

# *A Detailed Analysis of Family History and the Risk of Breast Cancer*

## **Abstract**

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The authors conducted a detailed analysis of the risk of developing breast cancer for women with a family history of breast cancer in a population based case control study. Cases were women who were diagnosed with breast cancer from 1987 through 1993 (n=673). Controls were demographically similar women who resided in the same towns as the cases (n=619). Any family history of breast cancer was associated with a 70 percent increased risk (95 percent confidence interval: 1.3, 2.2). Women with any first degree family history had a slightly greater increase in risk [Odds ratio = 1.7 (95 percent confidence interval: 1.3, 2.3)] than those with any second degree family history [Odds ratio= 1.5 (95 percent confidence interval: 1.1, 2.1)]. Postmenopausal women had further increases in these risks [Odds ratio = 2.0 (95 percent confidence interval: 1.4, 2.7) for any first degree family history and Odds ratio = 1.7 (95 percent confidence interval: 1.2, 2.6 for any second degree family history]. Postmenopausal women whose affected relative was diagnosed at an older age ( $\geq 55$  years) had a higher risk than those whose affected relative was diagnosed at a younger age ( $< 55$  years) [Odds ratio = 2.5 vs. 1.5 for only an affected first degree relative and Odds ratio =2.0 vs. 1.5 for only an affected second degree relative]. These results confirm that family history is an independent risk factor for breast cancer and suggest that its impact varies according to the characteristics of the affected relative. **Journal of Women's Cancer, Volume 5(1), Pg. 24-29, 2005.**

**I**t is well known that women with a family history of breast cancer have an increased risk of breast cancer themselves (1-7). Epidemiologic and genetic studies have shown that breast cancer aggregates within families (4, 8, 9). However, most family history studies have focused on risks associated with having an affected first degree relative, specifically a mother or sister (1, 2, 3, 5, 7, 8, 10, 11, 12, 13). Only a few studies have investigated risks associated with having affected second degree relatives or various combinations of affected relatives (4, 6, 14, 15, 16, 17). Furthermore, studies examining the age at diagnosis of the affected relative have produced mixed results (1, 3, 8, 14, 18-20). The current study provides a detailed analysis of the risk of breast cancer for women with a first or second degree family history of breast cancer, with various combinations and numbers of affected relatives, and according to the diagnosis age of the affected relative. Other studies assessing the risks associated with family history have used mortality from breast cancer as the outcome of interest (2, 7). use of immunohistochemistry (IHC) was based on the fact that the missense mutations normally result in an increased half-life of the protein product and a consequence accumulation of the mutant p53 protein in the nucleus. Because associations with mortality may be biased, we have used incident breast cancer cases as our outcome.

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**MATERIALS AND METHODS**

Cases were women who were diagnosed with cancer of the breast (n=858) from 1987 through 1993 among permanent residents of eight towns in the Cape Cod area of Massachusetts (Barnstable, Bourne, Falmouth, Mashpee, Sandwich, Brewster, Chatham and Provincetown) and reported to the state Cancer Registry. All cases were confirmed by review of medical and pathological records. Controls were similarly aged female residents of the same Cape Cod towns during the years from 1987 to 1993. Since many cases were elderly or deceased when the study began, three sources were used to identify controls efficiently. Living controls under 65 were chosen using random digit dialing, and those aged 65 and over were chosen randomly from lists of Medicare beneficiaries furnished by the Centers for Medicare and Medicaid Services (CMS). Deceased controls of similar age as deceased cases were chosen randomly from a file furnished by the Massachusetts Bureau of Health Statistics, Research and Evaluation.

Random digit dialing was implemented to select a random sample of living telephone subscribers under age 65 who lived in the eight Cape Cod towns during years that the cases were diagnosed. The 1990 U.S. Census (21) reported that more than 97 percent of housing units in Massachusetts had telephone service. Random digit dialing identified a total of 3,402 residential households (table 1). Approximately 68 percent did not have any residents who met the inclusion criteria. An additional 15 percent never answered the phone after many calls, and roughly 9 percent would not answer the screening questions that determined eligibility. Ultimately, 248 households were found with an eligible resident, of whom 157 were interviewed.

