Tumor Subtype
 - Intrinsic subtypes; molecular marker patterns
 - Outcomes
 - Survival rates; Locoregional recurrence

Breast CA Stage Distribution & Age





Breast Cancer Outcomes and Age

- Lower survival rates in younger breast CA pts
 - Partially explained by more advanced stage distribution, delays in diagnosis
- Numerous studies have demonstrated higher local/chest wall recurrence rates for young breast cancer patients
 - Higher local recurrence rates following breast conserving surgery partially explained by increased frequency of “extensive intraductal component”, making margin control more difficult

Normal Breast

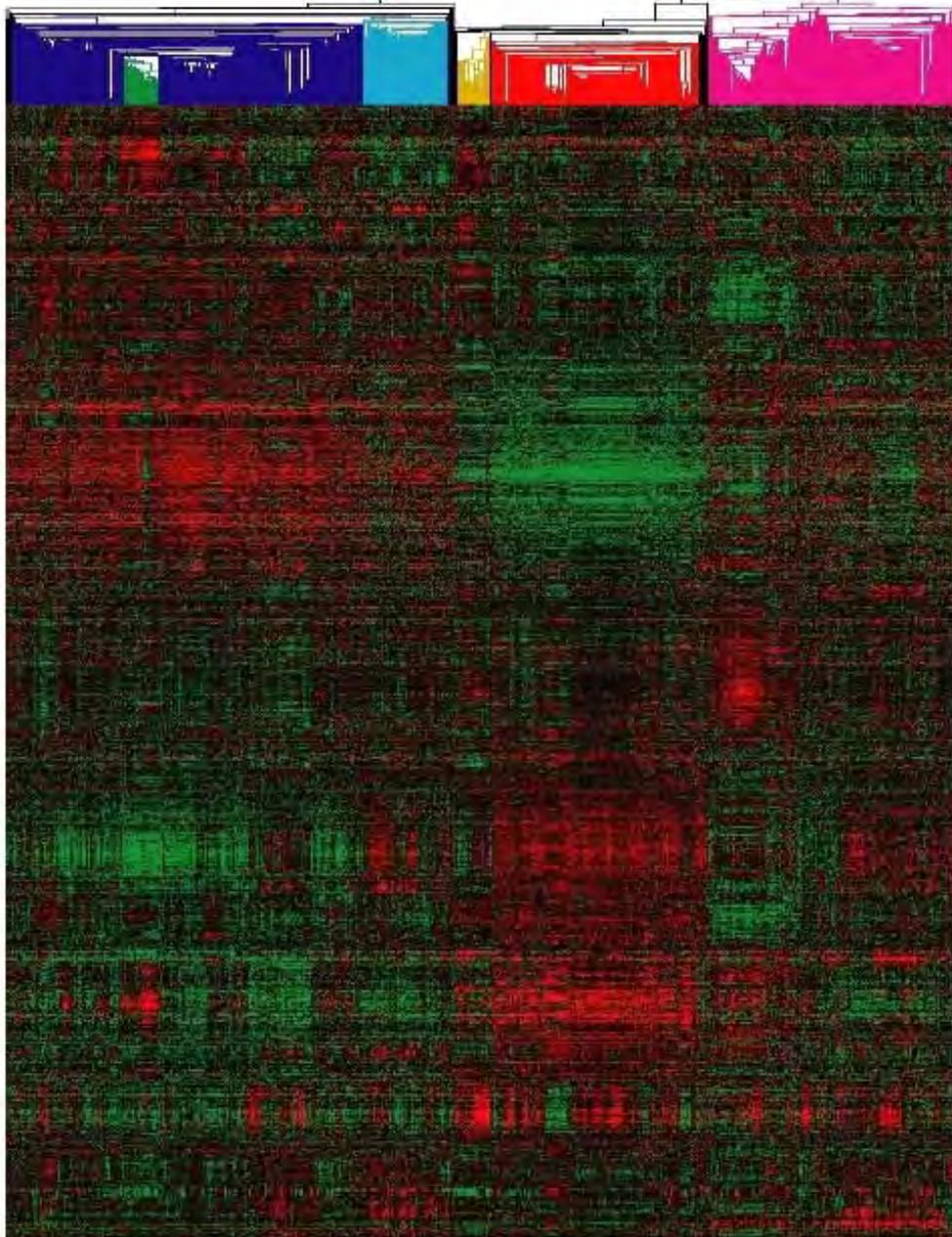
Claudin-low

Luminal A

Luminal B

Basal-like

HER2-enriched



Intrinsic Subtypes

Perou et al., Nature, 2000

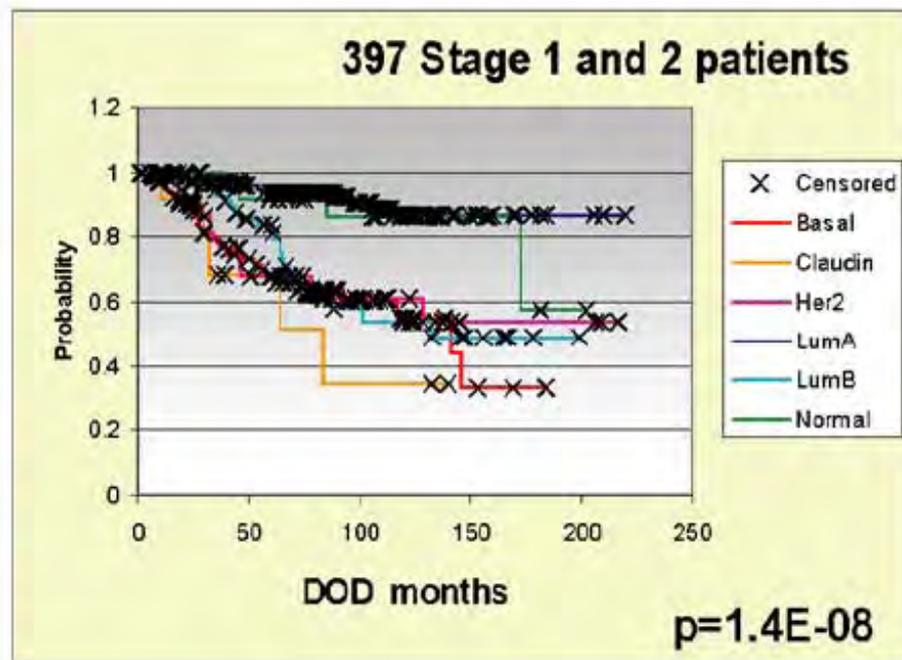
Sorlie et al., PNAS, 2001

