

# Family History and Breast Cancer Risk Among Older Women in the Breast Cancer Surveillance Consortium Cohort

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**IMPORTANCE** First-degree family history is a strong risk factor for breast cancer, but controversy exists about the magnitude of the association among older women.

**OBJECTIVE** To determine whether first-degree family history is associated with increased risk of breast cancer among older women, and identify whether the association varies by breast density.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective cohort study between 1996 and 2012 from 7 Breast Cancer Surveillance Consortium (BCSC) registries located in New Hampshire, North Carolina, San Francisco Bay area, western Washington state, New Mexico, Colorado, and Vermont. During a mean (SD) follow-up of 6.3 (3.2) years, 10 929 invasive breast cancers were diagnosed in a cohort of 403 268 women 65 years and older with data from 472 220 mammography examinations. We estimated the 5-year cumulative incidence of invasive breast cancer by first-degree family history, breast density, and age groups. Cox proportional hazards models were fit to estimate the association of first-degree family history with risk of invasive breast cancer (after adjustment for breast density, BCSC registry, race/ethnicity, body mass index, postmenopausal hormone therapy use, and benign breast disease for age groups 65 to 74 years and 75 years and older, separately). Data analyses were performed between June 2016 and June 2017.

**EXPOSURE** First-degree family history of breast cancer.

**MAIN OUTCOMES AND MEASURES** Incident breast cancer.

**RESULTS** In 403 268 women 65 years and older, first-degree family history was associated with an increased risk of breast cancer among women ages 65 to 74 years (hazard ratio [HR], 1.48; 95% CI, 1.35-1.61) and 75 years and older (HR, 1.44; 95% CI, 1.28-1.62). Estimates were similar for women 65 to 74 years with first-degree relative's diagnosis age younger than 50 years (HR, 1.47; 95% CI, 1.25-1.73) vs 50 years and older (HR, 1.33; 95% CI, 1.17-1.51) and for women ages 75 years and older with the relative's diagnosis age younger than 50 years (HR, 1.31; 95% CI, 1.05-1.63) vs 50 years and older (HR, 1.55; 95% CI, 1.33-1.81). Among women ages 65 to 74 years, the risk associated with first-degree family history was highest among those with fatty breasts (HR, 1.67; 95% CI, 1.27-2.21), whereas in women 75 years and older the risk associated with family history was highest among those with dense breasts (HR, 1.55; 95% CI, 1.29-1.87).

**CONCLUSIONS AND RELEVANCE** First-degree family history was associated with increased risk of invasive breast cancer in all subgroups of older women irrespective of a relative's age at diagnosis.

JAMA Intern Med. 2018;178(4):494-501. doi:10.1001/jamainternmed.2017.8642  
Published online February 12, 2018.

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Evidence of the association between the first-degree family history and the risk of invasive breast cancer among women 65 years and older (hereafter referred to as *older women*) is limited. Although family history is a strong risk factor for breast cancer among younger women,<sup>1,2</sup> controversy exists about the magnitude of the association between family history and breast cancer among older women. While some studies indicate that the risk associated with family history may be minimal for women after the age of 60 years,<sup>3</sup> other reports suggest that risk remains elevated among women 75 years or older.<sup>4</sup> Moreover, a systematic review suggests that family history and breast cancer risk vary according to the first-degree relative's age at diagnosis, especially whether it occurred before or after menopause.<sup>1</sup>

To our knowledge, the possibility that the association of the first-degree family history with incident breast cancer among older women varies by age and breast density has yet to be examined. The strength of the association between breast density and invasive breast cancer has been shown to decrease with increasing age up to the age of 65 years.<sup>5,6</sup> Although common genetic factors and modifiable exposures such as hormone use may be associated with both breast density and breast cancer risk,<sup>7-9</sup> the extent to which breast density modifies the association of family history with breast cancer risk among older women is poorly understood. Evaluating such relationships may help estimate late-life breast cancer risk and identify older women at elevated breast cancer risk who might benefit from continued mammography screening. The current US Preventive Services Task Force guidelines recommend biennial screening mammography in women 65 to 74 years old, but lack sufficient data to recommend screening in women 75 years and older.<sup>10</sup> With notable exceptions,<sup>4</sup> a major limitation of research addressing the association of family history and breast cancer to date includes the lack of data for women 75 years and older.<sup>3</sup>

