Risk Factors for Carcinoma *in Situ* of the Breast[1]

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Abstract

As more women obtain screening mammograms regularly and at younger ages, the diagnosis of breast carcinoma *in situ* becomes more frequent. To examine whether risk factors for carcinoma *in situ* correspond with risk factors for invasive breast cancer, we analyzed data from a population-based case-control study conducted in 1988–1990. We identified newly diagnosed cases of carcinoma *in situ* ($n = 301$) and invasive breast cancer ($n = 3789$) in women 18–74 years of age from Wisconsin's statewide tumor registry. Cases and population controls ($n = 3999$) completed structured telephone interviews. Overall, associations with risk of carcinoma *in situ* in relation to many reproductive life-style risk factors were similar to those associated with risk of invasive disease. Women who reported a family history of breast cancer had a 2-fold elevated risk of carcinoma *in situ* (odds ratio, 2.67; 95% confidence interval, 2.00–3.57). Personal history of benign biopsied breast disease also increased risk of carcinoma *in situ* (odds ratio, 2.19; 95% confidence interval, 1.62–2.95). Subgroup analysis suggested that high vitamin A intake and high alcohol intake may be associated with risk of ductal but not lobular carcinoma *in situ*. These data support the presence of common risk factors between *in situ* and invasive breast cancer.

Introduction

The widespread adoption of screening mammography in females >50 years of age in the 1980s resulted in a rise in the diagnosis of invasive breast cancer (1–5). During that time, the previously uncommon diagnosis of ductal and, to a lesser extent, lobular BCIS[3] (3) also increased markedly (1, 6–8). In Wisconsin, BCIS incidence increased >300% between 1980 and 1988 (5). Although the majority of treated BCIS cases perhaps will not subsequently develop to invasive cancer, ductal BCIS is generally recognized as the penultimate step in the progression of invasive tumors (9, 10). Lobular BCIS is less likely to progress to invasive cancer, but it is considered a marker for significantly increased risk of invasive breast cancer (10).

Despite the dramatic increase in incidence and the likelihood of carcinoma *in situ* to precede a diagnosis of invasive disease without definitive treatment, the epidemiology of BCIS is not well understood. It is not known whether BCIS shares some, or all, risk factors with invasive disease. Factors involved early in cancer development might be common to these two conditions. In contrast, factors involved in progression, including promoting agents such as estrogens, might be more strongly associated with invasive disease than with BCIS. To evaluate risk factors for BCIS, we conducted a population-based case-control study.

Materials and Methods

Identification of Cases. All female residents of Wisconsin with a new diagnosis of *in situ* or invasive breast cancer who were <75 years of age were eligible for this study. Cases were identified by Wisconsin's mandatory cancer registry during the period of April 1988 through December 1990. Information from the state registry was available on follow-up physician. According to an institutionally approved protocol, the physician of record for each eligible case was contacted by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers and known dates of diagnosis. For comparability with controls, cases <65 years of age without a driver's license (by self-report) were not eligible. Of the 354 eligible *in situ* cases, physicians refused contact for 40 (11%) cases, 2 (<1%) were deceased, 1 (<1%) could not be located, and 10 (3%) refused to participate. Of the 4563 eligible invasive cases, physicians refused contact for 380 (8.3%) cases, 271 (5.9%) were deceased, 11 (<1%) could not be located, and 112 (2.5%) refused to participate. Thus, data for 301 *in situ* cases (85%) and 3789 invasive cases (83%) were available for analysis.

Tumor registry reports included information regarding cancer site, morphology codes, extent of disease, demographics, diagnostic confirmation, and definitive therapy. *In situ* and invasive cases were distinguished according to the fifth digit behavior code (*in situ* = 2, invasive = 3) of the morphology code (11). For both *in situ* and invasive cases, 99% of diagnoses were confirmed through positive histology. Subtypes of BCIS cases were defined as lobular morphology 8520 (11) and ductal/nonlobular (8500, 8501, 8503, 8504, 8010, and 8140).

