HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2016 November 22.

Published in final edited form as:

Cancer Causes Control. 2015 December ; 26(12): 1771–1778. doi:10.1007/s10552-015-0670-9.

Risk Factors for Young-Onset Invasive and *In Situ* Breast Cancer

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Abstract

Purpose—Young-onset breast cancers tend to be more aggressive than later-onset tumors and may have different risk factor profiles. Among young-onset cases there may also be etiologic differences between ductal carcinomas *in situ* (DCIS) and invasive breast cancer, particularly if some factors promote malignant transformation.

Methods—We evaluated the association between several potential risk factors and young-onset breast cancer in the Two Sister Study (2008–2010), a sister-matched case-control study involving 1406 women diagnosed with breast cancer before age 50 (1185 invasive, 221 DCIS) and 1648 controls.

Results—Older age at menarche, younger age at menopause, premenopausal hysterectomy, early age at first-term pregnancy, obesity, and consumption of alcohol were associated with reduced risk of young-onset breast cancer. These patterns remained when we limited analysis to invasive breast cancers. In general, effect estimates were similar for young-onset invasive breast cancer and DCIS, although the number of DCIS cases was small.

Conclusions—In this sister-matched case-control study of young-onset breast cancer, many of the studied risk factors were associated with young-onset invasive breast cancer. There were few discernable differences in risk factors for young-onset DCIS versus young-onset invasive breast cancer.

Keywords

breast cancer; young-onset breast cancer; ductal carcinoma in situ; etiologic heterogeneity

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Author contributions: CRW, DPS, and LAD designed the study. KMO, JS, and CRW analyzed the data and wrote the manuscript, with contributions from DPS and LAD.

The authors have no financial or nonfinancial conflicts of interest to declare.

INTRODUCTION

Roughly 20% of invasive and 25% of *in situ* breast cancers diagnosed in the United States occur in women younger than 50. [1] Young-onset breast cancer tends to be more aggressive than later-onset disease, with higher stage and grade at presentation [2] and more estrogen receptor-negative or triple-negative subtypes. [3]

These clinical discrepancies may result from age-related etiologic differences. Several studies have evaluated established breast cancer risk factors specifically in young (usually age<50) or premenopausal women. Some of these factors, such as later age at menarche and later age at first full term pregnancy, show similar trends in young women. [4, 5] Others show opposite effects. For example, it is well-established that high body mass index (BMI) is inversely associated with breast cancer in young/premenopausal women, but positively associated with breast cancer in older/postmenopausal women. [5–7] This discrepancy is thought to be related to the relationship between adipose tissue, circulating estrogen levels, and estrogen metabolism. [7]

Ductal carcinoma *in situ* (DCIS) is a milk duct carcinoma that can become invasive and spread into surrounding tissues. [8] In the United States, approximately 20% of all young-onset cases have DCIS. [1] Researchers have long sought to understand the natural history of DCIS and identify factors that influence its invasive transformation. It is possible that among young-onset cases, DCIS and invasive breast cancer may have somewhat distinct etiologies.

Among women of all ages, there is some evidence that *in situ* breast cancer is associated with nulliparity, later age at first term pregnancy (i.e., at least 37 weeks gestation), later age at menopause, and low premenopausal BMI. [9–21]

On the other hand, findings on the relationships between *in situ* breast cancer and lactation, age at menarche, oral contraceptive use, and alcohol use have been inconclusive. [9, 13–15, 17–22] Few studies have looked at risk factors for DCIS that may be specific to young women.

In an effort to improve our understanding of the etiology of young-onset breast cancer, we conducted an epidemiologic study of invasive breast cancer and DCIS in young women. We considered several previously established risk factors for invasive disease in older women and ran separate analyses for all young-onset breast cancers combined versus controls, invasive breast cancer cases versus controls, and DCIS cases versus controls.

