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Benign breast disease and the risk of subsequent breast cancer in African American women

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Abstract

Benign breast disease (BBD) is an established risk factor for breast cancer among Caucasian women, but less is known about BBD in African American (AA) women. As AA women suffer from disproportionate mortality due to breast cancer, special focus on pathological characteristics that may influence disease risk is warranted.

Benign breast biopsies from AA women were identified by the University Pathology Group in Detroit, Michigan. AA women age 20 to 84 who underwent a breast biopsy from 1997 to 2000 were eligible for the study. Subsequent breast cancers were identified through a linkage with the Detroit SEER program. The first biopsy was reviewed by the pathologist, and lesions were classified following Dupont and Page criteria along with involution and other histologic features. Logistic regression was used to estimate the risk of developing a subsequent breast cancer with the histologic characteristics of BBD.

1,406 BBD biopsies from AA women were included in this study with a median follow-up of 10.1 years. The majority (68%) showed non-proliferative disease, 29% had proliferative disease without atypia, and 3% had proliferative disease with atypia. Subsequent incident breast cancers occurred in 55 women (3.9%). Women whose biopsies showed proliferative disease with atypia were over three-fold more likely to develop breast cancer as women who had non-proliferative disease (RR 3.29, 95% C.I. 1.21-8.93).

Better characterization of the risk of breast cancer among women with BBD, considering both ethnicity and detailed molecular findings, can lead to better surveillance, earlier diagnosis, and, potentially, improved survival.

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Background

Breast cancer (BrCa) is the most common cancer diagnosed in women in the United States, and the second leading cause of cancer-related deaths.(1) Racial disparities exist in both incidence and survival. In particular, African American (AA) women are at significantly greater risk of developing early onset BrCa (<35 years at diagnosis) and have poorer survival when compared to Caucasian women (1). The survival disparity can be partially explained due to a larger proportion of AA women being diagnosed at advanced stages of disease , with hormone receptor negative tumors, and tumors that display an aggressive histology type (2). There is a need to better understand the risk factors that may be unique to the AA population and that can identify high risk women who can benefit from closer surveillance, earlier diagnosis, and, ultimately, improved survival.

It is well established that Caucasian women with a history of benign breast disease (BBD) are at an increased risk for developing BrCa (3-7), but less is known about the risk of BrCa associated with BBD in AA women. Further classification of BBD show that there are distinct pathological features associated with higher BrCa risk. The classification system developed by Dupont and Page(8) is commonly used to examine BBD and BrCa risk, and consists of three categories: non-proliferative disease, proliferative disease without atypia, and proliferative disease with atypia, with the latter being associated with the highest risk of developing BrCa. Additional pathologic features such as columnar alterations, sclerosing adenosis, radial scars, lobular involution, and intraductal papillomas have also been associated with BrCa risk to varying degrees in mostly Caucasian populations (9-15).

AA and Caucasian populations differ with respect to several established risk factors for BrCa. AA women tend to have an increased body mass index, higher rates of obesity, higher parity, earlier age at first birth, and lower rates of breast feeding than Caucasian women (2, 12). These differences are hypothesized to affect the amount and duration of estrogen exposure, which may be linked to aggressive disease and poorer survival. It follows that risk factor differences might also play a role in the characteristics and development of BBD. The goal of this study is to determine if BBD is a similar risk factor for AA women, will increase our understanding of how BrCa develops in this population, and may help identify high risk women who could benefit from increased surveillance.

Methods

After receiving institutional review board approval, benign breast biopsies from AA women were identified from a database maintained by the University Pathology Group (UPG) in Detroit, Michigan. The UPG provides pathology services to eight general or specialty hospitals in the region, including those in the center of the city: Detroit Receiving Hospital, Harper University Hospital, Hutzel Women's Hospital, Sinai Grace Hospital and Karmanos Cancer Institute. AA women age 20 to 84 who underwent a breast biopsy at one of these institutions from 1997 to 2000 were eligible for the study. Exclusion criteria included: a history of invasive or in situ breast carcinoma prior to, or within six months, of the BBD biopsy, unilateral or bilateral mastectomy prior to or at diagnosis, prior breast reduction surgery, lipoma, fat necrosis, epidermal cysts, hematoma, accessory structure, phyllodes tumor, or a lymph node biopsy with no breast tissue.

