Research Article

Cancer Epidemiology, Biomarkers & Prevention

Emerging Trends in Family History of Breast Cancer and Associated Risk

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Abstract

Background: Increase in breast cancer incidence associated with mammography screening diffusion may have attenuated risk associations between family history and breast cancer.

Methods: The proportions of women ages 40 to 74 years reporting a first-degree family history of breast cancer were estimated in the Breast Cancer Surveillance Consortium cohort (BCSC: $N = 1{,}170{,}900$; 1996–2012) and the Collaborative Breast Cancer Study (CBCS: cases $N = 23{,}400$; controls $N = 26{,}460$; 1987–2007). Breast cancer (ductal carcinoma *in situ* and invasive) relative risk estimates and 95% confidence intervals (CI) associated with family history were calculated using multivariable Cox proportional hazard and logistic regression models.

Results: The proportion of women reporting a first-degree family history increased from 11% in the 1980s to 16% in 2010 to 2013. Family history was associated with a >60% increased risk of breast cancer in the BCSC (HR, 1.61; 95% CI, 1.55–1.66) and CBCS (OR, 1.64; 95% CI, 1.57–1.72). Relative risks decreased slightly with age. Consistent trends in relative risks were not observed over time or across stage of disease at diagnosis in both studies, except among older women (ages 60–74) where estimates were attenuated from about 1.7 to 1.3 over the last 20 years (P trend = 0.08 for both studies).

Conclusions: Although the proportion of women with a first-degree family history of breast cancer increased over time and by age, breast cancer risk associations with family history were nonetheless fairly constant over time for women under age 60.

Impact: First-degree family history of breast cancer remains an important breast cancer risk factor, especially for younger women, despite its increasing prevalence in the mammography screening era. *Cancer Epidemiol Biomarkers Prev; 26(12); 1753–60. ©2017 AACR.*

Introduction

Family history of breast cancer is widely recognized as an important risk factor for breast cancer. About 13% to 19% of women diagnosed with breast cancer have an affected first-degree relative (mother, daughter, or sister) compared with slightly fewer (8%–12%) of women without breast cancer (1, 2). Breast cancer risk increases with increasing number of affected first-degree relatives compared with women without a first-degree family history, increasing 1.5- to 4-fold as the number of diagnosed relatives increases (1, 3, 4).

Over the past three decades, the incidence of breast cancer has increased with the introduction and widespread use of mammography screening (5–7). The observed increase in breast cancer incidence has been most pronounced for ductal carcinoma *in situ* (DCIS; ref. 8), which increased 7-fold from 5.8 per 100,000 women in 1975 to 34.4 per 100,000 women in 2014 (9). Though not well studied, increase in DCIS and early stage breast cancer incidence associated with mammography screening has likely resulted in an increase in the proportion of women with a family history of breast cancer. If some of this increased incidence is due to overdiagnosis of clinically insignificant disease, this could result in a reduction in the risk of breast cancer associated with having a first-degree family history over time. In addition, because older women have a higher detection rate of DCIS and may be more likely to have indolent disease, the relative risk may decrease with increasing age if indolent disease does not have a genetic basis (10, 11). For example, a recent cohort study of women undergoing screening mammography in the United States observed a decrease in the relative risk of breast cancer associated with a family history from 1.9 to 1.5 with increasing age (2).

Using two large databases from the Breast Cancer Surveillance Consortium (BCSC) and the Collaborative Breast Cancer Study (CBCS), this study describes secular changes in the proportion of women with a self-reported first-degree family history of breast cancer over the past three decades, with the early study period coinciding with the surge in mammography utilization and increasing incidence of early-stage breast cancer. In addition, we assessed the relationship between a family history of breast cancer and breast cancer risk according to age and year of diagnosis as well as stage of disease.

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doi: 10.1158/1055-9965.EPI-17-0531

Materials and Methods

Study populations

We utilized two data sources: The BCSC and the CBCS. The BCSC is a National Cancer Institute–sponsored collaborative network of breast imaging registries established in 1994 (12–14). We included data from five BCSC registries: Kaiser Permanente Washington Registry, San Francisco Mammography Registry, Carolina Mammography Registry, New Hampshire Mammography Network, and Vermont Breast Cancer Surveillance System. These registries collect breast-imaging data among women in their catchment areas along with data on benign and malignant breast tumor diagnoses via linkage to tumor registries and pathology databases. Self-reported family history data were collected at the time of the mammography examinations through paper questionnaires (15). We included data on women without a personal history of breast cancer or breast reduction or augmentation who had information on first-degree family history of breast cancer self-reported at the time of a mammography examination from 1996 to 2012; cancer diagnoses were ascertained through December 2013. Family history was missing for 47,616 women, so these women were not eligible for this analysis. Each registry and the Statistical Coordinating Center (SCC) have received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act (HIPAA) compliant, were conducted in accordance with recognized ethical guidelines, and all registries and the SCC have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

The CBCS is a population-based case–control study that was carried out in Wisconsin, Massachusetts (apart from metropolitan Boston), Maine, and New Hampshire (16–18). Eligible case subjects were women identified by each state's cancer registry with a new breast cancer diagnosis. Similarly aged population controls were selected from lists of licensed drivers and Medicare beneficiaries. After obtaining informed consent from women to participate in the study, information on personal and family history of cancer and other study data were collected from participants between 1987 and 2007 via telephone interviews. Invasive breast cancer cases were enrolled during the entire study, whereas cases with DCIS were enrolled during 1997–2007. Family history was missing for 669 cases and 623 controls, so these women were not eligible for this analysis. Information regarding the pathologic confirmation and stage of disease at diagnosis was obtained from the cancer registry of each participating state. The study protocols were conducted in accordance with recognized ethical guidelines and were HIPAA compliant and approved by institutional review boards at the University of Wisconsin, Harvard University, and Dartmouth College.