Identification of Controls. Community controls were randomly selected from two sampling frames: those under age 65 years were selected from a list of licensed drivers, and controls aged 65–75 years were selected from a roster of Medicare beneficiaries compiled by the Health Care Financing Administration. Computer files of potential controls were obtained annually. The controls were selected to have an age distribution similar to that of the invasive breast cancer cases, but the selection otherwise was made at random. Controls had no previous diagnosis of breast cancer and met the eligibility

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[3] The abbreviations used are: BCIS, breast carcinoma *in situ*; OR, odds ratio; CI, confidence interval.

criterion of having a listed telephone number. Of the 4445 potential controls, 49 (1%) were deceased, 21 (<1%) could not be located, and 376 (9%) refused to participate. The overall response rate for control subjects was 90% ($n = 3999$).

Data Collection. Cases and controls were sent letters briefly describing the study before they were contacted by telephone. The 25-min telephone interview elicited information on reproductive experiences, including exogenous hormone use, history of beverage-specific alcohol use, selected dietary items, tallest adult height, and weight 5 years before interview, medical history, and demographic factors. Questions were included on participation in strenuous physical activity or team sports for ages 14–22 years; the number of years of participation, months during the year, and frequency of participation were requested for up to three activities or sports. The interview also included one question eliciting whether the women had ever had a mammogram; cases were asked about any mammography before their diagnosis. Information about the women's personal and family histories of breast cancer was obtained at the end of the interview to maintain blinding.

Reliability Study. After 6–12 months, we reinterviewed 211 control subjects to assess the reliability of the questionnaire. Overall, reproducibility was high. The κ statistic for a family history of breast cancer in a mother or sister was 0.85 (12). Spearman correlation coefficients for recent alcohol consumption ($r = 0.77$), recent body weight ($r = 0.92$), and duration of postmenopausal hormone use ($r = 0.99$) also demonstrated reliability (13–14).

Analyses. Only exposure status before an assigned reference date was used in this analysis. For cases, this was the date of breast cancer diagnosis. For comparability, control subjects were assigned a reference date corresponding to the average time from diagnosis to interview for the case group (~1 year). Age was defined as the age at diagnosis or reference date. Parity was the number of full-term pregnancies (defined as pregnancy >6 months resulting in live or still birth). Menopausal status was defined as postmenopausal if the subject reported a natural menopause or a bilateral oophorectomy prior to diagnosis or reference date. Women reporting hysterectomy alone were classified as postmenopausal if the age at surgery was greater than or equal to the 90th percentile of age at natural menopause for the control group (54 years for smokers and 55 for nonsmokers). Menopausal status was considered to be unknown for women with hysterectomy without bilateral oophorectomy if the age at surgery was between 42 and 54 years (or 55 years for nonsmokers).

A positive family history of breast cancer was defined as a diagnosis in a mother or sister. Alcohol intake was calculated as the sum of servings of beer, wine, and mixed drinks in the decade preceding the reference date; we assumed one serving of beer contained 12.8 g of alcohol, one 4-oz glass of wine contained 11 g, and one mixed drink contained 15 g (13). Frequency of physical activity was defined as the average number of episodes per week of ≤3 strenuous activities during the ages of 14–22 years. Body mass index was calculated as weight 5 years before interview (kg)/tallest adult height $(m)^2$. Daily β-carotene intake was evaluated as the content of β-carotene from raw and cooked spinach and carrots consumed 2 years before the interview (15). Postmenopausal hormone use was defined as the use of oral, injectable, or transdermal noncontraceptive hormones, including estrogens and/or progestins, for ≥3 consecutive months. The minimum duration of "ever" oral contraceptive use was also defined as 3 months.

