Epidemiology of Triple-Negative Breast Cancer:
Risk Factors and Early Detection

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Clinicopathology of Triple-Negative Breast Cancer

- Younger age distribution
  - Haffty et al: 63% TN <50 yo v. 45% for other subtypes
  - Dent et al: med. age 53 for TN v. 58 for other subtypes
  - Millikan et al: OR for Dx <40 = 4.5 (2.7-7.3) for TN
- Larger primary tumor size at diagnosis
  - Haffty: 58% T1 tumors for TN v. 79% T1 for others
  - Dent: mean tumor size 3.0 cm for TN v. 2.1 for others
- Association with hereditary susceptibility
  - BRCA1 mutation-associated cancers
  - Haffty: 26% of BCS-treated TN tumors were positive for BRCA mutation v. 1.7% of other subtypes

Epidemiology of TNBC

- Most established risk factors for breast cancer predict for estrogen receptor positive disease
  - Parity
  - Body mass index
  - Exogenous hormone exposure
- Concept: risk of TNBC may be associated with different complex of hereditary, reproductive, and environmental exposures

TNBC Risk Factors

- Women's CARE Study: Ha, Cancer Epi Bio Prev 2009
  - Mammographic density associated with increased risk for TNBC and also non-TNBC
- Carolina Breast Cancer Study: Millikan, BrCaResTr 2008
  - Multiparity; early childbearing; elevated waist-hip ratio associated with increased risk of TNBC
- Cancer Surveillance System (WA): Phipps, Cancer 2008
  - No difference in risk of TNBC vs non-TNBC associated with parity and age at first child-bearing
- Many studies demonstrating complex/mixed associations with limited age categories; weight; parity; and age at first childbearing

TNBC Risk Factors: Why Variation and Inconsistency?

- Triple-negative pattern:
  - Provides selected information regarding markers that these tumors fail to express
  - Provides NO information regarding what they DO express
  - TNBC is not a perfect surrogate for the basal breast cancer subtype
  - TNBC and basal breast cancers may represent a heterogeneous population of tumors
- One fairly consistent pattern: increased frequency of ER-negative/triple-negative/basal patterns among women with African ancestry (African American and African)
  - Opportunity to identify heritable risk factors by studying geographically-defined ancestry

BREAST CANCER IN AFRICAN AMERICANS

- ***Overall lower lifetime incidence***
- Higher mortality
- More advanced stage distribution
- ***Younger age distribution***
- ***Increased frequency of adverse prognostic tumor features***
- ***Higher incidence of male breast cancer***

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

		African American	*White American*
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%

Frequency of ER-Neg Breast Cancer NOT Explained by Stage Distribution: Age-specific incidence rates by ER status and race

