Breast Cancer in African-American Women

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Breast Cancer in African-American Women

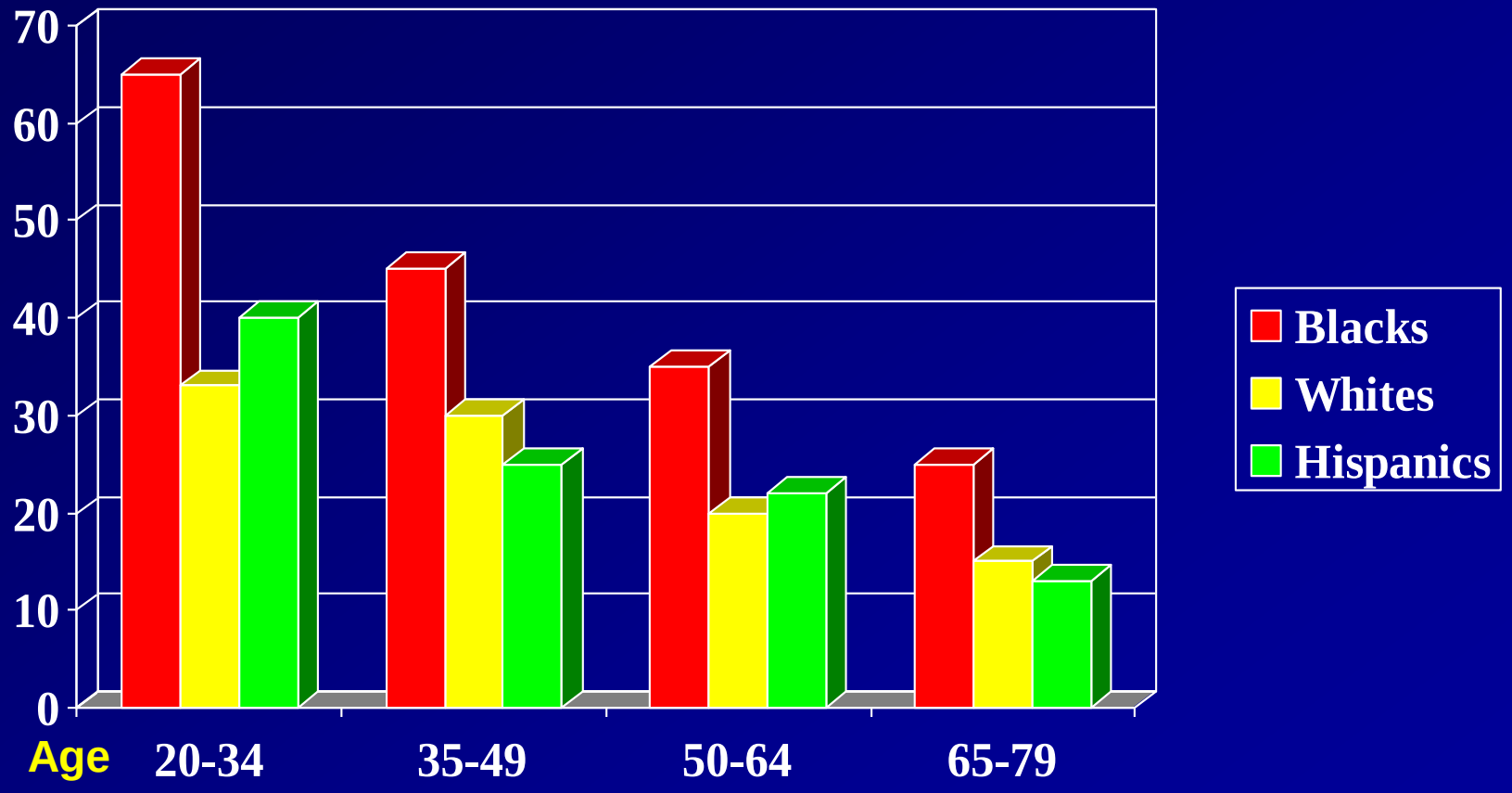
- Higher incidence overall of breast cancer in European-American women
- African-American women more likely to be diagnosed before age 40
- More aggressive tumors in African-American women
  - High grade
  - Negative for estrogen receptor expression
  - High mitotic index

