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Association Between Benign Breast Disease in African American and White American Women and Subsequent Triple-Negative Breast Cancer

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IMPORTANCE Compared with white American (WA) women, African American (AA) women have a 2-fold higher incidence of breast cancers that are negative for estrogen receptor, progesterone receptor, and *ERBB2* (triple-negative breast cancer [TNBC]). Triple-negative breast cancer, compared with non-TNBC, likely arises from different pathogenetic pathways, and benign breast disease (BBD) predicts future non-TNBC.

OBJECTIVE To determine whether AA identity remains associated with TNBC for women with a prior diagnosis of BBD.

DESIGN, SETTING, AND PARTICIPANTS This study is a retrospective analysis of data of a cohort of 2588 AA and 3566 WA women aged between 40 and 70 years with a biopsy-proven BBD diagnosis. The data—obtained from the Pathology Information System of Henry Ford Health System (HFHS), an integrated multihospital and multispecialty health care system headquartered in Detroit, Michigan—include specimens of biopsies performed between January 1, 1994, and December 31, 2005. Data analysis was performed from November 1, 2015, to June 15, 2016.

MAIN OUTCOMES AND MEASURES Subsequent breast cancer was stratified on the basis of combinations of hormone receptor and *ERBB2* expression.

RESULTS Case management, follow-up, and outcomes received or obtained by our cohort of 2588 AA and 3566 WA patients were similar, demonstrating that HFHS delivered care equitably. Subsequent breast cancers developed in 103 (4.1%) of AA patients (mean follow-up interval of 6.8 years) and 143 (4.0%) of WA patients (mean follow-up interval of 6.1 years). More than three-quarters of subsequent breast cancers in each subset were ductal carcinoma in situ or stage I. The 10-year probability estimate for developing TNBC was 0.56% (95% CI, 0.32%-1.0%) for AA patients and 0.25% (95% CI, 0.12%-0.53%) for WA patients. Among the 66 AA patients who developed subsequent invasive breast cancer, 16 (24.2%) developed TNBC compared with 7 (7.4%) of the 94 WA patients who developed subsequent invasive breast cancers and had complete biomarker data (P = .01).

CONCLUSIONS AND RELEVANCE This study is the largest analysis to date of TNBC in the context of racial/ethnic identity and BBD as risk factors. The study found that AA identity persisted as a significant risk factor for TNBC. This finding suggests that AA identity is associated with inherent susceptibility for TNBC pathogenetic pathways.

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Incidence of triple-negative breast cancer (TNBC), which is negative for the estrogen receptor (ER), the progesterone receptor (PR), and *ERBB2*, is 2-fold higher in African American (AA) women than in white American (WA) women.[1]

Most TNBC belongs to the inherently aggressive basal subtype and arises from different pathogenetic pathways compared to non-TNBC.[2,3] Benign breast disease (BBD) is associated with increased risk for ER-positive/non-TNBC.[4,5] In this study, we sought to determine whether AA identity is associated with TNBC among a cohort of AA and WA women who were initially diagnosed with BBD.

Key Points

Question Does race/ethnicity affect breast cancer risk among women with benign breast disease?

Findings A review of a cohort comprising 2588 African American (AA) women and 3566 white American (WA) women with biopsy-proven benign breast disease revealed subsequent ductal carcinoma in situ in 30 (1.18%) AA patients and 30 (0.85%) WA patients and subsequent invasive cancer in 73 (2.8%) AA patients and in 111 (3.1%) WA patients. Of the subsequent invasive cancers, triple-negative breast cancer was more common among AA members than among WA members of the cohort (16 [24.2%] vs 7 [7.4%], respectively).

Meaning African American identity is a risk factor for triple-negative breast cancer among women with benign breast disease.