Because random digit dialing is an inefficient way to identify elderly subjects, living controls 65 years of age and older were selected from a file of Medicare recipients provided by the CMS. Hatten estimated that Medicare recipients comprise 95 percent of individuals aged 65 years and older in the United States (22). Four hundred sixty-eight CMS controls were randomly chosen from residents of the eight Cape Cod towns using an age stratified sampling scheme. CMS controls who were deceased or were not residents of the study towns during the case ascertainment period were later excluded (table 1). Controls who died between January 1987 and December 1996 were randomly chosen from a file of all deaths that occurred among female residents of the eight Cape Cod towns.

Table 1. Selection and enrollment of breast cancer cases and controls.

	Cases	CMS* controls	Deceased controls	Random-digit dial controls
Selected	858	468	234	3,402
Excluded	54	16	20	515
Never located or contacted	25	74	34	2,639
Ineligible†	106	77	19	33
Physician or subject refusal	---	---	---	58
Target reached‡				
Interviewed	673	301	161	157

\* Centers for Medicare and Medicaid Services

† Includes women who did not meet the residence eligibility criteria, and CMS controls who died.

‡ Target number of interviews for RDD controls had been met.

All individuals, irrespective of the cause of death, were eligible for selection. Two hundred thirty-four deceased controls were chosen using a scheme that stratified on age and year of death. Deceased controls who were not study town residents during the case ascertainment period were later excluded.

Up to date addresses and telephone numbers of subjects, and, if necessary, their relatives, were identified from Cancer Registry and CMS records, physicians, tumor registrars, Bureau of Health Statistics' death, birth, and marriage records, state voter registration lists, drivers' license records, telephone books, directory assistance, and Internet resources. Following Cancer Registry policy, permission was obtained from treating physicians before interviewing living cancer cases. After obtaining verbal consent, trained staff carried out structured interviews to obtain information on family history of breast cancer, demographic characteristics, confounding variables such as age at diagnosis, age at first live birth or stillbirth, history of breast cancer and benign breast disease in the study subject.

Overall, 81 percent of the selected and eligible cases, 76 percent of CMS controls, 79 percent of deceased controls, and 83 percent of eligible and contacted random-digit dial controls were included in the final analysis (673 cases and 619 controls, table 1). Reasons for being excluded were failure to be located or contacted, failure to meet the eligibility criteria, inability to locate or obtain permission for interview from a treating physician (cases only), subject refusal, and reaching the target number of interviews (RDD controls only). The racial, vital status and geographic distribution of included and excluded eligible cases and non-RDD controls were quite similar. However,

excluded subjects tended to be older than included subjects (i.e., 55 percent and 58 percent of excluded cases and controls, respectively, were 70 years of age and older versus 40 percent each of included cases and controls)..

Respondent's health and cancer history information was ascertained from responses to survey questions. Family history of breast cancer was defined as having one or more blood relatives diagnosed with breast cancer. A first degree family history of breast cancer was defined as having an affected mother, sister(s) or daughter(s). A second degree family history of breast cancer was defined as having an affected grandmother(s) or aunt(s). Six main categories of family history were examined: any history, only first degree relative, any first degree relative, only second degree relative, any second degree relative, and a combination of first and second degree relatives. The specific affected relative (e.g., mother) and the number of affected relatives were also evaluated.

Women who only had an affected first degree relative or who only had an affected second degree relative were categorized as having an "only" first degree and "only" second degree history, respectively. Women who only had an affected first degree relative or who had affected first and second degree relatives were categorized as "any" first degree. Women who only had an affected second degree relative or who had affected first and second degree relatives were categorized as "any" second degree. Thus, a woman with only an affected sister was categorized as "only" first degree and "any" first degree history. A woman with an affected sister and aunt would be categorized as "any" first degree, "any" second degree and a combination of first and second degree. Overall, four hundred and ten subjects (31.7 percent) reported "any" family history of breast cancer.

First, crude associations for the various definitions of family history and the risk of breast cancer were computed if there were at least three exposed cases and three exposed controls. Next, subjects were stratified by potential confounding variables and Mantel Haenszel (MH) pooled estimates were calculated. A variable was considered a confounder if its pooled estimate differed from the crude estimate by 10 percent or more.

Multiple variable logistic regression models were used to control simultaneously for numerous confounders. Comparisons of the adjusted and crude estimates differed by less than ten percent for all of the variables assessed, including body mass index, race, education level, past use of hormone replacement therapy, past use of oral contraceptives, history of benign breast disease, and history of mammography.

