

Race Modifies the Association between Breast Carcinoma Pathologic Prognostic Indicators and the Positive Status for HER-2/*neu*

Azadeh T. Stark, Ph.D.¹
 Sarah Claud, M.P.H.²
 Alissa Kapke, M.S.³
 Mei Lu, Ph.D.³
 Michael Linden, M.D.⁴
 Jennifer Griggs M.D., M.P.H.⁵

¹ Josephine Ford Cancer Center and Department of Pathology, Henry Ford Health System, Detroit, Michigan.

² Division of Cancer Epidemiology and Prevention, Josephine Ford Cancer Center, Henry Ford Health System, Detroit, Michigan.

³ Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, Michigan.

⁴ Department of Pathology, Henry Ford Health System, Detroit, Michigan.

⁵ Department of Medicine, Hematology/Oncology and Department of Community and Preventive Medicine, University of Rochester, Rochester, New York.

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Address for reprints: Azadeh Stark, Ph.D., Josephine Ford Cancer Center, One Ford Place, 5C069, Detroit, MI 48202; Fax: (313) 874-6656; E-mail: astark1@hfhs.org

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BACKGROUND. Inferences about the variations in the biology of breast carcinoma between African-Americans and Caucasians have been reported. The difference in the prevalence of positive HER-2/*neu* breast carcinoma was evaluated and the race-specific risk was assessed for positive HER-2/*neu* among a cohort of women diagnosed with their first primary breast carcinoma, given the accepted prognostic pathologic indicators for positive HER-2/*neu* status.

METHODS. Demographic, clinical, and pathologic data were collected from existing databases. The status of HER-2/*neu* was considered positive if the immunohistochemistry score was 3⁺ or if the fluorescent in situ hybridization indicated a ratio greater than 2. Multivariable logistic regression was used to determine the race-specific risk for HER-2/*neu* positive breast carcinoma.

RESULTS. The difference in the prevalence of HER-2/*neu*-positive status between African-American and Caucasian women was not statistically significant ($P = 0.46$). For Caucasian women the likelihood for positive HER-2/*neu* was statistically significant and increased almost linearly within each stage with nuclear grade dedifferentiation relative to the reference group, women with Stage 1, Grade 1 carcinomas. For African-American women, this risk was not significantly associated with stage, nuclear grade, their interaction term, or other pathologic prognostic indicators.

CONCLUSIONS. The findings suggest that race modifies the association between the pathologic prognostic indicators of breast carcinoma and the likelihood of HER-2/*neu*-positive carcinoma. So far, clinical correlative studies of HER-2/*neu* have not included race as an independent variable. Concerns about the limited generalizability and the need for validation of the findings across racial lines have been expressed previously. *Cancer* 2005;104:2189–96.

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KEYWORDS: HER-2/*neu*, race, ethnicity, African American, Caucasian, breast carcinoma.

The human epidermal growth factor receptor-2 (HER-2/*neu*) is a well-characterized biomarker in the biology of breast carcinoma that has had immediate impact on clinical medicine. The positive status of HER-2/*neu* is associated with a younger age and several adverse prognostic factors, i.e., advanced stage, absence of estrogen and progesterone receptors, metastasis to axillary lymph nodes, and high nuclear grade.^{1–3} In addition, women diagnosed with positive HER-2/*neu* breast carcinoma generally have relative resistance to anthracycline-based chemotherapy, tamoxifen therapy, and have shorter disease-free and overall survival.^{1,4–7}

In general, African-American women are diagnosed with breast

carcinoma at a younger age, with carcinomas of larger size, high nuclear grade, and more axillary nodal involvement.⁸⁻¹² Independent studies support a higher prevalence of estrogen and progesterone receptor-negative carcinomas among African-American women even after adjusting for stage of carcinoma.¹³⁻¹⁵ Furthermore, the disease-free and overall survival of African-American women diagnosed with breast carcinoma has been reported to be shorter relative to Caucasian women.¹⁶⁻¹⁸ These clinical findings suggest that the biology of breast carcinoma potentially varies across racial lines. However, several molecular indices of breast carcinoma biology and their prevalence have been reported to be similar between African-American and Caucasian women.^{19,20} In view of these important observations, we evaluated the prevalence of positive HER-2/*neu* breast carcinoma in a cohort of African-American and Caucasian women diagnosed with invasive breast carcinoma. In addition, we evaluated race-specific risk for positive HER-2/*neu* breast carcinoma given the pathologic prognostic indicators used in clinical settings.