Methods

From January 1 through December 31, 2013, we queried the HFHS Pathology Information System to identify AA and WA women patients aged 40 to 70 years who were diagnosed with BBD by biopsy performed between January 1, 1994, and December 31, 2005. Patients with prior breast cancer were excluded. Patients whose breast cancer was diagnosed within 6 months of BBD biopsy were excluded to avoid including cases of coexisting BBD and cancer.

Self-reported race/ethnic identity, date of birth, and follow-up were obtained from electronic medical records at HFHS. Invasive carcinoma or ductal carcinoma in situ detected during follow-up was recorded as subsequent cancer.

An automated Dako immunostainer was used for ER/PR staining. *ERBB2* immunostaining was performed using HercepTest (Dako). Immunohistochemistry complied with established guidelines.[6,7] Briefly, tumors with less than 1% nuclear staining were scored as ER/PR-negative. *ERBB2* grading (0-3+) was based on the extent of membranous staining: 0 or 1+ was negative; 3+ was positive. Tumors with 2+ staining underwent fluorescent in situ hybridization. Benign breast disease was classified as fibrocystic/proliferative/hyperplasia without atypia, with atypia, or with lobular carcinoma in situ.

Distributions of clinicopathologic variables between AA and WA patients were compared using *t* test, Mantel-Haenszel test, or Wilcoxon rank sum test. Polychotomous multivariable logistic regression evaluated features that are associated with TNBC. Kaplan-Meier methods generated estimates of breast cancer incidence with log-rank *P* values. All statistical tests were 2-sided, and analyses were performed using SAS, version 9.3 (SAS Institute Inc), and known biomarker data.

The Henry Ford Health System (HFHS) Institutional Review Board approved this research, with informed-consent exemption. Data analysis was performed from November 1, 2015, to June 15, 2016.

Results

The study cohort included 2588 AA patients and 3566 WA patients. Mean age at BBD diagnosis was similar: 51.7 years for AA patients and 52.1 years for WA patients ($P = .07$). Mean follow-up was also similar: 10.3 years for AA patients and 10.2 years for WA patients. (There was no follow-up for 36 [1.4%] AA patients and 40 [1.1%] WA patients.) Benign breast disease biopsies evaluated screening mammography abnormalities in 2019 (78.0%) AA patients and 2800 (78.5%) WA patients; 555 (21.4%) AA patients and 748 (21.0%) WA patients underwent biopsy for clinical findings ($P = .47$). More than 90% of each subset had hyperplasia without atypia (2438 [94.2%] in AA patients and 3283 [92.1%] in WA patients). Atypia was more common among WA patients than among AA patients (283 [7.9%] vs 150 [5.8%], respectively; $P = .001$). Three (0.1%) patients in each subset had lobular carcinoma in situ.

Thirty (1.18%) AA patients and 30 (0.85%) WA patients were diagnosed with subsequent ductal carcinoma in situ ($P = .26$) at mean ages of 58.4 years and 61.8 years, respectively ($P = .16$) and at mean follow-up of 6.5 years and 6.1 years, respectively ($P = .64$). The ER was positive in 86.4% of AA ductal carcinoma in situ cases and 88.9% of WA ductal carcinoma in situ cases ($P = .81$). The PR was positive in 77.3% of AA ductal carcinoma in situ cases and 77.8% of WA ductal carcinoma in situ cases ($P = .97$).

Subsequent invasive breast cancer was diagnosed in 73 (2.8%) AA patients and 111 (3.1%) WA patients ($P = .58$) at similar follow-up intervals and mean ages (**Table 1**). Approximately half of each subset was diagnosed with stage I disease. Triple-negative breast cancer was detected in 3 times as many AA patients as in WA patients (16 [24.2%] vs 7 [7.4%], respectively; $P = .01$) with subsequent invasive breast cancer (**Table 2**).

Polychotomous logistic regression (performed on 157 cohort members who developed subsequent breast cancer) revealed that AA identity and high-grade disease were the 2 statistically significant features associated with TNBC. African American identity remained significantly associated with TNBC after adjusting for tumor grade. Among those who developed invasive breast cancer, the odds of TNBC vs ER/PR-positive/HER2-negative was 4.34 times (95% CI, 1.28-14.68; $P = .02$) higher in AA patients than in WA patients.