For both studies, we retrieved data on women who were between 40 and 74 years of age, including 1,170,900 women from the BCSC (of which 22,795 developed breast cancer) and 26,400 controls and 23,400 breast cancer cases from the CBCS. Family history of breast cancer was self-reported for first-degree relatives (i.e., mother, daughters, and sisters). In the BCSC, the mean follow-up time for women with a breast cancer diagnosis between qualifying entry mammogram and diagnosis was 821 days, and, for those censored, the mean follow-up time was 1,468 days. We defined breast cancer to be either DCIS or invasive carcinoma. Demographic data included self-reported race/ethnicity, and year and age at breast cancer diagnosis based on registry reports. Breast cancer stage was classified using the Surveillance Epidemiology and End Results Program summary stage as either DCIS, localized, or regional/distant (19).

Statistical analysis

We examined whether secular changes occurred in the proportion of women reporting a first-degree family history of breast cancer across the two studies and by age groups. Because women could contribute data for multiple mammograms in the BCSC cohort, data for one mammogram examination per woman per year were randomly selected for analysis to examine trends over time. Proportions of a family history of breast cancer for the two studies were adjusted for study site (BCSC registry and CBCS state) and age (to the 2000 U.S. standard population) using direct standardization (20); annual proportions are presented for the BCSC and biennial proportions are shown for the CBCS due to smaller sample sizes. Age-specific proportions were adjusted for study site only.

Separately for each of the two study populations, we estimated the relative risk of breast cancer among women with a first-degree family history compared with women with no first-degree family history by age, year (year of mammogram with self-reported family history for BCSC and year of diagnosis for CBCS), and stage at diagnosis using methods appropriate for each study design. Specifically, for the BCSC cohort, we randomly selected one mammogram per woman across all years of observation for analysis. We used Cox proportional hazards regression to estimate HRs and 95% confidence intervals (CI). Women in the BCSC entered the model beginning 3 months after their randomly selected mammogram to exclude cancers present at the time of the self-reported family history, and were censored following a breast cancer diagnosis, death, mastectomy, end of complete cancer capture, or at 10 years of follow-up. Models were adjusted for age, race/ethnicity, BCSC registry, and history of benign breast biopsy (either self-reported or pathology report confirmation). For CBCS case–control data, we used logistic regression to estimate ORs and 95% CI. Models were adjusted for age, race/ethnicity, state of residence, and self-reported history of benign breast biopsy. Statistical analysis was performed using SAS version 9.4 (SAS Institute).

Results

Table 1 describes the demographic characteristics of women in the two studies. On average, women in the BCSC were younger than women in the CBCS, reflecting that women in the BCSC were queried about their family history of breast cancer at the time of a screening or diagnostic mammogram, whereas women in the CBCS were queried at the time of a breast cancer diagnosis (with age-matched controls). Most women reported no history of benign breast biopsy in the BCSC (78.7%) and CBCS (81.2% of controls and 74.1% of cases). More women in the CBCS were non-Hispanic white (>96%) compared with the BCSC (67%).

The unadjusted proportion of women reporting a family history of breast cancer in the BCSC (12.4%) was similar to the controls in the CBCS (13.5%) and lower than in the CBCS cases (21.0%; Table 1). The reported prevalence of first-degree family history increased over time in both studies (Fig. 1). Specifically, the age-adjusted proportion of women reporting a family history

Table 1. Characteristics of participants in the BCSC (1996–2012) and CBCS (1987–2007)

	BCSC[a]	CBCS	
		Controls	Cases
	***N* = 1,170,900 (Col %)**	***N* = 26,460 (Col %)**	***N* = 23,400 (Col %)**
Age at enrollment			
40–49	471,306 (40.3)	5,381 (20.3)	4,790 (20.5)
50–59	363,237 (31.0)	8,663 (32.7)	7,561 (32.3)
60–74	336,357 (28.7)	12,416 (46.9)	11,049 (47.2)
Year of report			
1987–1993	NA (NA)	13,035 (49.3)	10,128 (43.3)
1994–1999	160,872 (13.7)	7,505 (28.4)	7,549 (32.3)
2000–2004	406,526 (34.7)	4,451 (16.8)	4,239 (18.1)
2005–2009	432,321 (36.9)	1,469 (5.5)	1,484 (6.3)
2010–2013	171,181 (14.6)	NA (NA)	NA (NA)
Benign breast biopsy			
No	921,231 (78.7)	21,485 (81.2)	17,341 (74.1)
Yes	199,791 (17.1)	4,319 (16.3)	5,489 (23.5)
Unknown	49,878 (4.3)	656 (2.5)	570 (2.4)
Race/ethnicity			
Non-Hispanic White	784,651 (67.0)	25,617 (96.8)	22,807 (97.5)
Other	223,743 (19.1)	742 (2.8)	522 (2.2)
Unknown	162,506 (13.9)	101 (0.4)	71 (0.3)
First-degree family history of breast cancer			
None	1,025,508 (87.6)	22,875 (86.5)	18,479 (79.0)
Any	145,392 (12.4)	3,585 (13.5)	4,921 (21.0)
1	101,911 (8.7)	3,284 (12.4)	4,283 (18.3)
>1	10,536 (0.9)	301 (1.1)	638 (2.7)
Unspecified[b]	32,945 (2.8)	0 (0)	0 (0)