MATERIALS AND METHODS

Setting

Members of the cohort were patients at the Henry Ford Health System (HFHS), the largest healthcare provider in southeastern Michigan. HFHS is a comprehensive, self-contained healthcare system, organized so that persons in the system receive every level of care from preventive and primary to subspecialty services. The majority of patients at the HFHS are insured through the Health Alliance Plan (HAP), which is a large, not-for-profit, mixed model HMO in southeastern Michigan. Electronic data across several departments and centers are readily available only for patients who have insurance through the HAP.

When a patient is first seen at any of the HFHS facilities for any reason, he or she is assigned a permanent and unique lifetime medical record number (MRN) which is entered into the Master Patient Index (MPI). The MPI resides within a larger relational database, the Corporate Data Store (CDS), serving as the central repository for data on patient encounters. Among the other databases within the CDS is information on the date of service, the physician at the clinical encounter, the place of the encounter, and the primary diagnosis. Most of the medical information generated from patient encounters is fed into the Medical Information Management System, which is the electronic version of medical records that contains physician notes, pathology diagnoses, radiology, and clinical laboratory results. Access to the databases is tightly monitored and is restricted to clinical and re-

search staff members. In 2003, over 560,000 people were cared for by HFHS, of whom 35% had declared their racial/ethnic heritage as African-American and 60% as Caucasian. The racial/ethnic heritage of the remaining 5% included Native-Americans, Hispanics, and Asian-American.

The data collection component of this project was exempt from requiring written informed consent because data were collected from already existing databases and no study participant was contacted. The Institutional Review Boards at HFHS approved this study protocol (IRB# 2403). This study is in compliance with the U.S. Congress Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Study Population

We identified members of the cohort who were diagnosed with their first primary breast carcinoma from the tumor registry of the HFHS. The other eligibility criteria were: 1) date of diagnosis no earlier than January 1, 2001, and no later than December 31, 2003; 2) breast carcinoma TNM Stages I-IV; 3) the diagnosis, initial treatment, and follow-up were performed at HFHS, 4) insurance through the HMO plan; and 5) racial heritage of either African-American or Caucasian.

Data Collection

Information on demographic variables (i.e., self-identified race, date of birth, and menopausal status), carcinoma pathologic parameters (i.e., TNM stage, nuclear grade, estrogen and progesterone receptors status, number nodal involvement, and status of HER-2/*neu* overexpression and/or amplification), and date of diagnosis were abstracted from electronic medical records. In 2001, the HFHS implemented an institutional policy that testing for HER-2/*neu* should be a component of diagnostic workup of any woman newly diagnosed with invasive breast carcinoma of any stage. For variables with missing values in electronic medical records, we reviewed hardcopies of medical records. Hardcopies of medical records were ordered through the Central Office of Research and Audit at HFHS. This approach enabled us to retrieve medical records for every study participant.