Breast Cancer in African-American Women

Breast cancers among young women have poorer prognosis

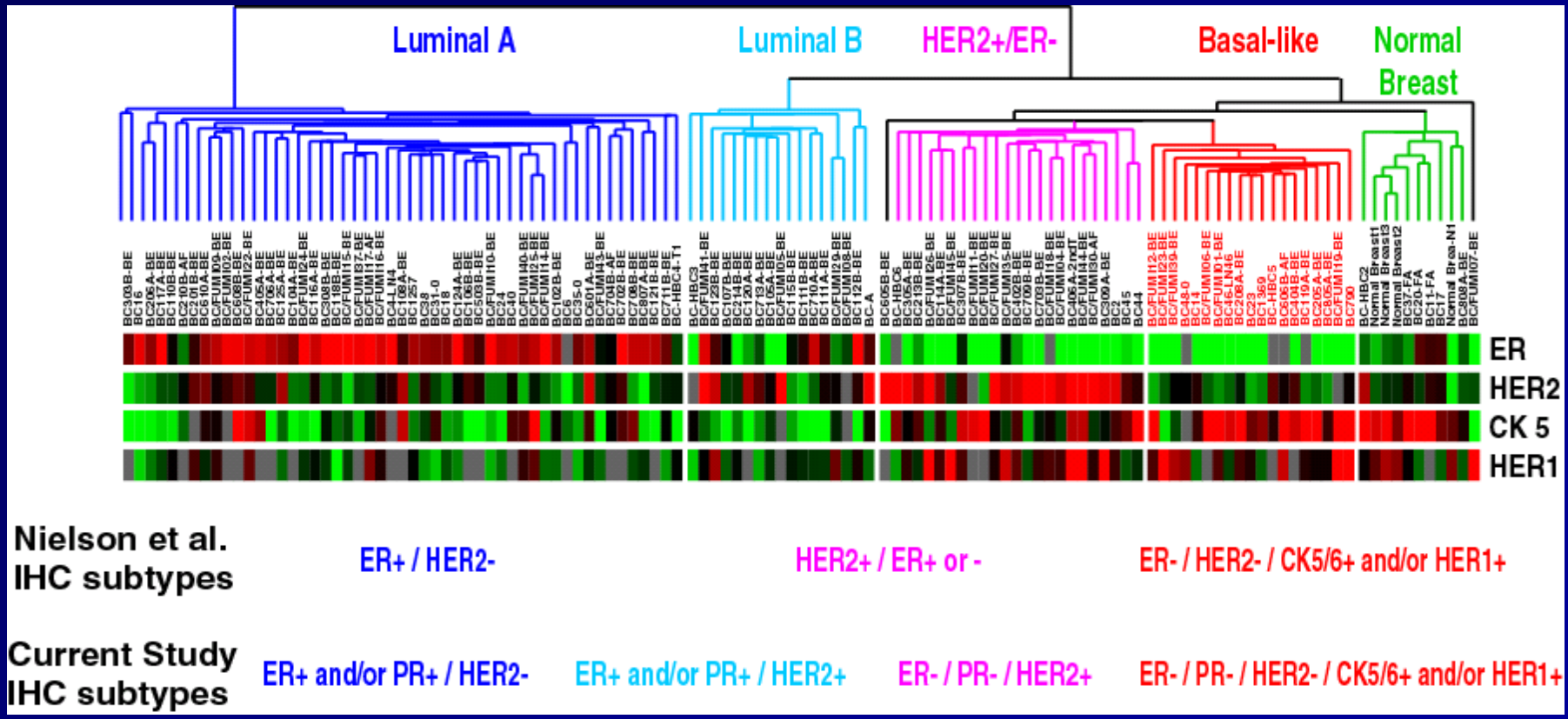
Is the higher incidence of more aggressive cancers among African-American women due to the earlier age at onset?

Proportion of ER-/PR- tumors by race in 13,239 women within age quartiles



Gapstur et al. Cancer, 1996

IHC surrogates for gene expression profiling



JAMA 2006, 295: 2492-2502.

Slide courtesy of R Millikan

Basal-like (TN) Breast Cancers

- More common in African-American than European-American women
- In CBCS (n=1,424 cases), 16% basal-like - different distributions by race, age (Millikan RC 2008)
- Women < 40 years have 4.5 times the risk of basal like breast cancer than those > 60, in comparison to luminal A

Menopausal status	EA (%)	AA (%)
Pre	14.5	27.2
Post	9.3	16

Race, Age and Breast Cancer Characteristics

- Unique molecular characteristics of tumors among younger women
  - Immune function, mTOR/rapamycin pathway, hypoxia, BRCA1, stem cell biology, apoptosis, histone deacetylase, signaling (Anders 2008)
- Differential tumor epithelial and stromal gene expression patterns between African-American and European-American women (Martin 2009)
  - Genes regulating angiogenesis and chemotaxis; unique interferon signature
    - Higher microvessel density and macrophage infiltration in tumors from African-American women

Breast Cancer in African-American Women

What is driving these differences in tumor subtypes?

- **epidemiologic risk factors? (modifiable)**
- **biology?**
- **genetics?**

What Risk Factors Differ by Subtype?

Carolina Breast Cancer Study, 1803 cases, 1,564 controls

	Luminal A OR (95% CI)	Basal-like OR (95% CI)	Basal-like Premenopausal	Basal-like Postmenopausal
Waist hip ratio				
<0.77	Referent	Referent	Referent	Referent
0.77-0.83	1.1 (1.1-1.7)	2.3 (1.5-3.5)	2.3 (1.3-4.1)	1.4 (0.7-2.8)
0.84+	1.5 (1.1-1.9)	2.3 (1.4-3.6)	1.9 (1.0-3.6)	1.4 (0.7-2.7)

Millikan Br Ca Trt Res 2008

What Risk Factors Differ by Subtype?

