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Breast Cancer Incidence in a Cohort of Women with Benign Breast Disease from a Multi-ethnic, Primary Health Care Population.

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Abstract

Background—Women with benign breast diseases (BBD), particularly those with lesions classified as proliferative, have previously been reported to be at increased risk for subsequent development of breast cancer (BC).

Methods—A cohort of 4970 women with biopsy-proven BBD, identified after histopathology review of BBD biopsies, was studied for determination of subsequent development of BC. We report on 4537 eligible women, 28% of whom are African American, whose BBD mass was evaluable for pathologic assessment of breast tissue. Ascertainment of subsequent progression to breast cancer from BBD was accomplished through examination of the tumor registries of the Henry Ford Health system, the Detroit SEER registry, and the State of Michigan cancer registry. Incidence rates (IR) are reported per 100,000 person years at risk (100k pyr). Poisson regression models were used to evaluate the association of demographic and lesion characteristics with BC incidence, using person years at the time of BBD diagnosis as the offset variable.

Results—The estimated overall BC IR for this cohort is 452 (95% confidence interval [CI] = 394 to 519) per 100k pyr. Incidence for women age 50 and older is 80% greater than for younger women ($p=0.007$, IRR=1.8, 95% CI= 1.36 to 2.36). Neither marital status ($p=0.91$, IRR=0.97, 95% CI= 0.73 to 1.29) nor race ($p=0.67$, IRR=0.9, 95% CI= 0.54 to 1.48) is associated with differences in BC IR. Compared to women with nonproliferative lesions, the risk for breast cancer is greater for women with ADH (IRR=5.0; 95%CI= 2.26 to 11.0; $p<0.001$) and other proliferative lesions (IRR= 1.7, 95% CI= 1.35 to 4.90, $p=0.004$). Breast cancer risk for woman with atypical lesions is significantly higher than for women with proliferative lesions without atypia (IRR=2.58, 95% CI= 1.35 to 4.90, $p=0.0039$).

Conclusion—Neither race nor marital status was a factor for breast cancer incidence from BBD in this cohort. Age retained its importance as a predictor of risk. BBD lesion histopathology in the outcome categories of either proliferative without atypia or proliferative with atypia are significant risk factors for BC, even when adjusted for the influence of demographic characteristics. The risks associated with BBD histological classifications were not different across races.

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INTRODUCTION

The breast is the site for numerous benign diseases. More than half of all women will develop some form of benign breast disease (BBD) after age 20 (1–3). Although a history of BBD indicates some increase in risk for breast cancer (BC), only a small fraction of those diagnosed ever develop malignant disease (2). For as long as benign breast diseases have been recognizable as distinct from breast cancers, the relationship of these benign conditions to development of malignant disease has been a topic of controversy (2–8)

A consensus was reached on the terminology for different types of benign breast proliferations and their associated relative risks for development of breast carcinoma in 1985 (9). It applied both to the type of pathologic findings to be included within BBD and to the grouping of the pathologic diagnoses into categories relative to the degree of invasive breast cancer risk deemed likely to be associated with each category. Another consensus group sponsored by the College of American Pathologists reported in 1998 on an updated version of the classification of BBD defined by risk for subsequent development of carcinoma (10). Their findings were as follows: 1) The lesions without significant increase in relative risk of cancer were nonproliferative or minimally proliferative; these included simple cystic changes, apocrine metaplasia, mild degrees of hyperplasia, and fibroadenoma (simple); 2) lesions associated with slightly increased relative risk (1.5 to 2 times) were moderate to florid degrees of hyperplasia (without atypia), papillomas with fibrovascular cores, and complex fibroadenomas. Here, controversy still exists regarding the significance of adenosis and its variant, sclerosing adenosis, but in general it appears that adenosis also may be associated with a relative risk similar to that of hyperplasia without atypia. Adenosis and hyperplasia together comprise the currently popular, although somewhat loose, category of proliferative breast disease; 3) the high-risk category (estimated as between five- and ten-fold increased risk) comprises atypical hyperplasias of ductal (ADH) and lobular types (ALH), which are defined as lesions having some histologic features of carcinoma *in situ* but not sufficient alteration to support an unequivocal diagnosis of carcinoma *in situ*. By definition, most of these lesions are incomplete forms of low-grade ductal carcinoma *in situ* or lobular carcinoma *in situ* and constitute a borderline group associated with moderately increased relative risk for invasive carcinoma. A family history of breast carcinoma doubles this risk for the individual (to 8–10 times) to about the risk that is associated with low-grade carcinoma *in situ* with no further treatment after biopsy.