Histology Review

The first biopsy, either core, excisional, or lumpectomy, with a diagnosis of BBD was reviewed by the blinded study pathologist (R.A-F.) using the original H&E slides. The study pathologist reviewed any questionable cases with the collaborating pathologist at the Mayo

clinic (D.W.V.), as well as a random sample of cases, with 10% of all cases receiving double review and discussion until consensus was reached. Lesions were classified based on the criteria developed by Dupont and Page (8) into three categories: non-proliferative disease, proliferative disease without atypia, or proliferative disease with atypia. The presence or absence of the following pathological features were also assessed for each biopsy: apocrine metaplasia, ductal hyperplasia, lobular hyperplasia, evidence of cysts, duct ectasia, fibrosis, intra-ductal papilloma, sclerosing adenosis, mucocele-like tumor, and columnar alteration. Additionally, the degree of atrophy was classified into three categories: none, 1 to 74 percent of the sample (partial involution), and 75 percent or greater (complete involution).

Follow-up

Information on the subsequent development of breast cancer was obtained from the Metropolitan Detroit Cancer Surveillance System (MDCSS), part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. The MDCSS is a population based cancer registry that collects incidence and follow-up information on all cancer cases diagnosed in the metropolitan Detroit area (Macomb, Oakland, and Wayne counties). The MDCSS catchment area covers the same geographic region that the UPG serves. Name, date of birth, and social security number were used to match records between the data sources, and follow-up data were available through the end of 2009. Follow-up information was also gathered by matching case information to the University Pathology Group's database. This database houses information on all specimens sent to the University Pathology Group, and contains detailed information on pathological findings.

Statistical Analysis

The distribution of pathologic characteristics of the breast biopsies were described using percentages. Associations between the histologic characteristics of BBD and the risk of developing a subsequent breast cancer were estimated using logistic regression to calculate relative risk ratios and 95% confidence intervals. Models were adjusted for age and year at biopsy and then stratified by age at biopsy (age less than 50 versus age 50 and over). In addition, standardized incidence ratios (SIR) and 95% confidence limits were calculated using data from the MDCSS database for AA women with breast cancer as reference, taking into account age at biopsy (in 5 year age groups) and calendar year. These analyses were completed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

The pathologic characteristics of BBD in our study were compared to those reported in the Mayo Clinic BBD cohort, which was originally described by Hartmann et al.(3) This cohort now includes 9,087 primarily Caucasian women who were diagnosed with BBD between the years 1967 to 1991 and were followed for a median duration of 18.7 years for a subsequent diagnosis of BrCa. Differences in the distribution of age at biopsy, involution, and overall impression between these two cohorts were assessed by using the 2-sample test for equality of proportions with a continuity correction (prop.test function) in the R statistical package (R version 2.8.0).

Results

A total of 1,406 eligible women were included in this study. The mean age at biopsy was 48.6, and approximately half the samples were from excisional biopsies (N=696, 49%). Based on the re-review, 965 (68%) showed non-proliferative disease, 407 (29%) had proliferative disease without atypia, and 44 (3%) had proliferative disease with atypia (Table 1). Subsequent incident breast cancers for 55 women (3.9%) were reported in the MDCSS database. The mean age at cancer diagnosis was 59.5, and the mean time from biopsy to BrCa diagnosis was 6.4 years. Overall, there was approximately a 50% increase in risk for

developing a subsequent breast cancer for the entire cohort compared to other AA women in the MDCSS (SIR=1.55, 95% C.I. 1.14-1.99, data not shown).