Abbreviations: Col, column; NA, not available.
[a]One randomly selected examination record per woman.
[b]Unknown number of affected family members (1 or more).

in the BCSC increased from 12.3% in 1996 to 16.0% in 2010 compared with controls in the CBCS where family history reporting increased from 10.6% in 1987 to as high as 14.0% in 2007. The proportion of women reporting a family history within the BCSC increased with age, especially in the most recent years (Fig. 2). The proportion with a family history increased over time for women ages 50 years and older, and the increase over time was largest for the oldest women. For example, among women ages 70 to 74 years, the proportion increased 56% from 13.9% in 1996 to 21.6% in 2012, whereas the proportion increased 49% from 11.5% in 1996 to 17.1% in 2012 among women ages 50 to 54 years, and was relatively flat at 12.2% to 13.1% among women ages 40 to 44 years.

Table 2 illustrates the increased risk of breast cancer associated with a family history overall and by year and stage of diagnosis. Overall, women with a first-degree family history had a more than 60% increased risk of breast cancer compared with women without a family history in both the BCSC (HR, 1.61; 95% CI, 1.55–1.66) and the CBCS (OR, 1.64; 95% CI, 1.57–1.72). Relative risks of breast cancer increased from 1.58 for women with one

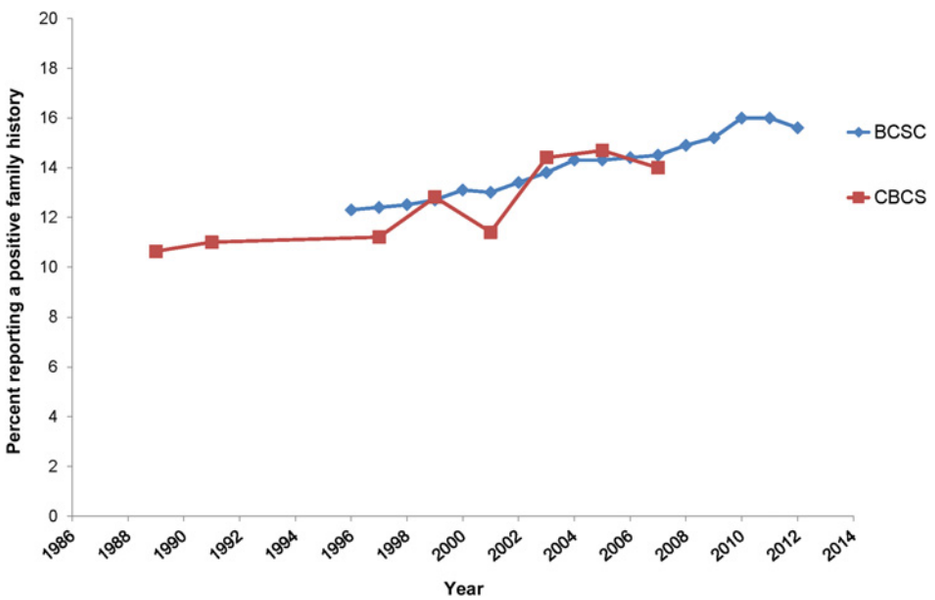

Figure 1.
Proportion of women ages 40 to 69 years reporting a positive first-degree family history of breast cancer in the BCSC (1996–2012) and the CBCS (1987–2007). Percentages are adjusted for study site (BCSC registry and CBCS state) and age based on the 2000 U.S. standard population. Each woman in the BCSC contributed one randomly chosen observation per year. CBCS limited to women without a personal history of breast cancer.