A. Non-T4 Patients

B. LABC Patients

C. IBC Patients

ER Positive
African-American
Caucasian

ER Negative
African-American
Caucasian

Incidence Rates per 100,000 woman-years

0.01
0.1
1
10
100

20 30 40 50 60 70 80 90

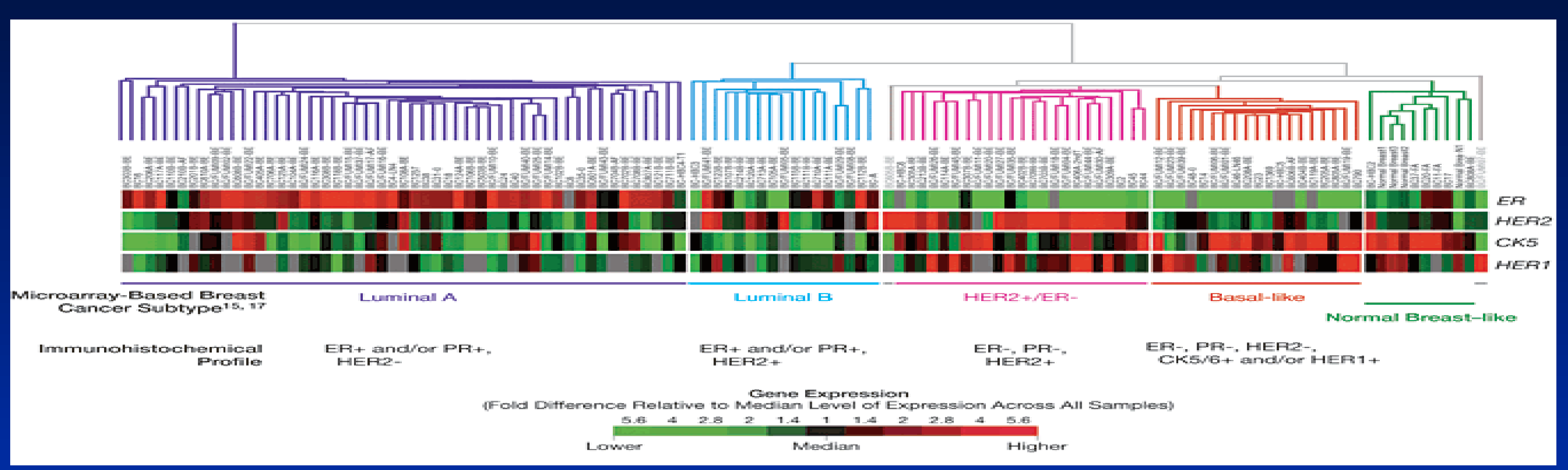
Age-at-Diagnosis

Hance, K. W. et al. J. Natl. Cancer Inst. 2005 97:966-975

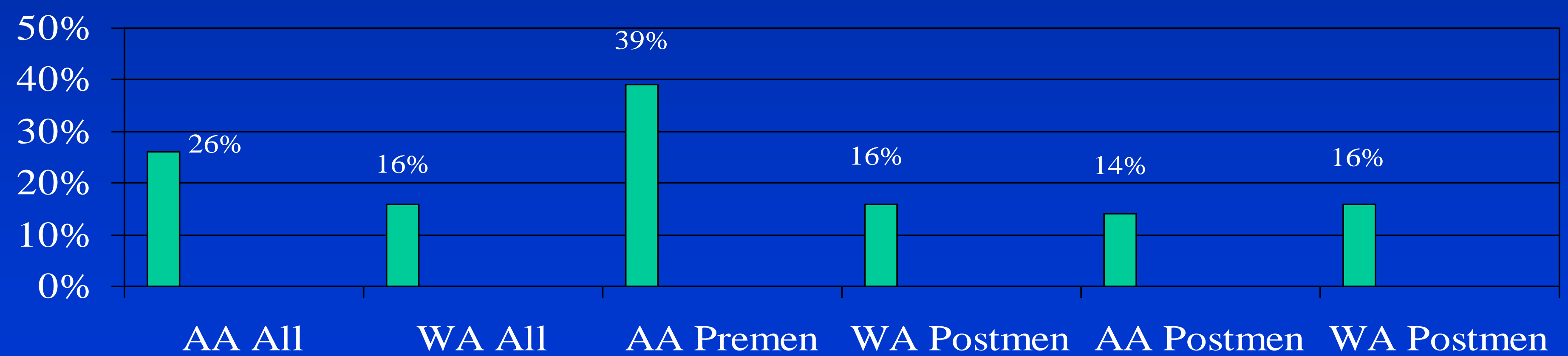
ER-Negative Breast Cancer: International Variations by SES

- Glasgow, Scotland *(Thomson et al, J Epi & Comm Health, 2001)*
  - 35% ER-negative for affluent women compared to 52% ER-negative for impoverished women
  - ER status missing for one-third of cases
- Glasgow, Scotland *(Carnon et al, BMJ 1994)*
  - 51% ER-negative for affluent women compared to 52% ER-negative for impoverished women
- Sweden National Health Care System *(Halmin et al Acta Oncologica, 2008)*
  - 37% ER-negative; no differences by SES
- London, England (Bowen et al Br J Cancer, 2008)
  - 34% ER-neg for British Black women compared to 25% ER-neg for British White women; results unchanged by SES stratification

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.

