

Breast cancer risk in young women and history of selected medical conditions

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Background Several common medical conditions are associated with altered hormone levels, and may thus plausibly influence breast cancer risk. Few studies have examined such relationships, and we utilized a population-based case-control study of young women in the US to examine breast cancer risk following a history of various medical conditions. Relationships between breast cancer and each medical condition examined are biologically plausible, and relevant in terms of public health.

Methods The study included 2173 breast cancer cases and 1990 population-based controls from three areas of the US, under 55 years, who were administered a questionnaire including details of physician-diagnosed medical conditions.

Results No significantly increased or decreased breast cancer risk was associated with a history of thyroid disease, gallbladder disease, colorectal polyps, diabetes, high blood pressure, high cholesterol or surgery for endometriosis. There was some evidence of an increased breast cancer risk associated with ovarian cysts among women who did not receive an oophorectomy (relative risk [RR] = 1.94, 95% CI : 1.0–3.9). Non-significant increases in breast cancer risk were observed following diagnoses of several other cancers, including thyroid cancer, basal cell carcinoma, Hodgkin's disease and malignant melanoma.

Conclusions To conclude, our generally null results from this large, population-based study support results from previous studies in providing reassurance that women with a history of several common medical conditions do not appear to be at an increased risk of breast cancer at a young age.

Keywords Breast cancer, medical history, diabetes, ovarian cysts

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Breast cancer is the most common female cancer in the US but, despite intensive research, only about half of the occurrence is due to established risk factors such as a family history of breast cancer, and reproductive and menstrual factors.^{1,2} Elevated levels of oestrogens are suspected to increase breast cancer risk,^{3,4} and other endogenous hormones such as progesterone,

ovarian and adrenal androgens, insulin, and thyroid hormones may also play a role.^{4–6} Several common medical conditions are associated with altered hormone levels, and may thus influence breast cancer risk. For example, clinical and experimental evidence suggests that decreased thyroid function may increase breast cancer risk,⁴ the prevalence of cholesterol gallstones is associated with use of exogenous oestrogens, and also with endogenous ovarian hormones,⁷ and non-insulin dependent diabetes mellitus (NIDDM) is characterized by high levels of circulating insulin, a known growth-promoting hormone for normal breast epithelial cells and breast cancer cells cultured *in vitro*.⁸ Other hormone-related disorders include endometriosis and ovarian cysts, whose relationship to breast cancer remains unresolved.^{9–12} Breast cancer may also be associated with several other cancers, including malignant melanoma, Hodgkin's disease, and cancers of the endometrium, ovary, colorectum, thyroid and salivary glands.^{13–15} Hypertension may reduce breast cancer risk by blocking oestrogen-stimulated growth through elevated levels of maternal serum α -fetoprotein,¹⁶ while low serum cholesterol may increase breast cancer risk in younger women.¹⁷

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Relationships between breast cancer and these medical conditions are biologically plausible, and relevant in terms of public health, yet relatively few epidemiological studies have examined them. Results from studies have been largely null, although, with one exception,¹⁸ confidence intervals (CI) were wide and associations could not be ruled out.^{11,19,20} Two case-control studies of male breast cancer have suggested associations with hyperthyroidism, gallstones, diabetes and high blood cholesterol.^{21,22}

The present analyses use data from a large population-based case-control study of breast cancer risk in young women.²³ As part of a detailed administered questionnaire, study subjects were asked about their previous medical history, providing an opportunity to examine associations between various medical conditions and breast cancer in this population.

Materials and Methods

This population-based case-control study was conducted in three geographical areas in the US covered by cancer registries—Atlanta, Seattle/Puget Sound and five counties in central New Jersey. Details have been published elsewhere.²³ Briefly, the present analyses consist of all women aged 20–44 years in Seattle and New Jersey, and aged 20–54 in Atlanta, who were newly diagnosed with *in situ* or invasive breast cancer during the period 1 May 1990 to 31 December 1992. Cases were identified through rapid ascertainment systems, and controls were chosen through random digit dialling and were frequency matched by geographical area and age to the expected distribution of cases. A 90.5% response rate to the telephone screener was obtained from 16 254 telephone numbers.