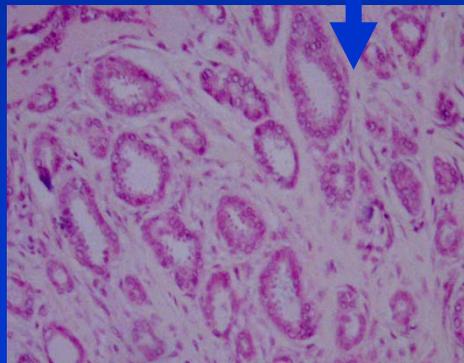
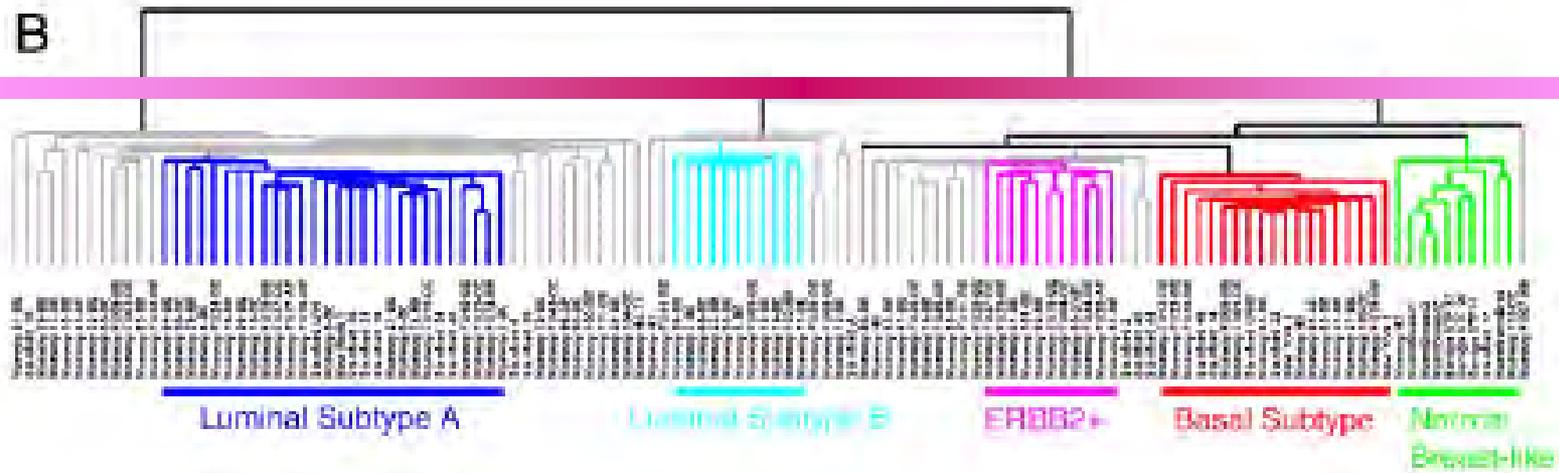
Sorlie et al., PNAS, 2003

Hu et al., BMC Genomics, 2006

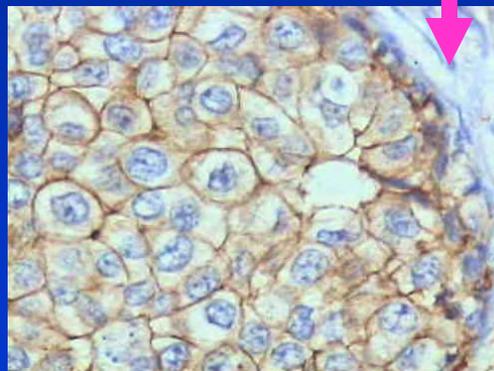
Herschkowitz et al., GB, 2007

Parker et al., JCO, Feb 2009

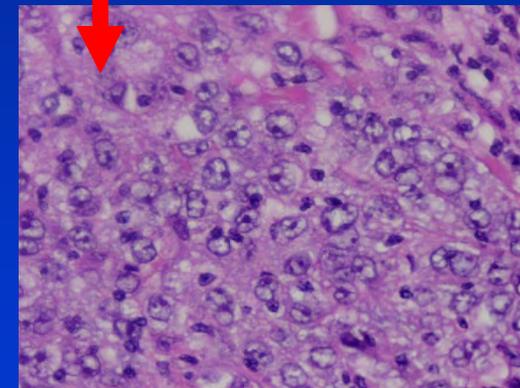




ER++, PR++, G1,2



HER2 ISH pos



“triple neg,” CK5/6+



“Basal-like” breast cancer

Gene expression profile

- Most tightly clustered subgroup in gene expression arrays
- CK 5/6 and 17 expression
- P53 mutations
- EGFR overexpression
- Mostly “triple negative”

BRCA1 connection

- ▣ Gene expression similar
- ▣ Morphology similar

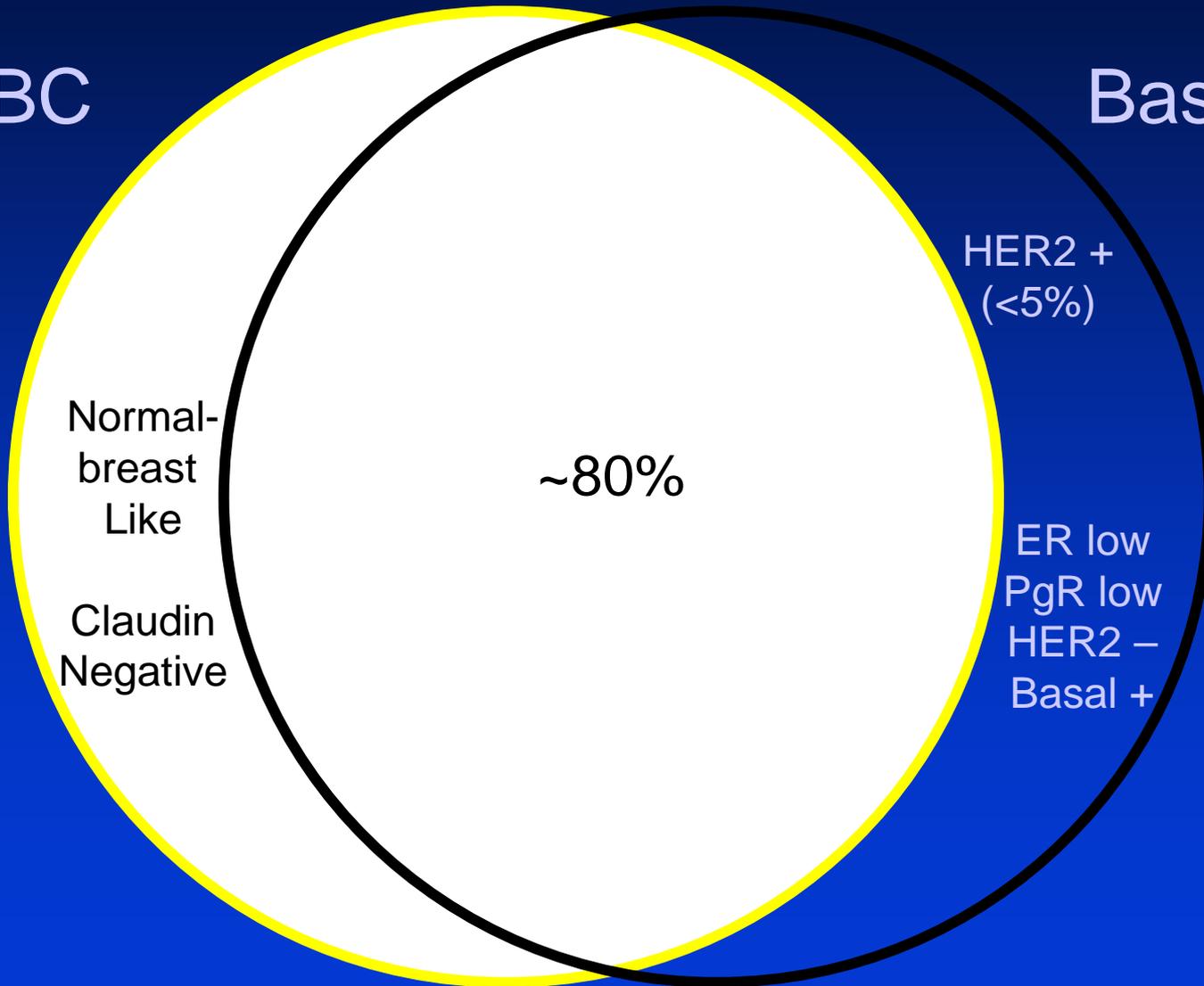
Morphology

- High grade
- Mainly ductal or medullary
- High mitotic count
- Scant stroma
- Central necrosis
- Pushing border
- Lymphocytic infiltrate
- Apoptotic figures

 TN is not a synonym for basal-like phenotype!