We used data from the population-based US Breast Cancer Surveillance Consortium (BCSC) prospective cohort study to quantify the risk of invasive breast cancer according to first-degree family history and Breast Imaging Reporting and Data System (BI-RADS) breast density among women 65 years and older receiving mammography in community practice. Although family history is not a modifiable risk factor, evaluating its impact is paramount for refining risk prediction tools and identifying high-risk older women for continued and potentially tailored mammography screening strategies.<sup>11</sup>

## Methods

### Study Population

The National Cancer Institute-funded BCSC (<http://www.bcsc-research.org>) is a community-based, geographically and racially/ethnically diverse cohort study that broadly represents the population of women presenting for screening mammography in the United States.<sup>12</sup> We included 7 BCSC registries located in New Hampshire, North Carolina, San Francisco Bay area, western Washington state, New Mexico, Colorado, and Vermont. Our sample consisted of 472 220 mammograms from

### Key Points

**Question** Is family history associated with breast cancer risk among older women, and if so, do any associations vary by breast density?

**Findings** In this cohort study of 403 268 women, first-degree family history was associated with an increased risk of breast cancer among women 65 years and older. Risk associated with family history was not significantly modified by breast density.

**Meaning** Family history should be considered when weighing harms and benefits of screening mammography in older women.

403 268 women 65 years and older who had at least 1 mammogram with self-reported information about first-degree family history between 1996 and 2012; women with missing family history data were excluded. For women with more than 1 mammogram during the study period, we selected the first mammogram within each age group. We excluded women with a breast cancer diagnosis prior to or within 3 months following their first eligible mammogram. Women were also excluded if they had breast implants or mastectomy, or if BI-RADS breast density was not available.

Each registry and the Statistical Coordinating Center have received institutional review board approval for consenting processes or a waiver of consent, enrollment of participants, and data linkages for research purposes. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and the Statistical Coordinating Center have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

### Measurement of Risk Factors

Risk factor information was obtained from self-report at the time of mammography, including age, family history in a first-degree relative, race/ethnicity, weight, height, postmenopausal hormone therapy use, and history of prior breast biopsies. Self-reported height and weight were used to calculate body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). Race and ethnicity were grouped as non-Hispanic white, non-Hispanic black, Asian/Pacific islander, Hispanic, mixed race, other).

Family history was evaluated as the main predictor variable. Wording on questionnaires varied by BCSC registry, but in general, women reported a first-degree relative with a breast cancer diagnosis, that is, mother, sister, or daughter (<http://www.bcsc-research.org/data/elements.html>). In addition, at a subgroup of facilities, women reported whether the diagnosis of breast cancer occurred at age younger than 50 years or 50 years or older for each first-degree relative. Community radiologists classified breast density on screening mammograms as part of routine clinical practice using the 4 American College of Radiology BI-RADS density categories<sup>13</sup>: a = almost entirely fat; b = scattered fibroglandular densities; c = heterogeneously dense; d = extremely dense. We grouped c and d categories together because category d is not common in older women. Age at the time of mammogram was

categorized based on US Preventive Services Task Force screening cutoffs for tabular presentation (65-74 and  $\geq 75$  years). Body mass index was categorized as less than 18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, or at least 35.0. Current use of postmenopausal hormone therapy at time of mammography was classified dichotomously based on women's self-report. Prior diagnoses of benign breast disease were collected by BCSC registries from pathology reports. We grouped each diagnosis from the pathology reports into 1 of 4 categories: nonproliferative, proliferative without atypia, proliferative with atypia, and lobular carcinoma in situ using the taxonomy proposed by Dupont and Page<sup>14</sup> and Page et al.<sup>15</sup> We classified the biopsy as diagnosis unknown if a woman reported a prior biopsy but pathology results were not available.

### Ascertainment of Breast Cancer Cases

The main outcome variable was incident invasive breast cancer. Diagnoses were obtained at each BCSC registry site through linkage with the regional population-based Surveillance, Epidemiology, and End Results program, state tumor registries, and pathology databases.