Structured face-to-face interviews were carried out, and complete interviews were obtained from 2202 of the 2551 eligible cases (86.3%) and 2009 of the 2571 eligible controls (78.1%). In order for the cases to be comparable with the controls, the 29 cases without residential telephones were excluded from the analyses. The 19 controls who had been previously diagnosed with breast cancer were also excluded from analyses. The study population consisted of the remaining 2173 cases and 1990 controls. Information on risk factors was truncated at the reference date (i.e. date of diagnosis for cases or the date of completion of the telephone screener for controls).

The interview included detailed information on reproductive and menstrual history, contraceptive behaviour and screening history. Subjects were also asked a series of questions on medical history in the period up to one year prior to the reference date, including whether they had ever received a diagnosis by a physician of thyroid disease, gallstones or gallbladder disease, 'sugar' diabetes (not during a pregnancy), polyps in the colon or rectum, high blood pressure (not during a pregnancy), high cholesterol, or a cancer other than that of the breast. For each condition, the year of first diagnosis and the method of treatment (hospitalization, surgery and/or medication) were recorded. Women were defined as having a history of endometriosis or ovarian cysts only if they had undergone surgery for these conditions. Women were defined as postmenopausal if they had either undergone a natural menopause, or surgery to remove both ovaries, or if their ovarian function was unknown but they were older than 51 years (assumed to be the median age of menopause²⁴). Alcohol intake was defined as

the lifetime average consumption up to 2 years before reference date.

Odds ratios (OR) and 95% CI were calculated by multiple logistic regression, adjusting for age at reference date as a continuous variable, and the following established or suspected risk factors as categorical variables: race, menopausal status, family history of breast cancer in a first degree relative, previous breast biopsy, a combination variable of number of full-term births and age at first full-term birth, number of mammograms received within the 5-year period prior to one year before reference date, recent body mass index (BMI), average lifetime alcohol consumption, and study site.

Results

The majority of subjects were <45 years (1647 cases, 1501 controls). There were 526 cases and 489 controls aged 45–54, and these were from Atlanta only. A higher proportion of women in this age group were black (22% of controls aged >45, compared with 14% of controls aged <45). However, OR associated with breast cancer risk factors were similar in both age groups (results not shown). Major risk factors were a family history in a first-degree relative, a previous breast biopsy, premenopausal status, low parity, and older age at first full-term birth. There was also some evidence of a relationship between breast cancer risk with BMI, alcohol consumption, and number of mammograms undergone in the previous 5 years. All of the above risk factors were adjusted for in analyses of each medical condition.

Results for thyroid diseases and gallbladder disease are shown in Table 1. Thyroid disorders as a group were not associated with breast cancer risk (OR = 0.94), although the risk was slightly increased among women who had received surgery (OR = 1.29). There was no significant variation in risk with duration of thyroid disease, type of thyroid disease or menopausal status at the time of breast cancer diagnosis (results not shown). There were insufficient patients to examine treatment effects by type of thyroid disease. A previous study suggested that women diagnosed with any thyroid disease before the age of 20 may be at a higher risk of breast cancer than those diagnosed as adults,¹¹ but there was no evidence of this in the present study (OR_{≤20 years} = 0.82, OR_{>20 years} = 0.99).

No association was seen between breast cancer and a previous diagnosis of gallstones or gallbladder disease (OR = 1.03, Table 1), although the risk was slightly higher among women with a diagnosis of gallbladder disease within the last 5 years (OR = 1.29).

A history of colorectal polyps was associated with a non-significantly reduced risk of breast cancer (OR = 0.77, Table 2). However, the number of subjects with a history of colorectal polyps was small, and there was no significant variation in risk with type of treatment, time since diagnosis of the polyps, or menopausal status (results not shown). Risk of breast cancer was slightly increased among women with a history of adult-onset diabetes (OR = 1.13, Table 2). Analyses were restricted to women with onset at age ≥30 since the vast majority of these cases will have NIDDM.²⁴ This increased risk was only evident among women who had received medication for their diabetes (OR = 1.39), and among women who had been diagnosed with diabetes 5 or more years prior to breast cancer diagnosis (OR_{≥5 years} = 1.38).