HER-2/*neu* Assessment and Scoring

Fluorescent in situ hybridization (FISH) and immunohistochemistry were used to assess amplification of the HER-2/*neu* gene and overexpression of its protein, p185 HER-2/*neu*, respectively. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using the HercepTest (Dako, Glostrup, Denmark) according to the manufacturer's

instructions. The DAKO HercepTest is an FDA-approved clinical test that qualitatively identifies by light microscopy p185 HER-2/*neu* overexpression in breast carcinoma cells. The relative overexpression of HER-2/*neu* was scored by a trained pathologist as 0, 1⁺, 2⁺, or 3⁺. The FISH method was performed on formalin-fixed, paraffin-embedded tissue sections using a DNA probe cocktail specific for the HER-2/*neu* gene locus (17q11.2-q12) and an internal control probe for chromosome 17 (CEP 17-D17Z1) (Vysis, Downers Grove, IL). After hybridization cells were scored and the ratio of HER-2/*neu* to CEP17 was calculated by a trained pathologist. The ratio of 2 or greater was considered positive for amplification.

For the purpose of the present study, HER-2/*neu* status was dichotomized as either positive or negative. A woman was classified as negative for HER-2/*neu* if her breast carcinoma tissue section received the designated score value of either 0 or 1; she was classified as positive if the score indicated a value of 3⁺. Specimens that were designated with a score value of 2⁺ for overexpression were further evaluated by the FISH technique. If the amplification ratio was greater than 2, then the study participant was classified as positive for HER-2/*neu*; otherwise, she was classified as negative.

Statistical Methods

We used descriptive statistics to summarize the characteristics of the study population. The variable 'age at the time of diagnosis' was categorized into 6 age groups: younger than 40, 40–49, 50–59, 60–69, 70–79, and 80 and older. Women were classified based on their menopausal status as either pre- or postmenopausal. The menopausal statuses of 12 women were marked as unknown. Axillary nodal involvement was classified into 3 groups: 1) negative for metastasis, 2) positive for metastasis, and 3) nodal metastasis was not evaluated. We classified the status of estrogen, progesterone, and HER-2/*neu* receptors into two phenotypes: positive and negative. Finally, the diagnosis of cancer TNM stage and nuclear grade were classified as I–IV and as 1–3, respectively. Differences in the distribution of these variables between African-American and Caucasian women were evaluated using the Student *t* test, Mantel-Haenszel chi-squared test of significance, and Wilcoxon Signed Rank test as appropriate. Study subjects were then stratified by their racial heritage and the association between the positive HER-2/*neu* status and pathologic and demographic variables were tested using the Spearman rank correlation for continuous variables or Mantel-Haenszel procedure for dichotomous variables. The Spearman rank correlation is the nonparametric statistic for

measure of association. The coefficient (*rho*) value of near unity indicates a good agreement, while a value of almost zero suggests a poor agreement, and a negative value indicates an inverse association. The Mantel-Haenszel statistic is based on 2 × 2 contingency distribution tables.

We applied multivariate logistic regression to determine the variables that are best associated with the risk of a positive HER-2/*neu* status in cancerous lesions of the breast tissue. In developing the best-fitted model, we first estimated the individual effect of each variable and interaction by race on HER-2/*neu* status. Variables were evaluated because of their potential biological impact (TNM stage, nuclear grade, histologic grade, number of axillary nodal involvement, and estrogen and progesterone receptors) or demographic influence (age at the time of diagnosis, menopausal status, and race). Correlations between different variables were estimated and multicollinearity was prevented by including in the model only variables with coefficient values of 0.7 or less.²¹ Variables with a *P*-value < 0.10 from the univariate analyses were considered the candidate variables. Interactions between variables also were tested at *P* = 0.10. The initial model was built using the forward selection approach. The interaction of race with lesion size, TNM stage, nuclear grade, and menopausal status on HER-2/*neu* were statistically significant (*P* < 0.03), and therefore were included in the model. The two variables estrogen and progesterone receptors were highly correlated (*r* = 0.76). Thus, the variable estrogen receptor was included in the final model because of its clinical significance and its biological interaction with HER-2/*neu*. The final model contained only variables that were significant at *P* = 0.05 and a three-way interaction term between TNM stage, nuclear grade, and race/ethnicity that remained significant at *P* = 0.02. All statistical tests were two-sided and analyses were performed using SAS v. 9.1 (SAS Institute, Cary, NC).