Table 2 describes the association between pathologic characteristics of the benign breast biopsies and subsequent BrCa development. Women whose biopsies were classified as having proliferative disease with atypia were over three times more likely to develop a subsequent breast cancer as women who had non-proliferative disease (RR=3.29, 95% C.I. 1.21-8.93). In addition, women with biopsies that displayed columnar alterations were associated with an increased risk for developing a subsequent breast cancer (RR=1.84, 95% C.I. 0.99-3.39), although this risk was only marginally statistically significant ($p=0.05$). Degree of involution was associated with a non-statistically significant reduction in risk of BrCa (RR=0.75, 95% CI: 0.37-1.55 for partial involution and RR=0.84, 95% CI: 0.34-2.07 for complete involution). When stratified by age at biopsy, proliferative disease with atypia for both age groups remained elevated but were no longer statistically significant (Supplemental Table 1). Women who were less than age 50 at biopsy and had columnar alterations (RR=2.26, 95% CI: 0.99-5.17) or cysts (RR=2.22, 95% CI: 1.02-4.85) were associated with an increased risk for developing a subsequent breast cancer, while women age 50 and greater were not (RR=1.30, 95% CI: 0.51-3.32 and RR=0.77, 95% CI: 0.34-1.72, respectively).

Compared to the women in the Mayo Clinic BBD cohort, AA women in the Detroit cohort were younger at biopsy and had less lobular involution (for the category complete involution, 19.1% in Detroit versus 21.9% in Mayo Clinic, $p=0.03$). Yet AA women had similar percentages of proliferative disease with atypia (3.2% in Detroit versus 3.7% in Mayo Clinic, $p=0.35$), (Table 3). The median time from BBD diagnosis to BrCa was 6.1 years for AA in Detroit, less than the 10.7 years in the mostly Caucasian Mayo Clinic BBD cohort, although this may be a function of fewer years of follow up time in Detroit versus a true biological difference.

Discussion

We report an association between BBD and an increased risk for developing a subsequent BrCa in AA women. Women who had proliferative disease with atypia were at the greatest risk, and the magnitude of this association is similar to those reported in primarily Caucasian populations (3, 6, 13). Biopsies showing columnar alterations were also associated with an increased risk of BrCa, primarily among younger AA women. Although there are conflicting reports regarding columnar alterations as a risk factor for BrCa, the current findings agree with results from studies done in primarily Caucasian populations (6, 10). Since columnar alterations are highly correlated with proliferative disease, it would be ideal to examine independent effects. Unfortunately, there weren't enough cases in this study to stratify by the presence of atypia. Unlike other reports (3, 6, 13), we did not see an association for proliferative disease without atypia and subsequent breast cancer risk, but this may be a function of sample size versus a true null association.

Our findings among AA women with prior benign breast biopsies and incident breast cancers suggest that results from the Mayo BBD Cohort study are likely to apply to AA populations. In fact, the SIR of 1.55 identified in our cohort is nearly identical to the findings reported by Hartmann et al. (RR=1.56, 95% CI: 1.45-1.68).[3] These findings also support previous work by Worsham et al. (16, 17) that showed the association between BBD and BrCa risk did not vary by race. AA women in our study were significantly younger when diagnosed with BBD and had less lobular involution than other reports of BBD in Caucasian populations. This is consistent with the epidemiology of BrCa in AA women, where BrCa is diagnosed at a younger age. Since involution is in part a function of the aging

process (18), it follows that there would be a smaller degree of involution in this population as well. Despite the younger ages at the time of the biopsy, the proportion of cases with proliferative disease was very similar for both populations. This suggests that breast changes happen at an accelerated rate in AA women or are modified by other factors (e.g. BMI or parity) that we could not evaluate in this study.