Reports of breast cancer (BC) incidence from BBD date back to the 1960's (11,12). Subsequent studies (13–17) indicate an incidence of BC from 1.4 to 2.7 times greater in women with histologically confirmed BBD than in the general population. More recent studies (18,19,20), support these observations and reiterate that the risk of developing breast cancer varies by category of benign breast disease and is directly related to the degree of epithelial atypia.

The majority of published studies have addressed breast cancer incidence and relative risks for BC from BBD in predominantly homogenous Caucasian-American populations (18–24). Important questions remain about breast cancer incidence from BBD and relative risks for BC in African American women with BBD. To our knowledge, this is a first report of a BBD cohort drawn from a multi-ethnic population with nearly 28% of eligible women who are African American. We report on the incidence rate of breast cancer for this multi-ethnic cohort drawn from a primary care population according to race, the histopathology of the BBD lesions, marital status, and the age at diagnosis of BBD. Additionally, this study provides the first suggestion of different risks for BC from BBD for women with ADH as opposed to ALH.

PARTICIPANTS AND METHODS

The Henry Ford Health System (HFHS) is one of the largest health care organizations in southeastern Michigan. It includes an HMO (Health Alliance Plan-HAP), a medical group (Henry Ford Medical Group, HFMG) and several satellite hospitals. The Henry Ford Hospital has 903 beds with associated ambulatory care centers providing more than 2.0 million patient visits annually. Most patients at HFHS reside in the three-county Metropolitan Detroit area. This study drew from a sizable pool of primary care patients serviced by HAP that is approximately 33% African-American.

Women were eligible for this study if they were 18 years or older, had a breast biopsy performed for diagnostic purposes, did not have a history of breast cancer, and were not diagnosed with breast cancer within 6 months of the index BBD diagnosis. Ascertainment of cohort subjects (before exclusions) was based on retrieval and review (by the primary pathologist) of all reports of biopsies with a BBD diagnosis within the Henry Ford Health system within the period from Jan 1981 to Dec 1994. Breast pathologists reviewed the histology for all eligible subjects of the study cohort using a detailed pathology review form designed to capture a broad spectrum of histological findings. The primary reference pathologist re-reviewed a 10% sample to assess intra-rater reliability. For women with more than 1 BBD biopsy, the earliest biopsy (index biopsy) was recorded and the diagnosis was based on the most advanced (serious) lesion in the index biopsy.

Because multiple lesions were common, women were classified according to the most advanced lesion using the following classification, listed in order of probable increasing risk of cancer: nonproliferative lesion, proliferative lesion, atypical lobular hyperplasia and atypical ductal hyperplasia. Women were classified as having a non-proliferative lesion if the pathologic diagnosis was simple fibrosis, cysts, simple apocrine metaplasia, or simple fibroadenoma. Women were classified as having a proliferative lesion if the pathologic diagnosis was mild or moderate/florid usual or apocrine hyperplasia, sclerosing adenosis, papilloma, complex fibroadenoma, or radial scar. When ADH or ALH was present with other pathologic lesions, a woman was classified as having either ADH or ALH.

Ascertainment of subsequent progression to breast cancer from BBD (breast cancer cases) was accomplished through examination of the tumor registries of the Henry Ford Health system, the Detroit SEER registry, and the State of Michigan cancer registry. Follow-up on women who did not develop cancer was obtained from the National Death Index, Equifax/ChoicePoint locator service, and HFHS databases. Cancer is defined using AJCC staging definitions and SEER summary stage. Women in any of the tumor registries with a diagnosis of carcinoma *in situ* or invasive cancer are classified as having cancer.