### Statistical Analysis

By design, all women had nonmissing age, family history, and breast density; individuals with missing values for specific covariates were excluded from any analysis using those variables. Treating the family history ascertainment as the unit of analysis, we evaluated the distribution of family history by demographic and clinical risk factors that were considered to be related to disease risk in older women. We evaluated the following family history categories: no first-degree family history vs any first-degree family history and family history by relative's ages at diagnosis (ie, age  $< 50$  vs  $\geq 50$  years).

We estimated separate models for women age 65 to 74 years and those 75 years and older. The method by Fine and Gray<sup>16</sup> was used to estimate the 5-year cumulative incidence function of invasive breast cancer by first-degree family history, breast density, and age groups considering ductal carcinoma in situ as a competing risk.<sup>17,18</sup> The regression models adjusted for BCSC registry, race/ethnicity, hormone therapy use, benign breast disease, and BMI. Adjusted marginal cumulative incidence functions within family history groups were estimated using the method of marginal standardization with the predicted function summed to a weighted average according to the observed covariate distribution in our study population.

We used Cox proportional hazards regression to model time to invasive breast cancer according to family history and age group, adjusted for BCSC registry, race/ethnicity, hormone therapy use, benign breast disease, and BMI. The model was also fit additionally adjusting for breast density, and fit including an interaction between family history and breast density to test for effect modification. Follow-up started 3 months after the first eligible mammogram. Women were censored at the time of death, diagnosis of ductal carcinoma in situ, mastectomy, end of complete cancer capture, or 10 years after study entry.

We performed a sensitivity analysis to assess whether the association between first-degree family history and breast can-

cer risk has attenuated over time among older women due to the family history data being older and potentially being less accurate than among more recently enrolled women. Specifically, we examined whether adjusting for calendar year, both as a main effect and with an interaction between calendar year and family history, affected the hazard ratios (HRs) for the association of family history and invasive breast cancer.

Two-sided statistical tests with  $P < .05$  were considered statistically significant. Statistical analyses were conducted using SAS software, version 9.1, of the SAS system for Windows (SAS Institute Inc) and R, version 3.2.2.

## Results

### Characteristics of the Study Population

During a mean (SD) follow-up of 6.3 (3.2) years (median, 6.8 years), 10 929 invasive breast cancers were diagnosed. **Table 1** shows the distribution of covariates across the strata of first-degree family history. A total of 38% of the study population was 75 years or older. The majority (71%) were non-Hispanic white, but 17% ( $n = 79\,156$ ) were African American, Asian, or Hispanic. Compared with women without a first-degree family history, those with any first-degree family history were proportionately more likely to be non-Hispanic white (77% vs 70%), and more likely to have benign breast disease (26% vs 20%). There was little variation in the proportions of breast density, hormone therapy use, and BMI and according to the presence of the first-degree family history, specifically having a relative who received a breast cancer diagnosis at age younger than 50 vs 50 years or older (**Table 1**). Among women reporting relatives with history of breast cancer, 62% ( $n = 46\,596$ ) reported their relatives' age at diagnosis. **eTables 1 and 2** in the **Supplement** present characteristics of the study population for women 65 to 74 years and 75 years and older. The younger age group (65-74 years) was proportionately more likely to use hormone therapy (22%) and have heterogeneously or extremely dense breasts (33%) than their older counterparts (**eTables 1 and 2** in the **Supplement**).

### Five-Year Cumulative Incidence of Invasive Breast Cancer by Family History, Breast Density, and Age Group

Five-year cumulative invasive breast cancer rates per 1000 persons increased with first-degree family history and age among women with heterogeneously or extremely dense breasts (65-74 years: with family history, 27; 95% CI, 22-30; and without family history, 20; 95% CI, 19-22;  $\geq 75$  years with family history: 28; 95% CI, 24-32; and without, 18; 95% CI, 16-20) (**Table 2**). The estimate per 1000 persons for women 65 to 74 years with first-degree relative's diagnosis at younger than 50 years was 28 (95% CI, 23-35) vs 24 (95% CI, 20-28) for women with relatives diagnosed at 50 years or older. The estimate per 1000 persons for women older than 75 years with the first-degree relative's diagnosis age at younger than 50 years was 26 (95% CI, 18-32) vs 27 (95% CI, 23-33) for women with relatives who received a breast cancer diagnosis at younger than 50 years.