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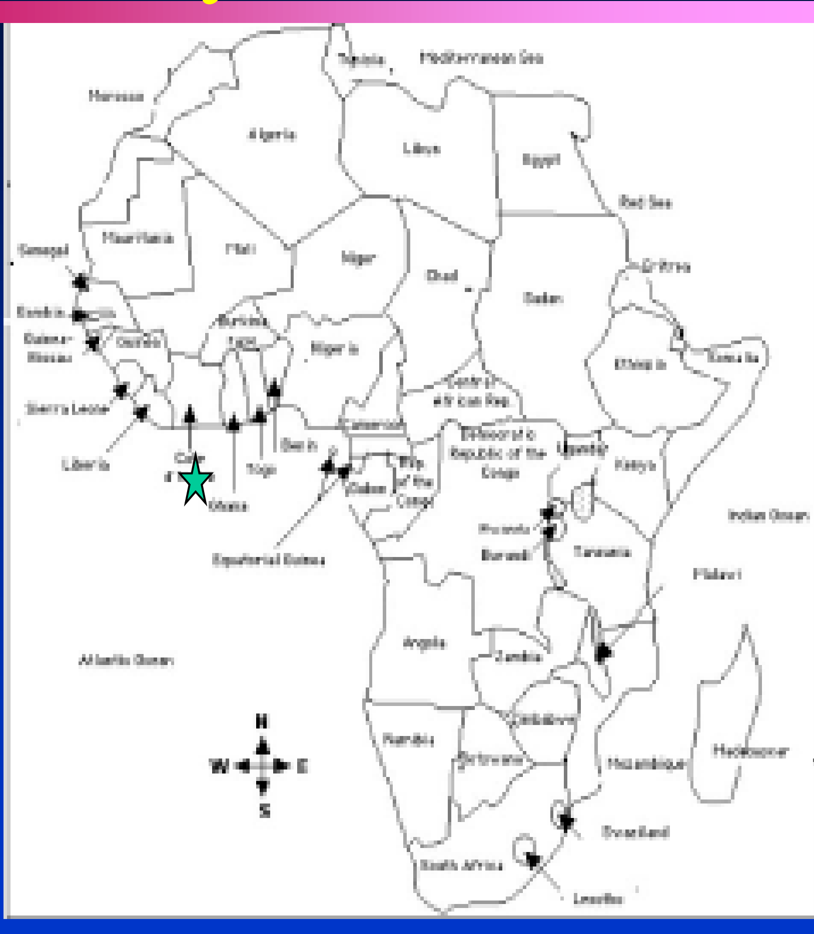
	Dataset/Sample Size	Frequency of Triple-Neg CA		
		AA	WA	P
Carey, 2006	97 premenopausal AA vs 164 premenopausal WA women; Carolina Breast Cancer Study	39%	16%	<0.001
Morris, 2007	2230 Thomas Jefferson Univ Hosp pts; 197,274 SEER pts	20.8%	10.4%	<0.0001
Lund, 2008	Population-based Atlanta GA cohort of 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

Racial/Ethnic Disparities in Triple-Negative Disease

- Implications for Screening
  - Breast CA incidence rates for women <40 (regardless of race/ethnicity) are unlikely to warrant modified mammographic screening recommendations
- Implications for Treatment
  - MDACC study of neoadjuvant CTX for triple-negative tumors (Dahwood et al, JCO Dec 2008)
  - 100 AA; 371 WA/Other
  - No differences in OS at 3years
- Conclusions:
  - Equality in treatment yields equality in outcome, but the treatment must match tumor subtype
  - Early detection is essential, regardless of race/ethnicity and regardless of tumor subtype