METHODS

We used data from the Two Sister Study, a sister-matched case-control study of young-onset breast cancer (2008–2010). The Two Sister Study is an offshoot of the Sister Study (2003–2009; http://www.sisterstudy.org), which enrolled 50,884 breast cancer-free women from the United States and Puerto Rico whose sister had been diagnosed with the disease. If a Sister Study participant's affected sister was diagnosed with invasive breast cancer or DCIS before age 50 and within the previous four years, the proband sister was recruited for the Two Sister

Study. Her matched controls included all of her full sisters already participating in the Sister Study. The final sample included 1419 cases and 1665 sister controls.

All participants completed the same baseline computer-assisted telephone interviews. Case sisters additionally answered questions about their breast cancer diagnosis and provided signed medical records releases. All participants gave their consent and the study was approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus group.

To minimize confounding by age and ensure comparable opportunity for exposure, we evaluated time-dependent covariates as of a family-specific index age. For each sibship, the index age was defined as the minimum of the age of the case at diagnosis and the age(s) of her sister control(s) at interview. In this way, the sisters were essentially matched on age.

We considered the following risk factors: age at menarche, menopausal status (premenopausal, postmenopausal with age at menopause <45, postmenopausal with age at menopause ≥45, or premenopausal with hysterectomy but retained ovarian tissue), number of full term pregnancies (lasting at least 37 weeks), ever use of oral contraceptives, height, average non-pregnant BMI during ages 30–39, average alcohol use during the previous 10 years, and smoking history (never, former or current). We also examined whether age at first full term pregnancy or breastfeeding affected the risk of breast cancer in parous women. Women were considered postmenopausal if their ovaries had been removed or if they had not had a menstrual period for one year while not pregnant or breastfeeding.

Invasive status was ascertained from case medical records, when available (88%), or self-report (11%). Women with both *in situ* and invasive tumor features were categorized as invasive.

We used conditional logistic regression to examine effects of the selected risk factors on all breast cancers, DCIS, or invasive breast cancer while accounting for sister-matching. [23] We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for each cancer type, relative to controls. Potential confounders included education, relative birth order among participating sisters, and all other evaluated risk factors, as described above. We used directed acyclic graphs to identify confounders. [24] Age, race, and family history of breast cancer were implicitly controlled for by the design. We also conducted trend tests for risk factors measured continuously.

Tests of homogeneity for invasive breast cancer versus DCIS were conducted using likelihood ratio tests. Here, we compared a model that included all breast cancer cases grouped together to a model that allowed for the exposure main effects to vary by invasive status. The difference in the deviances of the two models followed a chi-square distribution with p degrees of freedom, where p was the one less than the number of categories used to define the main exposure. All statistical analyses were conducted using SAS (9.3, SAS Institute, Cary, NC).

RESULTS

Of the 1419 Two Sister Study cases, 1185 (84%) had invasive breast cancer, 221 (15%) had DCIS, and 13 (1%) could not be classified (Table 1). Approximately 87% of all participants had completed education beyond high school and most participants were non-Hispanic white. Control sisters were 47.3 years old on average at interview, while invasive and DCIS cases were 44.1 and 44.8 years on average at diagnosis, respectively.

Early age at menarche (≤12 versus ≥14) was associated with increased risk of all young-onset breast cancer (OR=1.45, 95% CI: 1.11–1.89) and invasive breast cancer (OR=1.51, 95% CI: 1.13–2.01), specifically (Table 2). The relationship between age at menarche and young-onset DCIS was less clear (OR=1.05, 95% CI: 0.52–2.11), but the test for homogeneity indicated there was no significant difference between the effect estimates for invasive breast cancer versus DCIS (p=0.67). Compared with being premenopausal, early age at menopause (age <45) was associated with reduced risk of all young-onset breast cancer (OR=0.48, 95% CI: 0.33–0.69) and young-onset invasive breast cancer (OR=0.38, 95% CI: 0.25–0.58), but not young-onset DCIS (OR=1.38, 95% CI: 0.58, 3.30). A similar contrast was seen for having had a hysterectomy, in that the overall protective association was more pronounced for invasive breast cancer (OR=0.64, 95% CI: 0.44–0.93) than for DCIS (OR=0.96, 95% CI: 0.44–2.10). There was some evidence that the risk relationships with menopausal status are different for invasive breast cancer versus DCIS (p=0.06).