Case-control analysis	Luminal A OR (95% CI)	Basal-like OR (95% CI)
Parity		
Nulliparous	Referent	Referent
1	0.7 (0.5-1.0)	1.7 (0.9-3.0)
2	0.7 (0.6-1.0)	1.8 (1.1-3.1)
3+	0.7 (0.5-0.9)	1.9 (1.1-3.3)
Months breastfeeding per child		
Never	Referent	Referent
0-3.9	0.8 (0.7-1.0)	0.8 (0.6-1.2)
4+	0.9 (0.7-1.2)	0.6 (0.4-0.9)

Carolina Breast Cancer Study; Millikan Br Ca Trt Res 2008

Carolina Breast Cancer Study

	Luminal A OR (95% CI)	Basal-like OR (95% CI)	AA < 40y	AA 40-49y	EA < 40y	EA 40-49y
Parity and lactation						
Nulliparous	Referent	Referent				
1-2, never	0.7 (0.6-0.9)	1.8 (1.1-3.0)*				
1-2, ever	0.7 (0.5-0.9)	1.1 (0.6-2.0)				
3+, never	0.7 (0.5-0.9)	1.9 (1.1-3.3)*	18%	30%	5%	7%
3+, ever	0.7 (0.5-0.9)	1.3 (0.7-2.3)	9%	10%	10%	26%

For luminal A, parity reduces risk, regardless of number of children or breastfeeding; importance of terminal differentiation of breast ductal cells

Basal like – increased risk with parity ameliorated by breastfeeding

Risk Factors for Early Onset Breast Cancer among African-American Women

- **Black Women's Health Study (Palmer, PI)**
  - High parity IRR= 2.4 (CI=1.1-5.1) in women < 45; reduced risk in older women IRR = 0.5 (CI 0.3-0.9) (*JNCI* 2003)
  - High BMI inversely associated with risk in premenopausal women IRR=0.71, (CI 0.53-0.93); no association in postmenopausal (IRR=0.84, CI 0.63-1.12) (*CEBP* 2007)
  - Reduced risk with strenuous activity at age 21 for premenopausal (IRR=0.5, CI 0.3-0.8), but not postmenpausal women (*J Nat Med Assoc* 2001)

Breast Cancer in African-American Women

Need for very large sample sizes to subtype tumors, evaluate risk factors for subtypes by race, age

Developing P01 to pool studies (CBCS, Millikan; BWHS, Palmer; WCHS, Ambrosone)

Women's Circle of Health Study

- Grant developed in 2000
  - African-American women (and girls) have higher levels of estrogens, higher BNI, earlier age at menarche, earlier age at first birth, more children
  - Distribution of polymorphisms differs across racial and ethnic groups
  - Could these differences account for earlier onset and more aggressive disease?

Study Aims

1. **To investigate genetic, reproductive, hormonal and related risk factors in relation to breast cancer risk among African-American and Caucasian women.**

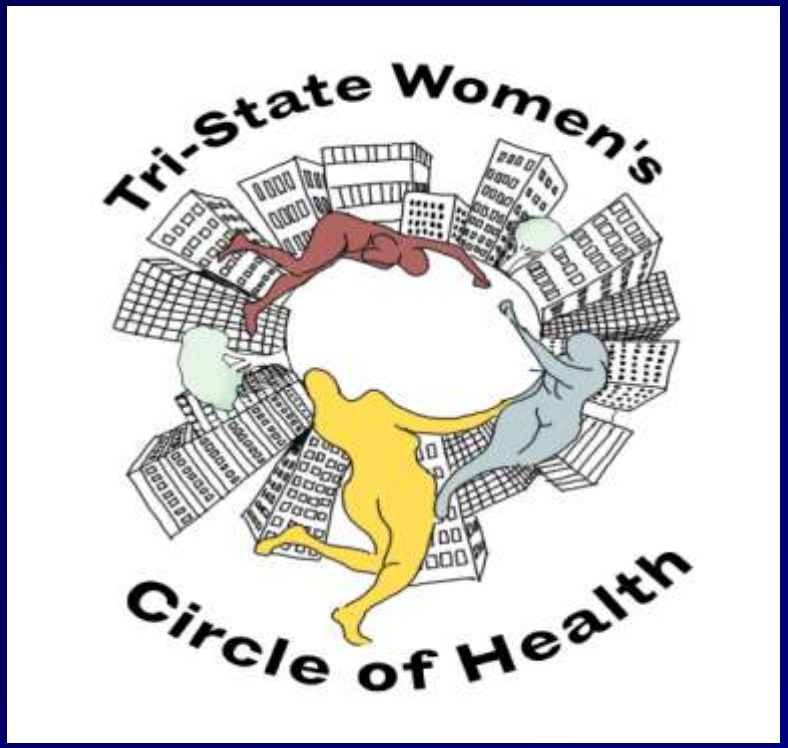
2. **To examine risk factors related to earlier age at diagnosis and more aggressive disease (ER-, high grade tumors).**

3. **To determine proportion of early age/aggressive breast cancer due to differential racial distribution of risk factors.**

Study Design

- First funded by DOD as part of Breast Cancer Center of Excellence for Biobehavioral Research (Bovbjerg, Center PI; Ambrosone, Project 1 [case control study] PI), Mount Sinai School of Medicine

- Obtained NCI funding to expand sample size, extend to Caucasians



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NEW JERSEY DEPARTMENT of HEALTH and SENIOR SERVICES

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Study Design

- Ascertainment of African-American (n=1200) and European-American (n=1200) women with incident, primary breast cancer through hospitals in the NY metropolitan area, and through NJ State Tumor Registry (SEER site)
  - Now limited to enrollment in NJ
- Equal number of healthy controls identified through random digit dialing
- Permission from physician to contact patient
- In-home interviews, sample collection

Recruitment Progress

The Women's Circle of Health:
Recruitment (as of May 5, 2009)

	Cases=1,249		Controls=1,085	
	AA*	White	AA*	White
NYC	338	340	356	338
NJ	251	320	93	298
Total	**589**	**660**	**449**	**636**
Goal:	*1,200*	*1,200*	*1,200*	*1,200*

**AA: African American*

Breast Cancer Detection among Younger and Older Women

How was your breast cancer found?