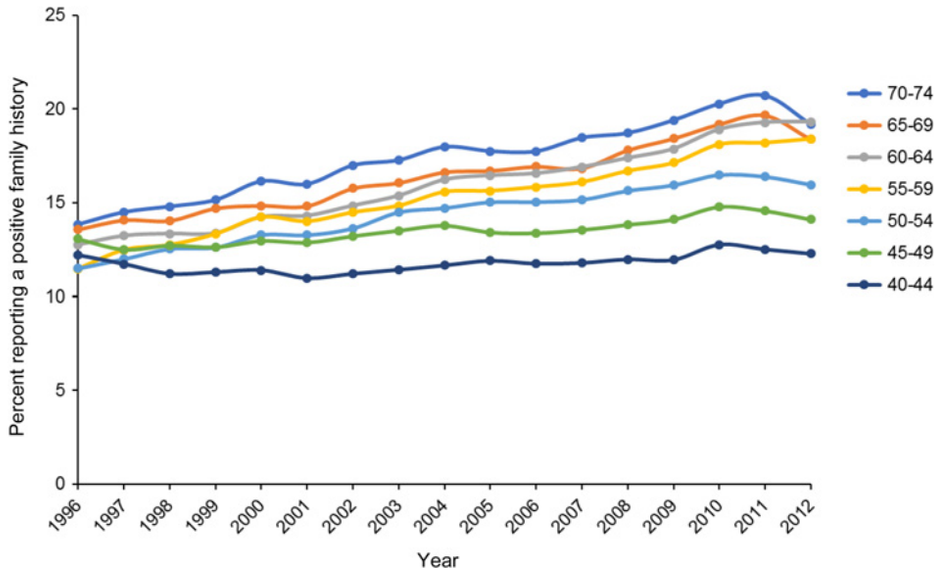

Figure 2.
Proportion of women ages 40 to 74 years reporting a positive first-degree family history of breast cancer by age and year, BCSC, 1996–2012. Percentages are adjusted for mammography registry. Each woman contributed one randomly chosen observation per year.

affected relative, to 1.88 in the BCSC and 2.47 in the CBCS for women with more than one affected relatives. When adjusting for age, the relative risk of breast cancer associated with a first-degree family history was essentially unchanged over the time period of the BCSC (*P* trend 0.40), and was modestly attenuated over time from 1.65 to 1.51 in the CBCS (*P* trend 0.06).

The proportion of cases in the CBCS reporting a first-degree family history of breast cancer was similar across stages at diagnosis for the case (age-adjusted percentages among women 40–69 years for DCIS: 23.8%; localized: 21.6%; regional/distant: 18.9%). Women with a family history of breast cancer had increased breast cancer risk at every stage of diagnosis in the BCSC and the CBCS (Table 2). Increased breast cancer risk was also observed throughout all time periods albeit to varying extents. For instance, among women in the BCSC, the relative risk associated with a family history increased over time from 1.54 to 1.82 for localized breast cancer (*P* trend 0.04) but not DCIS (*P* trend 0.26). However, attenuation over time in the relative risk of localized breast cancer associated with a positive family history from 1.73 to 1.44 was observed in the CBCS (*P* trend 0.03).

Compared with women without a first-degree family history of breast cancer, women with a first-degree family history of breast cancer had an increased risk of breast cancer at all ages, with the highest risk occurring among women ages 40 to 49 years in both the BCSC (HR, 1.81; 95% CI, 1.70–1.92) and the CBCS (OR, 1.88; 95% CI, 1.67–2.11; Table 3). Temporal trends in the associations were not strong within age strata, although relative risk estimates were attenuated in more recent years among older women (60–74) in both the BCSC (*P* trend 0.08) and the CBCS (*P* trend 0.08).

Discussion

We observed an increase in the proportion of women reporting a family history of breast cancer over time across two large, geographically diverse study populations. According to national surveillance statistics, mammography screening rates increased over time from about 29% in 1987 to over 70% since 2000 (21, 22). Increased uptake of screening mammography since the 1980s has resulted in an increase in breast cancer incidence especially in early-stage disease (23). Consequently, more women now report a family history of breast cancer.

In our study, the prevalence of women reporting a family history of breast cancer ranged from 11% observed during the late 1980s to 16% in 2010. Although the largest pooled analysis to date—performed in 2001 by the Collaborative Group on Hormonal Factors in Breast Cancer—estimated the prevalence of a positive family history to be around 12% (1), estimates of individual studies published over time vary. For instance, first-degree family history of breast cancer prevalence estimates from studies in the late 1970s and early 1980s ranged from 9% as observed by Bain and colleagues to as high as 22% in the Breast Cancer Detection Demonstration Project (24, 25). Studies published in the late 1980s up until 2012 including the National Health Interview Survey have estimated the prevalence of a positive family history of breast cancer to range from 11% to 19% (26–29).

The variations in the prevalence of breast cancer family history reported across studies may be explained by several factors. First, apart from differences in study design (e.g., case-control vs. prospective cohort), some studies have targeted specific population groups such as the Nurses' Health Study that has a fairly homogeneous socioeconomic status (28). Second, the age distribution has varied across studies, with some targeting women between ages 30 and 55 years and others such as Sellers and colleagues enrolling older women between ages 55 and 69 years (24, 27). Third, although a link between breast and ovarian cancer was observed for many decades (30), women with known deleterious *BRCA1/2* mutations have been increasingly studied ever since the discovery of these genes in 1994 (31, 32). Studies with more women with deleterious *BRCA* mutations (such as studies with a high number of Ashkenazi Jews) likely have a higher prevalence of a positive family history (33–35). Fourth, household size and birthrate in the United States have diminished over time, with estimates showing the average number of members per family in 2015 to be 3.1 compared with 3.5 in 1973 (36, 37). Hence, more recent generations have fewer siblings at risk for a breast cancer diagnosis.