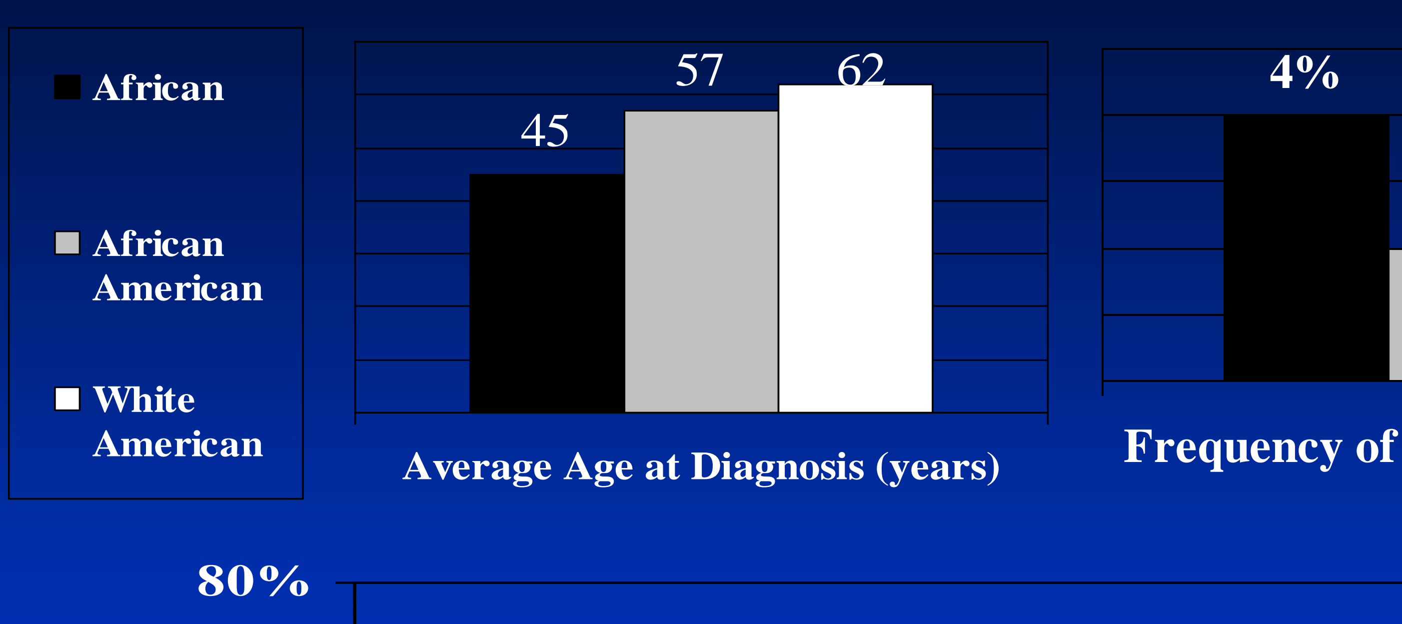
High-Risk Breast Cancer and African Ancestry

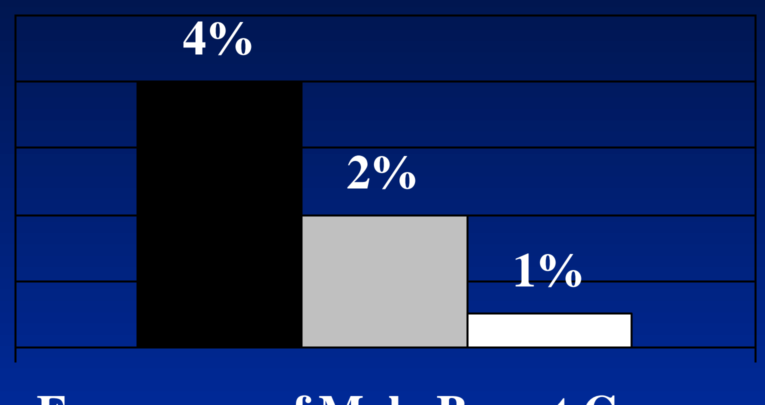
- Parallels between hereditary breast cancer and breast cancer in women with African ancestry
  - younger age distribution
  - increased prevalence of ER-neg, aneuploid tumors
  - higher risk of male breast cancer
- *Is African ancestry associated with a heritable marker for high-risk breast cancer subtypes?*