Table 1 Distribution of selected characteristics of 301 BCIS cases and 3789 invasive breast cancer cases from Wisconsin, 1988–1990

	In situ		Invasive	
	n	%	*n*	%
Age at diagnosis (yr)				
28–44	56	18.6	570	15.0
45–54	80	26.6	777	20.5
55–64	87	28.9	1047	27.6
65–74	78	25.9	1395	36.8
Histologic type				
Ductal	228	75.7	2709	71.5
Lobular	63	20.9	300	7.9
Other or not specified	10	3.3	780	20.6
Screening mammogram before diagnosis				
Yes	192	63.8	1775	46.9
No	75	24.9	1366	36.1
Not asked	34	11.3	648	17.0
Method of tumor detection				
Self	59	19.6	1756	46.3
Mammogram	182	60.5	1122	29.6
Health care practitioner	20	6.6	310	8.2
Other medical procedure[a]	4	1.3	6	0.2
Not asked	36	12.0	595	15.7

[a] Includes breast reduction surgery (two *in situ*, one invasive), biopsy (two *in situ*, two invasive), and other radiographic exams (three invasive).

ORs and 95% CIs obtained from polytomous logistic regression models were used to evaluate relative risks (16). All models included terms for age (5 categories), age at first birth (six categories), family history of breast cancer (no, yes, don't know), age at menopause (four categories, premenopausal, unknown), history of screening mammography (yes, no, don't know), and education (four categories); these covariates were chosen *a priori* as potential confounders. For each risk factor examined, models were fit twice: once with controls as the base category and once with invasive cases as the base category. Categorical variables were also represented as continuous variables when we assessed trends in separate models. Subjects with unknown values for any factors in the analyses were included using a separate dummy variable in the models (*e.g.*, personal history of benign breast disease, family history of breast cancer, and age at menopause).

Results

Most *in situ* tumors were classified as ductal ($n = 228$); 21% were lobular ($n = 63$; Table 1). Relative to invasive cases, BCIS cases were younger, were more likely to report obtaining a screening mammogram before their diagnosis (ductal *in situ*, 60.5%; lobular *in situ*, 74.6%; invasive, 46.9%), and were more likely to have their lesions detected through mammography (ductal *in situ*, 60.5%; lobular *in situ*, 61.9%; invasive, 29.6%).

Patterns of risk for BCIS according to several established risk factors for invasive breast cancer mirrored the associations expected for invasive tumors (Table 2). Using controls as the base category, a family history of breast cancer was associated with a 2-fold increase in risk of BCIS (OR, 2.67; 95% CI, 2.00–3.57). A personal history of biopsied benign breast disease was also associated with a 2-fold increased risk (OR, 2.19; 95% CI, 1.62–2.95). Later age at first birth increased risk, and higher parity decreased risk of BCIS. Age at menarche, age at menopause, and education were not significantly associated with risk of BCIS.

Elevated risk was found for BCIS using invasive cases as

Table 2 ORs and 95% CIs for BCIS and invasive breast cancer according to established risk factors for invasive breast cancer, Wisconsin 1988–1990