TNBC

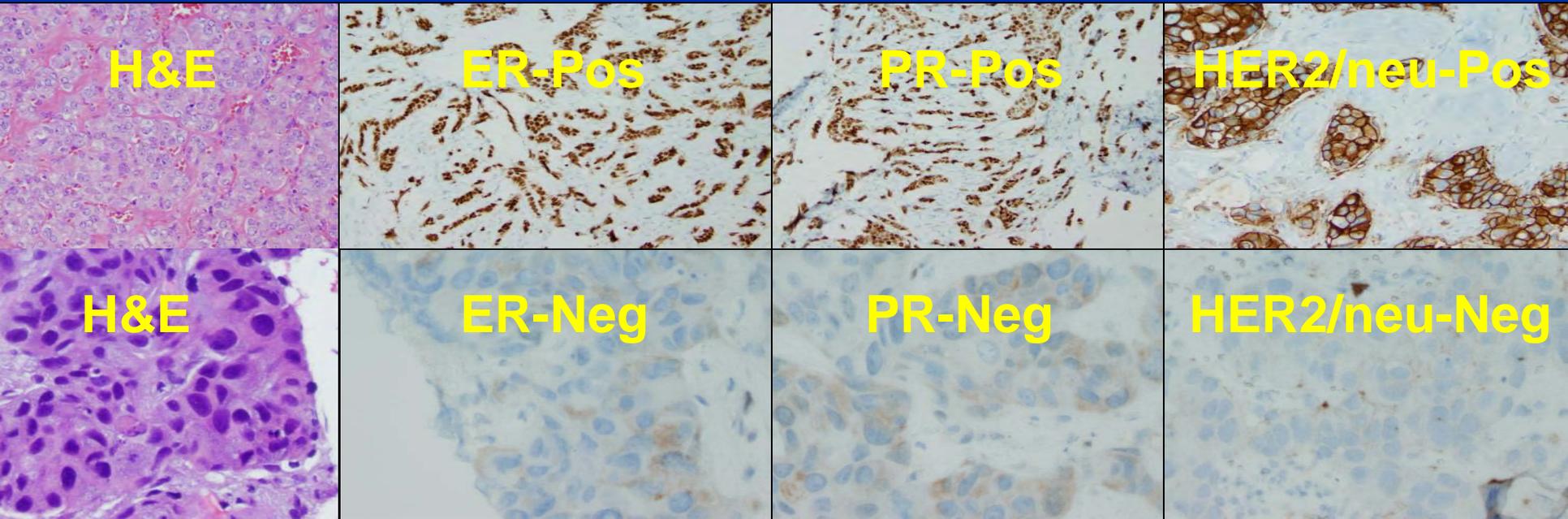
Basal-like





Clinical Relevance of “Triple-Negative” Breast Cancer

- Risk of metastatic spread exists for ALL breast cancers
 - Risk lower for early stage breast cancer*
 - Risk can be decreased with adjuvant systemic therapy*
 - Systemic therapy options determined by ER, PR, HER2/neu*
- Fewer systemic therapy options for TNBC
 - Inherently aggressive biologic behavior*
 - Endocrine therapy and trastuzumab will be ineffective*





Breast Cancer Subtypes/TNBC in Young Women

Risk of TNBC by Age, Population-Based California Cancer Registry, 1999–2003 (Bauer et al, Cancer 2007)

Age	Odds Ratio	95% CI
<40	1.53	1.37–1.70
40–49	1.20	1.10–1.31
50–59	1.12	1.02–1.22
60–69	1.00	1.00–1.00
70–79	0.90	0.81–0.99
80+	0.98	0.86–1.11



Race/Ethnicity-Associated Variation in Breast Cancer Among Young Women

- White Americans
- African Americans
- Hispanic/Latina Americans
- Asian Americans

Do we know how to appropriately define racial/ethnic identity???



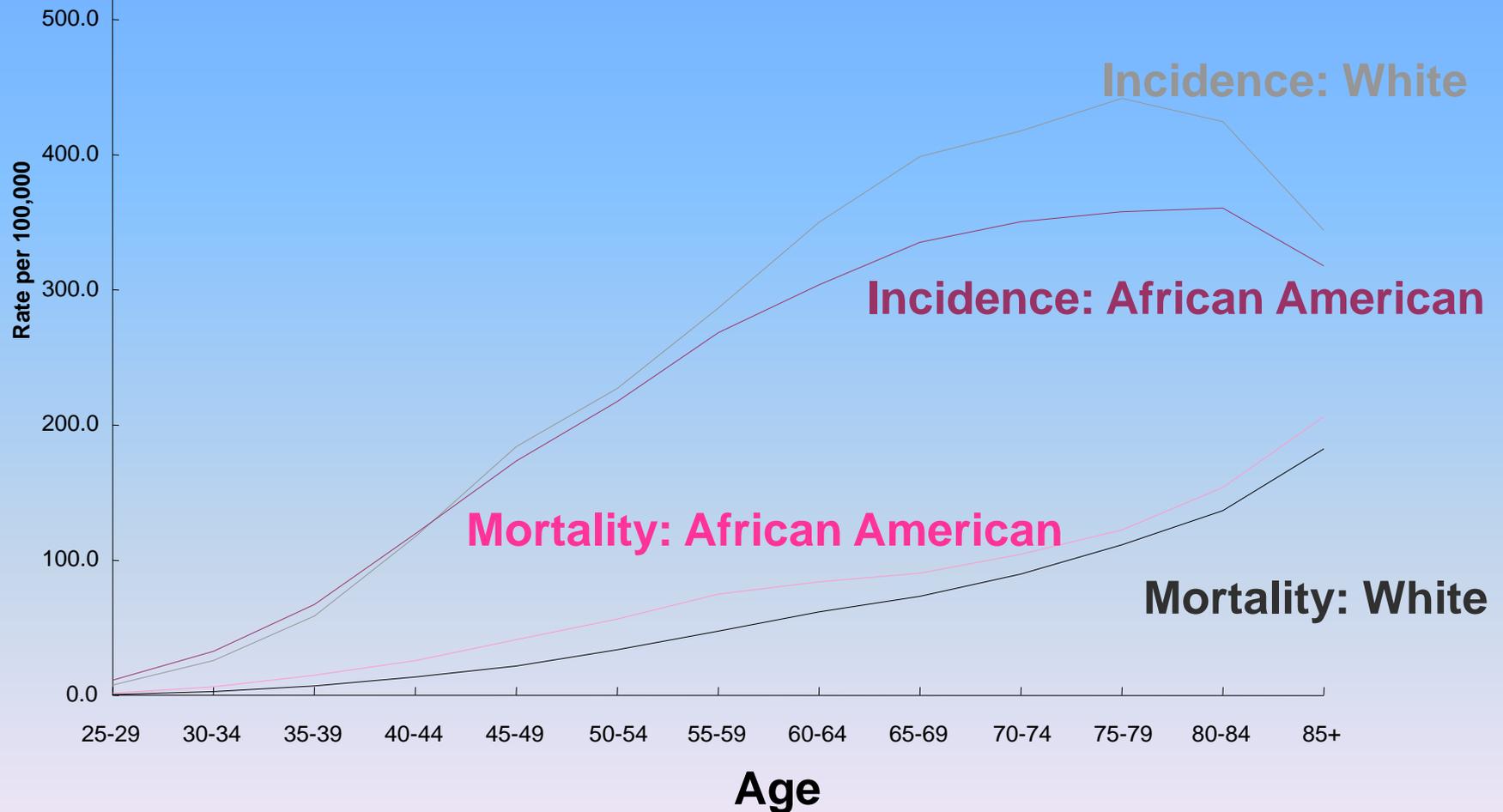
Race/Ethnicity-Associated Variation in Breast Cancer Among Young Women

- White Americans
 - Caucasians
 - European ancestry
- African Americans
 - African ancestry
 - Caribbean ancestry
 - South American ancestry
- Hispanic/Latina Americans
 - European/Spanish ancestry
 - South American ancestry
 - Central American ancestry
 - Cuban ancestry
- Asian Americans
 - Pacific Islanders
 - Japanese ancestry
 - Chinese ancestry

Heritable contributions from geographically-defined racial/ethnic ancestry to biology of breast cancer influenced by centuries of genetic admixture in the U.S.

