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Family history of cancer and risk of breast cancer in the Black Women's Health Study

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Abstract

Introduction—Relatively little research has been conducted on familial breast cancer in African American women.

Methods—Data from the Black Women's Health Study, a prospective cohort study of African American women, were used to assess breast cancer risk in relation to family history of cancer. Since 1995, participants have completed biennial postal questionnaires on health status, risk factors, and family history of cancer. Cox proportional hazards analyses were used to calculate incidence rate ratios (IRR) and 95% confidence intervals (CI) for family history of breast and other types of cancer.

Results—Among 57,364 participants who were cancer-free at baseline, 1,306 incident breast cancer cases occurred during 12 years of follow-up. The IRR for a first-degree family history of breast cancer relative to no family history was 1.78 (95% CI 1.55-2.06). IRRs varied by the age at diagnosis, from 1.60 ($\geq$ age 55) to 2.76 ($<$ age 35). Results were consistent across subtypes of breast tumor defined by estrogen and progesterone receptor status. Breast cancer risk was also associated with family history of colon cancer (IRR 1.35, 95% CI 1.12-1.63) and possibly with family history of leukemia (IRR 1.42, 95% CI 0.82-2.46).

Conclusions—These findings indicate a strong familial relationship for breast cancer in African American women. The associations with family history of colon cancer and leukemia warrant further investigation.

Introduction

Mortality from breast cancer is higher in African American women than U.S white women, both before age 40, when breast cancer occurs more commonly among black women, and also at older ages when breast cancer incidence is greater among white women [1-3]. The mortality differential does not appear to be entirely explained by differences in screening or treatment [3-7]. Observations that black women are more likely to develop aggressive tumors, receptor-negative tumors, and tumors that are less responsive to available treatments may be relevant to the disparity, and suggest an important genetic role [4,6]. To provide evidence of a genetic role in the etiology of breast cancer beyond that of high penetrance genes such as BRCA1 and BRCA2, we explored the relation of family history of cancer to incidence of breast cancer, overall and according to age and hormone receptor status of the tumors.

Methods

Study population

The Black Women's Health Study (BWHS) is an ongoing prospective cohort study of African American women from all regions of the United States [8]. In 1995, women enrolled in the study by completing questionnaires mailed to subscribers to Essence magazine (a popular magazine targeted to black women), members of several black professional organizations, and friends or relatives of early respondents. After exclusion of women who were outside the ages of 21 through 69 years, who did not fill out the questionnaire satisfactorily, or whose addresses were judged to be invalid, 59,000 women of ages 21 to 69 years comprised the study cohort. Institutional Review Boards of Boston University and Howard University approved the study protocol, with a waiver of documentation of informed consent.

Assessment of exposure

Follow-up questionnaires are mailed to participants every two years to update information on exposures and identify new occurrences of cancers and other serious illnesses. Follow-up has been complete for approximately 80% of the baseline cohort for each questionnaire cycle. The analysis reported here is based on data from the first 12 years of follow-up, from 1995 through 2007. The baseline questionnaire obtained information on family history of breast cancer, including whether the relative's breast cancer occurred before or after age 50, adult height, current weight, demographic characteristics, reproductive history, medical history, use of cigarettes and alcohol, usual diet, and other factors. In 1999, participants were asked to check which of the following relatives – mother, father, sister, brother, son, daughter -- had had breast cancer, lung cancer, colon cancer, rectal cancer, prostate cancer, or ovarian cancer; 87% of the baseline cohort completed the 1999 questionnaire. The 1999 questionnaire did not assess whether the relative's cancer was diagnosed before age 50 or after. Other cancers written in by participants were coded appropriately.

Case ascertainment

Incident cases of breast cancer are identified through responses on biennial follow-up questionnaires. The National Death Index is searched annually for all nonrespondents and is also used as a source of death certificate data for participants known to be deceased. Pathology data are obtained through participant medical records and through state cancer registries. Adequate pathology data were obtained for 1,144 of the 1,334 participants who reported an incident breast cancer and the diagnosis of breast cancer was confirmed for 99.1% of potential cases. Because the rate of confirmation was so high, we included as cases all self-reported breast cancers except the 11 that were disconfirmed by medical records. In addition, 17 breast cancer cases were censored because they had an earlier diagnosis of another type of cancer, leaving a total of 1,306 breast cancer cases for the present analysis.