Table 1. Characteristics of 403 268 Women by Family History of Breast Cancer in the Breast Cancer Surveillance Consortium

Characteristic	No. (%) <sup>a</sup>				
	All Mammograms (N = 472 220)	First-Degree Family History			
		None (n = 397 040)	Any (n = 75 180)	Relative's Diagnosis Age <50 y (n = 15 388)	Relative's Diagnosis Age ≥50 y (n = 31 208)
Age at study entry, y					
65-74	294 735 (60)	249 875 (61)	44 860 (57)	9128 (56)	18 699 (56)
≥75	177 485 (38)	147 165 (37)	30 320 (40)	6260 (41)	12 509 (40)
BI-RADS density <sup>b</sup>					
a	70 122 (15)	59 466 (15)	10 656 (14)	2147 (14)	4276 (14)
b	252 267 (53)	212 562 (54)	39 705 (53)	8068 (52)	16 081 (52)
c or d	149 831 (32)	125 012 (31)	24 819 (33)	5173 (34)	10 851 (35)
Race/ethnicity					
White, non-Hispanic	335 734 (71)	278 081 (70)	57 653 (77)	11 976 (78)	25 062 (80)
Black, non-Hispanic	26 267 (6)	23 005 (6)	3262 (4)	621 (4)	991 (3)
Asian/Pacific islander	23 589 (5)	21 329 (5)	2260 (3)	717 (5)	1219 (4)
Hispanic	29 300 (6)	25 578 (6)	3722 (5)	1038 (7)	1483 (5)
Other or mixed	4272 (1)	3589 (1)	683 (1)	223 (1)	338 (1)
Unknown	53 058 (11)	45458 (11)	7600 (10)	813 (5)	2115 (7)
Benign breast disease					
None (no prior biopsy)	374 462 (79)	318 710 (80)	55 752 (74)	11 176 (73)	23 025 (74)
Prior biopsy, unknown diagnosis	81 540 (17)	65 305 (16)	16 235 (22)	3399 (22)	6639 (21)
Nonproliferative	10 329 (2)	8382 (2)	1947 (3)	473 (3)	956 (3)
Proliferative without atypia	4598 (1)	3644 (1)	954 (1)	260 (2)	448 (1)
Proliferative with atypia	1014 (0.2)	798 (0.2)	216 (0.3)	58 (0.4)	105 (0.3)
Lobular carcinoma in situ	277 (0.1)	201 (0.1)	76 (0.1)	22 (0.1)	35 (0.1)
Postmenopausal hormone therapy use					
No	311 956 (66)	261 732 (66)	50 224 (67)	10 578 (69)	21 430 (69)
Yes	92 365 (20)	78 187 (20)	14 178 (19)	2629 (17)	5650 (18)
Unknown	67 899 (14)	57 121 (14)	10 778 (14)	2181 (14)	4128 (13)
BMI					
<18.5	4738 (1)	3965 (1)	773 (1)	164 (1)	348 (1)
18.5-24.9	92 171 (20)	76 219 (19)	15 952 (21)	3714 (24)	7633 (24)
25.0-29.9	73 905 (16)	61 039 (15)	12 866 (17)	3389 (22)	6085 (19)
30.0-34.9	34 016 (7)	28 030 (7)	5986 (8)	1608 (10)	2968 (10)
≥35.0	16 884 (4)	13 794 (3)	3090 (4)	882 (6)	1606 (5)
Unknown	250 506 (53)	213 993 (54)	36 513 (49)	5631 (37)	12 568 (40)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

<sup>a</sup> Some columns do not sum to 100% due to rounding.

<sup>b</sup> a Indicates almost entirely fat; b, scattered fibroglandular; c, heterogeneously dense; d, extremely dense. We grouped c and d categories together because they are not prevalent in older women.

### Hazard Ratios Associated With Invasive Breast Cancer Risk by Family History, Breast Density, and Age Group

We tested the proportional hazards assumption of family history using a  $\chi^2$  test of independence between the scaled Schoenfeld residuals and transformed survival time and the assumption was not violated ( $P = .82$ ).<sup>19</sup> The associations between family history and breast cancer were statistically significant in both age groups after adjustment for breast density, BCSC registry, race/ethnicity, BMI, hormone therapy use, and benign breast disease (Table 3). Family history was associated with a similar and statistically significantly increased risk of breast cancer among women age 65 to 74 years (HR, 1.48; 95% CI, 1.35-1.61) and women 75 years and older (HR, 1.44; 95% CI, 1.28-1.62); the test for interaction between age and family history was not significant (coeffi-