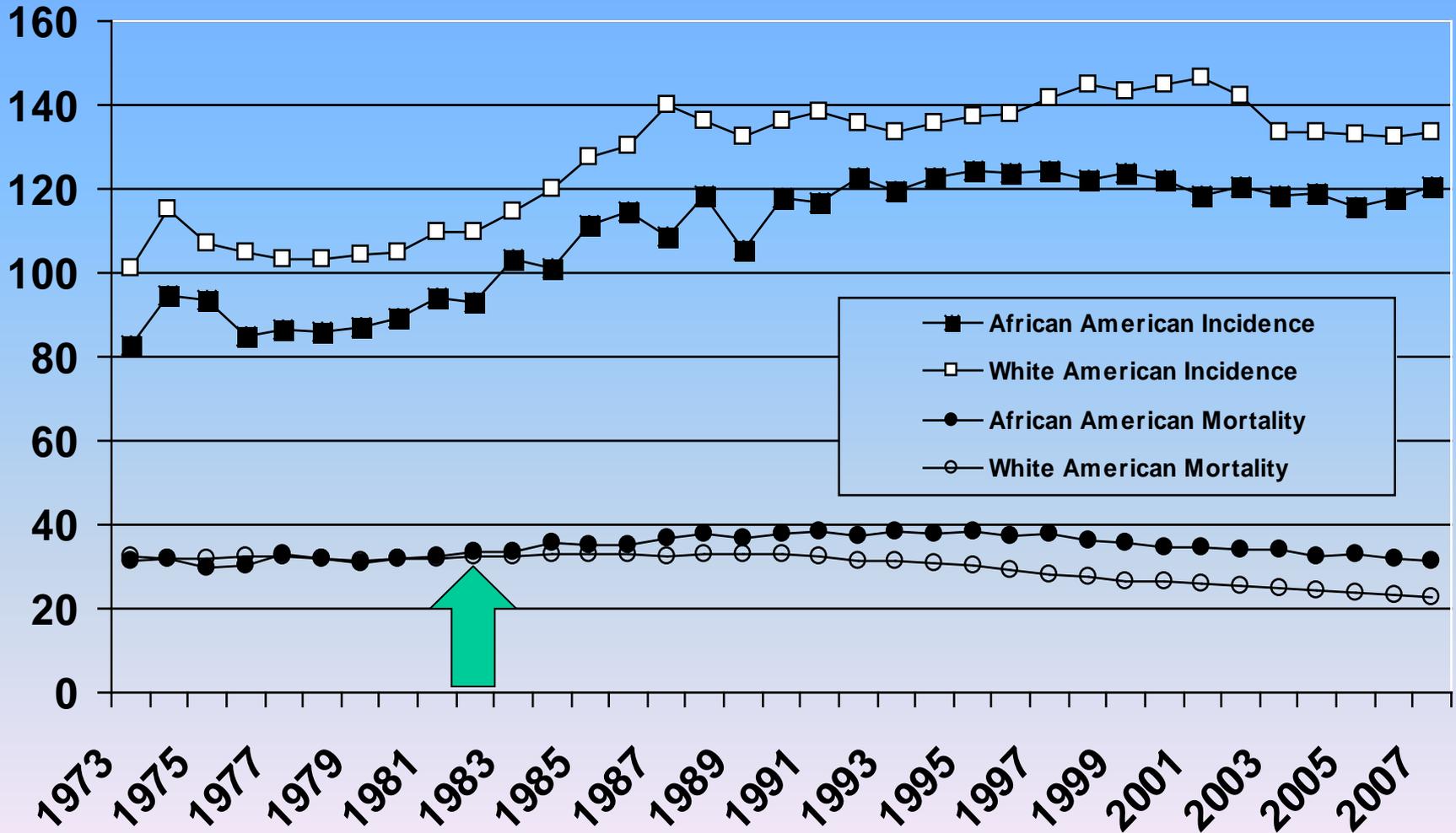


US Female Breast Cancer Incidence & Mortality by Age and Race, 2002-2006



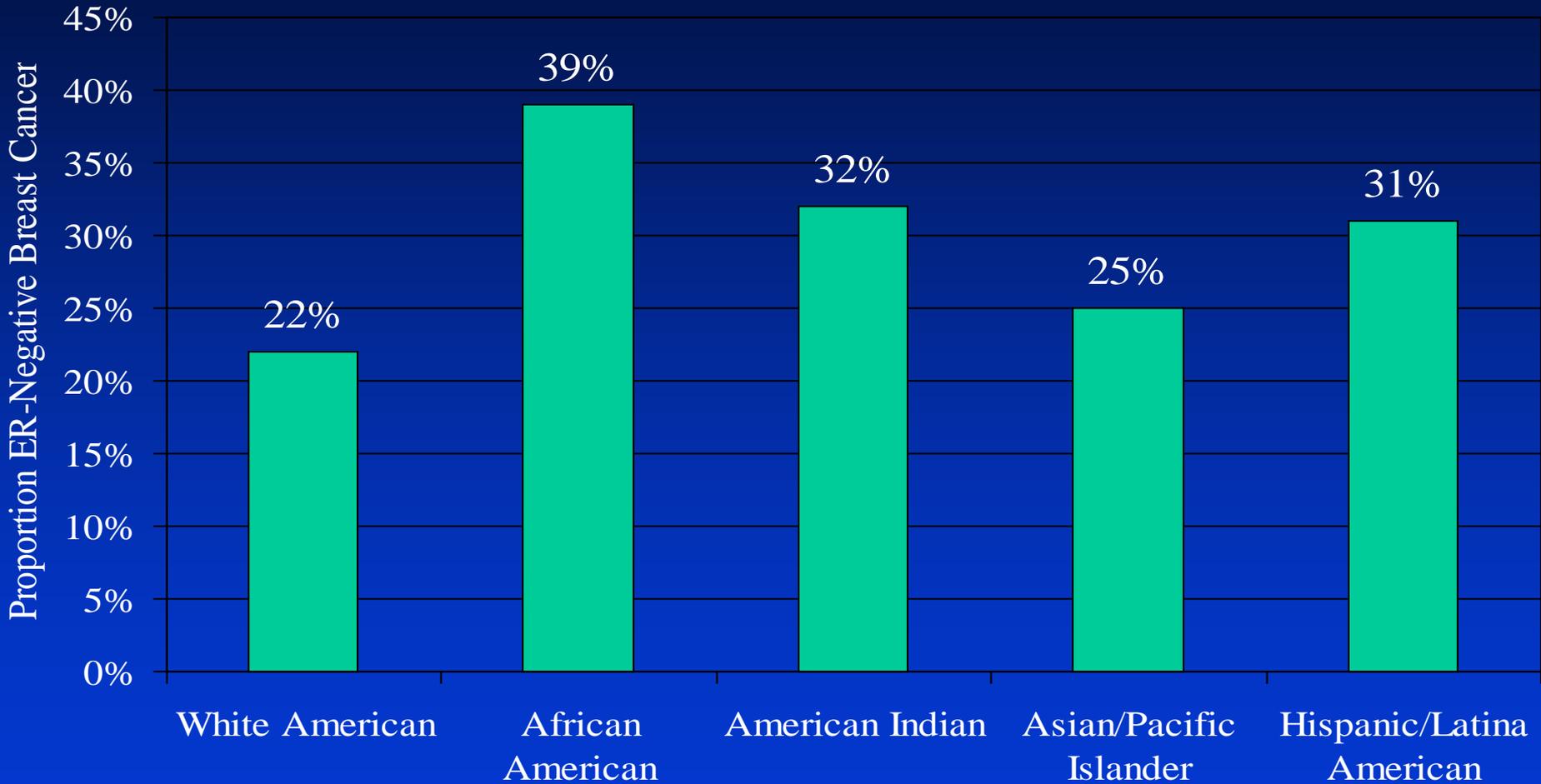


SEER Program: Breast Cancer Incidence and Mortality Rates, 1973-2007





Disparities in Breast Tumor Biology: ER-Negative Breast Cancer in the U.S.