	Controls	*In situ vs.* controls		Invasive *vs.* controls		*In situ vs.* invasive
	n	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]	OR (95% CI)[a]
Family history of breast cancer						
No history	3484	216	1	2990	1	1
Some history	442	71	2.67 (2.00–3.57)	691	1.92 (1.69–2.19)	1.39 (1.05–1.85)
Don't know	73	14	3.33 (1.84–6.03)	108	1.74 (1.28–2.36)	1.92 (1.07–3.42)
Biopsied benign breast disease						
No	3474	221	1	3155	1	1
Yes	453	68	2.19 (1.62–2.95)	542	1.44 (1.26–1.66)	1.52 (1.13–2.04)
Don't know	72	12	3.03 (1.55–5.93)	92	1.26 (0.89–1.70)	2.48 (1.28–4.79)
Age at menarche (yr)						
≥15	557	46	1	476	1	1
14	725	54	0.90 (0.59–1.35)	685	1.09 (0.93–1.29)	0.82 (0.54–1.24)
13	1137	82	0.82 (0.56–1.19)	1121	1.19 (1.03–1.39)	0.68 (0.47–1.00)
12	856	62	0.83 (0.55–1.23)	828	1.17 (1.00–1.38)	0.70 (0.47–1.05)
<12	680	54	0.87 (0.57–1.32)	618	1.13 (0.95–1.33)	0.77 (0.51–1.17)
Continuous per yr			1.02 (0.95–1.10)		0.97 (0.95–1.33)	1.06 (0.98–1.14)
			$P = 0.5$		$P = 0.4$	$P = 0.1$
Age at first birth[b] (yr)						
<20	624	34	1	519	1	1
20–24	1811	122	1.23 (0.82–1.84)	1598	1.06 (0.92–1.22)	1.16 (0.77–1.74)
25–29	826	70	1.53 (0.97–2.40)	835	1.19 (1.01–1.40)	1.29 (0.82–2.03)
≥30	274	25	1.70 (0.97–2.98)	320	1.33 (1.08–1.64)	1.28 (0.73–2.24)
Continuous per yr			1.03 (1.00–1.06)		1.02 (1.00–1.03)	1.01 (0.98–1.04)
			$P = 0.1$		$P = 0.01$	$P = 0.5$
Parity						
Nulliparous	495	50	1	530	1	1
1	360	39	0.86 (0.49–1.54)	383	0.91 (0.72–1.14)	0.95 (0.54–1.70)
2	981	62	0.51 (0.30–0.87)	963	0.89 (0.73–1.08)	0.58 (0.34–0.98)
3	873	73	0.69 (0.42–1.14)	765	0.81 (0.66–0.98)	0.85 (0.52–1.41)
4+	1290	77	0.52 (0.32–0.84)	1148	0.80 (0.67–0.97)	0.65 (0.40–1.05)
Continuous per pregnancy			0.91 (0.85–0.98)		0.96 (0.93–0.98)	0.96 (0.89–1.03)
			$P = 0.01$		$P < 0.001$	$P = 0.2$
Age at menopause (yr)						
<45	503	34	1	376	1	1
45–49	595	43	1.05 (0.66–1.68)	589	1.29 (1.08–1.55)	0.81 (0.51–1.30)
50–54	915	56	0.91 (0.58–1.42)	996	1.44 (1.22–1.70)	0.63 (0.40–0.99)
≥55	317	20	0.98 (0.55–1.76)	311	1.29 (1.04–1.60)	0.76 (0.42–1.36)
Premenopausal	981	87	1.05 (0.64–1.73)	895	1.26 (1.02–1.55)	0.83 (0.50–1.38)
Unknown age or status	688	61	1.32 (0.85–2.06)	622	1.27 (1.07–1.51)	1.04 (0.67–1.62)
Continuous per yr			1.00 (0.97–1.04)		1.03 (1.02–1.04)	0.98 (0.95–1.01)
			$P = 0.8$		$P < 0.001$	$P = 0.2$
Education						
No high school diploma	693	39	1	692	1	1
High school graduate	1835	127	1.11 (0.75–1.63)	1724	0.99 (0.87–1.13)	1.12 (0.76–1.64)
Some college	916	70	1.14 (0.74–1.75)	809	0.92 (0.79–1.08)	1.23 (0.81–1.89)
College graduate	555	65	1.54 (0.97–2.43)	564	1.06 (0.88–1.26)	1.45 (0.92–2.30)

[a] Adjusted as appropriate for age, age at first birth, family history of breast cancer, age at menopause, history of screening mammography, and education. In addition, the ORs and 95% CIs shown are mutually adjusted.
[b] Among parous women only.

the base category for both a family history of breast cancer (OR, 1.39; 95% CI, 1.05–1.85) and a personal history of benign breast disease (OR, 1.52; 95% CI, 1.13–2.04). Power was limited to rule out the possibility of modest associations seen for invasive breast cancer between risk of BCIS and other established risk factors, including reproductive factors and age at menopause.