	AA (%)		EA (%)	
	< 40	≥ **40**	< 40	≥ **40**
Self-exam	31	25	24	10
Accidental	40	22	35	18
MD exam	9	10	7	13
Mammogram	8	40	13	55

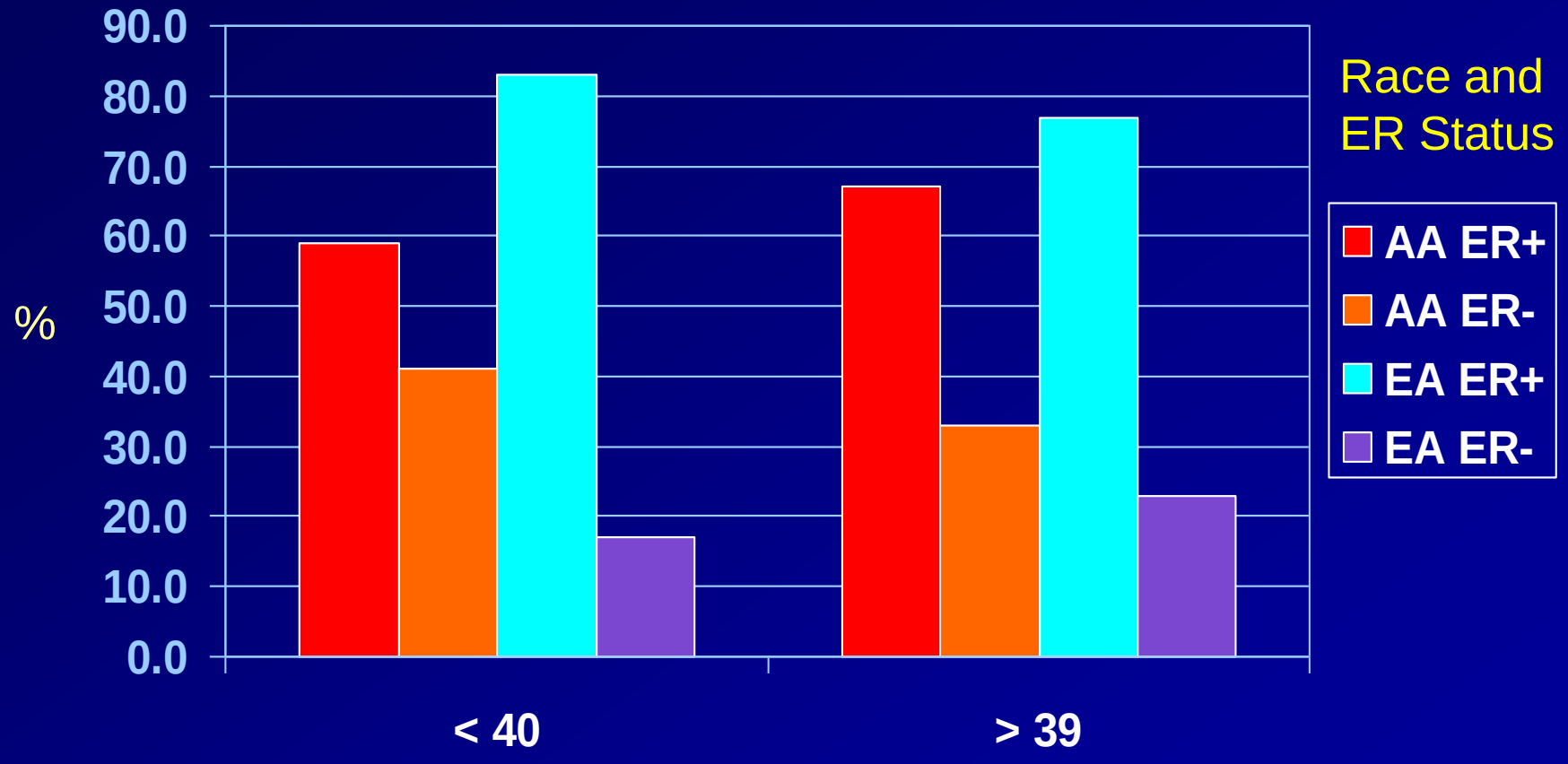
Ever have a screening mammogram

AA		EA	
< 40	≥ **40**	< 40	≥ **40**
40%	**84%**	**47%**	**93%**

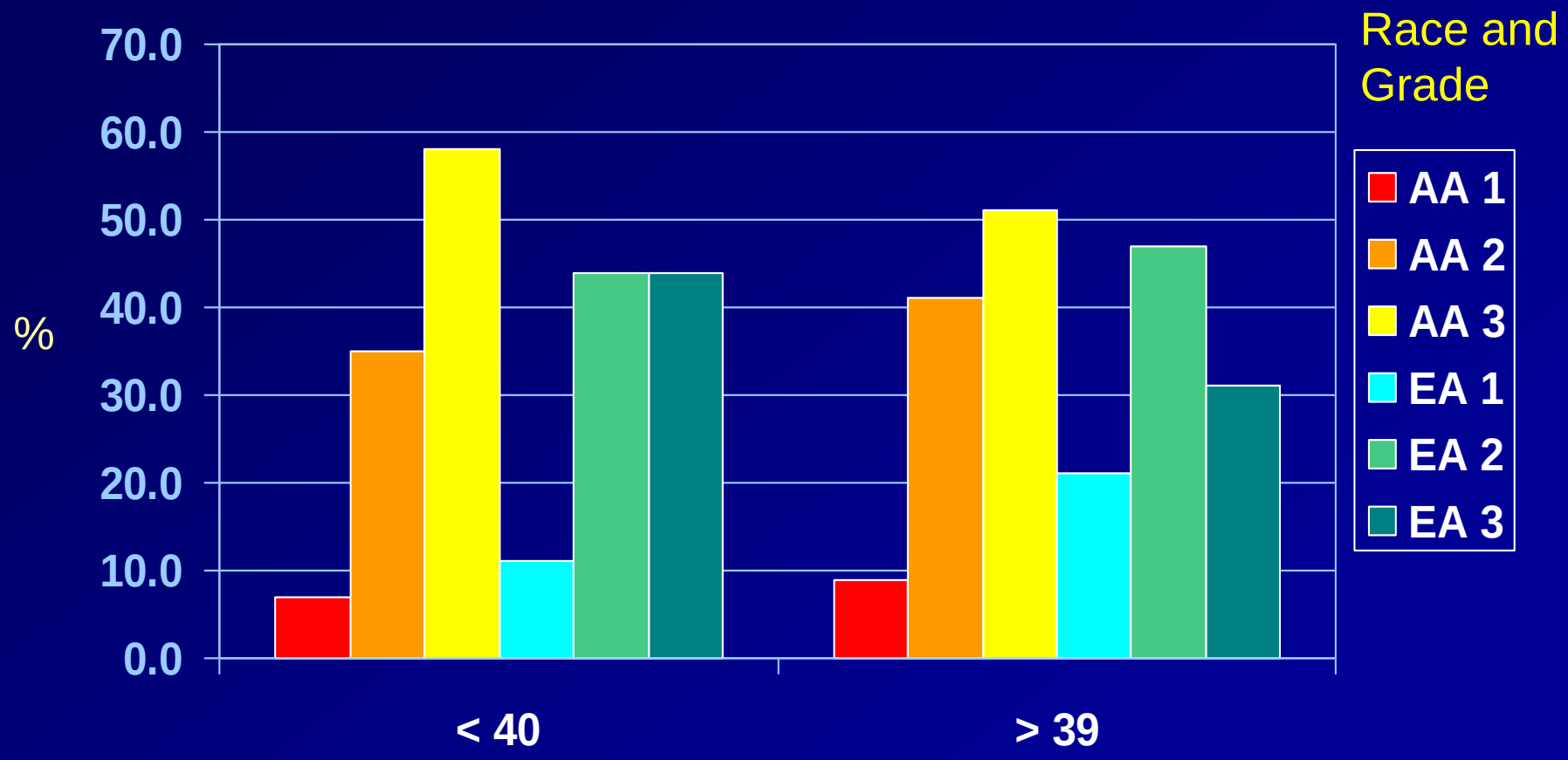