*Li et al; SEER Data, 1992-98
Arch Int Med 2003*

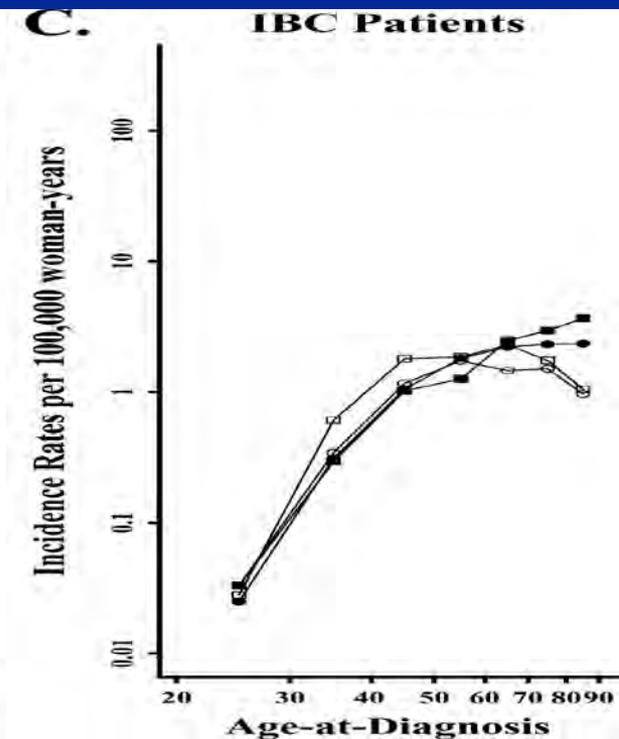
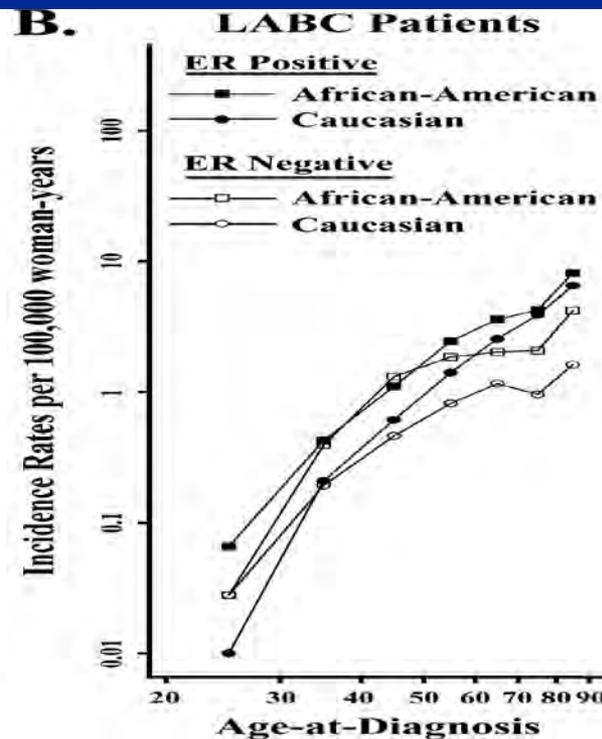
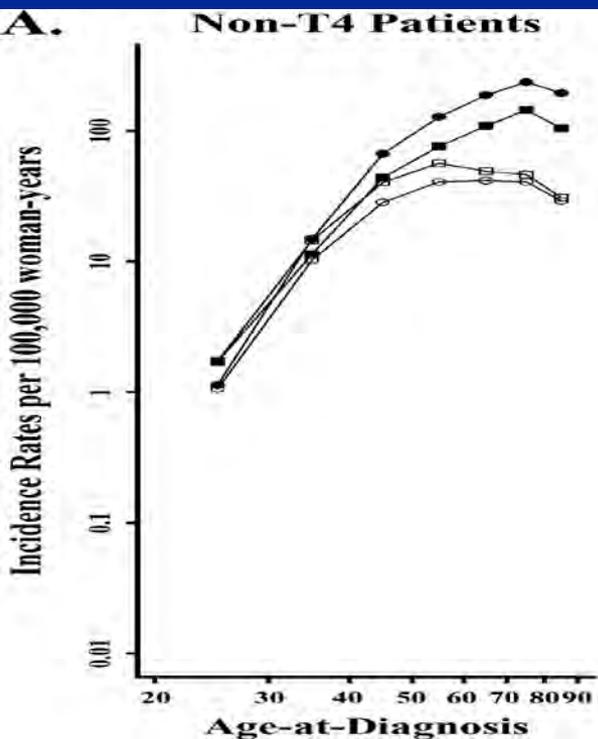
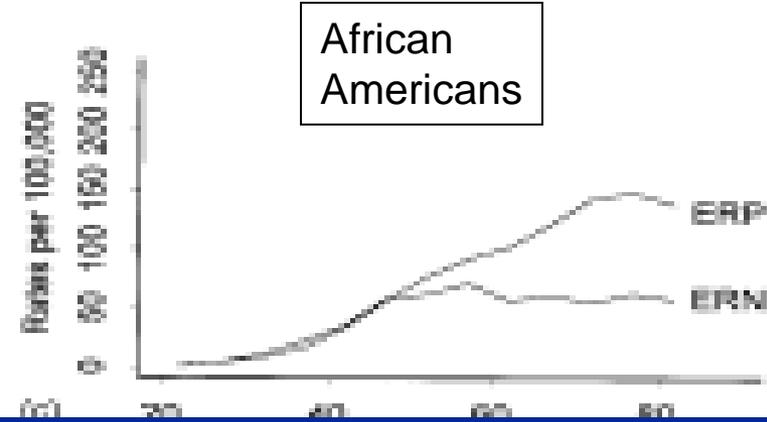
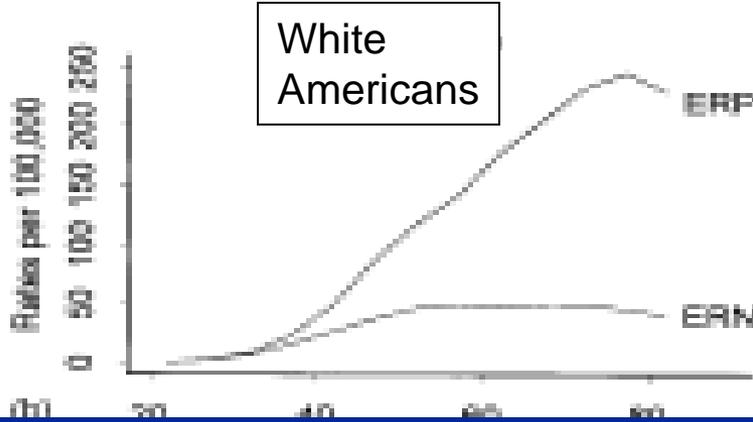


NCDB: Frequency of ER-Negative Tumors by Age, Stage, and Income 1998; N=170K; approximately 10% AA

		<i>African American</i>	<i>White American</i>
Age Category (years)	≤45	52%	35%
	46-60	41%	26%
	61-80	29%	17%
Stage	I	31%	17%
	II	42%	26%
	III	47%	32%
	IV	46%	30%
Income	<\$30,000	37%	23%
	\$30-\$45,000	39%	23%
	≥\$46,000	39%	21%