Associations between life-style factors and risk of disease are shown in Table 3. Alcohol consumption was associated with an increased risk for BCIS, so that the OR among women who drank at least 183 g/week (~2 drinks/day) was 2.34 (95% CI, 1.32–4.16 *versus* controls). The ORs for the extreme categories of physical activity, β-carotene intake (from cooked and raw spinach and carrots), and lactation duration were all less than unity. Greater body mass index was not significantly associated with BCIS among postmenopausal women. CIs for the risk estimates according to these life-style factors mostly contained one when comparing odds of BCIS to the odds of invasive breast cancer.

ORs for BCIS according to exogenous hormone use were modestly elevated (Table 4). The OR for oral contraceptive use was 1.24 (95% CI, 0.91–1.68 *versus* controls) and did not vary by duration of use. The OR for use of postmenopausal hormones within the past 5 years was 1.90 (95% CI, 1.24–2.92 *versus* controls). Risk did not differ appreciably according to preparation of use (estrogen alone or estrogen with progesterone; data not shown). Unexpectedly, ORs decreased rather than increased according to increasing duration of postmenopausal hormone use (P trend = 0.1). Risk estimates for BCIS associated with use of postmenopausal hormones were uniformly

Table 3 ORs and 95% CIs for BCIS and invasive breast cancer according to lifestyle risk factors for invasive breast cancer, Wisconsin 1988–1990

	Controls	*In situ vs.* controls		Invasive *vs.* controls		*In situ vs.* invasive
	n	*n*	OR (95% CI)[a]	*n*	OR (95% CI)[a]	OR (95% CI)[a]
Recent alcohol intake (g/wk)						
None	641	37	1	593	1	1
<39	2180	154	1.12 (0.76–1.63)	1954	1.01 (0.89–1.15)	1.10 (0.76–1.62)
39–90	641	53	1.26 (0.80–1.96)	626	1.11 (0.94–1.30)	1.13 (0.73–1.77)
91–182	323	28	1.34 (0.80–2.25)	330	1.17 (0.96–1.43)	1.14 (0.68–1.92)
≥183	139	21	2.34 (1.32–4.16)	218	1.76 (1.37–2.25)	1.33 (0.75–2.34)
Continuous per 26 g/wk			1.01 (0.99–1.04)		1.02 (1.00–1.03)	1.00 (0.98–1.02)
			$P = 0.2$		$P = 0.01$	$P = 0.8$
Early adulthood physical activity						
None	2466	186	1	2405	1	1
<7/wk	1373	104	0.93 (0.72–1.20)	1255	0.95 (0.86–1.05)	0.97 (0.76–1.26)
≥7/wk	73	3	0.56 (0.17–1.80)	41	0.57 (0.38–0.85)	0.97 (0.30–3.20)
Continuous per frequency/wk			0.99 (0.92–1.07)		0.96 (0.93–0.99)	1.03 (0.96–1.11)
			$P = 0.8$		$P = 0.02$	$P = 0.5$
Body mass index[b] (kg/m^2)						
<21	436	33	1	357	1	1
21–24	1173	88	1.03 (0.68–1.57)	1066	1.16 (0.98–1.37)	0.90 (0.59–1.36)
25–29	739	38	0.74 (0.45–1.20)	748	1.25 (1.05–1.49)	0.59 (0.36–0.96)
≥30	482	33	1.01 (0.60–1.68)	561	1.44 (1.19–1.75)	0.70 (0.42–1.17)
Continuous per 1 kg/m^2			1.00 (0.97–1.03)		1.02 (1.01–1.03)	0.98 (0.95–1.01)
			$P = 0.9$		$P = 0.001$	$P = 0.2$
Daily β-carotene intake quartile						
1 (<760 kIU)	955	76	1	944	1	1
2 (760–149 kIU)	977	81	1.09 (0.79–1.52)	913	0.95 (0.84–1.08)	0.90 (0.59–1.36)
3 (150–258 kIU)	969	89	1.18 (0.85–1.63)	914	0.95 (0.83–1.08)	0.59 (0.36–0.96)
4 (>258 kIU)	1098	55	0.68 (0.47–0.98)	1018	0.93 (0.82–1.06)	0.70 (0.42–1.17)
Continuous per 100 kIU			0.99 (0.99–1.00)		1.00 (1.00–1.00)	0.98 (0.95–1.01)
			$P = 0.1$		$P = 0.8$	$P = 0.2$
Duration of lactation[c]						
Never	1270	100	1	1170	1	1
Ever	2176	149	0.90 (0.68–1.18)	2044	1.02 (0.92–1.14)	0.91 (0.69–1.20)
<12 mo	1674	112	0.91 (0.68–1.22)	1586	1.04 (0.93–1.16)	0.88 (0.66–1.17)
12–23 mo	298	24	0.96 (0.60–1.55)	293	1.04 (0.86–1.25)	0.92 (0.57–1.49)
≥24 mo	204	13	0.73 (0.39–1.34)	165	0.85 (0.67–1.06)	0.86 (0.46–1.59)
Continuous per mo			1.00 (0.98–1.01)		1.00 (0.99–1.00)	1.00 (1.00–1.01)
			$P = 0.6$		$P = 0.1$	$P = 0.9$