cient: 0.0948; 95% CI, -0.0386 to 0.2282;  $P = .06$ ). As reported in Table 3, breast density did not significantly modify the association between family history and breast cancer, except perhaps in women 75 years and older with fatty breasts ( $P = .13$  for interaction). Specifically, for women age 65 to 74 years, the HR associated with family history was 1.67 (95% CI, 1.27-2.21) for women with fatty breasts vs 1.32 (95% CI, 1.15-1.52) for women with dense breasts. For women 75 years and older, the HR was 1.08 (95% CI, 0.74-1.57) for women with fatty breasts vs 1.55 (95% CI, 1.29-1.87) for women with dense breasts. The strength of the association between family history and breast cancer varied little according to first-degree relative's age at diagnosis (Table 3). Calendar year adjustment did not meaningfully change the estimates of association (data not shown).

**Table 2. Five-Year Cumulative Incidence of Breast Cancer by Family History of Breast Cancer, Breast Density, and Age Group, Breast Cancer Surveillance Consortium (BCSC)<sup>a</sup>**

Breast Imaging Reporting and Data System Density <sup>b</sup>	Incidence (95% CI), Cases per 1000 Women, by First-Degree Family History			
	None	Any <sup>c</sup>	Relative's Diagnosis Age <50 y	Relative's Diagnosis Age ≥50 y
Age 65-74 y				
a	10 (9-13)	17 (13-23)	16 (9-17)	13 (9-17)
b	15 (14-16)	24 (22-27)	23 (18-30)	22 (18-26)
c or d	20 (19-22)	27 (22-30)	28 (23-35)	24 (20-28)
Age ≥75 y				
a	13 (11-16)	14 (10-19)	20 (12-30)	13 (6-19)
b	16 (14-17)	23 (20-26)	18 (12-25)	26 (21-33)
c or d	18 (16-20)	28 (24-32)	26 (18-32)	27 (23-33)

<sup>a</sup> Multivariable models adjusted for BCSC registry, race/ethnicity, postmenopausal hormone therapy use, body mass index, and benign breast disease.

<sup>b</sup> a Indicates almost entirely fat; b, scattered fibroglandular; c, heterogeneously dense; d, extremely dense. We grouped c and d categories together because they are not prevalent in older women.

<sup>c</sup> Includes observations with missing relative's age at diagnosis.

**Table 3. Cox Regression Hazard Ratios for Effects of Breast Density and Family History of Breast Cancer on Invasive Breast Cancer by Age Group in the Breast Cancer Surveillance Consortium (BCSC)<sup>a</sup>**

Model	HR (95% CI) Relative to No First-Degree Family History		
	Any First-Degree Family History <sup>a</sup>	Relative's Diagnosis Age <50 y	Relative's Diagnosis Age ≥50 y
Age 65-74 y			
Model unadjusted for breast density	1.49 (1.36-1.62)	1.50 (1.28-1.76)	1.34 (1.18-1.52)
Model adjusted for breast density	1.48 (1.35-1.61)	1.47 (1.25-1.73)	1.33 (1.17-1.51)
Model stratified by BI-RADS density <sup>b</sup>			
a	1.67 (1.27-2.21)	1.57 (0.89-2.76)	1.23 (0.78-1.93)
b	1.58 (1.40-1.78)	1.53 (1.22-1.92)	1.47 (1.23-1.76)
c or d	1.32 (1.15-1.52)	1.39 (1.08-1.79)	1.20 (0.99-1.47)
Age ≥75 y			
Model unadjusted for breast density	1.45 (1.29-1.63)	1.32 (1.06-1.64)	1.56 (1.34-1.83)
Model adjusted for breast density	1.44 (1.28-1.62)	1.31 (1.05-1.63)	1.55 (1.33-1.81)
Model stratified by BI-RADS density <sup>b</sup>			
a	1.08 (0.74-1.57)	1.58 (0.87-2.86)	0.99 (0.56-1.75)
b	1.44 (1.22-1.69)	1.13 (0.81-1.57)	1.68 (1.36-2.08)
c or d	1.55 (1.29-1.87)	1.47 (1.05-2.04)	1.53 (1.20-1.95)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; HR, hazard ratio.