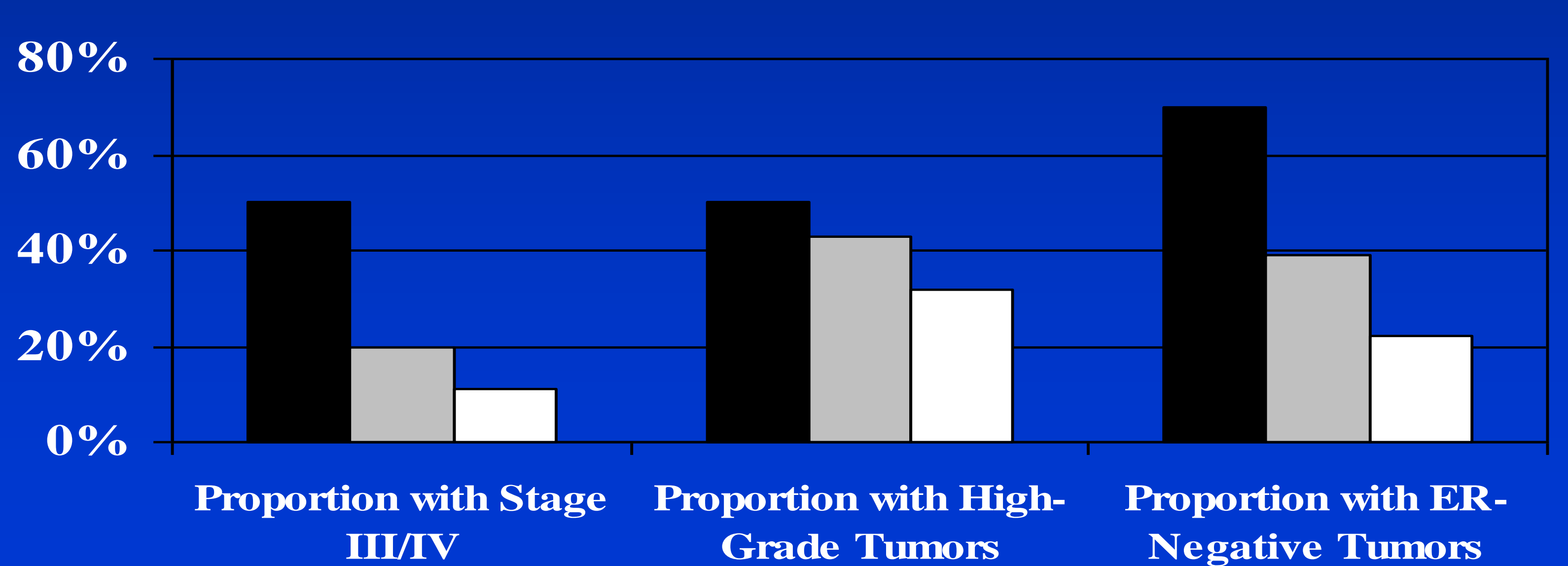


•Unique opportunity to gain insights regarding etiology of breast cancer disparities ***and*** the pathogenesis of triple-negative breast cancer

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







Research Project: UM International Breast Cancer Registry

To systematically evaluate African ancestry as a risk factor for ER/triple-negative, early onset breast cancer

- Multicenter/international study
  - African Americans
  - White Americans
  - Ghanaians
- Document correlation between quantified extent of ancestry (via genotyping) and risk for ER-negative/triple-negative breast cancer (via tumor studies)

UM-Ghana Research Project

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

- **Step 1:** Characterize the breast cancer burden of Sub-Saharan Western Africa
  - Komfo Anoyke Teaching Hospital
  - Kumasi, Ghana
  - Questionnaire data; breast tissue specimens; saliva specimens for DNA extraction/genotyping

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FOR RADIOTHERAPY &
NUCLEAR MEDICINE
KOMFO ANOKYE
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Research Project: UM/Ghana KATH Breast Cancer Registry

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

- **Step 2:** Compare the breast cancer phenotypes of White Americans, African Americans, and Ghanaian African women
  - Henry Ford Hospital, Detroit
  - Komfo Anoyke Teaching Hospital

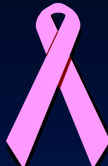
Preliminary Results (in press, *Cancer*)

	HFH WA N=1,008	HFH AA N=581	Ghana N=75	PValue
Mean Age	62.4	60.7	48.0	0.002
Mean Tumor Size	1.95	2.30	3.20	<.001
% Inv Ductal	81.4%	86%	66.7%	<.0001
Grade 3 (%)	29.3%	44.9%	76%	.007