Table 1 Relative risk (RR) of breast cancer in women with a history of thyroid disease or gallbladder disease

	Cases	Controls	RR ^a	95% CI
Thyroid disease				
Never diagnosed ^b	1952	1787	1.00	
Ever diagnosed ^c	215	196	0.94	0.8–1.2
Treatment				
Any medication	190	172	0.94	0.7–1.2
Any hospitalization	48	35	1.15	0.7–1.8
Any surgery	48	32	1.29	0.8–2.1
Untreated	15	17	0.78	0.4–1.6
Years since thyroid disease diagnosis^d				
1–4	40	44	0.79	0.5–1.2
5–9	32	26	1.17	0.7–2.0
10–14	31	31	0.86	0.5–1.4
15+	106	91	0.95	0.7–1.3
Gallbladder disease or gallstones				
Never diagnosed ^b	2046	1870	1.00	
Ever diagnosed ^c	123	118	1.03	0.8–1.4
Treatment				
Any medication	27	29	1.01	0.6–1.7
Any hospitalization	103	96	1.08	0.8–1.5
Any surgery	102	92	1.13	0.9–1.5
Untreated ^f	12	11	1.13	0.5–2.6
Years since gallstones or gallbladder diagnosis^g				
1–4	30	24	1.29	0.7–2.2
5–9	30	26	1.08	0.6–1.9
10+	62	66	0.97	0.7–1.4

^a Adjusted for age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, body mass index, and number of mammograms within the 5-year period prior to one year before diagnosis.

^b Reference group.

^c Excludes six cases and seven controls with unknown diagnosis.

^d Excludes six cases and four controls with unknown year of diagnosis.

^e Excludes four cases and two controls with unknown diagnosis.

^f Excludes two cases and two controls with unknown treatment.

^g Excludes one case and two controls with unknown diagnosis.

No significant association was seen between breast cancer and high blood pressure (OR = 0.86, Table 3), although there was a marginally significantly reduced risk among untreated women (OR = 0.72). No significant variation of OR was seen with time since first diagnosis of high blood pressure, or by whether the diagnosis was made pre- or post-menopausally. A previous study suggested that hypertension diagnosed before a last pregnancy has a protective effect on breast cancer,¹⁶ but we saw no evidence for this (OR = 1.04, 95% CI : 0.7–1.5). In contrast, there was a reduced risk among women diagnosed with high blood pressure after the end of their last pregnancy (OR = 0.76, 95% CI : 0.6–1.0).

High cholesterol levels were not associated overall with breast cancer risk (OR = 0.90, 95% CI : 0.7–1.1, Table 3). The OR did not vary between those diagnosed with breast cancer pre- and post-menopausally (results not shown).

Table 4 shows results of breast cancer risk following surgery for endometriosis or ovarian cysts. There was no overall association with surgery for endometriosis (OR = 1.14). The risk was greater among premenopausal women (OR = 1.68), especially among those with recent surgery (OR_{1–9 years} = 2.38, 95%

CI : 1.0–5.5, results not shown). There was no significant association between breast cancer and surgery for ovarian cysts (OR = 1.16). Oophorectomy is known to reduce the risk of breast cancer,¹² and the women who underwent partial or total oophorectomy as treatment for ovarian cysts had no altered risk of breast cancer (OR = 0.97). In contrast, women with ovarian cysts but no oophorectomy were at an increased risk of breast cancer (OR = 1.94, 95% CI : 1.0–3.9). This risk was particularly elevated among women with a recent surgery (OR_{1–9 years} = 3.45), although this was based on just six cases and two controls.

Relationships between breast cancer and previous diagnoses of other cancers are shown in Table 5. There was no significant overall association (OR = 1.11), and the risk did not vary with method of treatment. There was a greater risk among post-menopausal women (OR = 1.76) than among premenopausal women (OR = 1.05). No significant increase in breast cancer risk was associated with any individual cancer site, though there was some evidence of an increased risk with a previous diagnosis of thyroid cancer (OR = 2.04, 10 cases), basal cell carcinoma (OR = 2.01, 14 cases), Hodgkin's disease (OR = 1.80, 11 cases) and malignant melanoma (OR = 1.35, 16 cases, results not

Table 2 Relative risk (RR) of breast cancer in women with a history of colorectal polyps or diabetes