Increased parity was not associated with overall breast cancer risk (OR=1.08, 95% CI: 0.84–1.38 for ≥3 children versus no children), or risk of invasive breast cancer (OR=1.15, 95% CI: 0.88–1.50) or DCIS individually (OR=0.80, 95% CI: 0.38–1.66), though there was some evidence of an overall difference in effects by invasive status (p= 0.09). First term pregnancy after age 30 was associated with increased risk of invasive breast cancer (OR=1.58, 95% CI: 1.12–2.23 for age 30–34 versus age <25), with similar trends seen in the DCIS (OR=1.89, 95% CI: 0.72–4.95) and combined analysis (OR=1.65, 95% CI: 1.20–2.28). We also examined whether age at first full term pregnancy modified the effect of parity on young-onset breast cancer, and found that women who gave birth at age 28 (the median age at first birth) or later had increased risk of young-onset breast cancer if they went on to have additional pregnancies (OR=1.60, 95% CI: 0.95–2.70 for 2 vs. 1 pregnancies; OR=2.18, 95% CI: 1.06–4.49 for 3 or more versus 1 pregnancies). Increased parity was unrelated to the risk of young-onset breast cancer in women who gave birth before age 28.

Breast-feeding history and oral contraceptive use were not associated with all breast cancer, invasive breast cancer, or DCIS. Homogeneity p-values indicated that there were no significant differences between the effects of age at first birth, breastfeeding, or oral contraceptive use on invasive breast cancer versus DCIS. In additional analyses, we found no association between breastfeeding duration (never breastfed or breastfed <12 months versus breastfed ≥12 months) and all young-onset breast cancer (adjusted OR=1.08; 95% CI: 0.83, 1.42; restricted to parous women) or between recent use of oral contraceptives (OR= 1.08, 95% CI: 0.61, 1.89 for use in the last five years versus never use) and all young-onset breast cancer. The latter analysis was restricted to sister pairs in which the sisters' index age was

defined by the case sister's age at diagnosis so that we could be sure we were capturing the most relevant time period.

The positive association between parity and risk of any breast cancer among women with later first pregnancies is not likely to be attributable to pregnancy-induced breast cancer, as increasing time (in years) from last pregnancy to index age was not associated with disease (adjusted OR=1.04, 95% CI: 0.95–1.14). As with the recency of oral contraceptive use analysis, we limited this analysis to sister pairs in which the family-wide index age was determined by the case sister's age at diagnosis.

We found that obesity (BMI ≥30kg/m^2) at ages 30–39 was inversely associated with overall breast cancer (OR=0.74, 95% CI: 0.51–1.03 for BMI ≥30 versus <25) and invasive breast cancer (OR=0.71, 0.48–1.04), but was not related to DCIS (OR=1.06, 95% CI: 0.40–2.83) (Table 3). Relative to non-drinkers, alcohol consumption was associated with decreased risk of young-onset invasive breast cancer (OR=0.64, 95% CI: 0.45–0.91 for ≥161 drinks/year versus none). Alcohol intake was not related to DCIS (OR=1.44, 95% CI: 0.59–3.51), but the combined results showed the same pattern as invasive breast cancer alone (OR=0.72, 95% CI: 0.52–1.00). There was no association between height and breast cancer in any of the examined strata. Being a former smoker was associated with increased risk of invasive breast cancer (OR=1.24, 95% CI: 0.98–1.56). There was no evidence of heterogeneity by invasive status for BMI, height, alcohol intake or smoking history.

We ran sensitivity analyses excluding women whose medical records were not available (n=128 cases), but observed no meaningful differences between the observed associations and the original analyses (data not shown).

DISCUSSION

In our sister-matched, case-control study of breast cancer under age 50, older age at menarche, younger age at menopause, premenopausal hysterectomy, early age at first term pregnancy, obesity, and alcohol consumption were associated with reduced risk of young-onset breast cancer and also with young-onset invasive breast cancer, specifically. None of the explored risk factors was independently associated with young-onset DCIS, but the number of DCIS cases was small and effect estimates for DCIS were usually statistically consistent with those for invasive breast cancer. There was weak evidence of heterogeneity by invasive status for menopausal status and parity.