Classification of Subtypes

- Collection of tumor tissue blocks from hospitals
- Standardized grading by one pathologist at RPCI
- Construction of TMAs, staining for ER, PR, HER2, cytokeratins

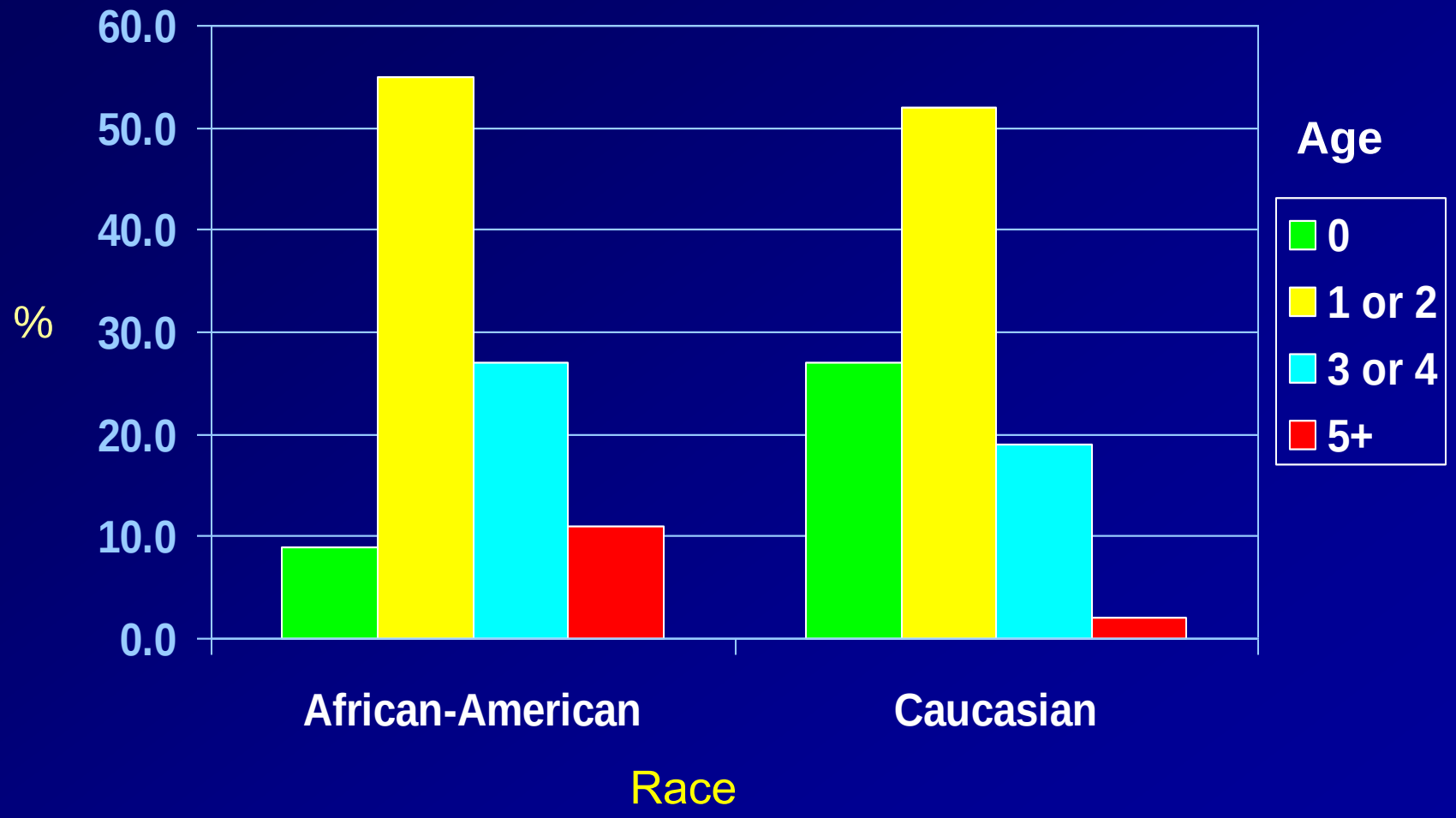
Estrogen Receptor Status by Race and Age (WCHS)