<sup>a</sup> Multivariable models adjusted for BCSC registry, race/ethnicity, body mass index, postmenopausal hormone therapy use, and benign breast disease.

<sup>b</sup> Includes observations with missing relative's age at diagnosis.

<sup>c</sup> a Indicates almost entirely fat; b, scattered fibroglandular; c, heterogeneously dense; d, extremely dense. We grouped c and d categories together because they are not prevalent in older women.

## Discussion

In this study of the relationships between first-degree family history of breast cancer, breast density, and risk of incident invasive breast cancer, we found that first-degree family history remained an important risk factor for breast cancer even among women older than 75 years and that breast density did not significantly modify the association except perhaps in women with fatty breasts. A first-degree family history led to an absolute increase in 5-year risk of breast cancer ranging from 1.2 to 10.3 percentage points depending on breast density status and age. For example, in women 65 to 74 years old with scattered fibroglandular densities, we observed an increase in 5-year risk of breast cancer from 15.1% (95% CI, 13.8%-16.3%) for women without a family history to 23.8% (95% CI, 21.5%-27.2%) for women with a family history. Similarly, among women 75 years and older with scattered fibroglandular densities, 5-year cumulative risk of breast cancer increased from 15.9% (95% CI, 14.4%-17.3%) for women without a family history to 23.1% (95% CI, 20.1%-26.5%) for women with a family history.

Although a first-degree relative's age at diagnosis is associated with differential magnitudes of breast cancer risk among

younger women,<sup>1</sup> our study shows that any first-degree family history, irrespective of a relative's age at diagnosis, increases the risk of breast cancer among older women. Our findings complement those in our previous study of younger women, which indicated that associations between family history and breast cancer did not change substantially when adjusted for breast density.<sup>20</sup>

Our results demonstrate that family history is associated with increased risk of invasive breast cancer in both age groups, 65 to 74 years and 75 years and older. In a population-based cohort study, the Iowa Women's Health Study of 36 658 participants observed from 1986 to 2001, the HR for the association of family history and breast cancer risk was 1.54 (95% CI, 1.24-1.93) for a first-degree family history vs none among women 75 years and older, consistent with our results.<sup>4</sup> Several studies report on breast cancer risk by family history and breast density among younger women.<sup>9,20,21</sup> In 3 nested case-control studies of 2322 younger women (1164 cases and 1158 controls; mean age, 57 years), the odds ratios for breast cancer risk were 1.37 (95% CI, 1.10-1.72) for having 1 affected relative and 2.45 (95% CI, 1.30-4.62) for having 2 or more affected relatives ( $P < .001$  for trend); adjustment for percent mammographic density reduced these odds ratios by 16% and



14%, respectively.<sup>9</sup> We extend the literature by showing that the association is similar by age and the first-degree relative's age at diagnosis. Further research is needed to elucidate the mechanisms underlying the observed relationships. For example, it is possible that women who had a young first-degree relative with breast cancer but did not develop the disease by age 65 years are less likely to carry the "high-risk" genetic predisposition of that relative. We also show that the association between any first-degree family history and breast cancer is statistically significant after adjustment for breast density and other breast cancer risk factors.

Although our study showed a clear and significant association between family history and increased breast cancer risk among older women, the magnitude of the association that we observed was lower than the pooled estimate reported in the meta-analysis by Pharoah et al<sup>1</sup> (relative risk [RR], 1.90; 95% CI, 1.7-2.0) as well as lower than the estimate in the study by Mavaddat et al<sup>22</sup> among women 60 years and older (odds ratio, 1.53; 95% CI, 1.37-1.70) and the estimate in the study by Colditz et al<sup>2</sup> with the relative's age at diagnosis younger than 50 years (RR, 1.70; 95% CI, 1.48-1.95) and 50 years and older (RR, 1.40; 95% CI, 1.27-1.54). The difference in effect estimates between the present study and these studies may be due to the fact that we included a population-based cohort of women 65 years and older who underwent screening mammography in US community practice, whereas Pharoah et al<sup>1</sup> included non-US studies and studies of women as young as 16 years. In addition, the studies by Mavaddat et al<sup>22</sup> and Colditz et al<sup>2</sup> included women younger than 65 years.