Our findings that later age at menarche, early menopause, having had a hysterectomy, and early age at first full-term pregnancy were associated with reduced risk of young-onset breast cancer are consistent with other studies. [4, 5, 25] Though we observed an inverse association between obesity and young-onset invasive breast cancer but not DCIS, the number of families with young-onset DCIS was small and previous investigations of BMI and breast cancer in young women have reported inverse associations with both tumor types. [11, 13, 20, 26]

In contrast with our findings, high alcohol consumption is usually observed to be associated with increased risk of young-onset invasive breast cancer, [20, 27, 28]. However, the

reported alcohol consumption in our study was relatively low, and the highest category of consumption in our study (≥161 drinks/year; category median= 312 drinks/year) was associated with null or even protective effects in other investigations, suggesting that if there is a U-shaped dose-response relationship, as has been observed in previous investigations of alcohol and young-onset breast cancer, [5, 28–30] our highest category has not reached the upturn.

Factors that influence mammography utilization are important to consider, as screening can detect tumors before they progress to invasive breast cancer. This is complicated by the fact that younger women are less likely to have regular mammograms, but more likely than older women to receive a DCIS diagnosis if a cancer is detected during screening. [31] The natural history of DCIS is not well understood, but this may mean that younger women are more likely to receive a false positive diagnosis. This, in turn, would result in attenuated effect estimates for DCIS-specific analyses.

Regardless of whether the DCIS diagnoses are true or false positives, the observed heterogeneity in risk estimates for invasive breast cancer versus DCIS among women with early menopause or hysterectomy could be a consequence of increased surveillance of women with gynecologic concerns and the fact that women with invasive breast cancer are excluded from having DCIS by our case definition. The fact that there was a higher percentage of DCIS than invasive breast cancer cases with maternal family history of breast cancer supports the possibility that women who are more likely to get screened also have a greater probability of being diagnosed with DCIS.

The observed inverse association between early menopause or hysterectomy and invasive breast cancer could also be attributable to reductions in circulating sex steroid hormones. [32] Women with earlier menarche and fewer pregnancies are exposed to more circulating sex steroid hormones in their lifetimes, which may explain their increased invasive breast cancer risk.

Our finding that later age at first birth was also associated with increased risk of invasive breast cancer, which appears to be exacerbated by additional births, is consistent with existing evidence that older breast tissue may be more susceptible to tumorigenesis when exposed to pregnancy-related growth and remodeling. [33] Women who give birth later also have fewer children on average.

Matching on sibship should control for some shared, unmeasured confounders. On the other hand, over-matching on shared exposures could negatively impact statistical efficiency. [34] To explore this possibility, we calculated intraclass correlation coefficients (ICC) for several of the examined risk factors, treating sisters as repeated measures within a family. We saw a moderate correlation between sisters' heights (ICC=0.53), but the ICCs for BMI, parity, alcohol, age at first birth, and age at menarche were all less than 0.3, indicating that over-matching is not a substantial concern in this analysis.

As relatively few of our cases were DCIS, we had limited power to look at risk factors for DCIS overall. We were able to test for heterogeneity, but identified few risk factors that could potentially promote or delay the DCIS to invasive transformation. Menopausal status

was a possible exception. We did not have sufficient power to explore even finer differences between DCIS and invasive breast cancer within tumor subtypes (e.g. estrogen receptor or triple-negative status).

In summary, late menarche, early menopause, premenopausal hysterectomy, early age at first full term pregnancy, moderate consumption of alcohol and adult obesity may protect against invasive breast cancer in young women. With the possible exception of menopausal status, we observed overall concordance between risk factors for young-onset DCIS and invasive breast cancer.

Acknowledgments

We thank Drs. Min Shi and Matthew Longnecker of the National Institutes of Environmental Health Sciences for helpful comments on this paper.