Information on estrogen receptor (ER) status and progesterone receptor (PR) status was obtained either from pathology reports or from state cancer registry data. Among those for whom such data were available, 64.9% were classified as ER+ and 35.1% as ER-, and 50.7% as PR+ and 49.3% as PR-. A comparison of characteristics of cases with known receptor status and those with unknown status indicated that the two groups were similar with regard to family history of breast cancer, age at diagnosis, education, parity, and body mass index.

Statistical Analysis

Age-stratified Cox proportional hazards regression models were used to derive incidence rate ratios (IRR) and 95% confidence intervals (CI) for breast cancer in relation to family history of breast cancer [9]. Each participant contributed follow-up time from baseline in 1995 until

the occurrence of any cancer (other than nonmelanoma skin cancer), death, loss to follow-up, or end of follow-up, whichever occurred first. Departures from the proportional hazards assumption were tested by a likelihood ratio test comparing models with and without age by covariate interaction terms. SAS statistical software (version 9.1; SAS Institute, Inc.) was used. We present age-adjusted IRRs and multivariable IRRs obtained from models that controlled for established breast cancer risk factors, including age at menarche (<12, 12-13, 14+), age at first birth (<20, 20-24, 25-29, 30+), number of births (1, 2, 3+), menopausal status (pre, post, uncertain), female hormone use (never, <5 years duration, 5+ years duration), and frequency of alcohol consumption (<1 drink/week, 1-3/week, 4-6/week, 7+/week). Because data on family history of cancers other than breast cancer were collected in 1999 rather than at baseline in 1995, we carried out a sensitivity analysis which considered follow-up from 1999 through 2007 only.

Results

During follow-up from 1995 through 2007, 1306 incident breast cancer cases occurred among 57,364 BWHs participants who were cancer-free at baseline. A history of breast cancer in one or more first-degree relatives (mother, sister, or daughter) was reported by 17.5% of cases, with 1.0% reporting a family history in two or more first-degree relatives. The multivariable IRR for having at least one first-degree family member with breast cancer relative to none was 1.78 (1.55-2.06) (Table 1). The comparable IRR for breast cancer in two or more first-degree relatives was 2.09 (1.18-3.69). A test for departure from the proportional hazards assumption showed a significant interaction by age ($p = 0.03$). Stronger associations were observed for breast cancer diagnosed at a young age: the IRRs were 2.76 for breast cancer diagnosed before age 35 and 1.60 for cancer diagnosed at ages 55 and older.

As shown in Table 2, the relative's age at diagnosis of breast cancer modified the association of family history with breast cancer risk among women who developed breast cancer before age 45: the multivariable IRR for having a first-degree relative who developed breast cancer before age 50 was 2.83 (95% CI 2.00-4.01) whereas the IRR for having a relative who developed breast cancer at 50 and older was 1.73 (95% CI 1.06-2.83). For cancers that occurred at ages 45 and older, there was little difference in risk according to the relative's age at diagnosis.

The relation of family history to risk of breast cancer according to ER and PR status is shown in Table 3. Family history was associated with breast cancer risk among tumor types ER+/PR+, ER+/PR-, and ER-/PR-; no association was observed for tumors that were ER-PR+, but there were only eleven such cases. The highest IRR observed was for the association of family history with ER+/PR+ tumors.

Because we asked about other cancer types in family members, we were also able to assess the relation of family history of each of the most frequently occurring cancers to risk of breast cancer (Table 4). Family histories of lung, ovarian, and prostate cancer were not associated with risk of breast cancer. However, IRRs were 1.35 (95% CI 1.12-1.63) for having a first degree relative with colon cancer and 1.42 (95% CI 0.82-2.46) for having a first degree relative with leukemia. Since participants were asked about family history of these types of cancer in 1999 rather than at baseline in 1995, we repeated the analyses with 1999 as start of follow-up (847 breast cancer cases included) and found similar results: for family history of colon cancer, the IRR was 1.32 (95% CI 1.05-1.67) and for family history of leukemia, it was 1.68 (95% CI 0.90-3.13) (data not shown).