Table 2. Relative risks of breast cancer associated with a first-degree family history of breast cancer by year and stage of disease at diagnosis, BCSC 1996–2012 and CBCS 1987–2007

Variable	BCSC			CBCS		
	Total at entry ($N = 1{,}170{,}900$)	*N*, Cases ($N = 22{,}795$)	HR (95% CI)[a]	Controls ($N = 26{,}460$)	Cases ($N = 23{,}400$)	OR (95% CI)[a]
Any first-degree family history	145,392	4,422	1.61 (1.55–1.66)	3,585	4,921	1.64 (1.57–1.72)
1	101,911	2,953	1.58 (1.52–1.64)	3,284	4,283	1.57 (1.49–1.65)
>1	10,536	407	1.88 (1.70–2.07)	301	638	2.47 (2.15–2.84)
Unspecified[b]	32,945	1,062	1.60 (1.50–1.70)	0	0	
Year of diagnosis						
1987–1993	NA	NA	NA	13,035	10,128	1.65 (1.54–1.78)
1994–1999	160,872	5,700	1.60 (1.49–1.70)	7,505	7,549	1.74 (1.59–1.90)
2000–2004	406,526	9,744	1.64 (1.56–1.73)	4,451	4,239	1.50 (1.34–1.67)
2005–2009	432,321	6,883	1.67 (1.57–1.77)	1,469	1,484	1.51 (1.24–1.82)
2010–2013	171,181	468	1.68 (1.35–2.07)	NA	NA	NA
Trend			$P = 0.40$			$P = 0.06$
Stage of disease at diagnosis						
DCIS	1,170,900	4,979	1.63 (1.51–1.75)	10,966	2,328	1.78 (1.59–1.99)
Localized	1,170,900	11,454	1.68 (1.61–1.76)	26,460	12,767	1.69 (1.60–1.79)
Regional/distant	1,170,900	5,123	1.58 (1.47–1.70)	26,460	6,198	1.46 (1.36–1.57)
Stage and year of diagnosis						
DCIS						
1987–1993	NA	NA	NA	NA	NA	NA
1994–1999	160,872	1,207	1.77 (1.54–2.04)	7,105	1,337	1.90 (1.64–2.19)
2000–2004	406,526	2,047	1.54 (1.37–1.73)	2,392	832	1.59 (1.31–1.94)
2005–2009	432,321	1,612	1.63 (1.44–1.84)	1,469	159	1.71 (1.15–2.54)
2010–2013	171,181	113	1.59 (1.02–2.49)	NA	NA	NA
Trend			$P = 0.26$			$P = 0.27$
Localized						
1987–1993	NA	NA	NA	13,035	5,587	1.73 (1.59–1.88)
1994–1999	160,872	2,806	1.54 (1.40–1.69)	7,505	4,166	1.78 (1.61–1.96)
2000–2004	406,526	4,943	1.73 (1.61–1.86)	4,451	2,235	1.56 (1.37–1.77)
2005–2009	432,321	3,478	1.73 (1.59–1.87)	1,469	779	1.44 (1.15–1.81)
2010–2013	171,181	227	1.82 (1.35–2.45)	NA	NA	NA
Trend			$P = 0.04$			$P = 0.03$
Regional/distant						
1987–1993	NA	NA	NA	13,035	3,072	1.53 (1.37–1.70)
1994–1999	160,872	1,202	1.61 (1.40–1.86)	7,505	1,673	1.52 (1.32–1.75)
2000–2004	406,526	2,314	1.56 (1.39–1.74)	4,451	1,046	1.28 (1.07–1.53)
2005–2009	432,321	1,500	1.58 (1.39–1.79)	1,469	407	1.42 (1.06–1.88)
2010–2013	171,181	107	1.66 (1.06–2.60)	NA	NA	NA
Trend			$P = 0.76$			$P = 0.12$

Abbreviation: NA, not available.

[a]Models adjusted for single year of age, race/ethnicity, history of benign breast biopsy, and registry/state of residence. Reference category for all models defined as women reporting no family history of breast cancer (BCSC, $n = 1{,}025{,}508$; CBCS controls $n = 22{,}875$, cases $n = 18{,}479$).

[b]Unknown number of affected family members (1 or more).

Previous research has differed in breast cancer risk estimates associated with a family history, which may reflect variations in study design and time of data collection. Pharaoh and colleagues (38), in their 1997 systematic review and meta-analysis, observed breast cancer–relative risk estimates among women with an affected first-degree relative that ranged from 1.2 to 8.8 across studies conducted over a period of six decades, with most studies reporting relative risks between 2 and 3. We report relative risk estimates toward the lower ends of these ranges, between about 1.3 and 2.5.

Studies characterizing the relationship between presence of family history and breast cancer stage at diagnosis, though less well described, have highlighted certain relationships. For instance, among women with invasive breast cancer at diagnosis, women with a positive family history tended to have smaller tumors with more favorable prognostic outcomes (39, 40); however, results have been mixed with other studies suggesting no relationship with stage of disease (41, 42). Stage at diagnosis could be related to family history through mechanisms working in different ways; women undergoing routine mammography screening are more likely to be diagnosed with breast cancer at an earlier stage, whereas breast cancer tumors with more aggressive features tend to be diagnosed at later stages (43). In the CBCS, family history was more common in earlier as compared with later staged breast cancer. Family history of breast cancer may be a stronger risk factor for women with early-stage breast cancer because women with a family history are more likely to seek screening. Due to limitations in the accuracy of self-reported health information, studies have not historically collected information on whether family members with breast cancer were diagnosed with DCIS or invasive breast cancer.