Statistical Methods

Definitions—Risk for breast cancer from BBD is defined as new cases divided by number in the cohort, whereas incidence rate (IR) is defined as new cases divided by person years at risk, thus accounting for differences in follow-up time. The incidence rate ratio (IRR) is defined as the ratio of incidence rates in those exposed to that of those unexposed.

Chi square tests were used to test differences in proportions. Tests for trend were used to assess whether there were differences between groups in increasing severity of BBD lesions. Differences in age and in length of follow-up were tested with two-sample t-tests for 2-group comparisons and with one-way analysis of variance when there were more than 2 groups. Multinomial logistic models were used to assess the association of demographic characteristics with differences in type of BBD lesion expressed as relative risks (RR). Incidence rates (IR) are reported per 100,000 person years at risk (100k pyr). Poisson regression models were used

to evaluate the association of demographic and lesion characteristics with breast cancer incidence using person years since BBD diagnosis as the offset variable.

RESULTS

Final BBD cohort

From the original cohort of 5354 women, 4970 women were eligible for pathologic assessment. Approximately 5% (243) of the cohort were determined to be ineligible, most commonly for reasons of age (50% of ineligible women) or because the index biopsy was performed for reasons other than diagnosis of benign breast disease (30% of ineligible women). At pathology review, specimens from approximately 2% (108) of the 5111 eligible women contained no breast tissue and, therefore, could not be evaluated for the pathologic characteristics under consideration. In addition, approximately 0.6% (33) of the cohort had insufficient mammary tissue for evaluation of the presence of a BBD lesion. Finally, 433 women with no BBD lesion on histopathology review of BBD biopsy slides were excluded to yield the final BBD cohort of 4537 BBD subjects (original BBD cohort 4970-433=4537). We report on 4537 women, 91% of the initial cohort, with BBD mass who were both eligible and evaluable for pathologic assessment of breast tissue.

Nearly 28% of eligible women are African American; 63% were younger than 50 years at time of index biopsy, and 40% were never married (Table 1).

Most of the women (70%) had more than a single lesion evaluated at the time of index biopsy. The number of lesions biopsied ranged from 1 to 10 and there is an association between the number of lesions biopsied and the pathology of the most advanced lesion; the number of lesions biopsied increases with the diagnosis of more advanced lesions (Spearman's $\rho = 0.53$, $p < 0.001$).

Approximately 5% (246) of the cohort had atypical lesions at index biopsy; 4% (179) had atypical ductal hyperplasias (ADH), and 1% (67) had atypical lobular hyperplasias (Table 2A). Other proliferative lesions were identified in approximately 56% (2542) of the cohort; 39% (1749) had only nonproliferative lesions.

There are significant differences between older women and younger women in the pathologic diagnosis of the index lesion ($p < 0.001$) (Table 2B). Older women are more likely to have atypia than are younger women ($p < 0.001$) and married women are somewhat less likely to have nonproliferative lesions than unmarried women ($p = 0.056$). However, none of these differences is large.

Length of follow-up information was obtained on 95% (4326/4537) of the cohort and was similar for all of the subgroups examined.

Subsequent to, and more than 6 months after, the index biopsy, 202 women in the cohort were diagnosed with breast cancer. Overall, the estimated rate of breast cancer in this cohort is 452 per 100k pyr, with a wide range in the annual incidence (Table 3); the annual breast cancer incidence rates varied from a minimum of 203 cases per 100k pyr in 1990 to 641 cases per 100k pyr in 1986, but we detected no temporal pattern ($p = 0.35$). Approximately 20% of these women had stage 0 or *in situ* breast cancer at diagnosis (41/202), 63% (126/202) had stage I or higher stage disease, and for 17% (35/202), stage could not be determined from either the HFHS tumor registry or from SEER.