[a] Adjusted as appropriate for age, age at first birth, family history of breast cancer, age at menopause, history of screening mammography, and education. In addition, the ORs and 95% CIs shown are mutually adjusted.
[b] Among postmenopausal women only.
[c] Among parous women only.

greater than estimates for invasive disease, although most CIs for the comparisons included one.

Although the sample size constrained our evaluation, we did observe some differences between risk factors for lobular BCIS ($n = 63$) and ductal BCIS ($n = 228$) using controls as the base category. OR estimates for lobular BCIS were somewhat greater in magnitude than for ductal BCIS according to a personal history of benign breast disease and age at first birth (Table 5). The reduction in risk of BCIS according to high intake of vitamin A appeared restricted to ductal BCIS, whereas high intake of alcohol significantly increased risk of ductal BCIS but not lobular BCIS. Associations between risk of both BCIS subtypes and other factors, such as family history and use of exogenous hormones, were similar.

Discussion

We found that many risk factors for carcinoma *in situ* of the breast were similar to those established for invasive breast cancer. Common factors included family history, reproductive events such as age at first birth and parity, as well as exposures more proximate to diagnosis such as recent alcohol consumption. Some factors consistently associated with invasive breast cancer, such as age at menopause and body mass index, were not strongly associated with BCIS in this study. However, sample sizes were too small to detect possible modest associations between risk of BCIS and several other factors. Because the majority of cases were ductal, this analysis primarily reflects risk factors for this lesion.

Other studies have found similar risk factors for both invasive cancer and BCIS (17–24). OR estimates in our study are generally comparable to those from these other reports. In particular, our risk estimate for a positive family history of invasive breast cancer in a first-degree relative (OR, 2.7) is similar to most (17, 19, 20) but not all (21, 22) other studies that report 2- to 3-fold increases in risk. Our risk estimates for benign breast disease and age at first birth are similar to other reports (17, 19, 21, 24). Few studies have examined other life-style factors.

Most other reports (18, 19, 23, 25–28) have also described elevated risks associated with postmenopausal hormone use. The prevalence of postmenopausal hormone use has been increasing (29), and use of screening mammography has also been increasing since the 1980s (30). These two behaviors are highly correlated

Table 4 ORs and 95% CIs for BCIS and invasive breast cancer according to exogenous hormone use, Wisconsin 1988–1990

