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## 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 aged 40–74 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 2010–13. Family history was associated with a >60% increased risk of breast cancer in the BCSC (hazard ratio=1.61;95%CI=1.55–1.66) and CBCS (odds ratio=1.64;95%CI=1.57–1.72). Relative risks decreased slightly with age. Consistent trends in

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relative risks were not observed over time or across stage of disease at diagnosis in both studies, except among older women (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).

**Conclusion**—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.

**Implication**—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.

### Keywords

Breast cancer; family history; risk factors; mammography; self-report; prevalence

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### Introduction

Family history of breast cancer is widely recognized as an important risk factor for breast cancer. About 13–19% of women diagnosed with breast cancer have an affected first-degree relative (mother, daughter or sister) compared to slightly fewer (8–12%) of women without breast cancer (1, 2). Breast cancer risk increases with increasing number of affected first-degree relatives compared to 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) (8), which increased seven-fold from 5.8 per 100,000 women in 1975 to 34.4 per 100,000 women in 2014 (9). Though not well studied, increases 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 over-diagnosis 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, since 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 US 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 and the Collaborative Breast Cancer Study, this study describes secular changes in the proportion of women with a self-reported first-degree family history of breast cancer over the past 3 decades, with the early study period coinciding with the surge in mammography utilization and increasing incidence of early-stage breast cancer. Additionally, 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.

## Materials and Methods

### Study populations

We utilized two data sources: The Breast Cancer Surveillance Consortium (BCSC) and the Collaborative Breast Cancer Study (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 was 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 pathological 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 40–74 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 ductal carcinoma *in situ* (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 (SEER) 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. Since 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 to 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 hazard ratios (HR) 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 odds ratios (OR) 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, Cary, NC).

### 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 (Figure 1). Specifically, the age-adjusted proportion of women reporting a family history in the BCSC increased from 12.3% in 1996 to 16.0% in 2010 compared to 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 (Figure 2). The proportion with a family history increased over time for women aged 50 years and older, and the increase over time was largest for the oldest women. For example, among women aged 70–74 years, the proportion increased 56% from 13.9% in 1996 to 21.6% in 2012, while the proportion increased 49% from 11.5 in 1996 to 17.1 in 2012 among women aged 50–54 years, and was relatively flat at 12.2% to 13.1% among women aged 40–44 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 to 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 affected relative, to 1.88 in the BCSC and 2.47 in the CBCS for women with more than one affected relative. 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 to 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 aged 40–49 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 et al. 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 (NHIS) 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 30–55 years and others such as Sellers et al. enrolling older women between ages 55–69 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 US have diminished over time, with estimates showing the average number of members per family in 2015 to be 3.1 compared to 3.5 in 1973 (36, 37). Hence, more recent generations have fewer siblings at risk for a breast cancer diagnosis.

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 et al. (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 – 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 towards the lower ends of these ranges, between about 1.3 to 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 since 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 to localized and DCIS stages, although 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 over-diagnosis, 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). Over-diagnosis 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 over-diagnosis 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 over-diagnosis, 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.