The distribution of cases within the 3 Dupont and Page categories were nearly identical between the Detroit cohort and the Mayo clinic cohort. In comparison, the proportion of non-proliferative disease and proliferative disease without atypia between the Detroit cohort and the Henry Ford Health system cohort reported by Worsham, et al (16) differed (non-proliferative disease: 67.8% in the Detroit cohort versus 38.5% in the Henry Ford cohort). The difference may be due to pathological interpretation, which is reduced in the Detroit and Mayo cohorts because of joint training and discussion of a subset of cases. It may also be due to differences in the years included in the cohort and the indication for biopsy. The Henry Ford Health system cohort included biopsies between 1981-1994, whereas the Detroit cohort was from 1997-2000, when more needle biopsies were being performed.

The association with breast cysts and the development of subsequent breast cancer in younger AA women may be unique to the AA population. While most published literature suggests cysts are non-proliferative lesions that aren't associated with future breast cancer risk (9, 19), the report from Worsham et. al. (17), in a racially diverse population, also showed the presence of cysts to be associated with a significant increase in breast cancer risk. This finding warrants further investigation among AA women.

Aside from lack of behavioral risk factor information, there are other limitations in this work that should be considered. The logistic regression results used women with non-proliferative disease as the reference group. Since women with non-proliferative disease are at an increased risk of breast cancer (3), the relative risks presented are likely an underestimate of the risk compared to the general population. This study is also limited by the small number of subsequent BrCa events. A larger cohort of BBD in AA women is needed to fully examine risk stratified by age and to examine some of the less frequent pathologic categories. Additionally, this study lacked breast density data, which would allow for a more detailed assessment of the independent effects of BBD.

This study does have some notable strengths, including an adequate sample size to estimate risk of BrCa after a diagnosis of BBD in AA women. In addition, the pathological characterization was standardized with the Mayo cohort, allowing us to compare study populations. There was standardized pathology review using up-to-date criteria, and including less described features such as involution, and the original pathologist working with the Mayo cohort (D.W.V.) trained the Detroit pathologist (R.A.F.) during her residency and has continued to provide consultation over the last decade. Lastly, follow up continues in this cohort, and will be expanded to additional BBD cases.

In conclusion, we report risk estimates for AA women with benign breast biopsies showing proliferative disease with atypia and increased breast cancer risk. While these pathological characteristics appear to result in similar risk profiles as those seen among Caucasian women, it is likely other factors vary with respect to predictive potential. For example, while the Breast Cancer Risk Assessment tool has been integrated into clinical practice, the CARE model appears to be more appropriate for AA women. The CARE model used data from 3,283 African American women enrolled in a case-control study and race-specific SEER rates to estimate relative and population attributable risks, and was validated using data from African American women in the Women's Health Initiative (for post-menopausal women) and the STAR trial (20). While the CARE model is reported to provide a better risk

assessment for African American women, it underestimates the risk associated with previous breast biopsies in this population (20). Better characterization of the risk of breast cancer among women with BBD, considering both ethnicity and detailed molecular findings, can lead to better surveillance, earlier diagnosis, and, ultimately, improved survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical characteristics of benign breast biopsies among African Americans from the University Pathology Group in Detroit, MI from 1997-2000.

Characteristic	N (%)
Age at biopsy	
<40	304 (22%)
40-49	497 (35%)
50-59	321 (23%)
60-69	173 (12%)
70+	111 (8%)
Biopsy Type ^a	
Excisional	685 (49%)
Core/Needle	717 (51%)
Apocrine Metaplasia ^b	
No	965 (69%)
Yes	439 (31%)
Ductal Hyperplasia ^c	
None	964 (69%)
Atypical	18 (1%)
Mild	218 (16%)
Moderate	198 (14%)
Lobular Hyperplasia	
No	1384 (98%)
Yes	22 (2%)
Presence of cysts ^d	
No	837 (60%)
Yes	567 (40%)
Duct Ectasia	
No	1346 (96%)
Yes	60 (4%)
Fibrosis ^e	
No	526 (40%)
Yes	617 (47%)
Marked	163 (12%)
Intra-Ductal Papilloma ^f	
No	1268 (90%)
Single	123 (9%)
Multiple	14 (1%)
Sclerosing adenosis ^g	
No	1314 (94%)
Yes	91 (6%)
Columnar alteration ^h	