	Controls *n*	*In situ vs.* controls		Invasive *vs.* controls		*In situ vs.* invasive
		n	OR (95% CI)[a]	*n*	OR (95% CI)[a]	OR (95% CI)[a]
Oral contraceptive use						
Never	2518	166	1	2392	1	1
Ever	1422	130	1.24 (0.91–1.68)	1337	1.17 (1.03–1.32)	1.06 (0.78–1.44)
Duration (yr)						
<2	456	41	1.21 (0.81–1.79)	446	1.20 (1.02–1.41)	1.01 (0.68–1.49)
2–5	445	39	1.17 (0.77–1.77)	422	1.17 (0.99–1.38)	1.00 (0.66–1.52)
>5	521	50	1.33 (0.90–1.95)	469	1.13 (0.96–1.32)	1.18 (0.80–1.73)
Continuous per yr			1.02 (0.99–1.05)		1.01 (0.99–1.02)	1.01 (0.98–1.04)
			$P = 0.3$		$P = 0.3$	$P = 0.5$
Postmenopausal hormone use[b]						
Never	1498	82	1	1443	1	1
Ever	626	65	1.92 (1.34–2.75)	591	1.17 (1.01–1.34)	1.65 (1.15–2.36)
Time since last use (yr)						
<5	363	39	1.90 (1.24–2.92)	286	1.02 (0.85–1.22)	1.87 (1.21–2.87)
5–19	191	17	1.75 (1.00–3.05)	223	1.35 (1.09–1.67)	1.30 (0.75–2.25)
≥20	72	9	2.53 (1.18–5.42)	82	1.34 (0.95–1.88)	1.88 (0.88–4.02)
Duration (yr)						
<2	182	25	2.41 (1.48–3.92)	179	1.14 (0.91–1.43)	2.12 (1.30–3.44)
2–4	143	14	1.91 (1.04–3.50)	147	1.28 (1.00–1.65)	1.49 (0.81–2.72)
5–9	121	11	1.66 (0.85–3.25)	100	1.05 (0.79–1.40)	1.58 (0.80–3.10)
≥10	180	15	1.53 (0.84–2.80)	165	1.17 (0.93–1.49)	1.30 (0.71–2.39)
Continuous per yr			1.02 (1.00–1.05)		1.01 (1.00–1.02)	1.02 (0.99–1.04)
			$P = 0.1$		$P = 0.2$	$P = 0.3$

[a] Adjusted as appropriate for age, age at first birth, family history of breast cancer, age at menopause, history of screening mammography, and education. In addition, the ORs and 95% CIs shown are mutually adjusted.
[b] Among postmenopausal women only.

(31). Furthermore, the effects of postmenopausal hormones on the density of breast tissue (32–34) may increase the likelihood of biopsy and the serendipitous finding of BCIS, particularly of lobular BCIS. Thus, it is difficult to disentangle the independent effects of postmenopausal hormones on BCIS incidence. Restricting our control group to women with a history of screening mammography did attenuate risk estimates for BCIS associated with use of postmenopausal hormones (OR, 1.43; 95% CI, 1.00–2.04 for ever use) as well as benign breast disease (OR, 1.56; 95% CI, 1.16–2.10) and family history of breast cancer (OR, 2.39; 95% CI, 1.78–3.21). These three factors tend to be present in women who have greater health care use, which includes mammography and clinical breast examination. Yet, the prevalence of past mammography use in our BCIS case group was high (72% among cases who answered the screening question), and our estimates, including the complete control group, are reassuringly similar to those from two studies involving completely screened populations (20, 21, 23).

The observed differences in risk factors for lobular and ductal BCIS are notable, although limited by our sample size. Few studies have specifically examined risk factors for lobular and ductal BCIS. Our results agree with those of Weiss *et al.* (17) in that the magnitude of the risk estimates for lobular BCIS associated with benign breast disease and age at first birth were greater than for ductal BCIS. Unlike the results reported here, Weiss *et al.* (17) found greater ORs for family history with ductal BCIS than with lobular BCIS. As Weiss *et al.* note, though, sample sizes for lobular BCIS were small and the estimates were not stable. Distinctive etiological pathways may be responsible for differing associations between risk factors and subtypes of BCIS. Indeed, two recent reports suggest that risk estimates for invasive disease may vary by histological subtype (28, 35).