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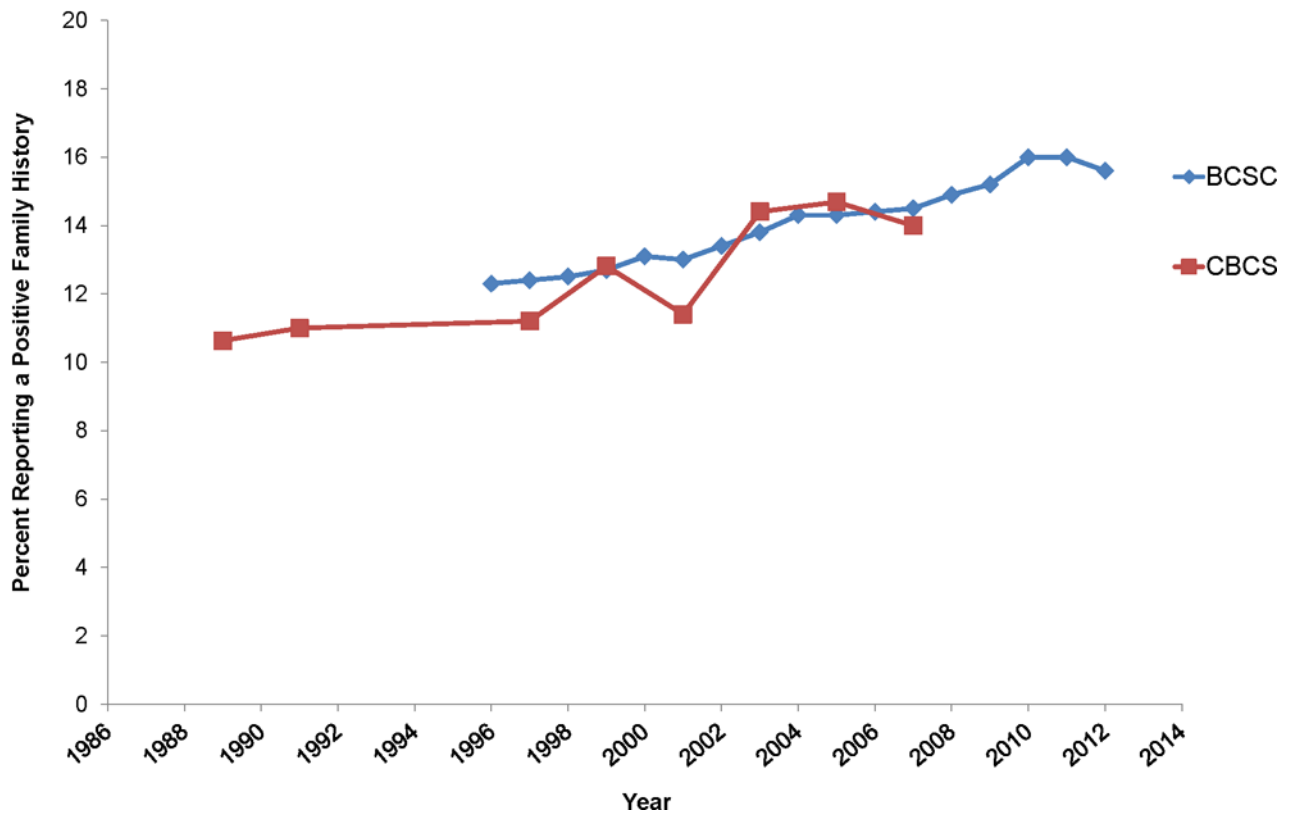
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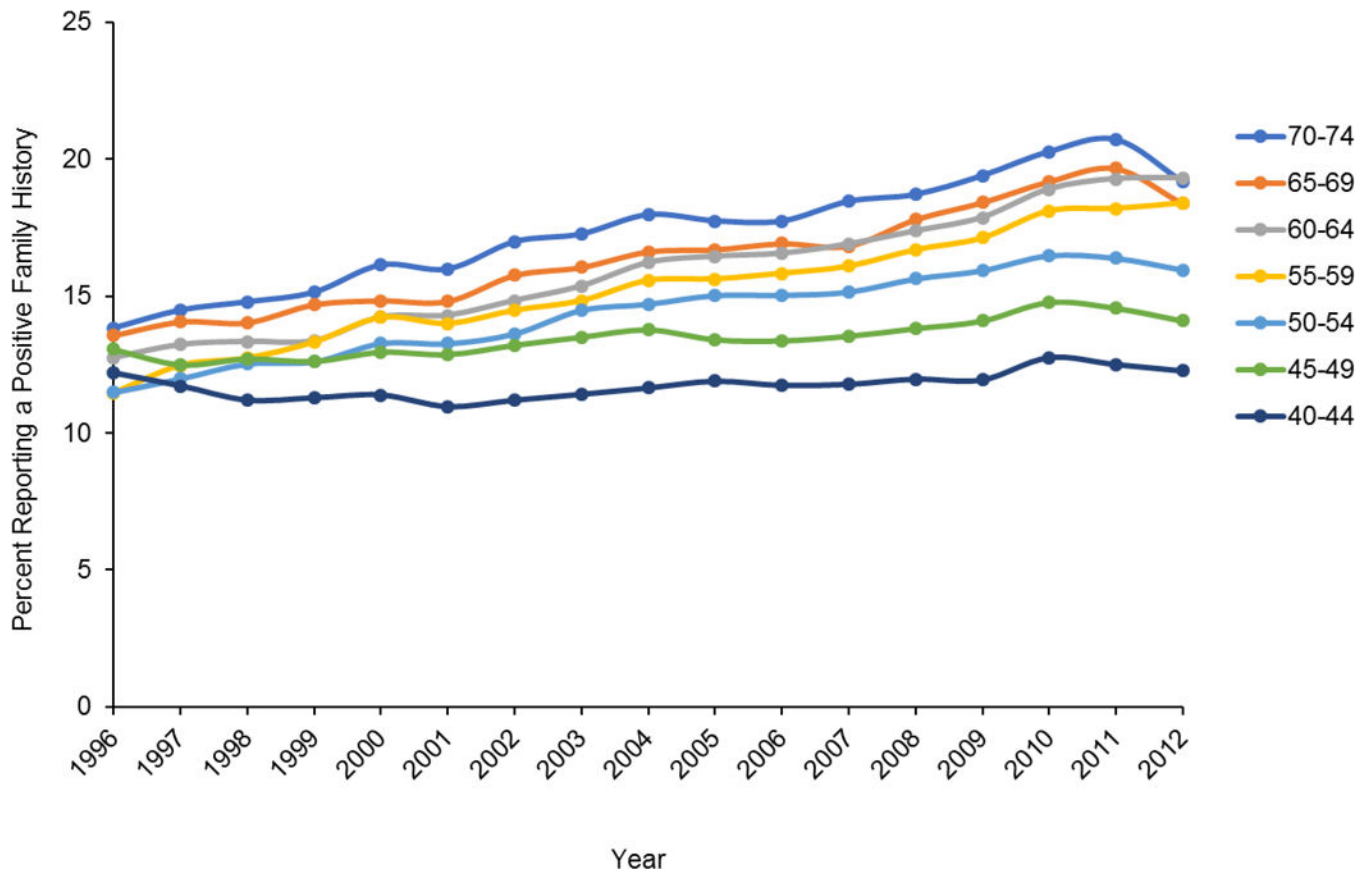
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**Figure 1.**