The breast cancer incidence rate (IR) for women age 50 and older is considerably higher (Table 4) as compared to women younger than 50 (624 vs. 348 per 100k pyr; IRR=1.8, 95% CI=1.36

to 2.36, $p=0.007$). Neither marital status (IRR=0.96, 95% CI=0.73 to 1.29, $p=0.91$), nor race ($p=IRR=0.9$, 95% CI=0.54 to 1.48, 0.67) is associated with differences in breast cancer incidence (Table 4). Compared to women with nonproliferative lesions, the risk for breast cancer is greater for women with ADH (IRR=5.0; 95% CI: 2.26, 11.0; $p<0.001$), ALH (IRR=3.2, 95% CI: 0.83, 12.4) and other proliferative lesions (IRR: 1.7, 95% CI: 1.35, 4.90, $p=0.004$). Breast cancer risk for woman with atypical lesions is significantly higher than for women with proliferative lesions without atypia (IRR=2.58, 95% CI= 1.35 to 4.90, $p=0.0039$). We tested for race and lesion type interaction and found the risks associated with BBD lesion histology outcome (lesion severity) was not different across races ($p=0.44$).

Poisson regression analysis to assess the simultaneous importance of demographics and lesion type for risk of breast cancer showed no statistically significant lack of fit.

There were 202 cancers in the cohort of 4537; 167 that were staged (126 invasive, 41 CIS) and 35 unstaged, yielding an overall IR of 452 breast cancer cases per 100k pyr (95% CI= 394 to 519). When only the staged 126 invasive cancers were considered as the progression to breast outcome, the estimated BC IR is 263 (95% CI =246 to 352) per 100k pyr. When the staged 126 invasive cases were pooled with the 35 missing stage (161 cases), the estimated BC IR is 377 (95% CI =321 to 440) per 100pyr. Poisson models of breast cancer incidence rates accounting for outcome to breast cancer progression $n=126$ and $n=161$ retained identical results as $n=202$.

Cumulative breast cancer incidence by type of lesion (Figure 1) indicates that women with atypical lesions are at greater risk for breast cancer than women with other types of breast lesions (RR=4.6; 95% CI: 2.93, 7.37; $p<0.0001$). At 5 years of follow-up, the cumulative breast cancer incidence was 6% among women with lesions of atypia, which was approximately 4 times higher than for women with nonproliferative and proliferative lesions. There was not a significant difference in risk between women with nonproliferative and proliferative lesions (RR=1.2, 95% CI: 0.71, 2.17; $p=0.44$) at 5 years, but at 10 years of follow-up, risk was significantly higher among women with atypia or proliferative lesions as compared to women with nonproliferative lesions (atypia RR=4.7; 95% CI: 2.76, 8.11, $p<0.001$; proliferative RR=1.66; 95% CI: 1.10, 2.48; $p=0.014$).

DISCUSSION

Our cohort of 4537 women with biopsy-proven BBD is distinct from previously reported benign breast disease studies for several reasons. Derived from a multi-ethnic, primary care patient population serviced by an HMO that is also a health insurance provider (Health Alliance Plan), it draws from an urban population in Detroit and includes a large proportion of all women in the southeastern metropolitan sectors of Detroit. The strengths of this study lie in the multi-ethnic character of the population studied with nearly 28% of eligible women who are African American and its successful collection of follow-up information on 95% (4326/4537) of the cohort. The most distinctive contribution of the study is the uniform detailed histopathology review of the BBD lesions. The re-review of BBD biopsies captured every designation of BBD lesion type encountered in the index biopsy, classifying with great specificity the different lesions in the categories of nonproliferative, proliferative without atypia, and proliferative with atypia.

Our data show no detectable temporal pattern for annual breast cancer incidence rates (Table 3). Although we cannot compare these results directly with published studies using standardized incidence rates (13–20), they clearly fall within a similar range.

In this multi-ethnic, primary care cohort, 28% of women were African American. Neither race nor marital status was a factor for breast cancer incidence from BBD. The risk associated with BBD lesion histology outcome (lesion severity) was not different across races.