Kaplan-Meier risk estimates are shown in the **Figure**. There were no significant differences between AA patients and WA patients when all phenotypes were grouped together (log-rank $P = .45$), with an estimated 10-year incidence of 2.5% (95%

Table 1. Clinicopathologic Characteristics of Patients Diagnosed With Subsequent Invasive Breast Cancer[a]

Variable	No. (%) African American Patients (n = 73)	No. (%) White American Patients (n = 111)	*P* Value
Age at diagnosis of breast cancer, mean (SD)	61.6 (9.4)	61.9 (9.2)	.73
Length of time between diagnosis of BBD and breast cancer, mean (SD), y	6.9 (4.4)	6.2 (3.8)	.23
Estrogen receptor			
Positive	49 (70.0)	90 (83.3)	.04
Negative	21 (30.0)	18 (16.7)	
Missing	3	3	
Progesterone receptor			
Positive	43 (65.6)	85 (79.2)	.009
Negative	27 (34.4)	22 (20.8)	
Missing	3	4	
ERBB2			
Positive	9 (13.6)	17 (17.9)	.47
Negative	57 (86.6)	78 (82.1)	
Missing[a]	7	16	
AJCC stage			
IA	21 (20.8)	30 (21.6)	.77
IB	24 (23.8)	39 (28.0)	
IIA	9 (8.9)	11 (7.9)	
IIB	11 (10.9)	20 (14.3)	
IIIA	3 (3.0)	4 (2.9)	
IIIC	1 (1.0)	0	
IV	2 (2.0)	5 (3.6)	
Missing	2	2	
Histologic grade			
1	13 (18.8)	30 (27.8)	.08
2	29 (42.0)	48 (44.4)	
3	27 (39.1)	30 (27.8)	
Missing	4	3	

Abbreviations: AJCC, American Joint Committee on Cancer staging system; BBD, benign breast disease.

[a] *ERBB2* testing is not routinely performed for cases of ductal carcinoma in situ; it became a standardized component of invasive breast cancer biomarker assays at the Henry Ford Health System in 2001.

Table 2. Distribution of Phenotypes Among Patients Who Developed Subsequent Invasive Breast Cancer

Subtype	No. (%) African American Patients (n = 66)	No. (%) White American Patients (n = 94)	*P* Value
ER^+ and/or PR^+, $ERBB2^-$	41 (62.1)	70 (74.5)	.01
ER^+ and/or PR^+, $ERBB2^+$	6 (9.1)	11 (11.7)	
ER^-, PR^-, $ERBB2^+$	3 (4.5)	6 (6.4)	
ER^-, PR^-, and $ERBB2^-$	16 (24.2)	7 (7.4)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

CI, 1.9%-3.2%) and 3.2% (95% CI, 2.6%-4.0%), respectively. Most subsequent invasive breast cancers were non-TNBC for both AA and WA patients; however, risk of subsequent TNBC was significantly higher for AA patients than for WA patients (log-rank $P = .004$), and risk of subsequent non-TNBC was higher for WA patients than for AA patients (log-rank $P = .048$). Ten-year estimates for incidence of TNBC were 0.56% (95% CI, 0.32%-1.0%) and 0.25% (95% CI, 0.12%-0.53%) for AA patients and WA patients, respectively. Ten-year estimates for incidence of non-TNBC were 1.76% (95% CI, 1.27%-2.43%) and 2.85% (95% CI, 2.30%-3.55%) for AA patients and WA patients, respectively.