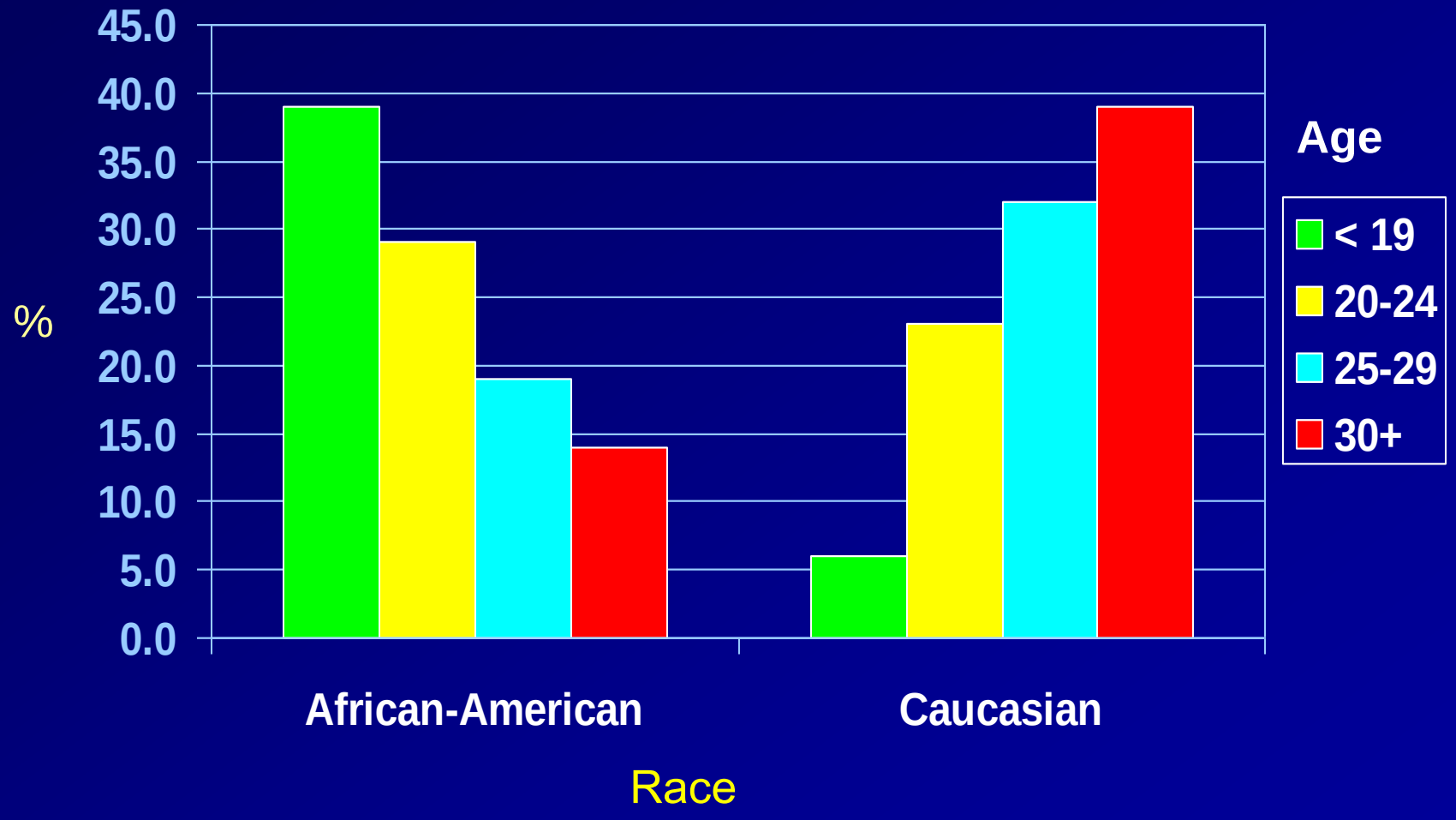
Tumor Differentiation by Race and Age (WCHS)