We observed a much higher prevalence of proliferative lesions without atypia (56%) and of atypical lesions at index biopsy (5%; 4% ADH, 1% ALH), with a lower prevalence of nonproliferative lesions (39%) (Table 2A), in contrast to the observations by Hartmann et al, 2005 (18); the differences may reflect the population makeup from which study cohorts were drawn.

This study found higher breast cancer risk among women with atypical hyperplasia and corroborates studies indicating that the risk of developing breast cancer is directly related to the degree of epithelial atypia (18–25). We were able to refine the risks for epithelial lesions in the most serious risk category of atypia, which includes atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). Prior studies have reported risks for atypia combining ADH and ALH into a single category of epithelial atypia. We observed that, compared to women with nonproliferative disease, the risk for BC with ADH is 4 times greater ((95% CI 1.98 to 9.48) and the risk for women with ALH is approximately 3 times greater ((95% CI 0.78 to 11.02). To our knowledge, our study is the first to suggest that BC risk from BBD for women with ADH may be higher than for women with ALH. However, the lack of significant relative risk differences between ADH and ALH (RR= 1.45, 95% CI 0.36 to 5.99) most likely reflect the small numbers of women with ALH as a sole lesion.

Several studies support the finding of no increased risk for women with nonproliferative findings with no family history or a weak family history of breast cancer (18,26,27). However, when lesions in the nonproliferative and proliferative categories were combined as lower-category lesions (LC-BBD), significantly increased risk of breast cancer was noted compared to the overall risk for women in that age range who did not develop LC-BBD (28). During the follow-up period, breast cancer was eventually diagnosed in nearly 13% of our study population with ADH and 9% with ALH, as compared to 5% with proliferative lesions without atypia and 3% of nonproliferative diagnoses (Table 4).

Age retained its importance as a predictor of risk with older women more likely to have atypia than are younger women, a finding supported by other recent studies (27, 29). One explanation for this finding may be that it reflects the time required for a multistep, progressive accumulation of destabilization events, hallmarks of sporadic cancer. The observation that older women are more likely to present with atypia can be offered as evidence of a temporal, morphologic continuum in the progression of breast cancer from precursor benign lesions. Support for the latter is also strengthened by the cumulative breast cancer incidence by type of lesion upon follow-up. In our study, at 5 years of follow-up no significant difference in risk between women with nonproliferative lesions or with proliferative lesions without atypia was observed, even though the risk was 4 times higher for women with atypia. At 10 years of follow-up, however, cumulative breast cancer incidence was significant for both women with proliferative lesions without atypia and women with atypia.

Female breast cancer incidence rates vary considerably across racial and ethnic groups. Incidence rates continue to increase in Caucasian American women (0.4% per year for 1987–2000), but have stabilized in African American women since 1992 (30). The prevalence of several established risk factors differs across racial and ethnic subpopulations and these may contribute to the higher incidence rates in whites compared with other racial and ethnic groups (30). A known risk factor relates to specific diagnoses among benign proliferative breast lesions (18–25). This first large multi-ethnic cohort study shows a similar prevalence of the major histological subtypes of benign breast disease for African American women comprising nearly

28% of the study group as for the non-African American. Additionally, the risks associated with BBD histological classifications were not different across races.

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Cumulative Breast Cancer Incidence by Type of Most Serious BBD Lesion

Figure 1.

The plot of cumulative breast cancer incidence (CI) by type of lesion, shows that women with atypical lesions have consistently higher breast cancer incidence (RR=4.6; 95% CI= 2.93 to 7.37, $p<.0001$). At 5 years of follow-up, the cumulative breast cancer incidence was 6% among women with lesions of atypia, which was approximately 4 times higher than for women with non-proliferative and proliferative lesions. There was not a significant difference in CIs among non-proliferative and proliferative lesions (RR=1.2, 95% CI= 0.71 to 2.17, $p=0.44$) at 5 years, but at 10 years of follow-up, the CI was significantly higher among women with atypia or proliferative lesions as compared to women with non-proliferative lesions (atypia RR=4.7, 95% CI= 2.76 to 8.11, $p<.001$; Proliferative RR=1.66; 95% CI= 1.10 to 2.48, $p=0.014$).