Discussion

Triple-negative breast cancer has become a surrogate for the aggressive basal breast cancer subtype in clinical practice,[2] is a marker of hereditary breast cancer susceptibility, is more common among AA women, and has different risk factors. Multiple pregnancies, for example, reduce the likelihood of developing ER-positive breast cancer, but multiparity appears to increase the risk of TNBC.[2]

Benign breast disease that results in multiple biopsies is a well-established breast cancer risk factor and is a key element of

the Gail individualized breast cancer risk-assessment model.[8] Benign breast disease without atypia approximately doubles breast cancer risk.[9] Histopathologic indices of abnormal proliferation confer higher risks: 4- to 5-fold relative risk for atypia and 10-fold relative risk for lobular carcinoma in situ.[9-11] Several studies have confirmed that BBD is a breast cancer risk factor in both AA and WA women.[12,13]

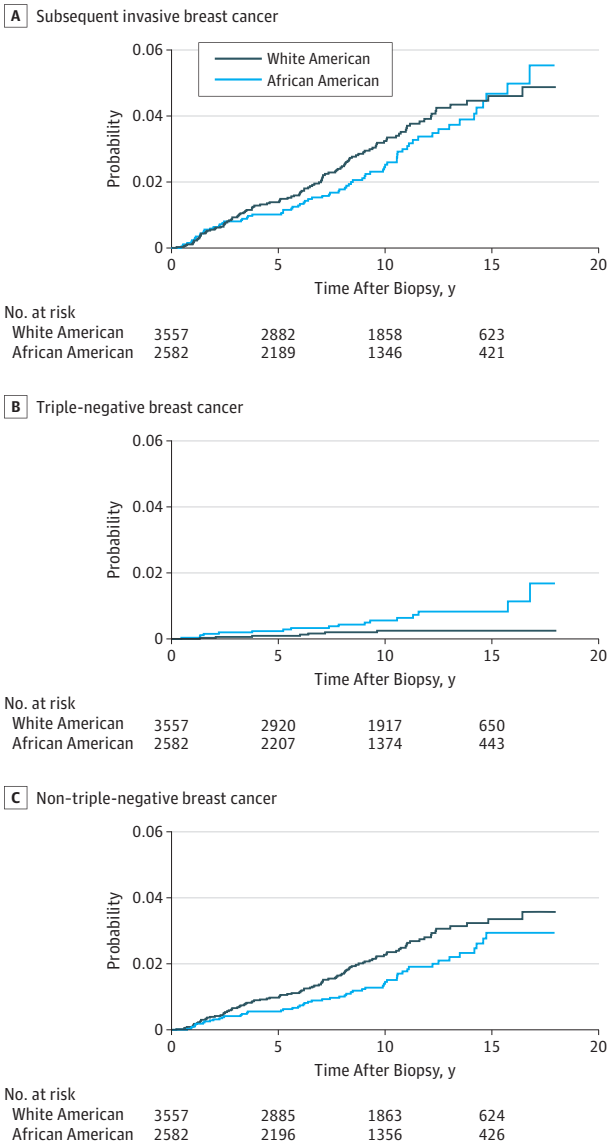
Until recently, studies that correlate BBD with breast cancer risk grouped all phenotypes together. Insights regarding the diversity of breast cancer prompted scrutiny of BBD and phenotype-stratified risk. One model of breast cancer pathogenesis suggests that fibrocystic proliferative changes are precursors for relatively more indolent patterns, including ER-positive disease.[3] The Mayo Clinic BBD cohort demonstrated that 84% of 1273 cancers detected among more than 13 000 BBD cases were ER-positive.[4] Similarly, the Cancer and Steroid Hormone Study found that BBD was associated with increased risk for luminal A breast cancer but not hormone receptor–negative or TNBC disease.[5]

The etiology of the association between TNBC and AA identity is poorly understood, but environmental, reproductive, and genetic factors have been proposed.[14] The contribution of germline genetic factors is supported by studies that demonstrated an increased frequency of TNBC among western sub-Saharan African women, a population likely to have shared ancestry with AA women as a consequence of the colonial transatlantic slave trade.[14,15]

Although the majority of cancers that developed in our cohort of AA and WA patients with BBD were ER positive, AA identity was a statistically significant risk factor for TNBC. This finding suggests that African ancestry is not only associated with a woman's inherent susceptibility for pathways to developing TNBC but also relevant in discussions of chemoprevention.