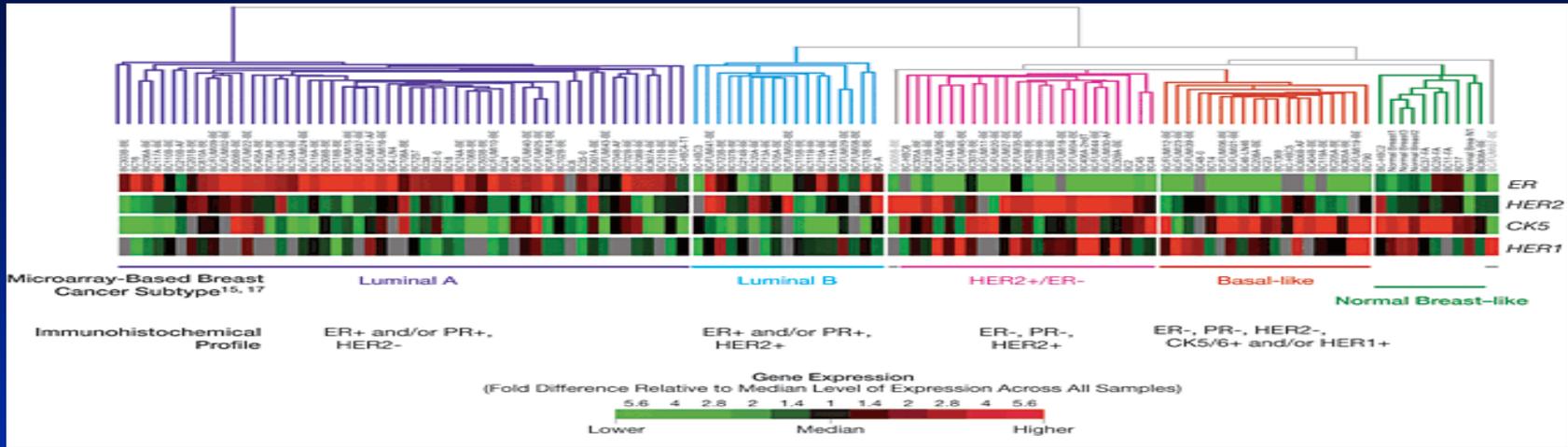


Breast Cancer Incidence: Estrogen Receptor-Positive (ERP) vs Estrogen Receptor-Negative (ERN)

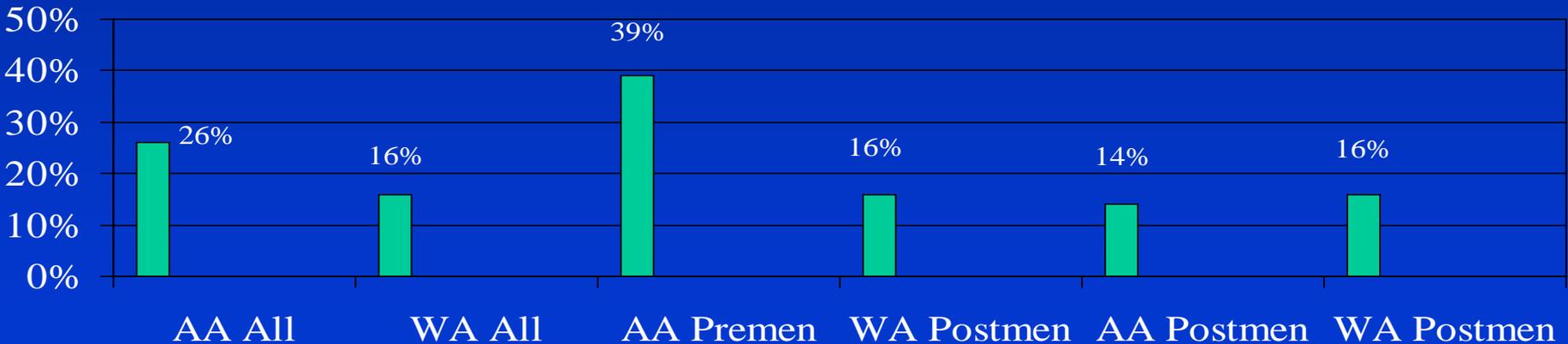




Microarray and Immunohistochemistry to Identify of Breast Tumor Subtypes



Carolina Breast Cancer Study: Frequency of “basal subtype” by IHC



Carey, L. A. et al. JAMA
2006;295:2492-2502.



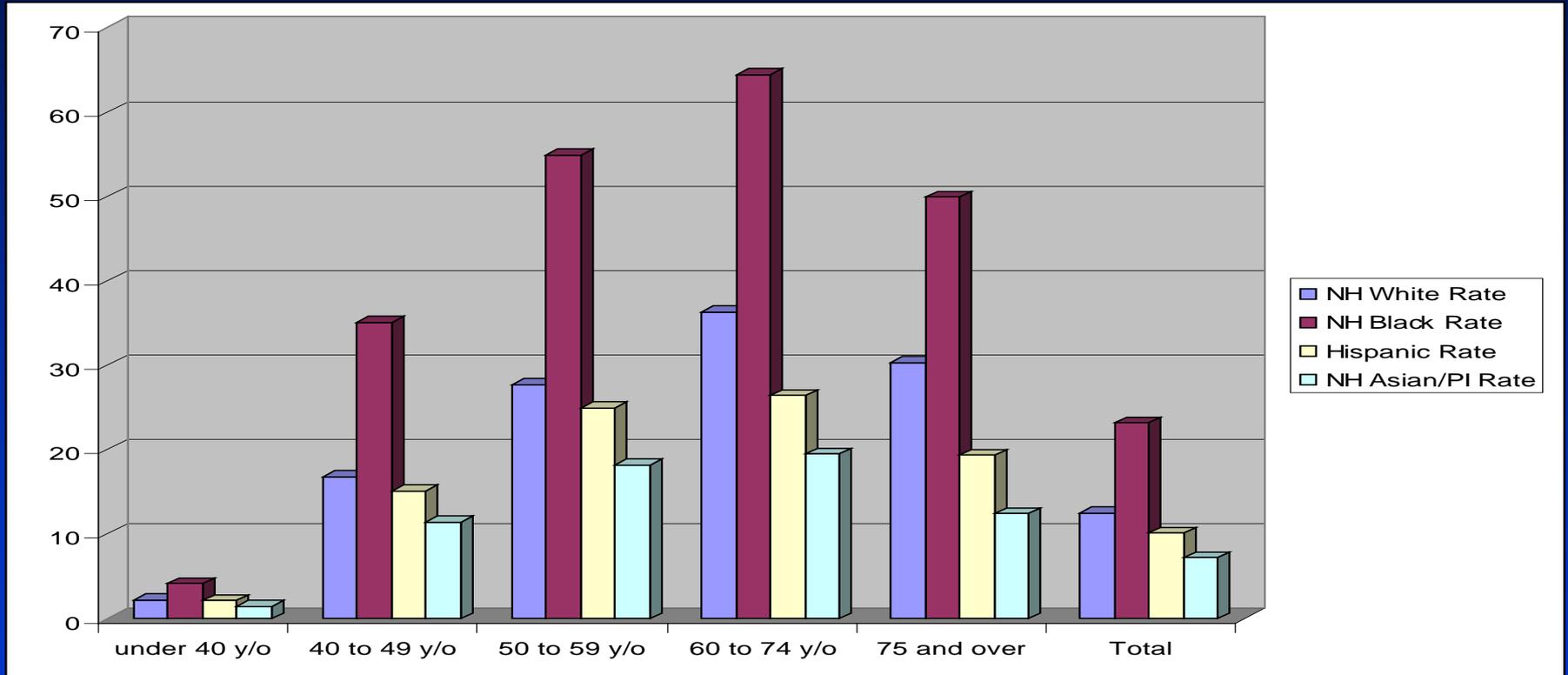


	Dataset/Sample Size	Frequency of Triple-Neg CA		
		AA	WA	P
Carey, 2006	97 premenopausal AA vs 164 premenopausal WA women; Carolina Breast Cancer Study	39%	16%	<0.001
Morris, 2007	2230 Thomas Jefferson Univ Hosp pts; 197,274 SEER pts	20.8%	10.4%	<0.0001
Lund, 2008	Population-based Atlanta GA cohort of 116 AA, 360 WA pts	46.6%	21.8%	<0.001
Lund, 2008	167 AA and 23 WA from Grady Hospital; Atlanta, GA	29.3%	13.0%	0.05
Moran, 2008	99 AA; 968 WA BCS pts from Yale Univ School of Medicine	21%	8%	<0.0001