Funding sources: This work was supported by the Intramural Research Program of the National Institutes of Health; National Institute of Environmental Health Sciences (grant numbers Z01-ES044005 [DPS] and Z01-ES102245 [CRW]); and Susan G. Komen for the Cure (grant number FAS0703856 to CRW).

Abbreviations

BMI	Body mass index
CI	Confidence interval
DCIS	Ductal carcinoma *in situ*
OR	Odds ratio

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Table 1

Descriptive characteristics of Two Sister Study participants

Characteristics; N (%)	Controls (n=1665)	Invasive cases (n=1185)	Ductal carcinoma *in situ* cases (n=221)	Case, invasive status unknown (n=13)
Index age				
<40	334 (20)	258 (22)	37 (17)	1 (8)
40–<45	602 (36)	413 (35)	77 (35)	6 (46)
≥45	729 (44)	514 (43)	107 (48)	6 (46)
Breast cancer diagnosis age				
<40	–	180 (15)	22 (10)	0 (0)
40–<45	–	347 (29)	65 (29)	5 (38)
≥45	–	658 (56)	134 (61)	8 (62)
Race				
Non-Hispanic White	1485 (89)	1043 (88)	198 (90)	11 (85)
Non-Hispanic Black	73 (4)	57 (5)	11 (5)	2 (15)
Hispanic	63 (4)	50 (4)	7 (3)	0
Other	43 (3)	35 (3)	5 (2)	0
Relative birth order among participating sisters				
First (oldest)	915 (55)	435 (37)	85 (38)	7 (54)
Second	606 (36)	667 (56)	121 (55)	4 (31)
Third or younger	144 (9)	83 (7)	15 (7)	2 (15)
Education				
High school or less	217 (13)	155 (13)	21 (10)	1 (8)
Some college but no degree	279 (17)	176 (15)	31 (14)	3 (23)
Associate or technical degree	252 (15)	166 (14)	32 (14)	2 (15)
Bachelor degree	524 (31)	390 (33)	84 (38)	4 (31)
Master or doctoral degree	393 (24)	298 (25)	53 (24)	3 (23)
Maternal history of breast cancer				
Yes	285 (17)	194 (16)	51 (23)	5 (38)
No	1371 (83)	985 (84)	168 (77)	8 (62)

The following variables had missing data: Race (1 control), Maternal history of breast cancer (9 controls, 2 ductal carcinoma in situ cases, 5 invasive cases)

Table 2

Odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between established reproductive risk factors and young-onset invasive and DCIS breast cancer, Two Sister Study (2008–2010)