Characteristic	N (%)
No	1167 (83%)
Yes	222 (16%)
Atypia	15 (1%)
Mucocele-like Tumor ⁱ	
No	1402 (100%)
Yes	3 (0%)
Atrophy ^j	
None	248 (21%)
Partial	727 (60%)
Complete	230 (19%)
Overall Impression ^k	
Non-Proliferative Disease	945 (68%)
Proliferative Disease without Atypia	405 (29%)
Proliferative Disease with Atypia	44 (3%)

Unknown values (a-4, b-2, c-8, d-2, e-100, f-1, g-1, h-2, i-1, j-201, k-12)

Table 2

The association between pathologic characteristics of benign breast biopsies and subsequent breast cancer risk in African American women in Detroit, MI.

	Breast Cancer Status		Relative Risk ^a	
	Negative	Positive	(95% C.I.)	p value
Apocrine Metaplasia				
No	927	38	1.0 (Ref)	
Yes	422	17	0.93 (0.52-1.67)	0.80
Ductal Hyperplasia				
None	928	36	1.0 (Ref)	
Yes	415	19	1.14 (0.64-2.01)	0.66
Lobular Hyperplasia				
No	1330	54	1.0 (Ref)	
Yes	21	1	1.08 (0.14-8.21)	0.94
Cyst				
No	809	28	1.0 (Ref)	
Yes	540	27	1.41 (0.82-2.42)	0.21
Duct Ectasia				
No	1294	52	1.0 (Ref)	
Yes	57	3	1.33 (0.40-4.41)	0.64
Fibrosis				
No	505	21	1.0 (Ref)	
Yes	749	31	0.97 (0.55-1.71)	0.91
Intra-Ductal Papilloma				
None	1220	48	1.0 (Ref)	
1 or more	130	7	1.26 (0.55-2.84)	0.59
Sclerosing adenosis				
No	1266	48	1.0 (Ref)	
Yes	84	7	2.20 (0.96-5.01)	0.06
Columnar alteration				
No	1127	40	1.0 (Ref)	
Yes	222	15	1.84 (0.99-3.39)	0.05
Atrophy				
None	237	11	1.0 (Ref)	
Partial	700	27	0.75 (0.37-1.55)	0.44
Complete	218	12	0.84 (0.34-2.07)	0.71
Overall Impression				
Non-Proliferative Disease	912	33	1.0 (Ref)	
Proliferative Disease without Atypia	388	17	1.16 (0.64-2.12)	0.62
Proliferative Disease with Atypia	39	5	3.29 (1.21-8.93)	0.02

^a adjusted for age and year at biopsy

Table 3

Comparison of benign breast disease characteristics between the Detroit, African American cohort and the Mayo Clinic cohort

	Detroit (N, %)	Mayo (N, %)	p value
Age at Biopsy			
<40	304, 21.6%	1603, 18.3%	<0.01
40-49	497, 35.4%	2446, 28.0%	<0.01
50-59	321, 22.8%	2109, 24.1%	0.30
60-69	173, 12.3%	1600, 18.3%	<0.01
70+	111, 7.9%	978, 11.2%	<0.01
Atrophy/Involution ^a			
None	248, 20.6%	1627, 18.6%	0.11
Partial	727, 60.3%	5197, 59.5%	0.60
Complete	230, 19.1%	1912, 21.9%	0.03
Overall Impression ^b			
Non-Proliferative Disease	945, 67.8%	5736, 65.7%	0.13
Proliferative Disease without Atypia	405, 29.1%	2677, 30.6%	0.24
Proliferative Disease with Atypia	44, 3.2%	323, 3.7%	0.35

^aUnknown for 201 Detroit cases,

^bUnknown for 12 Detroit cases