Population-Based Incidence Rates of TNBC, by Race/Ethnicity and Age:

Implications for Screening Recommendations



USPSTF updated mammography recommendations may worsen breast cancer outcome disparities between AA and WA women (CANCER, 2011)



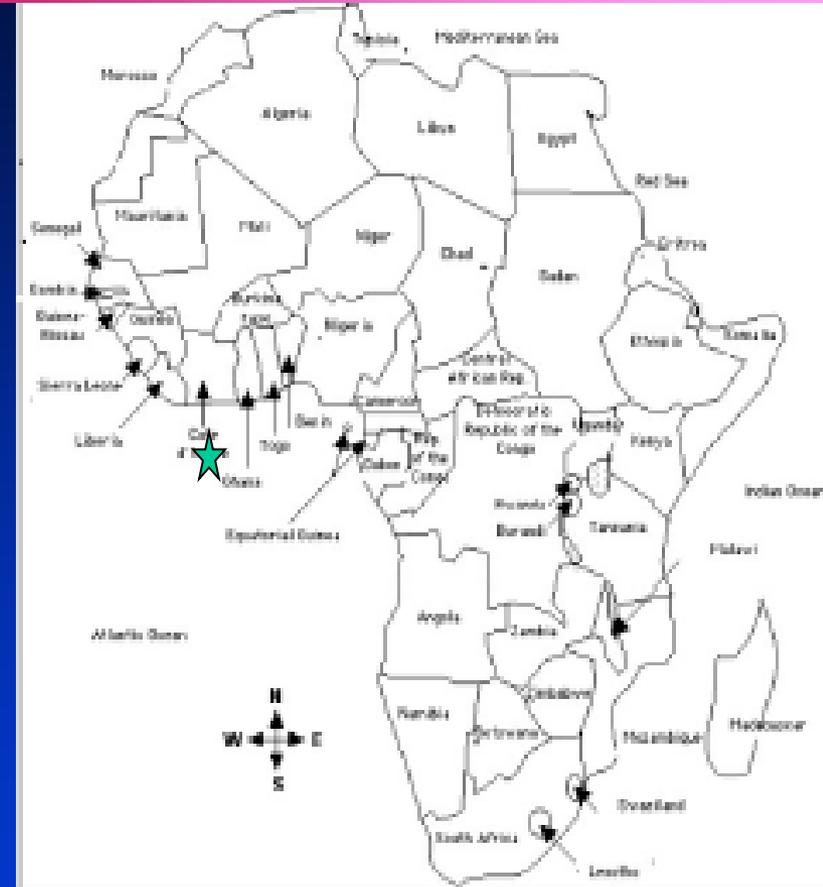
Risk Factors for Biologically-Aggressive Breast Cancer in Young Women

- Millikan R et al, CBCS (*Breast Cancer Res Tr* 2008)
 - “traditional” risk factors (↓parity; ↑age at FLB) increased risk of luminal A breast cancer
 - Basal-like breast cancers associated with ↑parity; ↓age at FLB; ↓breastfeeding; and abdominal adiposity
 - Estimate: 2/3 basal-like breast cancer in premenopausal African American women could be prevented by modifiable risk factors
- John et al, San Francisco Bay Area Breast Cancer Study: WA, AA, and HA Premenopausal breast cancer cases and controls (*Amer J Epi*, 2011)
 - Across all three groups, ↑ BMI and abdominal adiposity inversely associated with risk of ER-positive breast cancer but no association with ER-neg disease



Risk Factors for TNBC: African Ancestry???

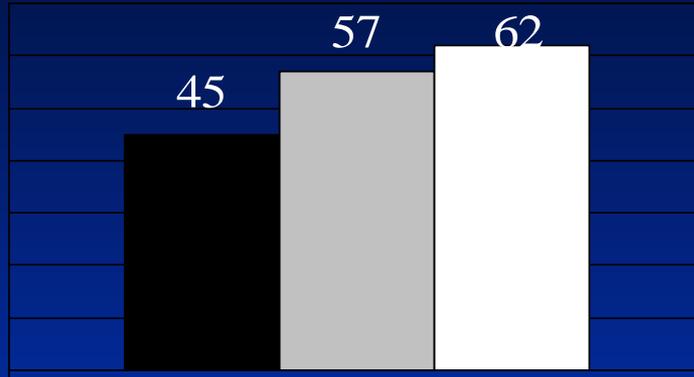
- Parallels between hereditary breast cancer and breast cancer in women with African ancestry
 - younger age distribution
 - increased prevalence of ER-neg, aneuploid tumors
 - higher risk of male breast cancer
- *Is African ancestry associated with a heritable marker for high-risk breast cancer subtypes?*
- Unique opportunity to gain insights regarding etiology of breast cancer disparities **and** the pathogenesis of triple-negative breast cancer



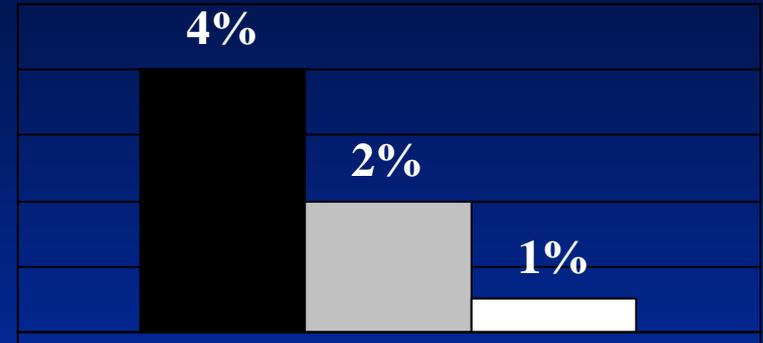


Breast CA in African American, Sub-Saharan African, and White American Women

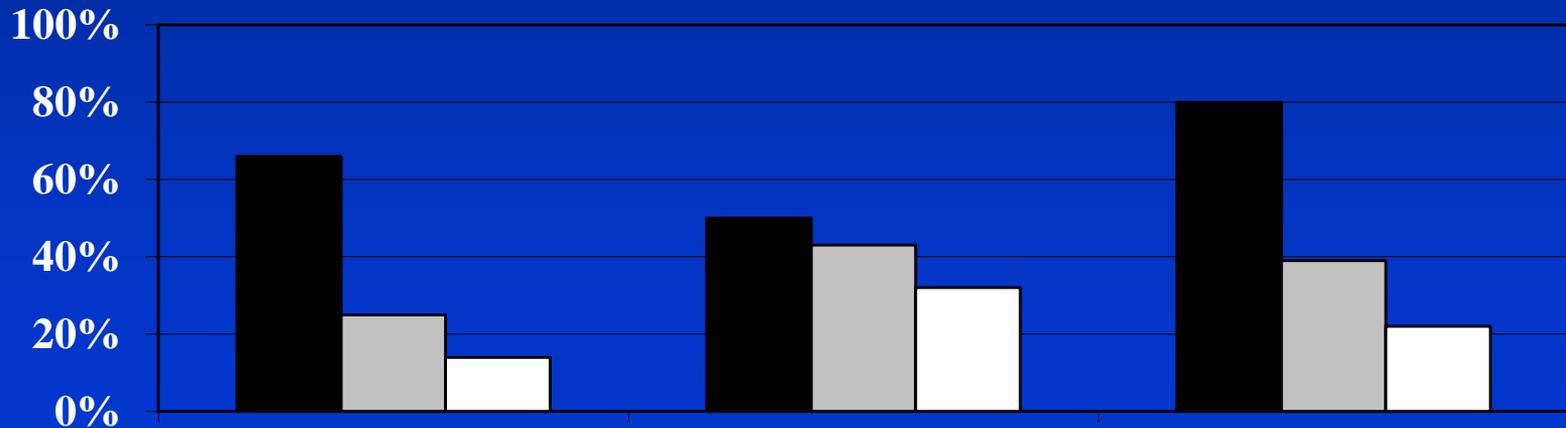
■ African
■ African American
■ White American