As an integrated health care system, HFHS is well suited to study breast cancer disparities because it comprises multiple facilities and hospitals that provide care to large indigent as well as affluent populations in diverse communities of metropolitan Detroit and southeast Michigan; it also offers a robust employee-based insurance plan (Health Alliance Plan). Our study revealed that HFHS's AA and WA patients with BBD received or obtained similar care management, follow-up, and outcomes, providing evidence that the health care system delivers equitable quality of care.

Figure. Rates of Subsequent Breast Cancer for African American and White American Patients, by Phenotype



A, Probability of subsequent invasive breast cancer after benign breast disease (log rank, $P = .45$). B, Probability of triple-negative breast cancer after benign breast disease (log rank, $P = .004$). C, Probability of non–triple-negative breast cancer after benign breast disease (log rank, $P = .048$).

Conclusions

To our knowledge, this study is the largest report on TNBC in the context of racial/ethnic identity and BBD as risk factors. We acknowledge the limitation of self-reported race/ethnicity; future research will attempt to account for admixture and risk factors, such as obesity and family history. We hope that our observations will be reevaluated in other communities.

ARTICLE INFORMATION

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Rockville, Maryland (Patriotis); Fox Chase Cancer Center, Philadelphia, Pennsylvania (Engstrom).

Author Contributions: Drs Newman and Stark had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Newman, Stark, Chitale, Pepe, Worsham, Nathanson, Miller, Patriotis, Engstrom.
Acquisition, analysis, or interpretation of data: Newman, Stark, Chitale, Pepe, Longton, Worsham, Nathanson, Miller, Bensenhaver, Proctor, Swain, Engstrom.
Drafting of the manuscript: Newman, Stark, Worsham.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Newman, Stark, Pepe, Longton.
Administrative, technical, or material support: Newman, Stark, Chitale, Nathanson, Miller, Proctor, Patriotis, Engstrom.

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REFERENCES

1. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst*. 2015;107(6):djv048.

2. Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer. *Ann Surg Oncol*. 2015;22(3):874-882.

3. Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, Marchió C, Reis-Filho JS. Breast cancer precursors revisited: molecular features and progression pathways. *Histopathology*. 2010;57(2):171-192.

4. Visscher DW, Frost MH, Hartmann LC, et al. Clinicopathologic features of breast cancers that develop in women with previous benign breast disease. *Cancer*. 2016;122(3):378-385.

5. Gaudet MM, Press MF, Haile RW, et al. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. *Breast Cancer Res Treat*. 2011;130(2):587-597.

6. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Oncol Pract*. 2010;6(4):195-197.

7. Wolff AC, Hammond ME, Hicks DG, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.

8. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

9. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353(3):229-237.

10. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast—risk assessment and management options. *N Engl J Med*. 2015;372(1):78-89.

11. King TA, Pilewskie M, Muhsen S, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. *J Clin Oncol*. 2015;33(33):3945-3952.

12. Worsham MJ, Abrams J, Raju U, et al. Breast cancer incidence in a cohort of women with benign breast disease from a multiethnic, primary health care population. *Breast J*. 2007;13(2):115-121.

13. Cote ML, Ruterbusch JJ, Alosh B, et al. Benign breast disease and the risk of subsequent breast cancer in African American women. *Cancer Prev Res (Phila)*. 2012;5(12):1375-1380.

14. Newman LA. Disparities in breast cancer and African ancestry: a global perspective. *Breast J*. 2015;21(2):133-139.

15. Jiagge E, Jibril AS, Chitale D, et al. Comparative analysis of breast cancer phenotypes in African American, white American, and West versus East African patients: correlation between African ancestry and triple-negative breast cancer. *Ann Surg Oncol*. 2016;23(12):3843-3849.