Discussion

The present findings of a 78% increased risk of breast cancer for African American women who have a first degree relative with breast cancer demonstrate a familial component to breast cancer in African-American women. The association with family history was stronger for breast cancer diagnosed before age 45, and also stronger if the relative with cancer had been diagnosed at a young age. An association with family history of breast cancer was observed for both ER+ and ER- breast cancer.

There have been only three studies, each with a case-control design, that provide data on family history of breast cancer in black women [10,11,12]. In a hospital-based case-control study, the odds ratio for having a first-degree relative with breast cancer was 2.8 [10]. The other two case-control studies used a cohort approach in which the relative's cancer status was the outcome. In the Cancer and Steroid Hormone study, the relative risk estimates were 2.02 for mothers of cases relative to mothers of controls, and 1.65 for sisters of cases relative to sisters of controls [11]. In the more recent Women's CARE study, the estimated relative risk for breast cancer among all first degree relatives of the cases was 1.78 [12]. Our prospective cohort study yielded an identical overall relative risk estimate of 1.78.

The present results are also similar to results from studies of Asian and Caucasian women. In the most informative data on Asian women, from a large cohort study of women in Shanghai, the estimated relative risk for having at least one first degree relative with breast cancer was 1.74 [13]. In the most informative study of family history and breast cancer risk in Caucasian women, a pooled analysis of 52 case-control and cohort studies, the estimated relative risk associated with having a single first degree relative with the disease was 1.80, for two relatives it was 2.93, and for three or more it was 3.90 [14]. The similarity of findings in different ethnic groups suggests that genetic factors probably do not explain ethnic disparities in breast cancer incidence, such as the disproportionately high incidence of breast cancer in young African American women.

We found that the association of family history of breast cancer with breast cancer risk was present in all combinations of ER/PR status except for ER-/PR+, a group for which numbers were too small for informative analysis. These results are in agreement with findings from a large cohort of women from the Group Health screening program from Western Washington state [15]. The Iowa Women's Health Study cohort found that an association was present in all categories of receptor status except ER+/PR- [16]. In our study, the IRR for positive family history was highest for ER+/PR+ tumors although not statistically different from IRRs for the other subtypes. These results illustrate the importance of assessing family history in relation to specific subtypes of breast cancer.

Relatively few studies have examined whether having a family history of other types of cancer predicts risk of breast cancer. In the CARE study, family history of ovarian cancer was associated with breast cancer risk in white women but not in black women [12]. On the other hand, family history of cervical cancer was associated with breast cancer in black, but not white women [12]. In the Shanghai Women's Health Study, a family history of leukemia was associated with increased risk of breast cancer overall and family histories of lung cancer and esophageal cancer were associated with early onset breast cancer [14]. In a Danish population-based registry linkage study, family histories of ovarian and cervical cancers were associated with overall breast cancer risk, and family histories of colon and gall bladder cancer were associated with early breast cancer [17]. In a Swedish registry study, family histories of colorectal, ovarian, and pancreatic cancers were associated with breast cancer risk [18]. Family history of colon cancer, but not ovarian cancer, was associated with an increased risk of breast cancer in a primarily Caucasian population from the Southwestern U.S [19]. In the present

study of African American women, no association was observed with family history of lung, prostate, or ovarian cancer. However, women who reported a first degree relative with colon cancer had a 35% increased risk of breast cancer. This is of interest because African Americans have a higher incidence of colon cancer than do other U.S. ethnic groups [20]. We also observed an increased IRR, not statistically significant, for leukemia, in agreement with results from the Shanghai study. In the only study that reported on the accuracy of self-reports of family history of cancer by ethnic group, there was no difference in accuracy by race/ethnicity [21].

A potential limitation of the present study, shared by previous epidemiologic studies of family history of breast cancer, is the lack of information on which participants had mutations in the BRCA1 or BRCA2 genes. As a result, it was not possible to estimate the magnitude of the IRR associated with a positive family history of breast cancer separate from the effects of these rare, high-penetrance genes. However, the prevalence of these genes is quite low in African American women, with the best estimates indicating a prevalence of 1.4% for the BRCA1 gene and 2.6% for the BRCA2 gene [22].