Proportion of women aged 40–69 years reporting a positive first-degree family history of breast cancer in the Breast Cancer Surveillance Consortium (BCSC, 1996–2012) and the Collaborative Breast Cancer Study (CBCS, 1987–2007). Percentages are adjusted for study site (BCSC registry and CBCS state) and age based on the 2000 US 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 aged 40–74 years reporting a positive first-degree family history of breast cancer by age and year, Breast Cancer Surveillance Consortium, 1996–2012.

Percentages are adjusted for mammography registry. Each woman contributed one randomly chosen observation per year.

Characteristics of participants in the Breast Cancer Surveillance Consortium (BCSC, 1996–2012) and Collaborative Breast Cancer Study (CBCS, 1987–2007)

Table 1

	BCSC <sup>a</sup>		CBCS	
	Controls N=26,460	Cases N=23,400	Col %	Col %
<b>Age at enrollment</b>				
40–49	471,306	40.3	5,381	20.3
50–59	363,237	31.0	8,663	32.7
60–74	336,357	28.7	12,416	46.9
<b>Year of report</b>				
1987–1993	NA	NA	13,035	49.3
1994–1999	160,872	13.7	7,505	28.4
2000–2004	406,526	34.7	4,451	16.8
2005–2009	432,321	36.9	1,469	5.5
2010–2013	171,181	14.6	NA	NA
<b>Benign breast biopsy</b>				
No	921,231	78.7	21,485	81.2
Yes	199,791	17.1	4,319	16.3
Unknown	49,878	4.3	656	2.5
<b>Race/ethnicity</b>				
Non-Hispanic White	784,651	67.0	25,617	96.8
Other	223,743	19.1	742	2.8
Unknown	162,506	13.9	101	0.4
<b>First-degree family history of breast cancer</b>				
None	1,025,508	87.6	22,875	86.5
Any	145,392	12.4	3,585	13.5
1	101,911	8.7	3,284	12.4
>1	10,536	0.9	301	1.1
Unspecified <sup>b</sup>	32,945	2.8	0	0

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; CBCS, Collaborative Breast Cancer Study; Col, column; NA, not available.

One randomly selected examination record per woman.  
Unknown number of affected family members (1 or more).

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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		
	N, total at Entry (N=1,170,900)	N, Cases (N=22,795)	HR (95% CI) <sup>a</sup>	Controls (N=26,460)	Cases (N=23,400)	OR (95% CI) <sup>a</sup>
<b>Any first-degree family history</b>	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 <sup>b</sup>	32,945	1,062	1.60 (1.50–1.70)	0	0	
<b>Year of diagnosis</b>						
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
<b>Stage of disease at diagnosis</b>						
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)
<b>Stage and year of diagnosis</b>						
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)

Variable	BCSC		CBCS		OR (95% CI) <sup>a</sup>
	N, total at Entry (N=1,170,900)	N, Cases (N=22,795)	Controls (N=26,460)	Cases (N=23,400)	
2000–2004	406,526	4,943	4,451	2,235	1.56 (1.37–1.77)
2005–2009	432,321	3,478	1,469	779	1.44 (1.15–1.81)
2010–2013	171,181	227	NA	NA	NA
Trend					P=0.03
Regional/distant					P=0.04
1987–1993	NA	NA	13,035	3,072	1.53 (1.37–1.70)
1994–1999	160,872	1,202	7,505	1,673	1.52 (1.32–1.75)
2000–2004	406,526	2,314	4,451	1,046	1.28 (1.07–1.53)
2005–2009	432,321	1,500	1,469	407	1.42 (1.06–1.88)
2010–2013	171,181	107	NA	NA	NA
Trend					P=0.12

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; CBCS, Collaborative Breast Cancer Study; HR, hazard ratio; NA, not available; OR, odds ratio.

<sup>a</sup>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).

<sup>b</sup>Unknown number of affected family members (1 or more).

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) <sup>a</sup>	Controls (N=26,460)	Cases (N=23,400)	OR (95% CI) <sup>a</sup>
<b>Age at breast cancer diagnosis (years)</b>						
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)
<b>Age and year of diagnosis</b>						
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)	414	382	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

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; CBCS, Collaborative Breast Cancer Study; HR, hazard ratio; NA, not available; OR, odds ratio.

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).

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