TABLE 1
DEMOGRAPHIC CHARACTERISTICS (FINAL BBD COHORT N=4537)

	N (Pct)
African American	
Yes	1228 (28%)
No (includes white, other, unknown)	3309 (72%)
Age	
50 yrs or older	1682 (37%)
49 yrs or younger	2855 (63%)
Ever married	
Yes	2703 (60%)
No	1798 (40%)

Table 2A
MOST SERIOUS LESION AT INITIAL BIOPSY

	N	Percent
Non Proliferative	1749	39%
Proliferative	2542	56%
ALH	67	1%
ADH	179	4%

TABLE 2B
DIFFERENCE IN LESION TYPE BY DEMOGRAPHIC CHARACTERISTICS

	Nonproliferative	Proliferative	ALH	ADH	Sig ^{<i>l</i>}
African American					0.049
Yes	479 (39%)	701 (57%)	15 (1%)	33 (3%)	
No	1256 (38%)	1818 (56%)	52 (2%)	146 (4%)	
Age					<0.001
50 Yrs or older	579 (34%)	956 (57%)	34 (2%)	113 (7%)	
49 Yrs or younger	1170 (41%)	1586 (56%)	33 (1%)	66 (2%)	
Ever Married					0.056
Yes	1003 (37%)	1549 (57%)	45 (2%)	106 (4%)	
No	734 (41%)	966 (54%)	22 (1%)	73 (4%)	

^{*l*}Test for differences in trend in proportions

TABLE 3
 ESTIMATED BREAST CANCER INCIDENCE RATES (PER 100,000 PERSON YEARS AT RISK) AND
 LOWER/UPPER BOUNDS OF 95% CONFIDENCE INTERVAL

Year of BBD Diagnosis	Cancers	Person Years at Risk	Breast Cancer Incidence Rate*	95% C.I.
1981	13	2748	473	(275, 815)
1982	13	3068	424	(246, 730)
1983	14	3064	457	(271, 771)
1984	14	2419	579	(343, 977)
1985	8	3291	243	(122, 486)
1986	27	4211	641	(440, 935)
1987	26	4682	555	(378, 816)
1988	14	3687	380	(225, 641)
1989	19	3525	539	(344, 845)
1990	6	2953	203	(91, 452)
1991	15	2666	563	(339, 933)
1992	13	3189	408	(237, 702)
1993	9	2386	377	(196, 725)
1994	11	2812	391	(217, 706)
Overall	202	44700	452	(394, 519)

*
 per 100,000 person years at risk

TABLE 4
CANCER INCIDENCE RATE (IR) BY DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	N (%) with Cancer	IR ¹ (95% C.I.)	IRR ² (95% C.I.)	Signif. ³
African American				0.67
Yes	52 (4.2%)	420 (320, 551)	0.9 (0.54, 1.48)	
No	150 (4.6%)	468 (399, 549)	1.0	
Age 50 or older				0.007
Yes	105 (6.2%)	624 (515, 755)	1.8 (1.36, 2.36)	
No	97 (3.4%)	348 (285, 425)	1.0	
Ever Married				0.907
Yes	122 (4.5%)	448 (375, 535)	0.97 (0.73, 1.29)	
No	79 (4.4%)	460 (369, 573)	1.0	
Lesion Type				<.0001
ADH	23 (12.9%)	1411 (938, 2124)	5.0 (2.26, 11.0)	
ALH	6 (9.0%)	907 (408, 2020)	3.2 (0.83, 12.4)	
Proliferative Lesion	125 (4.9%)	491 (412, 586)	1.7 (1.02, 2.95)	
Non-proliferative Lesion	48 (2.7%)	283 (213, 375)	1.0	

IR¹=incidence rate;

IRR²=incidence rate ratio

Signif³=significance: p<0.05