The following variables were included in the final regression models because they were design variables or well-established risk factors for breast cancer: age at diagnosis or index year, vital status at interview, prior history of breast cancer in the study subject, prior history of medical treatment with ionizing, radiation, age at first live or stillbirth and history of mammography.

Because previous research has suggested that menopausal status differentially modifies a woman's risk of breast cancer (1, 14), we repeated these analyses among postmenopausal women. There were too few premenopausal women to estimate precisely the risk among these subjects.

We also stratified subjects by age at diagnosis of the woman's affected relative(s) (<55 and > 55) (23) and calculated crude and adjusted estimates for each stratum. If a subject had two affected first degree or two affected second degree relatives and age at diagnosis information was available for both relatives, the younger age was used. Women with affected first and second-degree relatives were omitted from this analysis.

Values for family history of breast cancer were imputed for subjects if information on the particular family history variable was missing for more than 10 percent of subjects. Sixteen percent of subjects were missing breast cancer information on grandmothers and 11 percent were missing information on aunts. Breast cancer histories were imputed using a random number imputation using the prevalence proportions of breast cancer for grandmothers (5 percent) and aunts (13 percent) among subjects with no missing values (24). Crude estimates of effect for subjects with and without imputed values were nearly identical, and so we present the analyses without imputations.

RESULTS

The characteristics of the study population are presented in table 2. Cases and controls were similar for most demographic and breast cancer risk factors. The mean age for cases and controls was 65 years. The majority of respondents were living at the time of interview, postmenopausal, white, and educated beyond high school. Crude estimates of effect according to family history of breast cancer are presented in table 3. Compared to women with no family history, subjects with an affected first degree relative had the greatest risk of breast cancer [Odds ratio (OR) = 1.9 (95 percent confidence interval: 1.4, 2.6) for only first degree and OR = 1.8 (95 percent confidence interval: 1.4, 2.4) for any first degree].

TABLE 2.: Case/control characteristics.

Characteristic	Cases (n=673)	Controls (n=619)
Mean Age (years)(SD)	65 (13.0)	65 (13.8)
Age (years) (%)†		
<50	16.5	16.6
50 -59	12.2	13.6
60 -69	31.5	29.9
70 -79	28.5	26.2
≥ 80	11.3	13.7
Body mass index (kg/m <sup>2</sup> )(%)‡		
< 21	22.0	19.9
21 - 25	46.3	49.3
25 - 29	22.0	22.9
> 29	9.7	7.9
Race (%)		
White	98.4	95.8
Other	1.6	4.2
Vital status at interview (%)		
Living	71.8	74.0
Deceased	28.2	26.0
Menopausal status (%)†		
Premenopausal	11.1	15.5
Postmenopausal	88.9	84.5
Education Level (%)† < High School		
High school graduate 1-3 years college/vocational	9.7	12.4
College degree/graduate work	35.4	33.1
Unknown	28.8	28.0
	24.8	25.7
	1.3	0.8
Past use of hormone replacement therapy (%)‡		
Yes	21.7	22.5
No	70.7	71.7
Unknown	7.6	5.8
Past oral contraceptive use (%)‡		
Yes	21.4	21.7
No	70.0	71.1
Unknown	8.6	7.2
Age (years) at first live or stillbirth (%)		
Nulliparous	24.1	20.2
< 24	29.4	34.6
24 - 29	30.8	31.3
≥ 30	14.5	12.6
Unknown	1.5	1.3
History of breast cancer (%)‡		
Yes	5.3	4.7
No	94.7	94.0
Unknown	0.0	1.3
History of benign breast disease (%)‡		
Yes	21.7	19.1
No	65.4	73.8
Unknown	12.9	7.1
History of medical treatment with ionizing radiation (%)‡		
Yes	4.0	6.8
No	92.9	90.6
Unknown	3.1	2.6
History of mammography (%)‡		
Yes	90.6	78.5
No	5.4	14.2
Unknown	4.0	7.3

\* At diagnosis year for cases and index year for controls. † Body mass index calculated using subject's usual weight. ‡ Prior to diagnosis year for cases and index year for controls.