Many factors are likely to influence women's use of screening mammography (44). Women with a family history of breast cancer are more likely to adhere to mammography screening guidelines including more recent and frequent screens (45, 46). The risk of being diagnosed with regional/distant breast cancer among women with a positive family history appears to be slightly lower compared with localized and DCIS stages, although

Table 3. Relative risks of breast cancer associated with a family history of breast cancer by age and year of diagnosis, BCSC 1996–2012 and CBCS 1987–2007

	BCSC			CBCS		
	Total at entry ($N = 1,170,900$)	Cases ($N = 22,795$)	HR (95% CI)[a]	Controls ($N = 26,460$)	Cases ($N = 23,400$)	OR (95% CI)[a]
Age at breast cancer diagnosis (years)						
40–49	471,306	6,626	1.81 (1.70–1.92)	5,381	4,790	1.88 (1.67–2.11)
50–59	363,237	7,454	1.60 (1.51–1.69)	8,663	7,561	1.56 (1.43–1.69)
60–74	336,357	8,715	1.50 (1.42–1.58)	12,416	11,049	1.63 (1.52–1.74)
Age and year of diagnosis						
Age 40–49 years						
1987–1993	NA	NA	NA	1,856	1,180	1.82 (1.46–2.27)
1994–1999	55,606	1,517	1.75 (1.54–2.00)	1,987	2,057	2.07 (1.72–2.48)
2000–2004	158,384	2,825	1.86 (1.69–2.05)	1,156	1,139	1.73 (1.37–2.18)
2005–2009	180,850	2,132	1.79 (1.61–2.00)	382	414	1.43 (0.96–2.15)
2010–2013	76,466	152	2.36 (1.64–3.40)	NA	NA	NA
Trend			$P = 0.28$			$P = 0.23$
Age 50–59 years						
1987–1993	NA	NA	NA	3,738	2,621	1.54 (1.34–1.77)
1994–1999	45,363	1,901	1.55 (1.38–1.74)	2,553	2,703	1.60 (1.38–1.85)
2000–2004	129,101	3,270	1.63 (1.49–1.79)	1,791	1,644	1.38 (1.15–1.64)
2005–2009	137,325	2,157	1.77 (1.60–1.96)	581	593	1.80 (1.33–2.44)
2010–2013	51,448	126	1.48 (0.97–2.25)	NA	NA	NA
Trend			$P = 0.24$			$P = 0.88$
Age 60–74 years						
1987–1993	NA	NA	NA	7,441	6,327	1.68 (1.54–1.84)
1994–1999	59,903	2,282	1.61 (1.45–1.77)	2,965	2,789	1.69 (1.48–1.94)
2000–2004	119,041	3,649	1.52 (1.40–1.65)	1,504	1,456	1.50 (1.26–1.80)
2005–2009	114,146	2,594	1.47 (1.34–1.62)	506	477	1.29 (0.94–1.76)
2010–2013	43,267	190	1.34 (0.95–1.87)	NA	NA	NA
Trend			$P = 0.08$			$P = 0.08$

Abbreviation: NA, not available.

[a]Models adjusted for single year of age, race/ethnicity, and history of benign breast biopsy and registry/state of residence. Reference category for all models defined as women reporting no family history of breast cancer (BCSC, $n = 1,025,508$; CBCS controls $n = 22,875$, cases $n = 18,479$).

this was more strongly evident in the CBCS than the BCSC. Reasons are not apparent for the observation that the relative risk associated with a family history increased over time for localized breast cancer in the BCSC and decreased over time in the CBCS. Despite this finding, family history should not be discounted as an important risk factor for breast cancer.

The risk of breast cancer among women with a positive family history was fairly constant across all time periods among younger (<60) women. Although *P* values for trend were only borderline significant, risk estimates did decline by about 50% over time among older women in both study populations. Interestingly, the increase in the proportion of women with a family history over time was slightly larger for this older age group. It is not surprising we did not see an attenuation of the relative risks among younger women given the changes in proportion with a family history were small in this group. From the 1980s up until the early 2000s, women increasingly utilized mammography screening, resulting in a rise in breast cancer incidence. Previous research suggests that some screen-detected breast cancer cases might reflect overdiagnosis, which is defined as breast cancer cases detected at screening that would not otherwise have been clinically evident during a woman's life time (47). Overdiagnosis estimates range from 10% to 30%, with estimates varying by study methodology (excess incidence under screening vs. statistical modeling accounting for lead-time bias), age, and study population (47–51). Though overdiagnosis cannot be ruled out, our findings suggest that family history has less impact on breast cancer incidence as women age, similar to previous reports (1, 52). However, the lack of family history data as far back as the late 1970s and early 1980s may have limited the identification of significant changes in family history risk estimates.

The two data sources used for our study have provided insight regarding increased breast cancer risk among women with a family history reported over time. By including two large multi-site studies with different designs, we could compare results and time periods for consistencies in patterns. The population-based sampling of the CBCS and the prospective design of the BCSC are additional strengths to this analysis. However, some limitations should be considered. Information on family history of breast cancer was self-reported, but women tend to report such information reliably (53, 54). Only first-degree family history of breast cancer was ascertained, so that risk from paternal relatives was under-represented. All women in the BCSC have had a mammogram (either screening or diagnostic), so they may be more likely to have a family history of breast cancer than the general population, although the prevalence of a family history was very similar between the BCSC and the CBCS.