RESULTS

We identified 937 women with primary breast carcinoma, Stages I–IV, from the tumor registry at HFHS. After reviewing the medical records, a total of 186 of the members were excluded because: 1) primary carcinoma was diagnosed before 2001 (*n* = 52); 2) referral to HFHS for second opinion (*n* = 41); 3) treatment was not performed at HFHS (*n* = 74); 4) male breast carcinoma (*n* = 3); 5) pathology diagnosis of Stage 0 (*n* = 4); and 6) metastasis to the breast (*n* = 6). For patients presenting with bilateral breast carcinoma (*n* = 15), we included data for the most severe diagnosis. For example, for women with the diagnoses of invasive carcinoma in one breast and carcinoma in situ in

TABLE 1
Demographic Characteristics of the Study Sample and Cancer Pathologic Prognostic Indicators at Initial Clinical Presentation by Race

Variable	African American <i>n</i> = 249	Caucasian <i>n</i> = 502	<i>P</i> value
Age (mean ± SD, yrs) ^a	60 (± 14)	62 (± 13)	< 0.001 ^b
Menopausal status			0.18
Pre	55 (22.4)	90 (18.3)	
Post	191 (77.6)	403 (81.7)	
Unknown	3	9	
Stage at diagnosis			< 0.001 ^c
I	108 (44.4)	271 (56.1)	
II	90 (37.0)	166 (34.4)	
III	20 (8.2)	31 (6.4)	
IV	25 (10.3)	15 (3.1)	
Unknown	9	19	
HER-2/ <i>neu</i> status			0.46 ^d
Negative	170 (68.3)	356 (70.9)	
Positive	79 (31.7)	146 (29.1)	
Estrogen receptor status			< 0.001 ^c
Negative	87 (37.3)	98 (21.0)	
Positive	146 (62.7)	369 (79.0)	
Unknown	16	35	
Progesterone receptor status			< 0.001 ^c
Negative	109 (46.8)	139 (29.8)	
Positive	124 (53.2)	328 (70.2)	
Unknown	16	35	
Tumor grade			< 0.001 ^c
1 Well differentiated	57 (23.7)	165 (34.8)	
2 Moderately differentiated	83 (34.4)	176 (37.1)	
3 Poorly differentiated	101 (41.9)	133 (28.1)	
Unknown	8	28	

^a Mean ± standard deviation in years.

^b Student *t* test.

^c Wilcoxon Rank Test.

^d Mantel-Haenszel chi-squared test of significance.

the other (*n* = 7), data on the prognostic pathologic markers of the invasive lesions were collected. For the remaining eight women with the diagnoses of invasive carcinomas in both breasts, we included data for carcinomas with more advanced TNM stage and/or nuclear grade.

A total of 751 women were eligible to be included in the study. Of those, 33.2% (*n* = 249) had identified their racial heritage as African-American and 66.8% (*n* = 502) as Caucasian (Table 1). On average, African-American women were younger (60 ± 14) than the Caucasian women (62 ± 13) (*P* < 0.001). The proportion of African-American women diagnosed with more advanced stages of carcinoma (III and IV) was almost twofold higher than for Caucasian women (*P* < 0.001). Similarly, the percentage of African-American women (*n* = 101, 42%) diagnosed with poorly differentiated

nuclear grade was higher than Caucasian women (*n* = 133, 28%; *P* < 0.001). The diagnosis of estrogen and progesterone receptor-negative breast carcinoma was more common among African-American women (*n* = 87, 37%, and *n* = 109, 47%) than Caucasian women (*n* = 98, 21%, and *n* = 139, 30%; *P* < 0.001). Finally, about 32% (*n* = 79) of African-American women and 29% (*n* = 146) of Caucasian women were diagnosed with HER-2/*neu*-positive breast carcinomas. This difference did not reach the level of statistical significance (*P* = 0.46).