Subjects with a second degree family history had a smaller increased risk [OR = 1.5 (95 percent confidence interval: 1.1, 2.2) for only second degree and OR = 1.5 (95 percent confidence interval: 1.1, 2.1) for any second degree].

The risks associated with having a specific affected relative or a combination of affected relatives are presented in table 4. Subjects with an affected mother or sister were at greatest risk (OR = 1.8 for mother and OR = 2.0 for sisters). Women with an affected daughter, aunt, and grandmother were at less increased risk (OR = 1.5, 1.4 and 1.5, respectively). For women with two or more affected relatives, the greatest risk was seen for women with an affected mother and sister [OR = 2.0 (95 percent confidence interval: 0.7, 6.5)]. In fact, as the number of affected first degree relatives increased, so did a woman's risk of breast cancer (OR=1.8 for one relative, OR=2.5 for two or more). This pattern was not seen for the number of affected second degree relatives.

After adjusting for age at diagnosis or index, vital status, history of breast cancer, history of ionizing radiation, age at first live or stillbirth, and history of mammography, nearly identical odds ratios were computed for all definitions of family history. Adjusted odds ratios are presented in tables 3 and 4. Crude and adjusted estimates for the various family history definitions among postmenopausal subjects are presented in tables 5 and 6. For most definitions, the risks for postmenopausal women were slightly higher than the estimates computed for all study subjects. The largest risks were seen for postmenopausal women with an affected mother (adjusted OR = 2.4), an affected sister (adjusted OR=2.0), and an affected aunt (adjusted OR=1.9). As expected, having two or more affected first degree relatives further increased the risk for postmenopausal women (adjusted OR = 2.7). The age at which a woman's relative was diagnosed with breast cancer influenced her risk of breast cancer. Having a first degree relative diagnosed with breast cancer at age 55 years or older was associated with a greater increased risk [OR = 2.1 (95 percent confidence interval: 1.4, 3.3) for only a first degree relative affected] than having a first degree relative diagnosed at less than age 55 years [OR = 1.4 (95 percent confidence interval: 0.9, 2.3) for only a first degree relative affected]. An increased risk was also seen for women with a second degree relative diagnosed at age 55 years or older [OR = 1.8 (95 percent confidence interval: 1.1, 3.0)]

for only a second degree relative affected] but not for women with a second degree relative diagnosed at less than 55 years of age [OR = 1.1 (95 percent confidence interval: 0.5, 2.2) for only a second degree relative affected]. We also examined the age at diagnosis of the affected relative among postmenopausal cases and controls. Risk estimates for the family history definitions among postmenopausal women were higher for women whose relatives were diagnosed at age 55 years or older than women whose relatives were diagnosed at less than 55 years of age (e.g., OR = 2.5 for age > 55 years and OR = 1.5 for age < 55 years for only a first degree family history of breast cancer, and OR = 2.0 for age > 55 and OR = 1.5 for age < 55 for only a second degree family history of breast cancer).

## DISCUSSION

We found an increase in the risk of breast cancer among women with a family history of breast cancer compared to women with no such history. Women with any family history of breast cancer had a 70 percent increased risk of breast cancer. Consistent with several previous reports (1, 3, 7, 11, 12, 13, 14, 17, 25, 26), we found that a first degree family history of breast cancer imparted an 80-90 percent increased risk and that a second degree family history was associated with a 60 percent increased risk. Furthermore, we found that a woman's risk of breast cancer increased as the number of affected first degree relatives' increased. Like other studies, women with both a mother and sister affected had a 90 percent increased risk (1, 2).

When the data were limited to postmenopausal women, the risks were further increased. Unfortunately, the study population included too few premenopausal women to calculate precisely the odds ratios among these cases and controls. Other studies have also found that postmenopausal women with a positive family history have elevated risks (1, 11, 14, 18, 27, 28). Research addressing a postmenopausal woman's risk of breast cancer according to the age at which her family member was diagnosed with cancer has produced conflicting results (1, 3, 5, 8, 14, 18, 29). In some studies the risks were more elevated when the relative was diagnosed at a younger age (e.g., 8) while in others the risk was more elevated when the relative was diagnosed at an older age (e.g., 29). In our study, postmenopausal women with a relative diagnosed at a later age (> 55 years) were at greater risk than if the relative was younger (< 55 years) at diagnosis.

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