	Cases	Controls	RR ^a	95% CI
Colorectal polyps				
Never diagnosed ^b	2136	1951	1.00	
Ever diagnosed ^c	34	38	0.77	0.5–1.3
Treatment				
Any medication	6	13	0.43	0.2–1.2
Any hospitalization	15	12	0.96	0.4–2.1
Any surgery	19	20	0.79	0.4–1.5
Untreated	13	10	1.12	0.5–2.6
Years since polyps diagnosis^d				
1–4	12	14	0.76	0.3–1.7
≥5	21	24	0.72	0.4–1.3
Diabetes				
Never diagnosed ^b	2125	1949	1.00	
Diagnosed aged ≥30 years ^c	33	31	1.13	0.7–1.9
Treatment				
Any medication	27	21	1.39	0.8–2.6
Any hospitalization	7	8	0.84	0.3–2.5
Untreated	9	12	0.50	0.2–1.5
Years since diabetes diagnosis				
1–4	12	16	0.86	0.4–1.9
≥5	21	15	1.38	0.7–2.8

^a Adjusted for age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, body mass index, and number of mammograms within the 5-year period prior to one year before diagnosis.

^b Reference group.

^c Excludes three cases and one control with unknown diagnoses.

^d Excludes one case with unknown year of diagnosis.

^e Fourteen cases and 9 controls diagnosed before age 30 are excluded. Excludes one case with unknown year of diagnosis.

shown). However, the numbers of events were small and lacked power to detect a significantly increased risk. There was no evidence of an increased risk of breast cancer following diagnoses of cancer of the cervix, uterus or ovary.

Discussion

The largely null results in this study support previous studies,^{11,18–20} and provide further reassurance that young women with these conditions are not at an increased risk of breast cancer. The study is large and has the advantage of being population-based rather than hospital-based. However, the young age range results in few women with some of the medical conditions under study, and true associations with breast cancer may therefore not have been detected. Further, the study was designed to assess breast cancer risk in relation to oral contraceptive use, and questions on medical history were relatively brief. A potential source of bias is that medical history is defined as self-reported physician-diagnosed disease and was not verified. However, it has been shown that self-reporting of most chronic conditions (including thyroid diseases, diabetes, gallbladder disease, hypertension, and cancer), and recall of prior hospitalization and surgery is reasonably accurate,^{25–27} although self-reported high cholesterol may be less so.²⁸ It is possible that non-differential misclassification may have contributed to the null findings. Any bias due to cases recollecting medical history more completely than controls would

tend to increase relative risks,²⁹ and would not explain the null results observed.

Despite clinical observations of thyroid disease in breast cancer patients,⁴ there is little epidemiological support for an association.^{4,18,19,30,31} Details of the types of medication used for treatment of thyroid disease were not available in our study, and it is possible that treatment of hyperthyroidism with radioactive iodine ¹³¹I may be associated with an increased risk of breast cancer, but evidence for this is not conclusive.^{4,11,32} Our results provide further evidence that young women with thyroid disease are at no altered risk of breast cancer.

Both gallbladder disease and breast cancer are more prevalent in females than in males, and also in developed countries, possibly suggesting common hormonal and dietary risk factors.⁶ Increased risks of cancers of the breast, reproductive system and gastrointestinal tract in women with gallstone disease aged <50 have been seen,³³ but our results support most other studies in finding no association.^{11,18–20,34,35}

Colorectal adenomatous polyps are precursor lesions for most colorectal cancers,³⁶ and several studies have found an association between breast and colorectal cancers, suggesting shared risk factors.^{14,15} Two studies found an increased prevalence of colorectal polyps in breast cancer cases compared with hospital controls^{37,38} but our null finding supports more recent work.^{39,40}

Breast cancer shares several risk factors with NIDDM, including increased prevalence in females compared with males,

Table 3 Relative risk (RR) of breast cancer in women with a history of physician-diagnosed high blood pressure or high cholesterol