We stratified the study population by racial heritage and evaluated the association of the HER-2/*neu*-positive status for age and the pathologic prognostic indicators within each stratum. We conducted bivariate logistic regression models to test the interaction between race and each independent variable and the difference between the interactions (Table 2). For African-American women, neither age nor the pathologic prognostic indicators were statistically significant predictors for positive HER-2/*neu* status. In contrast, for Caucasian women these variables were significantly associated with positive HER-2/*neu* status. The differences in the interaction between race and TNM stage (*P* = 0.006), race and nuclear grade (*P* = 0.007), and race and lesion size (*P* = 0.049) were statistically significant.

We also calculated the multivariable race-specific relative risk and 95% confidence intervals (CI) for positive HER-2/*neu* status and the pathologic prognostic markers (Table 3). For Caucasian women, we observed a significant statistical interaction between TNM stage and nuclear grade. Within each TNM stage the risk of positive HER-2/*neu* status increased almost linearly with the degree of nuclear dedifferentiation, although the CI was large because of the relatively small numbers. Women diagnosed with Stage I, Grade 2 breast carcinomas had more than a threefold increased risk (relative risk [RR] = 3.65, 95% CI 1.71–7.79) for positive HER-2/*neu* status compared with the reference group, women with a diagnosis of Stage I, Grade 1 breast carcinoma. The RR increased to 4.81 (95% CI, 2.08–11.1) for women with Stage I, Grade 3 diagnosis. For women diagnosed with TNM Stage II, nuclear Grade 1, the estimated risk increased by almost twofold (RR = 2.30, 95% CI 0.84–6.24) relative to the reference group. For women diagnosed with the same TNM stage but nuclear Grades 2 and 3, the RRs were 3.42 (95% CI 1.52–7.73) and 4.44 (95% CI 2.00–9.86), respectively. The RR for positive HER-2/*neu* status for women who were diagnosed with advanced TNM stages (III and IV) and Grade 2 increased to 11.7 (95% CI 3.86–35.6). This risk was

TABLE 2
Association of Race and Pathologic Prognostic Indicators with Positive HER-2/*neu* Status: Bivariable Logistic Regression Analyses

Prognostic marker	African-American women			Caucasian women			Interaction difference <i>P</i>
	N = 249			n = 502			
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>	
Age	0.99	0.14–2.79	0.57	0.98	0.97–1.00	0.04	0.45
Estrogen receptor	1.56	0.89–2.72	0.12	1.52	0.95–2.43	0.08	0.94
Progesterone receptor	1.72	1.00–2.98	0.05	1.53	1.00–2.34	0.05	0.74
Nuclear grade	1.12	0.79–1.58	0.51	2.05	1.57–2.68	<0.0001	0.007
TNM stage	1.12	0.79–1.60	0.52	2.15	1.60–2.88	<0.0001	0.006
Nodal metastasis	1.20	0.67–2.16	0.54	2.05	1.33–3.14	0.001	0.15
Lesion size	1.06	0.95–1.19	0.29	1.26	1.11–1.42	0.0003	0.049

TABLE 3
Race, TNM Stage, Nuclear Grade and Risk of Positive HER-2/*neu* Status: Multivariable Logistic Regression Analysis^{a,b}

	N	Relative risk	95% CI
African-American women			
TNM Stage 1			
Grade 1	12/25	1.00	—
Grade 2	16/29	0.89	0.34–2.33
Grade 3	7/18	0.67	0.21–2.13
TNM Stage 2			
Grade 1	3/12	0.42	0.10–1.84
Grade 2	11/15	1.24	0.42–3.68
Grade 3	12/36	0.54	0.20–1.45
TNM Stages 3 and 4			
Grade 1	Not enough data	—	—
Grade 2	3/8	0.61	0.13–2.81
Grade 3	14/13	1.76	0.61–5.09
Caucasian women			
TNM Stage 1			
Grade 1	12/113	1.00	—
Grade 2	28/59	3.65	1.71–7.79
Grade 3	19/32	4.81	2.08–11.1
TNM Stage 2			
Grade 1	8/27	2.30	0.84–6.24
Grade 2	19/42	3.42	1.52–7.73
Grade 3	23/41	4.44	2.00–9.86
TNM Stages 3 and 4			
Grade 1	Not enough data	—	—
Grade 2	11/8	11.7	3.86–35.6
Grade 3	11/4	25.1	6.57–95.6

^a Adjusting the other covariates in the model.