Previous studies have demonstrated that the RR for the high-penetrance susceptibility genes *BRCA1* and *BRCA2* is somewhat more attenuated at later ages.<sup>23</sup> Furthermore, the cumulative effect of single-nucleotide polymorphisms as a polygenic risk score is reported to be slightly attenuated in women older than 65 years compared with younger women<sup>22</sup>; there is evidence of attenuated effect size but consistent risk effect of both high-penetrance and low- to moderate-penetrance common variants. The prevalence of first-degree family history in our cohort of women undergoing screening mammography (approximately 16%; data not shown) was approximately 4% higher than that among women 60 years or older in the US National Health Interview Survey.<sup>24</sup> A somewhat higher prevalence of family history in our cohort is unsurprising because women with a family history are more likely to be screened with mammography.<sup>25,26</sup> Although family history of breast cancer highly influences older women's decisions to continue screening,<sup>27</sup> advancing age is a major risk factor for breast cancer, peaking between 75 and 79 years.<sup>28</sup> Hence, estimating the impact of established breast cancer risk factors in the elderly is needed to facilitate individualized cancer screening decisions.<sup>29,30</sup>

Women 75 years and older had the highest prevalence of family history in our cohort. Because older women are more likely to have larger families and, potentially, older first-degree relatives, and because older age is a strong risk factor for breast cancer, the increased family history is likely due to the higher prevalence in older relatives.

Our study relied on BI-RADS breast density measurements reported by radiologists at multiple radiology facilities within BCSC registries; interobserver agreement on BI-RADS categories is moderate.<sup>31</sup> In addition, we collected self-reported information on first-degree family history at the time of mammography, lessening the possibility of recall bias. Any misclassification due to self-report is likely to have been random, leading to an underestimation of the association between first-degree family history and breast cancer.

### Limitations

Our study was limited to simple first-degree family history, and we were unable to compare the associations as a function of simple vs extended family history. Evidence from the BCSC suggests that a history of breast cancer in both first- and second-degree relatives is more strongly associated with breast cancer than simple first-degree family history.<sup>20</sup> Moreover, because our study population consisted of women undergoing screening mammography, we were unable to compare screened vs nonscreened cohorts.

This study has several strengths, including the largest, population-based sample of socioeconomically and ethnically diverse older women in the United States, prospective cohort design, large number of outcomes, and complete breast cancer follow-up. We were also able to account for the confounding influence of several key factors including benign breast disease, adiposity, postmenopausal hormone therapy, and race/ethnicity. We examined the association of first-degree family history and breast cancer separately by breast density status and age group that included a large proportion of women 75 years or older.

### Conclusions

In summary, first-degree family history was associated with invasive breast cancer risk among older women ages 65 to 74 years and 75 years or older. This association did not vary significantly by first-degree relative's age at diagnosis. Furthermore, breast density did not significantly modify the association of family history with invasive breast cancer risk. Based on this pattern of findings, clinicians should continue to ask older women about family history of breast cancer to personalize mammography screening strategies. Crucially, family history needs to be taken into account when considering the potential benefits vs harms of continued mammography in this population.

#### ARTICLE INFORMATION

**Accepted for Publication:** December 21, 2017.

**Published Online:** February 12, 2018.

doi:10.1001/jamainternmed.2017.8642

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**Obtained funding:** Braithwaite, Miglioretti, Kerlikowske.

**Administrative, technical, or material support:** Braithwaite, Demb, Buist, Kerlikowske.

**Study supervision:** Braithwaite, Miglioretti, Kerlikowske.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This work was supported by a National Institutes of Health, National Cancer Institute (NIH/NCI)–funded Program Project (PO1 CA154292). It was also supported by an NIH/NCI–funded Research Project Grant (1R01CA207361-01A1). Data collection was additionally supported by the Breast Cancer Surveillance Consortium (HHSN261201100031C); Vermont Breast Cancer Surveillance System data collection was also supported by U54CA163303 from NIH/NCI. The collection of cancer and vital status data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. A full description of these sources is available at <http://www.bcscc-research.org/work/acknowledgement.html>.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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**Additional Contributions:** We thank the BCSC investigators, participating mammography facilities, radiologists, and participating women for the data they have provided for this study.

**Additional Information:** Procedures for requesting BCSC data for research purposes are detailed at <http://www.bcscc-research.org>.

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