	HFH WA N=1,008	HFH AA N=581	Ghanaian N=75	P-Value
ER Negative	21.9%	36.1%	76%	<.0001
PR Negative	30.1%	44.9%	66.7%	<.0001
HER-2 Neg	76.7%	75.1%	(46/48) 95.8%	<.0001
$ER^-/PR^-/HER2^-$	16.0%	26.4%	(37/45) 82.2%	.<.0001

Patterns Among Locally-Advanced, Grade 3 Tumors

	HFH WA	HFH AA	Ghanaian	P-Value
ER Negative	50.0%	67.4%	77.2%	<.041
PR Negative	60.7%	76.1%	69.2%	0.374
HER-2/neu Negative	46.4%	63.0%	94.7%	<0.01
ER/PR/HER2 Negative	15.4%	41.9%	83.3%	<0.01



Other African Datasets

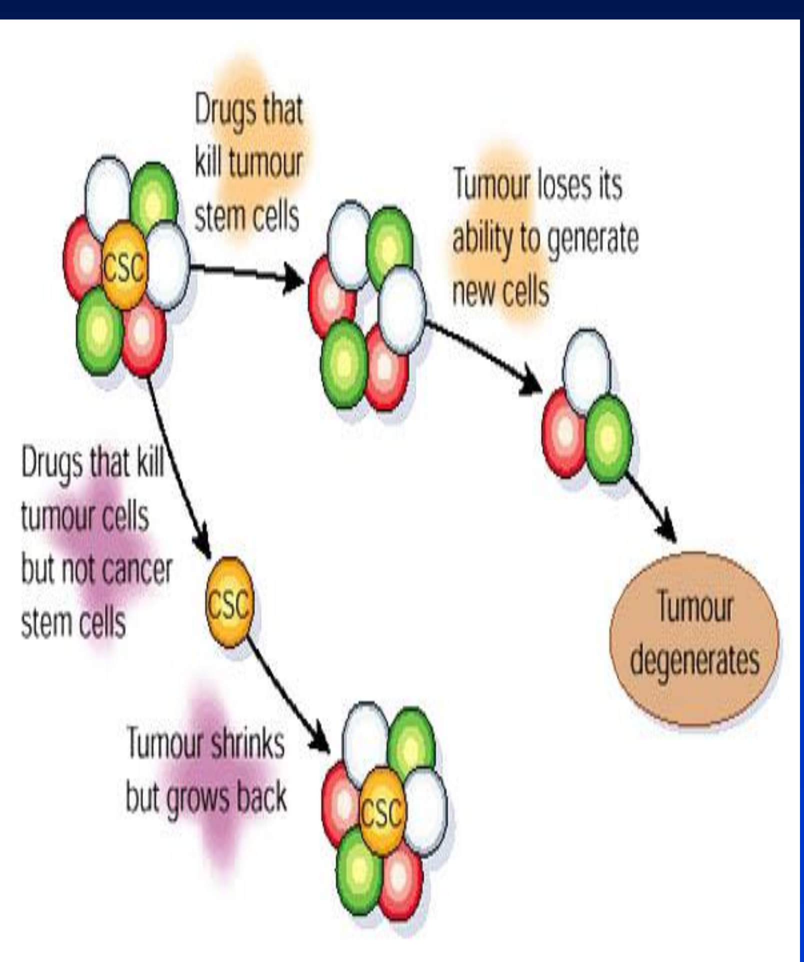
- Huo et al (Olopade) JCO 2009
  - 378 breast cancers from Nigeria and Senegal
  - 1996-2007
  - Mean age 45 yrs
  - 76% ER-negative
  - 73% triple-negative
- Bird et al Ann Surg Onc 2008
  - 120 breast cancers from Kenya
  - 2001-2007
  - Median age 47 yrs
  - 76% ER-negative
  - 44% triple-negative (subset of 34 tumors)

Research Project: UM International Breast Cancer Registry

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

- Step 3: Explore other, novel aspects of tumor biology in women with African ancestry
  - Breast cancer stem cells; EZH2
  - Are there differences in the oncogenic potential of mammary tissue that are associated with African ancestry?