Strengths of the study are the large size of the cohort and the duration of follow-up which resulted in a large number of breast cancer cases, thus permitting estimation of IRRs with narrow confidence bounds. One advantage of studying this relation in a cohort versus a case-control study is that it was possible to directly compare incidence rates in persons with and without a family history. Another is that there would not have been differential reporting of family history of cancer based on the respondents' own case status. While there was undoubtedly underreporting of family members with cancers, the underreporting would have been non-differential.

In summary, our prospective study of African American women supports a genetic etiology for breast cancer in this population group. The magnitude of the association and the relatively stronger association with early onset disease are consistent with findings from Asian-ancestry and European-ancestry populations. In addition, our data suggest a familial link of colon cancer, and possibly leukemia, with breast cancer.

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Table 1

Risk of breast cancer in relation to family history of breast cancer

Participant's age (years)	First-degree family history	Breast cancer cases	Person-years	Age-adjusted incidence rate ratio (95% CI)	Multivariable incidence rate ratio (95% CI)
<35	No	56	134,325	1.00	1.00
	Yes	10	7,812	2.77 (1.41-5.45)	2.76 (1.40-5.43)
35-44	No	289	180,741	1.00	1.00
	Yes	53	16,311	1.93 (1.44-2.59)	1.93 (1.44-2.60)
45-54	No	382	141,747	1.00	1.00
	Yes	85	17,066	1.81 (1.43-2.30)	1.81 (1.43-2.29)
≥ 55	No	350	83,921	1.00	1.00
	Yes	81	12,302	1.60 (1.25-2.03)	1.60 (1.25-2.04)
Overall	No	1,077	540,734	1.00	1.00
	Yes	229	53,491	1.79 (1.55-2.06)	1.78 (1.55-2.06)

Table 2

Risk of breast cancer in relation to family history of breast cancer according to whether the relative was diagnosed with breast cancer before age 50*

Participant's age (years)	Relative's age at diagnosis (years)	Breast cancer cases	Age-adjusted incidence rate ratio (95% CI)	Multivariable incidence rate ratio (95% CI)
<45	<50	35	2.78 (1.96-3.94)	2.83 (2.00-4.01)
	≥50	17	1.77 (1.09-2.88)	1.73 (1.06-2.83)
	unknown	11	1.25 (0.68-2.28)	1.26 (0.69-2.30)
≥45	<50	62	1.70 (1.31-2.21)	1.72 (1.32-2.22)
	≥50	56	1.57 (1.20-2.06)	1.55 (1.12-2.03)
	unknown	48	1.89 (1.41-2.53)	1.90 (1.42-2.55)
Overall	<50	97	1.98 (1.61-2.44)	2.00 (1.63-2.47)
	≥50	73	1.62 (1.27-2.05)	1.59 (1.25-2.02)
	unknown	59	1.72 (1.33-2.24)	1.73 (1.33-2.25)

* Data on relative's age at diagnosis not available for relatives whose breast cancers were reported only on the 1999 questionnaire.

Table 3

Risk of breast cancer according to tumor receptor status in relation to family history of breast cancer

Receptor status of case tumor	First-degree family history	Breast cancer cases	Age-adjusted incidence rate ratio (95% CI)
ER+/PR+	No	235	1.00
	Yes	61	2.19 (1.65-2.90)
ER+/PR-	No	67	1.00
	Yes	13	1.59 (0.87-2.88)
ER-/PR+	No	10	1.00
	Yes	1	0.82 (0.10-6.41)
ER-/PR-	No	171	1.00
	Yes	31	1.56 (1.06-2.29)
Unknown	No	594	1.00
	Yes	123	1.73 (1.43-2.11)

Table 4

Risk of breast cancer in relation to family history of prostate cancer, lung cancer, colon cancer, ovarian cancer, and leukemia

Family history of	Breast cancer cases	Age-adjusted incidence rate ratio (95% CI)
Prostate cancer	133	1.07 (0.89-1.28)
Lung cancer	129	1.02 (0.85-1.22)
Colon cancer	125	1.35 (1.12-1.63)
Ovarian cancer	51	1.00 (0.76-1.33)
Leukemia	13	1.42 (0.82-2.46)