Characteristics	Control Sisters (n=1648) No. (%)	Invasive Cases (n=1185) No. (%)	DCIS Cases (n=221) No. (%)	Adjusted OR All cases vs. controls (95% CI)	Adjusted OR Invasive cases vs. controls (95% CI))	Adjusted OR DCIS cases vs. controls (95% CI)	Homogeneity p-value[a]
Age at Menarche[b]							
≥14	433 (26)	259 (22)	55 (25)	1.00	1.00	1.00	
12 or 13	942 (57)	699 (59)	127 (57)	1.29 (1.06, 1.57)	1.29 (1.04, 1.60)	1.27 (0.76, 2.12)	p= 0.67
<12	272 (17)	227 (19)	39 (18)	1.45 (1.11, 1.89)	1.51 (1.13, 2.01)	1.05 (0.52, 2.11)	
Trend test				p =0.005	p = 0.005	p = 0.79	
Menopausal status, index age[c]							
Premenopausal	1379 (84)	1070 (90)	186 (84)	1.00	1.00	1.00	
Postmenopausal, age at menopause <45 y	116 (7)	40 (3)	15 (7)	0.48 (0.33, 0.69)	0.38 (0.25, 0.58)	1.38 (0.58, 3.30)	
Postmenopausal, age at menopause ≥45 y	29 (2)	16 (1)	3 (1)	0.56 (0.29, 1.10)	0.68 (0.32, 1.43)	0.42 (0.09, 2.10)	p= 0.06
Premenopausal hysterectomy, with retained ovarian tissue	122 (7)	59 (5)	17 (8)	0.68 (0.48, 0.94)	0.64 (0.44, 0.93)	0.96 (0.44, 2.10)	
Parity as of index age[d]							
Nulliparous	352 (21)	252 (21)	47 (21)	1.00	1.00	1.00	
1 child	256 (16)	186 (16)	38 (17)	0.99 (0.76, 1.28)	0.91 (0.69, 1.22)	1.54 (0.73, 3.26)	
2 children	613 (37)	458 (39)	90 (41)	1.15 (0.92, 1.43)	1.12 (0.88, 1.42)	1.43 (0.77, 2.65)	p= 0.09
≥3 children	426 (26)	289 (24)	46 (21)	1.08 (0.84, 1.38)	1.15 (0.88, 1.50)	0.80 (0.38, 1.66)	
Trend test				p = 0.61	p = 0.17	p = 0.17	
Age at first pregnancy lasting ≥37 weeks (as of index age)[e]							
<25 y	465 (37)	270 (30)	54 (32)	1.00	1.00	1.00	
25–29 y	456 (36)	341 (38)	52 (31)	1.28 (0.98, 1.66)	1.35 (1.02, 1.79)	0.83 (0.39, 1.77)	
30–34 y	233 (19)	214 (24)	40 (24)	1.65 (1.20, 2.28)	1.58 (1.12, 2.23)	1.89 (0.72, 4.95)	p= 0.32
≥35 y	100 (8)	64 (7)	22 (13)	1.22 (0.80, 1.87)	1.12 (0.70, 1.80)	1.35 (0.42, 4.33)	
Trend test				p = 0.03	p = 0.11	p = 0.23	
Breastfeeding History (among parous women; as of index age)[f]							
Never	265 (20)	181 (19)	28 (16)	1.00	1.00	1.00	

Characteristics	Control Sisters (n=1648) No. (%)	Invasive Cases (n=1185) No. (%)	DCIS Cases (n=221) No. (%)	Adjusted OR All cases vs. controls (95% CI)	Adjusted OR Invasive cases vs. controls (95% CI))	Adjusted OR DCIS cases vs. controls (95% CI)	Homogeneity p-value[a]
Ever	1030 (80)	752 (81)	146 (84)	1.08 (0.80, 1.48)	1.02 (0.72, 1.44)	1.24 (0.56, 2.73)	p= 0.27
Use of oral contraceptives as of index age[g]							
Never User	167 (10)	112 (9)	27 (12)	1.00	1.00	1.00	
Ever User	1479 (90)	1073 (91)	194 (88)	0.96 (0.74, 1.24)	1.03 (0.77, 1.36)	0.65 (0.34, 1.23)	p= 0.19

Abbreviations: Odds Ratio (OR), 95% Confidence Interval (95% CI), Ductal Carcinoma *in situ* (DCIS)

The following variables had missing data: Age at menarche (1 control), Menopausal status (2 controls), Parity (1 control), Breastfeeding (1 control), Use of oral contraceptives (2 controls). 13 cases were missing invasive status were removed, along with their 17 matched controls.

[a] Likelihood ratio test for homogeneity between the invasive-specific OR and the DCIS-specific OR.

[b] Adjusted for education (high school or less, some college but no degree, associate or technical degree, bachelor degree, master or doctoral degree), relative weight at age 10 (lighter, same, heavier), childhood physical activity (0, <2 hrs, 2–<4, ≥4 hrs/wk)

[c] Adjusted for education, age at menarche (<12, 12 or 13, >13), birth order (1, 2, or 3+) BMI in 30s (<18.5, 18.5–24.9, 25.0–29.9,≥30.0 kg/m), parity (0, 1–2, 3+ births), smoking (ever/never)

[d] Adjusted for education, age at menarche, birth order, oral contraceptive use (never/ever), age at first live birth (continuous, data for nulliparous women imputed with mean value)

[e] Among women with at least one term pregnancy; Adjusted for education, age at menarche, birth order, oral contraceptive use (never/ever)