Breast Cancer Stem Cells



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

Cell Stem Cell

C Ginestier, M Wicha, G Dontu, et al

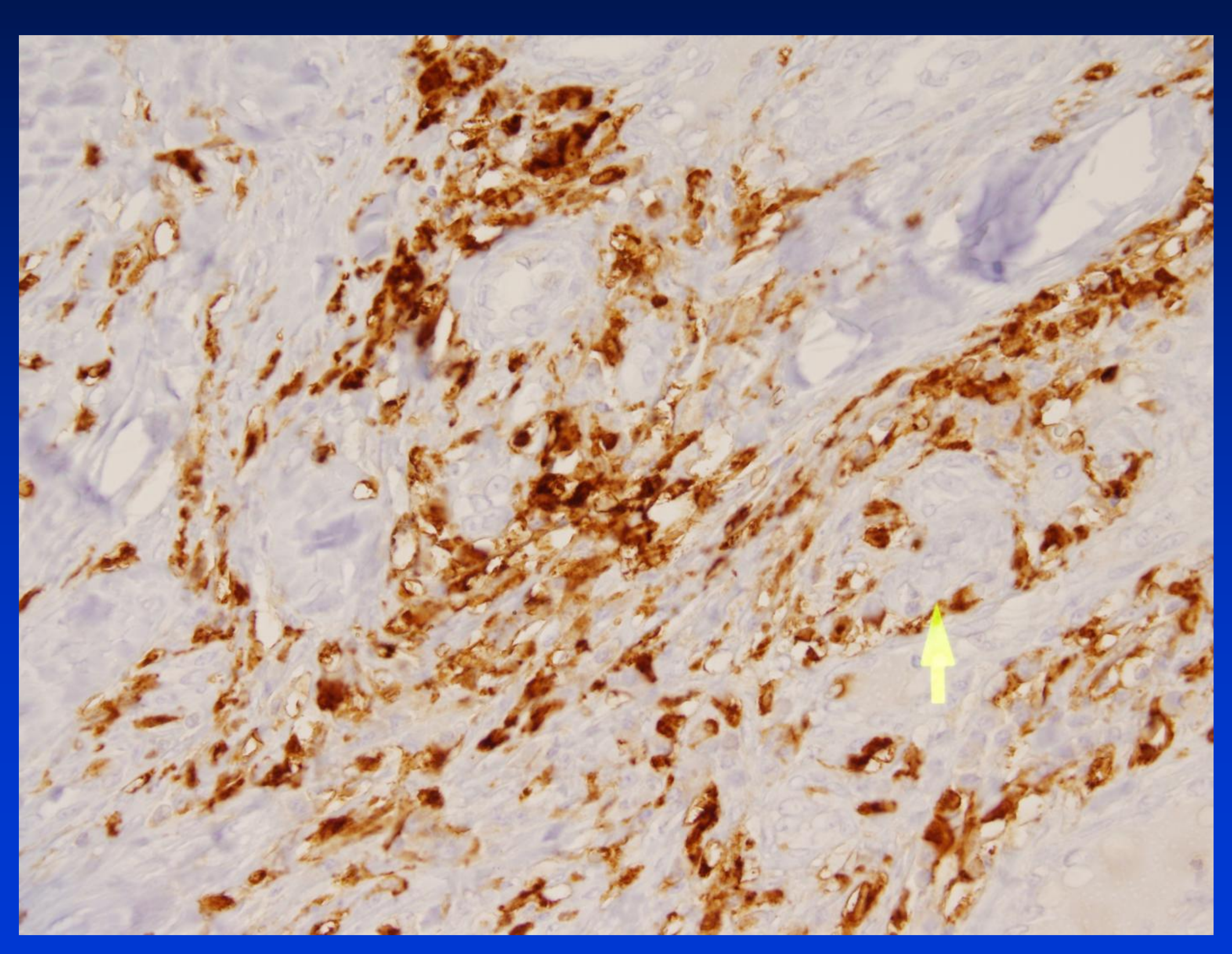
University of Michigan
Laboratoire d'Oncologie Moléculaire, Centre de Recherche en Cancérologie de Marseille, France