	Cases	Controls	RR ^a	95% CI
High blood pressure (HBP)				
Never diagnosed with HBP ^b	1895	1693		
Ever diagnosed ^c	274	292	0.86	0.7–1.1
Treatment				
Any medication	189	187	0.94	0.7–1.2
Any hospitalization	17	28	0.61	0.3–1.2
Untreated ^d	82	104	0.72	0.5–1.0
Years since HBP diagnosis^e				
1–4	84	90	0.90	0.7–1.2
5–9	71	77	0.85	0.6–1.2
≥10	112	121	0.81	0.6–0.1
High cholesterol				
Never diagnosed with high cholesterol ^b	1859	1676	1.00	
Ever diagnosed ^f	299	290	0.90	0.7–1.1
Treatment				
Any medication	25	17	1.43	0.8–2.7
Untreated ^g	272	271	0.87	0.7–1.1
Years since high cholesterol diagnosis^h				
1–4	230	234	0.86	0.7–1.1
5–9	46	38	1.03	0.7–1.6
≥10	21	14	1.38	0.7–2.8

^a Adjusted for age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, body mass index, and number of mammograms within the 5-year period prior to one year before diagnosis.

^b Reference group.

^c Excludes four cases and five controls with unknown diagnoses.

^d Excludes three cases with unknown treatment.

^e Excludes seven cases and four controls with unknown year of diagnosis.

^f Excludes 15 cases and 24 controls with unknown diagnoses.

^g Excludes two cases and one control with unknown treatment history.

^h Excludes two cases and four controls with unknown year of diagnosis.

central obesity (for postmenopausal women), and, possibly, a protective effect of physical activity.⁴¹ Insulin is an important growth factor for human breast cancer cells cultured *in vitro*⁸ and it is interesting to note that significant associations with breast cancer risk have been noted with serum C-peptide levels⁴² (an accurate estimate of insulin secretion) and with circulating concentrations of insulin-like growth factor.⁴³ In most investigations, however, no association has been seen between breast cancer and diabetes,^{11,19,21,44,45} although a recent study did support a modest elevation in risk for postmenopausal breast cancer.¹⁸ The lack of an association for the most part could be due to the natural history of NIDDM, which is characterized by hyperinsulinaemia in early stages, followed by hypoinsulinaemia as the disease progresses.⁴⁶

The slightly reduced breast cancer risk associated with a previous diagnosis of high blood pressure did not vary with menopausal status, in contrast to two other studies where a history of high blood pressure was associated with a reduced risk of breast cancer in premenopausal women, but an increased risk in postmenopausal women.^{19,20} In the present study, there was no evidence of an increased risk associated with use of medications, contrasting with studies from the 1970s that suggested that reserpine was associated with breast cancer, a

relationship that has not been subsequently confirmed.¹⁷ One study of women aged under 55 found a significantly reduced risk of breast cancer among parous women whose high blood pressure was diagnosed prior to the end of their most recent pregnancy.¹⁶ However, this result was not supported in a larger study,¹⁹ or in the present study.

Several cohort studies have found no association between breast cancer risk and total serum cholesterol,^{47–50} although in one study higher cholesterol levels were associated with a significantly lower risk of breast cancer among women aged under 50.⁵¹ The slightly reduced risk seen in the present study is likely to be due to chance, but possibly also to the cholesterol-lowering effect of the preclinical cancer,^{17,52} as the reduction was seen only among women with a recent diagnosis of high cholesterol. Our study is limited by the lack of biological samples and by the self-reported history of high cholesterol, which was largely untreated.

Both endometriosis and ovarian cysts are associated with increased levels of ovarian hormones.^{9,10} The suggested increased breast cancer risk among premenopausal women in this study following surgery for endometriosis supports findings from several previous studies.^{11,53} The extent to which this relationship is biological or due to shared risk factors remains

Table 4 Relative risk (RR) of breast cancer in women with previous surgery for endometriosis or ovarian cysts