The relation between several risk factors—including postmenopausal hormone use, benign breast disease, and family history—was stronger for BCIS than for invasive disease. Colditz *et al.* (26) reported a slightly higher risk estimate for BCIS associated with recent hormone use than for invasive disease, as did we. The higher observed risks, in this study and in others (19, 23), may be attributable to surveillance bias when screening is associated both with detection and the risk factors. However, among the published studies that included BCIS and postmenopausal hormone use (18, 19, 23, 25–28), the highest elevated risk estimate was reported from the Breast Cancer Detection Demonstration Project [2.3; 95% CI, 1.3–3.9 for use of estrogen and progestin (23)]. This study perhaps was the most valid assessment of risk factors for BCIS because all participants received regular examinations.

Studies of BCIS should provide an opportunity to observe whether exposures exert their effects early or late in the tumorigenic process (36). To date, studies—including our own—have confirmed a few associations between selected factors and both invasive and *in situ* breast disease, whereas small sample sizes have limited the ability to rule out effects between BCIS and some established risk factors for invasive disease. More precise evaluation of any risk factor differences according to histology will depend upon larger study populations.

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Table 5 ORs and 95% CIs for BCIS according to histologic type, Wisconsin 1988–1990

	Controls *n*	Lobular BCIS ($n = 63$)		Ductal/nonlobular BCIS ($n = 238$)	
		n	OR (95% CI)[a]	*n*	OR (95% CI)[a]
Family history of breast cancer					
No	3484	44	1	172	1
Yes	442	17	2.95 (1.65–5.27)	54	2.68 (1.93–3.72)
Benign breast disease					
No	3474	37	1	184	1
Yes	453	22	3.86 (2.19–6.81)	46	1.88 (1.32–2.68)
Age at first full-term birth (yr)					
<20	603	5	1	28	1
20–24	1817	28	1.84 (0.69–4.87)	95	1.14 (0.73–1.77)
25–29	836	19	2.75 (0.97–7.81)	51	1.30 (0.79–2.15)
≥30 or nulliparous	743	11	2.12 (0.70–6.47)	64	1.88 (1.16–3.06)
Daily β-carotene intake quartile					
1 (<760 kIU)	955	12	1	64	1
2 (760–149 kIU)	977	17	1.40 (0.66–2.98)	64	1.03 (0.71–1.48)
3 (150–258 kIU)	969	18	1.50 (0.71–3.18)	71	1.13 (0.79–1.61)
4 (>258 kIU)	1098	16	1.36 (0.63–2.94)	39	0.54 (0.35–0.84)
Continuous per 100 kIU			1.01 (1.00–1.02)		0.99 (0.98–1.00)
			$P = 0.2$		$P = 0.004$
Alcohol intake (g/wk)					
None	641	11	1	26	1
<39	2180	34	0.68 (0.33–1.39)	120	1.31 (0.84–2.05)
39–90	641	7	0.45 (0.17–1.21)	46	1.68 (1.01–2.79)
≥91	462	11	1.03 (0.43–2.47)	38	1.82 (1.07–3.08)
Continuous per 26 g/wk			0.99 (0.92–1.07)		1.00 (0.99–1.02)
			$P = 0.9$		$P = 0.8$
Use of oral contraceptives					
Never	2518	32	1	134	1
Ever	1422	29	1.19 (0.64–2.21)	101	1.25 (0.89–1.77)
Use of postmenopausal hormones[b]					
Never use	1498	18	1	64	1
Time since last use (yr)					
<5	363	9	1.63 (0.69–3.89)	30	2.03 (1.24–3.34)
≥5	263	7	2.46 (0.95–6.40)	19	1.83 (1.05–3.20)

[a] Adjusted as appropriate for age, age at first birth, family history of breast cancer, age at menopause, and education. In addition, the ORs and 95% CIs shown are mutually adjusted.
[b] Among postmenopausal women only.

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