Average Age at Diagnosis (years)



Frequency of Male Breast Cancer



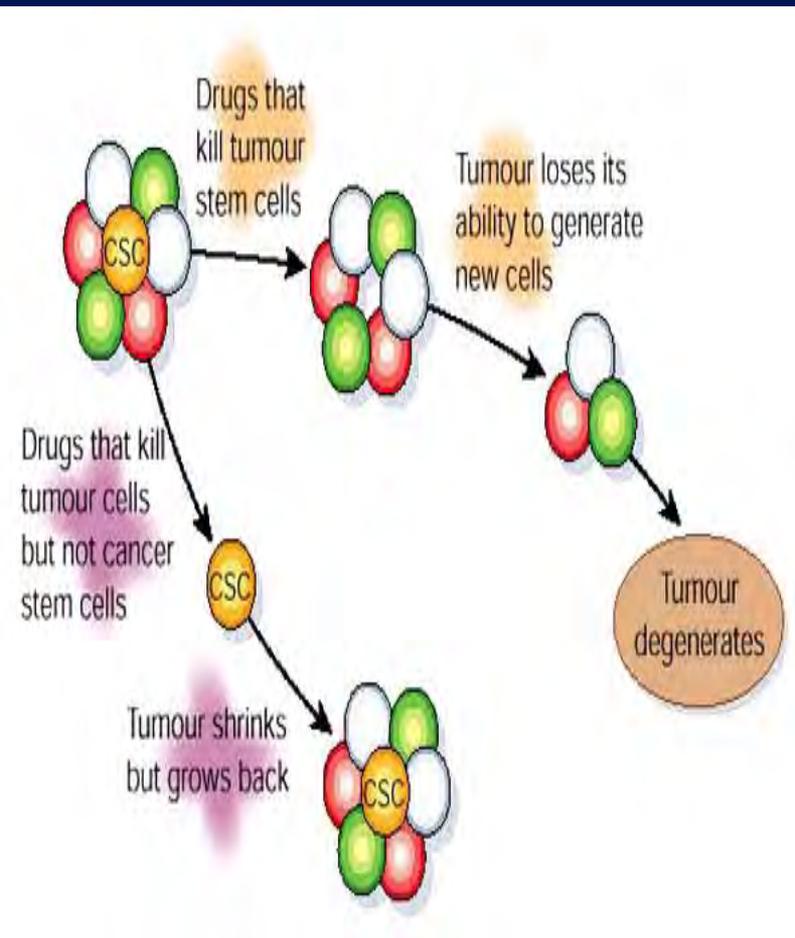
Proportion with TNBC

Proportion with High-Grade Tumors

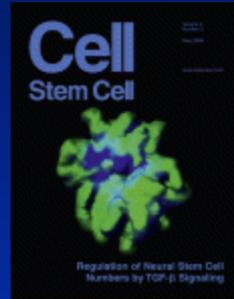
Proportion with ER-Negative Tumors



Breast Cancer Stem Cells



“ALDH1 Is a Marker of Normal and Malignant Human Mammary Stem Cells and a Predictor of Poor Clinical Outcome”

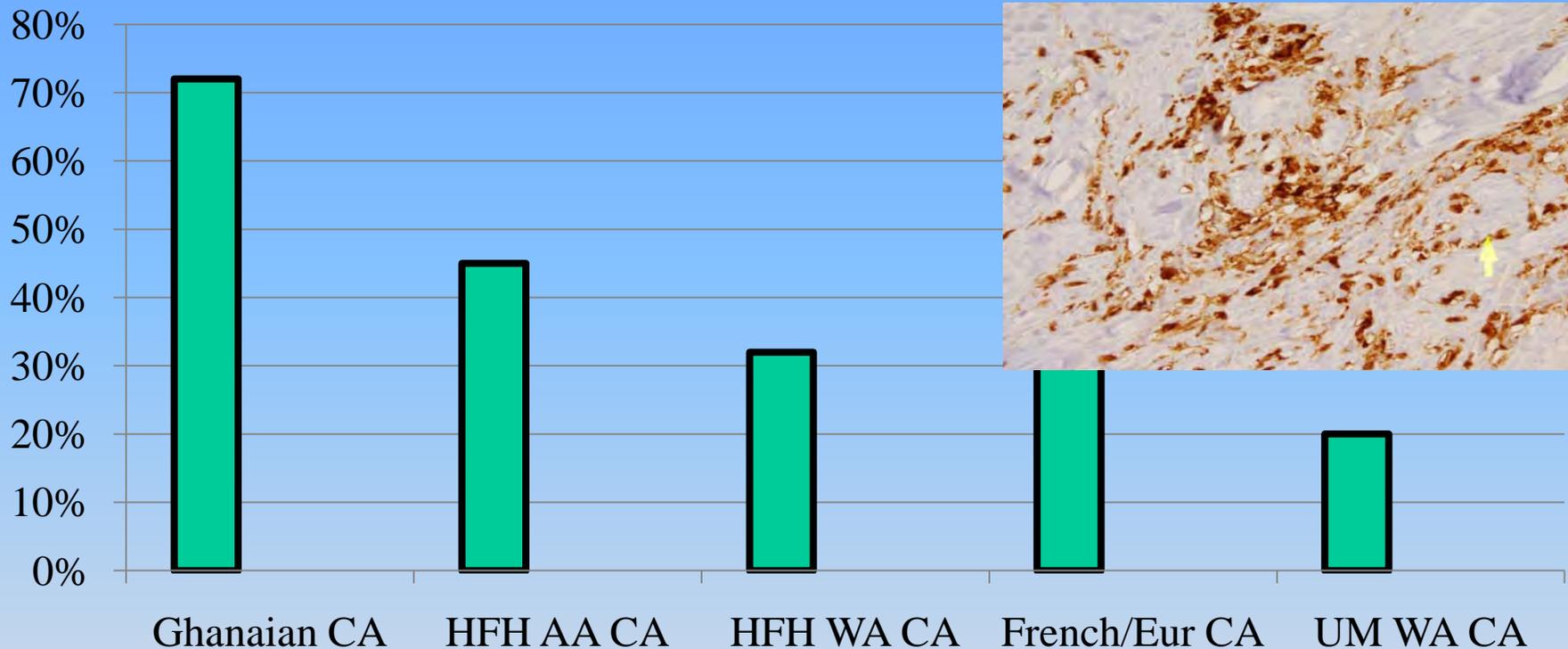


C Ginestier, M Wicha, G Dontu, et al

University of Michigan
Laboratoire d'Oncologie Moléculaire,
Centre de Recherche en
Cancérologie de Marseille, France
November 2007, Pages 555-567



ALDH-1 Staining by Race/Ethnicity



- Consistent with results in Uganda breast cancer pts (Nalwoga et al, Br J Cancer 2010)
- 69 benign Ghanaian breast specimens studied at UM – 42 (61%) ALDH1-positive



Summary and Conclusions

- Breast cancer risk increases with age, but young women account disproportionately for breast cancer mortality
 - Advanced stage distribution and inherently more aggressive disease biologically
- African American women have increased risk for breast cancer in premenopausal age range compared to White American women and increased risk for ER-neg/TNBC that is most notable in the premenopausal age range



Summary and Conclusions

- Future research directions:
 - Identify therapeutic targets for treatment of TNBC
 - Study heritable and modifiable risk factors for early-onset and biologically-aggressive breast cancer patterns
 - Improve screening for appropriately-selected young women
 - Improve data collection on breast cancer risk in premenopausal women of other racial/ethnic backgrounds
 - Refine our definitions for racial/ethnic identity so that they are more scientifically relevant