In conclusion, the prevalence of a self-reported family history of breast cancer has increased over time, especially among older women, coinciding with the observed trend in increased breast cancer incidence following widespread mammography use. However, breast cancer risk associated with family history by age and stage at diagnosis does not seem to have changed significantly over time, except possibly among women 60 and older. This suggests that any breast cancer overdiagnosis, which had been highlighted in prior studies as a factor influencing the rise in breast cancer incidence, appears to have had little impact on the breast cancer risk associated with a family history, particularly in younger women. The relevance of a family history of breast cancer should not be discounted even as breast cancer incidence and mammography use have stabilized in recent times.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acknowledgments

This work was supported by the NIH under NCI grants P30 CA014520, P01 CA154292, U01 CA199218, R01 CA067264, and R01 CA047147. Collection of BCSC data was supported by the NCI grant P01 CA154292, contract HHSN261201100031C, and grant U54 CA163303. The collection of BCSC 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. For a full description of these sources, please see http://www.bcsc-research.org/work/acknowledgement.html.

The authors wish to thank Julie McGregor, Kathy Peck, and Laura Stephenson of the Wisconsin Cancer Reporting System for their contributions to data collection and study management for the CBCS. We thank the BCSC investigators, participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at: http://www.bcsc-research.org/.

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Received June 14, 2017; revised August 11, 2017; accepted September 22, 2017; published OnlineFirst October 6, 2017.

References

1. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001;358:1389–99.
2. Tice JA, Miglioretti DL, Li CS, Vachon CM, Gard CC, Kerlikowske K. Breast density and benign breast disease: risk assessment to identify women at high risk of breast cancer. J Clin Oncol 2015;33:3137–43.
3. Kharazmi E, Chen T, Narod S, Sundquist K, Hemminki K. Effect of multiplicity, laterality, and age at onset of breast cancer on familial risk of breast cancer: a nationwide prospective cohort study. Breast Cancer Res Treat 2014;144:185–92.
4. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med 2012;156:635–48.
5. Feuer EJ, Wun LM. How much of the recent rise in breast cancer incidence can be explained by increases in mammography utilization? A dynamic population model approach. Am J Epidemiol 1992;136:1423–36.
6. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. Cancer J Clin 2014;64:52–62.
7. Glass AG, Lacey JV Jr., Carreon JD, Hoover RN. Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. J Natl Cancer Inst 2007;99:1152–61.
8. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302:1685–92.
9. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al. SEER Cancer Statistics Review, 1975—2014 [Internet]. Bethesda, MD: National Cancer Institute; 2016. Available from: https://seer.cancer.gov/csr/1975_2014/.
10. van Luijt PA, Heijnsdijk EA, Fracheboud J, Overbeek LI, Broeders MJ, Wesseling J, et al. The distribution of ductal carcinoma in situ (DCIS) grade in 4232 women and its impact on overdiagnosis in breast cancer screening. Breast Cancer Res 2016;18:47.
11. Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. J Natl Cancer Inst 2002;94:1546–54.
12. Ballard-Barbash R, Taplin SH, Yankaskas BC, Ernster VL, Rosenberg RD, Carney PA, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. Am J Roentgenol 1997;169:1001–8.
13. Onega T, Goldman LE, Walker RL, Miglioretti DL, Buist DS, Taplin S, et al. Facility mammography volume in relation to breast cancer screening outcomes. J Med Screen 2016;23:31–7.
14. National Cancer Institute. Breast Cancer Surveillance Consortium: evaluating screening performance in practice [Internet]. Bethesda, MD: National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services; 2004.
15. Breast Cancer Surveillance Consortium. Data elements and questionnaires [Internet] Seattle, WA: BCSC Statistical Coordinating Center; 2017. Available from: http://www.bcsc-research.org/data/elements.html.
16. Newcomb PA, Trentham-Dietz A, Hampton JM, Egan KM, Titus-Ernstoff L, Warren Andersen S, et al. Late age at first full term birth is strongly associated with lobular breast cancer. Cancer 2011;117:1946–56.
17. Sprague BL, Trentham-Dietz A, Newcomb PA, Titus-Ernstoff L, Hampton JM, Egan KM. Lifetime recreational and occupational physical activity and risk of in situ and invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:236–43.
18. Nichols HB, Trentham-Dietz A, Sprague BL, Hampton JM, Titus-Ernstoff L, Newcomb PA. Effects of birth order and maternal age on breast cancer risk: modification by whether women had been breast-fed. Epidemiology 2008;19:417–23.
19. Young JL Jr, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA, editors. SEER Summary Staging Manual -2000: codes and coding instructions. Bethesda, MD: National Cancer Institute; 2001.
20. Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. Health People Statistical Notes, no. 20. Hyattsville, MD: National Center for Health Statistics. January 2001; 2001, pp. 1–10.
21. National Center for Health Statistics. Health, United States, 2014: with special feature on adults aged 55–64. Hyattsville, MD: National Center for Health Statistics; 2015.
22. White A, Thompson TD, White MC, Sabatino SA, de Moor J, Doria-Rose PV, et al. Cancer screening test use - United States, 2015. MMWR Morb Mortal Wkly Rep2017;66:201–6.
23. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER cancer statistics review, 1975–2012. Bethesda, MD: National Cancer Institute; 2015.
24. Bain C, Speizer FE, Rosner B, Belanger C, Hennekens CH. Family history of breast cancer as a risk indicator for the disease. Am J Epidemiol 1980;111:301–8.
25. Brinton LA, Hoover R, Fraumeni JF Jr. Interaction of familial and hormonal risk factors for breast cancer. J Nat Cancer Inst 1982;69:817–22.
26. Egan KM, Stampfer MJ, Rosner BA, Trichopoulos D, Newcomb PA, Trentham-Dietz A, et al. Risk factors for breast cancer in women with a breast cancer family history. Cancer Epidemiol Biomarkers Prev 1998;7:359–64.