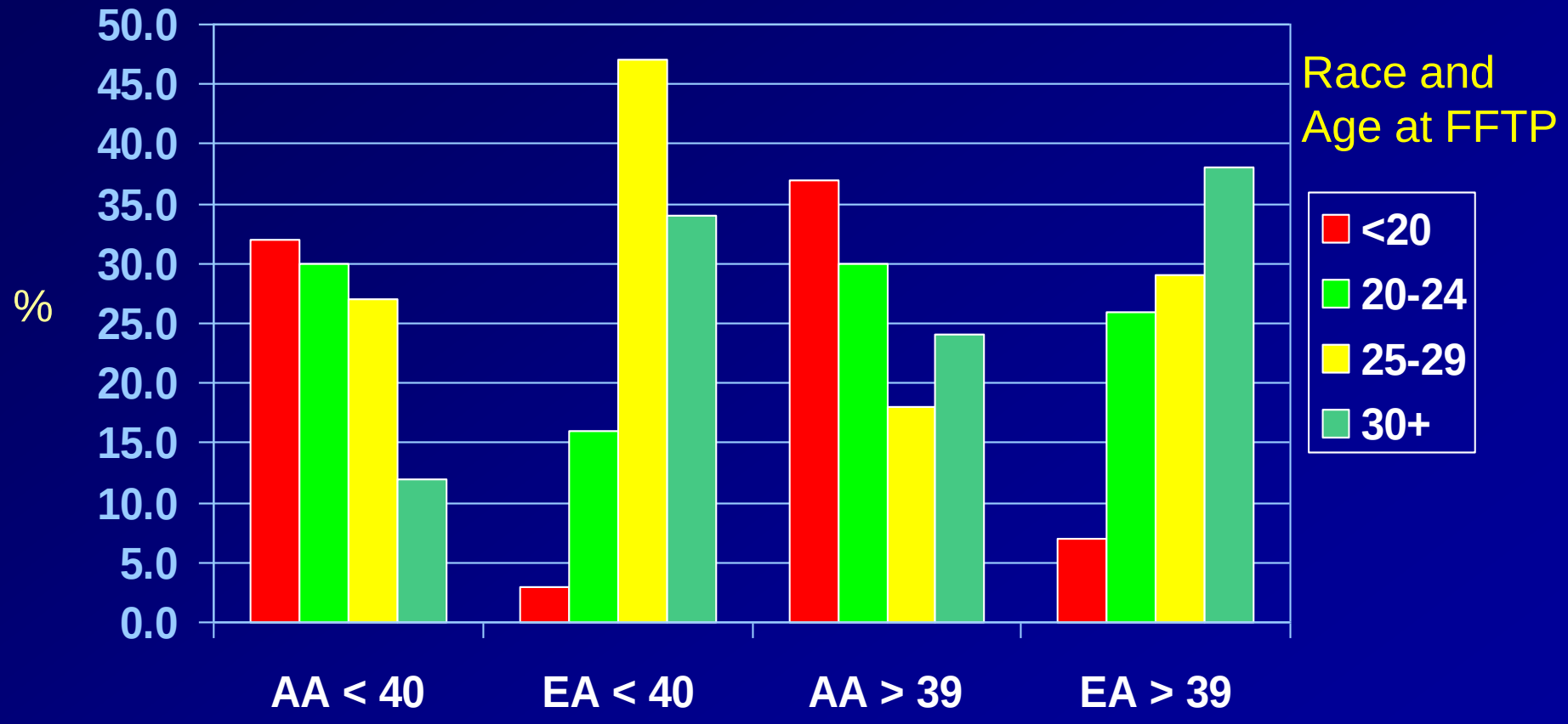
Parity by Race among Cases (WCHS)



Age at First Full Term Pregnancy by Race (WCHS)



Age at FFTP by Race and Age (WCHS)



GWAS of Breast Cancer in African-American Women (Haiman, PI)

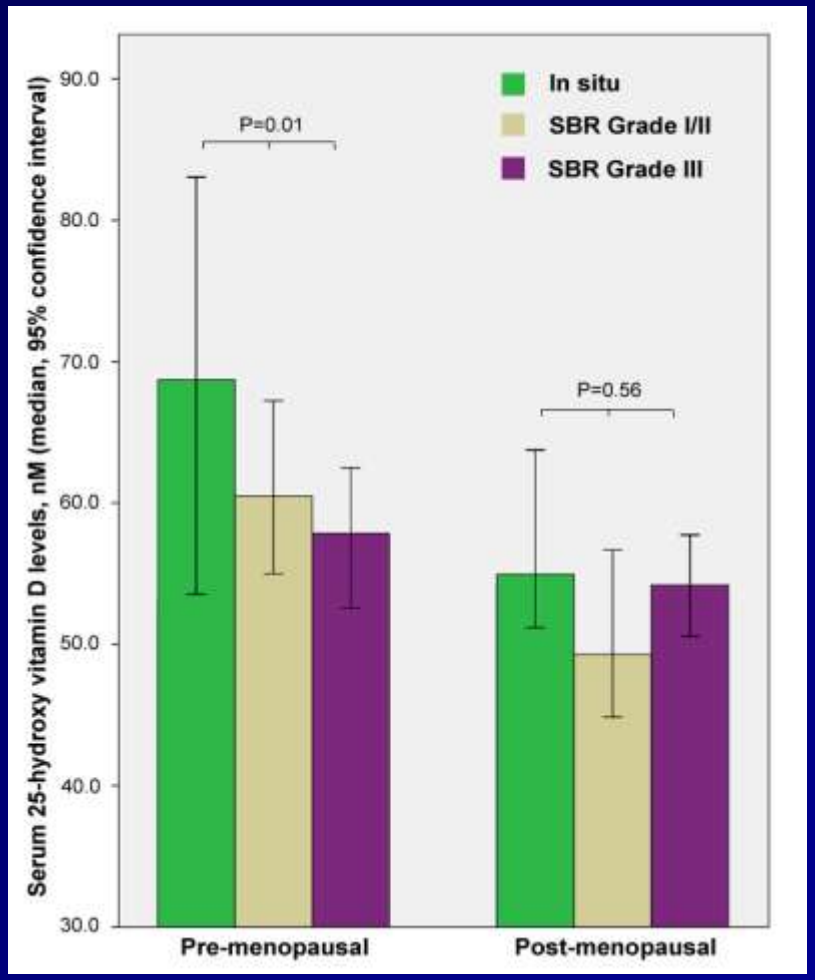
- 12 Participating studies
  - 4,684 cases, 4,506 controls
- Illumina 1M chip
- Risk variants found in EA GWAs – slight associations in AAs (FGFR2, 8q24, MAP3K1)
- Additional unique SNPs identified (ORs=1.2), specific to ER- breast cancer
- Stratify by age at onset