^b *P* interaction for stage, grade, and race significant at 0.02.

increased by more than twofold (RR = 25.1, 95% CI 6.57–95.6) when the nuclear grade was classified as poorly differentiated or Grade 3. For African-American women, the risk for positive HER-2/*neu* status was not statistically significant with TNM stage, nuclear grade, or their interaction term or other pathologic prognostic indicators.

DISCUSSION

The results from clinical correlative studies indicate that amplification of the HER-2/*neu* gene and/or overexpression of its protein are associated with the adverse pathologic prognostic characteristic of breast carcinoma, that is, absence of hormone receptors,

high nuclear grade, advanced TNM stage, and younger age.^{22,23} It is well accepted that more African-American women are diagnosed with breast carcinomas with these adverse pathologic characteristics.⁹⁻¹² Therefore, in general, the proportion of African-American women diagnosed with HER-2/*neu*-positive breast carcinoma is expected to be higher than Caucasian women. However, neither the findings from the present study nor from the previous studies suggest any difference in the prevalence of HER-2/*neu*-positive breast carcinomas between African-American and Caucasian women.^{19,20,24} Additional statistical analyses showed that racial heritage modified the risk for positive HER-2/*neu* status breast carcinoma. We do not expect that our findings were confounded by potential biases in clinical assessment of HER-2/*neu* or by differential access to healthcare. In January 2001, the Henry Ford Health System implemented an institutional policy that the assessment of amplification of HER-2/*neu* gene and/or overexpression of its protein, p185 HER-2/*neu*, should be a component of the diagnostic workup of any woman diagnosed with any stage of invasive breast carcinoma. Therefore, by focusing on women who were diagnosed with breast carcinoma after January 2001 we excluded any potential bias in clinical assessment of HER-2/*neu*. Also, because the study population was insured through the same capitated health insurance, the potential socioeconomic bias through limited or no access to healthcare was minimized for this group of women.

Recently, Taucher et al.²⁴ suggested a very small probability of HER-2/*neu* overexpression in breast carcinoma of the subgroup of women diagnosed with estrogen receptor-positive and low or moderate nuclear grade breast carcinoma. Results from the present study also support the low likelihood of HER-2/*neu*-positive breast carcinoma among estrogen receptor-positive and well-differentiated nuclear grade breast carcinoma; however, only for Caucasian women. Our data suggest that race modifies the association between the accepted pathologic prognostic characteristics of breast carcinoma with HER-2/*neu* gene amplification and/or overexpression of its p185 protein. Because of the small number of women in this study, the results presented here are not definitive. Nevertheless, the findings of the present study suggest that pathologic predictive indicators for HER-2/*neu* gene amplification and/or overexpression of its protein may differ for African-American women.

Inferences about the potential biological differences between African-American and Caucasian women are supported by results from independent population-based and clinical studies. Wojcik et al.²⁵ reported survival differences between African-American