November 2007, Pages 555-567

ALDH-1 Staining by Race/Ethnicity

- Ghanaian Cases:
  - 20/23 **(87%)**
- University of Michigan White American cases:
  - 24/146 **(19%)**
- French/European cases:
  - 102/345 **(30%)**
- White American/European ER-negative cases
  - 39/80 **(50%)**
- *Consistent with results in Uganda breast cancer pts (Nalwoga et al, Br J Cancer 2010)*

ALDH1/Breast CA Stem Cell Marker: Ghanaian Breast Cancer Case



Breast Cancer Screening and TNBC Risk

- "Traditional" screening recommendations
  - Annual mammography starting at age 40 years
- Recent controversy based upon USPSTF update on screening recommendations,
  - *Ann Int Medicine November 2009*
  - "USPSTF recommends against routine screening mammography in women aged 40-49 years...The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years."

Screening for Breast Cancer

Study	Age at Entry	Accrual Interval	F/U (yrs)	Mamm Interval	Mam Views	↓Mortality 40-49 yo
HIP	40-49	1963-66	18	12	2	22
Kopperberg	40-49	1977-89	15	24	1	22
Ostergotland	40-49	1978-89	14	24	1	8
Malmo	45-49	1977-90	13	18-24	1,2	28
Edinburgh	45-49	1978-85	13	24	1,2	18
Gothenberg	39-49	1982-84	12	18	1,2	29
Stockholm	40-49	1981-86	11	28	1	5
Canada NBSS	40-49	1980-85	11	12	2	0

Potential for underestimation of mammography benefits

Invitation studies; ITT analysis design

Lack of sophistication in mammography technology

Possible flawed randomization in Canadian trial

USPSTF Update: Background

- Cancer Intervention and Surveillance Modeling Network (CISNET; Mandelblatt et al) and meta-analysis (Nelson et al) commissioned to re-evaluate mammography randomized controlled trials
- Two Modeling Strategies:

Number Needed to Screen to Save One Life by Age
40-49: 1900
50-59: 1300
60-69: 400

Life-Years Gained per 1000 Women Screened
Annual mammography starting at age 40 vs at age 50: median 33 yrs gained (range 11-58)

USPSTF Update: Background

- Two Modeling Strategies:

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Life-Years Gained per 1000 Women Screened

Annual mammography starting at age 40 vs at age 50: median 33 yrs gained (range 11-58)

"If the goal of a national screening program is to reduce mortality in the most efficient manner, then programs that screen biennially from age 50...are among the most efficient... If the goal of a screening program is to efficiently maximize the number of life-years gained, then the preferred strategy would be to screen starting at age 40 years"

USPSTF Comments Regarding "High-Risk" Subsets

- USPSTF states that screening recommendations are intended for "average-risk" women; may not necessarily apply to women with hereditary susceptibility
  - No comment regarding particular racial/ethnic subsets related to population-level risk for early-onset breast cancer
- CISNET authors commented on uncertainties of mammography data for African American women

Implications of USPSTF Recommendations Related to Breast Cancer Disparities

Age-Specific Incidence

AA Inc
WA Inc

per 100,000 population

350
300
250
200
150
100
50
0

30-34 35-39 40-44 45-49 50-54 55-59

Age-Specific Mortality

AA Mort
WA Mort

per 100,000 population

80
70
60
50
40
30
20
10
0

30-34 35-39 40-44 45-49 50-54 55-59

Age (years)

Breast Imaging/Screening and TNBC

- Ko et al, Eur Radiol 2007 and Yang et al, Br Cancer Res Tr 2008: TNBC more likely to present as a mass or asymmetric density without microcalcifications
- Yang et al, Int J Rad Onc Biol Phys 2009: No difference in frequency of TNBC between mammo-occult and mammo-apparent breast cancers
- Ma et al, Cancer Epi Bio Prev 2009: mammographic density associated with risk of both TNBC and non-TNBC
- Dogan et al, AJR 2010: potential added-value of MRI to evaluate TNBC

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