	Cases	Controls	RR ^a	95% CI
Surgical diagnosis of endometriosis				
Never diagnosed ^b	2120	1947	1.00	
Ever diagnosed	53	43	1.14	0.7–1.8
Years since surgery^c				
1–9	28	19	1.37	0.7–2.5
≥10	24	18	1.22	0.6–2.3
Premenopausal women				
Never diagnosed ^b	1919	1725	1.00	
Ever diagnosed	37	19	1.68	0.9–3.0
Postmenopausal women				
Never diagnosed ^b	298	213	1.00	
Ever diagnosed	16	24	0.50	0.2–1.1
Surgical diagnosis of ovarian cysts				
Never diagnosed ^d	1932	1748	1.00	
Ever diagnosed	64	49	1.16	0.8–1.7
Treatment				
Oophorectomy ^e	38	36	0.97	0.6–1.6
No oophorectomy	27	13	1.94	1.0–3.9
Years since surgery^f				
1–9	6	2	3.45	0.7–17.5
10–19	10	5	1.75	0.6–5.3
≥20	9	6	1.35	0.5–3.9
Premenopausal women^g				
Never diagnosed ^d	1798	1624	1.00	
Ever diagnosed with cysts, undergone oophorectomy	29	17	1.56	0.8–2.9
Ever diagnosed with cysts, no oophorectomy	26	12	1.99	1.0–4.0

^a Adjusted for age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, body mass index, and number of mammograms within the 5-year period prior to one year before diagnosis.

^b Reference group for analyses of endometriosis.

^c Excludes one case and six controls with unknown year of diagnosis.

^d Reference group for analyses of ovarian cysts. Excludes 170 cases and 187 controls who had a partial or total oophorectomy prior to the development of ovarian cyst.

^e Includes partial oophorectomy.

^f Among women without an oophorectomy only. Excludes two cases with unknown year of diagnosis.

^g Only two postmenopausal women (one case and one control) with ovarian cysts had not had an oophorectomy.

unclear. Breast cancer and ovarian cysts also share risk factors such as nulliparity, early age at menarche and late age at first birth,¹⁰ but previous studies have not found an association between breast cancer and ovarian cysts among premenopausal women,^{11,18,19} possibly because of the inclusion of women who had undergone an oophorectomy.

No significant association between breast cancer and a history of a previous cancer was seen in this study. However, numbers are small and the data are consistent with previously observed associations between breast cancer and malignant melanoma, thyroid cancer and Hodgkin's disease.^{13,54,55} Oestrogen receptors have been found in malignant melanoma cells, suggesting that oestrogens may be involved in the aetiology.¹³ The increased risk of breast cancer following Hodgkin's disease may be a treatment effect of radiotherapy or chemotherapy,⁵⁵ although an increased risk has also been seen among the few patients receiving neither radiotherapy nor chemotherapy.⁵⁴ The present study is too small to evaluate the effect of treatment for other cancers on subsequent breast cancer risk. Ovarian cancer

and breast cancer share several risk factors such as nulliparity and late age at menopause, and the observed OR associated with ovarian cancer (OR = 1.21) may be an underestimate, as the three cases and three controls each underwent surgery for ovarian cancer, which would reduce the risk of breast cancer.¹²

To conclude, our generally null results from this large, population-based study support results from previous studies in providing reassurance that women with a history of several common medical conditions do not appear to be at an increased risk of breast cancer at a young age. Many of these conditions, however, were relatively rare among our younger study subjects. Given that many of these conditions could potentially be biologically related to subsequent breast cancer risk, future studies should continue to investigate effects among older women.

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Table 5 Relative risks (RR) of breast cancer in women with a previous diagnosis of cancer

	Cases	Controls	RR ^a	95% CI
Never previously diagnosed with cancer^b	2071	1913	1.00	
Ever diagnosed with cancer^c	101	77	1.11	0.8–1.5
Treatment^d				
Any medication	23	19	1.08	0.6–2.0
Any hospitalization	63	50	1.13	0.8–1.7
Any surgery	97	72	1.13	0.8–1.6
Years since diagnosis of first cancer^c				
1–4	22	26	0.76	0.4–1.4
5–9	26	14	1.52	0.8–3.0
≥10	52	37	1.18	0.8–1.8
Premenopausal women				
Never diagnosed ^b	1858	1667	1.00	
Ever diagnosed	80	64	1.05	0.8–1.5
Postmenopausal women				
Never diagnosed ^b	211	240	1.00	
Ever diagnosed	21	13	1.76	0.7–4.5

^a Adjusted for age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, body mass index, and number of mammograms within the 5-year period prior to one year before diagnosis.

^b Reference group.

^c Excludes one case with unknown diagnosis.

^d Excludes three cases and two controls who did not report any treatment.

^e Excludes one case with unknown year of diagnosis.

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