and Caucasian women who had equal and free access to healthcare services through the Department of Defense (DoD). Their findings suggested that for African-American women the risk of breast carcinoma mortality relative to the race-specific national average was reduced. However, these women still had about a 50% higher risk relative to Caucasian women who were recipients of DoD health services (RR = 1.45, 95% CI 1.20-1.76). The risk was reduced to 1.41 (95% CI 1.16-1.70) after adjusting for TNM stage and demographic variables. Their finding suggests that equal access to healthcare delivery reduces but does not extirpate the gap in the overall survival between African-American and Caucasian women. Furthermore, the demographic and pathologic prognostic indicators of cancer do not fully explain the differences in treatment outcome of breast carcinoma and survival differences. In a more recent report, Jatoui et al.²⁶ reported that since 1981 the disparity in the age-adjusted breast carcinoma survival had widened between African-American and Caucasian women with equal and free access to the DoD healthcare system. The authors suggested that access to the healthcare system most likely is not the sole reason for the difference in breast carcinoma survival. Griggs et al.²⁷ argue that the disparity in breast carcinoma survival can be partially attributed to the systematic differences in the administration of adjuvant chemotherapy given to African-American women. Findings from their study suggest that African-American women receive lower chemotherapy dose proportion and dose intensity, independent of body weight and white blood cell counts. The association between race and lower chemotherapy dose proportion and dose intensity was strengthened after controlling for potential confounding factors: carcinoma pathology, comorbidities, estimated household income, type of insurance, medical reasons for dose change, and treatment delays, including missed appointments.

Newman et al.¹⁸ proposed a founder mutation effect in the biology of breast carcinoma in African-Americans. This observation has been supported by similarities in the pathologic characteristics of cancerous lesions of the breast among African-American women and women diagnosed with BRCA mutation breast carcinoma and the similarity between breast carcinoma epidemiology of African-American and native African women.¹⁸ Findings from several studies support differences in molecular and genetic perturbations in breast carcinoma of African-American and Caucasian women.²⁸⁻³⁰ Recently, Jones et al.²⁹ reported a fourfold (OR = 4.00, 95% CI 1.77-9.01) increase in the risk of p53 mutation in breast carcinoma of African-American women relative to Caucasians.

The risk remained relatively unchanged (OR = 4.29, 95% CI 1.32–13.94) after adjusting for age, socioeconomic status, severe obesity, and carcinoma pathologic characteristics. Higher levels of constitutively active estrogen receptor $_{\alpha}$ exon 5 Δ and exon 3 Δ and the increased concentration of estrogen receptor $_{\alpha}$ relative to estrogen receptor $_{\beta}$ have been detected in cancerous lesions of the breast of African-American women compared with Caucasian women.³⁰ It has been proposed that the relative changes of estrogen receptor isoforms can potentially modify the estrogen-mediated signaling, which may contribute to the more aggressive biology of breast carcinoma in African-American women.³⁰ Collectively, research supports that improving access to healthcare and improving the quality of care will diminish some of the observed disparity in breast carcinoma survival. However, the presumption of variations in the biology of cancer should not be ignored.

The concern about the limited generalizability of results and the need for validation of the findings across racial lines has been expressed for more than a decade.³¹ We reviewed a large body of clinical literature reporting on the association between HER-2/*neu* gene amplification and/or overexpression of its p185 protein in breast carcinoma. None of these reports included race as an independent variable. Most likely, the low number of African-American participants and the general assumption about the homogeneity of the biology of breast carcinoma across racial lines were the reasons. To our knowledge, this is the first report to suggest that the association between HER-2/*neu* amplification and/or overexpression with adverse pathologic prognostic characteristics of breast carcinoma differs between African-American and Caucasian women. We can only speculate that variation in the biology of breast carcinoma modifies this association. Yet we do not reject the hypothesis that race, a proxy for socioeconomic status, is an intervening factor in the observed differences in the biology of breast carcinoma between the two racial groups of women. It has been suggested that the differences in phenotypic expression of molecular indices of breast carcinoma biology or lack of them is mediated entirely through socioeconomic status.^{32,32}

Despite the passage of more than a decade since the enactment of the Revitalization Act of 1993, the number of African-American women participating in breast carcinoma research is still significantly lower than Caucasian women.^{33,34} This is in contrast to the observation of a comparable number of African-American and Caucasian men participating in prostate carcinoma clinical research.³³ Equal participation of African-American women in breast carcinoma research

is needed for validation of the clinical application of many promising biomarkers.

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