[f] Adjusted for education, age at first live birth (continuous), alcohol use (ever/never), smoking, birth order

[g] Adjusted for education, age at menarche, birth order

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Table 3

Odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between other established risk factors and young-onset invasive and DCIS breast cancer, Two Sister Study (2008–2010)

Characteristics	Control Sisters (n=1648) No. (%)	Invasive Cases (n=1185) No. (%)	DCIS Cases (n=221) No. (%)	Adjusted OR All cases vs. controls (95% CI)	Adjusted OR invasive cases vs. controls (95% CI)	Adjusted OR DCIS cases vs. control (95% CI)	Homogeneity p-value[a]
Height[a]							
<64 inches	491 (30)	343 (29)	60 (27)	0.96 (0.78, 1.18)	0.94 (0.75, 1.17)	1.11 (0.65, 1.90)	
64–66.9 inches	692 (42)	494 (42)	101 (46)	1.00	1.00	1.00	p= 0.90
≥67 inches	465 (28)	348 (29)	60 (27)	1.03 (0.84, 1.25)	1.02 (0.82, 1.26)	1.14 (0.68, 1.91)	
Trend test				p = 0.59	p = 0.57	p = 0.93	
Body mass index ages 30–39[b]							
<24.9 kg/m^2	1191 (72)	851 (72)	171 (77)	1.00	1.00	1.00	
25.0–29.9 kg/m^2	310 (19)	245 (21)	36 (16)	1.03 (0.82, 1.29)	1.06 (0.83, 1.34)	0.97 (0.47, 2.01)	p= 0.63
≥30.0 kg/m^2	143 (9)	83 (7)	14 (6)	0.74 (0.51, 1.03)	0.71 (0.48, 1.04)	1.06 (0.40, 2.83)	
Trend test				p = 0.26	p = 0.33	p = 0.94	
Alcohol use in the 10 years preceding index age[c]							
Nondrinker	149 (9)	133 (11)	19 (9)	1.00	1.00	1.00	
Social (<10 drinks/year)	174 (11)	92 (8)	18 (8)	0.61 (0.42, 0.89)	0.57 (0.38, 0.85)	1.03 (0.40, 2.69)	
10–38 drinks/year	434 (26)	322 (27)	65 (29)	0.81 (0.59, 1.12)	0.72 (0.52, 1.02)	1.80 (0.79, 4.10)	
39–161 drinks/year	451 (27)	327 (28)	63 (29)	0.77 (0.56, 1.05)	0.66 (0.47, 0.94)	1.68 (0.74, 3.82)	p= 0.42
≥161 drinks/year	437 (27)	310 (26)	56 (25)	0.72 (0.52, 1.00)	0.64 (0.45, 0.91)	1.44 (0.59, 3.51)	
Trend test				p = 0.22	p = 0.08	p = 0.33	
Smoking history as of index age[d]							
Non-smoker	1080 (66)	758 (64)	150 (68)	1.00	1.00	1.00	
Former smoker	388 (24)	304 (26)	54 (24)	1.13 (0.92, 1.40)	1.24 (0.98, 1.56)	0.68 (0.40, 1.16)	p= 0.21
Current smoker	177 (11)	122 (10)	17 (8)	0.94 (0.69, 1.26)	0.96 (0.69, 1.33)	0.75 (0.33, 1.70)	

Abbreviations: Odds Ratio (OR), 95% Confidence Interval (95% CI), Ductal Carcinoma *in situ* (DCIS)

The following variables had missing data: Body mass index (4 controls, 6 invasive cases), Alcohol use (20 controls, 1 invasive case), Smoking history (3 controls, 1 invasive case). 13 cases were missing invasive status were removed, along with their 17 matched controls.

[a]Adjusted for education

[b] Adjusted for education, childhood physical activity, alcohol (ever/never), smoking (ever/never), parous at age 30 (yes/no), age at menarche, birth order

[c] Adjusted for education, birth order, smoking (ever/never)

[d] Adjusted for education, alcohol use (ever/never), birth order