27. Sellers TA, Kushi LH, Potter JD, Kaye SA, Nelson CL, McGovern PG, et al. Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. N Eng J Med 1992;326: 1323–9.
28. Colditz GA, Kaphingst KA, Hankinson SE, Rosner B. Family history and risk of breast cancer: nurses' health study. Breast Cancer Res Treat 2012;133: 1097–104.
29. CDC/National Center for Health Statistics. About the national health interview survey [Internet]. Atlanta, GA: CDC/National Center for Health Statistics; 2015. Available from: http://www.cdc.gov/nchs/nhis/about_nhis.htm
30. Lynch HT, Guirgis HA, Albert S, Brennan M, Lynch J, Kraft C, et al. Familial association of carcinoma of the breast and ovary. Surg Gynecol Obst 1974;138:717–24.
31. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378:789–92.
32. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71.
33. Claus EB, Schildkraut J, Iversen ES Jr., Berry D, Parmigiani G. Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. J Nat Cancer Inst 1998;90:1824–9.
34. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.
35. Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Res 2006;66:8297–308.
36. US Census Bureau. Historical households tables: Table HH-6. Average population per household and family: 1940 to present [Internet]. Suitland, MD: US Department of Commerce, November 2016. Available from: https://www.census.gov/data/tables/time-series/demo/families/households.html.
37. National Center for Health Statistics. Vital statistics of the United States, 2003, Vol. I. Hyattsville, MD: Centers for Disease Control and Prevention; 2005.
38. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997;71:800–9.
39. Molino A, Giovannini M, Pedersini R, Frisinghelli M, Micciolo R, Mandara M, et al. Correlations between family history and cancer characteristics in 2256 breast cancer patients. Br J Cancer 2004;91:96–8.
40. Malone KE, Daling JR, Doody DR, O'Brien C, Resler A, Ostrander EA, et al. Family history of breast cancer in relation to tumor characteristics and mortality in a population-based study of young women with invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:2560–71.
41. Melvin JC, Wulaningsih W, Hana Z, Purushotham AD, Pinder SE, Fentiman I, et al. Family history of breast cancer and its association with disease severity and mortality. Cancer Med 2016;5:942–9.
42. Wobbes T, van de Wiel MP, van der Sluis RF, Theeuwes AG. The effect of familiality on clinical presentation and survival in mammary carcinoma. Eur J Surg Oncol 1987;13:119–21.
43. Crispo A, Barba M, D'Aiuto G, De Laurentiis M, Grimaldi M, Rinaldo M, et al. Molecular profiles of screen detected vs. symptomatic breast cancer and their impact on survival: results from a clinical series. BMC Cancer 2013;13:15.
44. Walter LC, Lindquist K, Covinsky KE. Relationship between health status and use of screening mammography and Papanicolaou smears among women older than 70 years of age. Ann Int Med 2004;140:681–8.
45. Tracy KA, Quillin JM, Wilson DB, Borzelleca J, Jones RM, McClish D, et al. The impact of family history of breast cancer and cancer death on women's mammography practices and beliefs. Genet Med 2008;10:621–5.
46. Murabito JM, Evans JC, Larson MG, Kreger BE, Splansky GL, Freund KM, et al. Family breast cancer history and mammography: Framingham Offspring Study. Am J Epidemiol 2001;154:916–23.
47. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, M W. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380:1778–86.
48. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 2012;367:1998–2005.
49. Duffy SW, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L, et al. Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. Breast Cancer Res 2005;7:258–65.
50. Baines CJ, To T, Miller AB. Revised estimates of overdiagnosis from the Canadian National Breast Screening Study. Prev Med 2016;90:66–71.
51. Biesheuvel C, Barratt A, Howard K, Houssami N, Irwig L. Effects of study methods and biases on estimates of invasive breast cancer overdetection with mammography screening: a systematic review. Lancet Oncol 2007;8: 1129–38.
52. Murff HJ, Peterson NB, Greevy R, Zheng W. Impact of patient age on family cancer history. Gen Med 2006;8:438–42.
53. Chang ET, Smedby KE, Hjalgrim H, Glimelius B, Adami HO. Reliability of self-reported family history of cancer in a large case-control study of lymphoma. J Nat Cancer Inst 2006;98:61–8.
54. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;146:244–8.