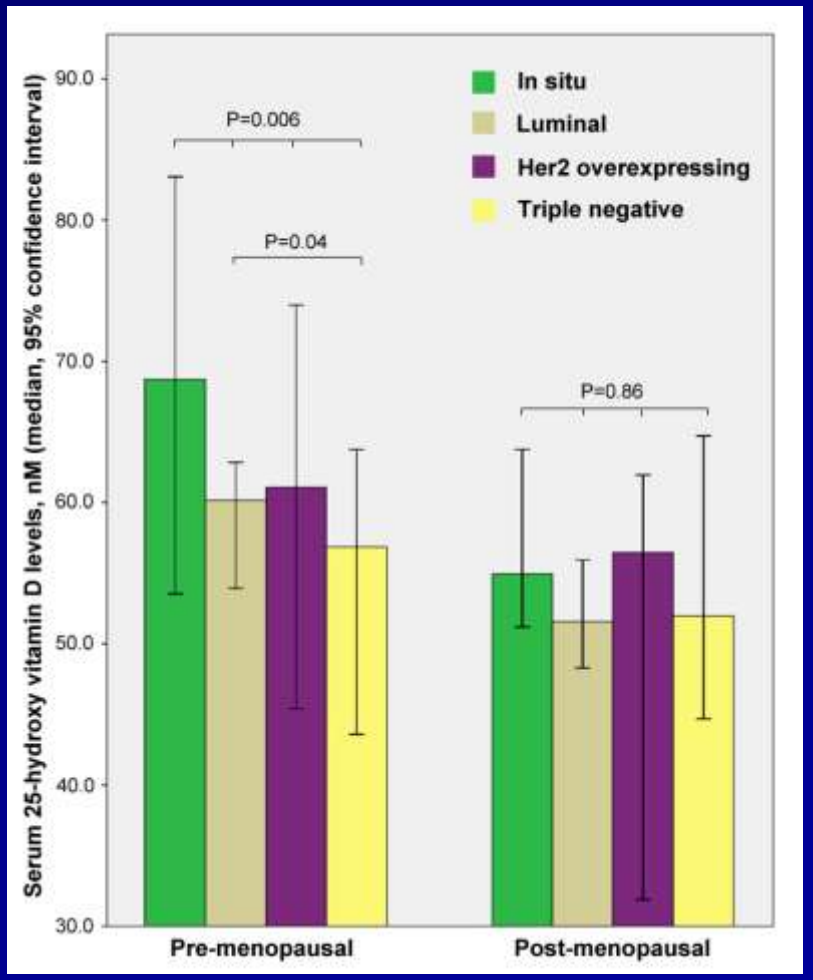
Breast Cancer in African-American Women: an 'Out of Africa' Hypothesis

- Higher pigmentation in Africans –
  - adequate absorption of vitamin D in sub-Saharan environment
  - High prevalence of vitamin D deficiencies in African-Americans
  - Distributions of polymorphisms in Vitamin D receptor and VDR metabolism varies by ancestry

- Relationship between Vitamin D levels and basal-like breast cancers?

Vitamin D levels according to clinical characteristics by menopausal status





Funded by BCRF

Vitamin D and Early, Aggressive Breast Cancers in African-American Women

- Low vitamin D levels associated with high grade, triple negative breast cancers ONLY among premenopausal women

- Ongoing assessment in relation to early onset, aggressive breast cancer in African-American women in WCHS study; vitamin D receptor polymorphisms

Breast Cancer in African-American Women: an 'Out of Africa' Hypothesis

- Adaptation to endemic infectious disease (malaria) in Africa
- Development of robust immune/inflammatory response – differential distributions of SNPs in these pathways
- Relationship with high grade, early onset breast cancers?

Early, Aggressive Breast Cancers in African-American Women

- Racial differences in tumor characteristics *appear to be* independent of early age at onset
- Intensive research to identify modifiable risk factors for early aggressive breast cancers

In collaboration with……

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Multiple clinical and scientific collaborators

Number of Children by Race and Age among Breast Cancer Cases (WCHS)