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Body mass index and risk of second primary breast cancer: The WECARE Study

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Abstract

The identification of potentially modifiable risk factors, such as body size, could allow for interventions that could help reduce the burden of contralateral breast cancer (CBC) among breast cancer survivors. Studies examining the relationship between body mass index (BMI) and CBC

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The WECARE Study Collaborative Group details are given in Appendix.

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have yielded mixed results. From the population-based, case–control, Women's Environmental, Cancer and Radiation Epidemiology (WECARE) Study, we included 511 women with CBC (cases) and 999 women with unilateral breast cancer (controls) who had never used postmenopausal hormone therapy. Rate ratios (RR) and 95% confidence intervals (CI) were used to assess the relationship between BMI and CBC risk. No associations between BMI at first diagnosis or weight-change between first diagnosis and date of CBC diagnosis (or corresponding date in matched controls) and CBC risk were seen. However, obese (BMI ≥ 30 kg/m^2) postmenopausal women with estrogen receptor (ER)-negative first primary tumors (*n* = 12 cases and 9 controls) were at an increased risk of CBC compared with normal weight women (BMI < 25 kg/m^2) (*n* = 43 cases and 98 controls) (RR = 5.64 (95% CI 1.76, 18.1)). No association between BMI and CBC risk was seen in premenopausal or postmenopausal women with ER-positive first primaries. Overall, BMI is not associated with CBC risk in this population of young breast cancer survivors. Our finding of an over five-fold higher risk of CBC in a small subgroup of obese postmenopausal women with an ER-negative first primary breast cancer is based on limited numbers and requires confirmation in a larger study.

Keywords

BMI; Second primary contralateral breast cancer; ER-negative

Introduction

The relationship between body mass index (BMI) and risk of a first primary breast cancer is modulated by menopausal status. Most studies have found BMI to be inversely associated with premenopausal breast cancer risk [1]. Conversely, BMI has been positively associated with postmenopausal breast cancer risk [1], especially among women with no history of postmenopausal hormone therapy (HT) use [2–4]. Studies have also shown that this relationship is limited to, or is more pronounced in, estrogen receptor (ER) and/or progesterone receptor (PR) positive tumors [5–7]. The association between BMI and breast cancer risk in postmenopausal women is largely mediated by endogenous hormone levels [8, 9], and may be attributed to the aromatization of estrogen in peripheral adipose tissue. The inverse relationship seen in premenopausal women may be due to irregular menstrual cycles and anovulation associated with a high BMI [10].

Studies examining the relationship between BMI and second primary breast cancer in the contralateral breast (CBC) have been mixed, with some showing no association [11–13] and others (including both premenopausal and postmenopausal women) showing a positive relationship [14–18]. Most known risk factors for CBC are not readily modifiable (i.e., family history, *BRCA* mutation status). BMI is a potentially modifiable risk factor, which could allow for targeted interventions that would help reduce the burden of CBC among breast cancer survivors.

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a population-based case–control study comparing women with CBC (cases) to those with unilateral breast cancer (UBC) (controls). The objective of this analysis is to determine the association between BMI and CBC risk in premenopausal and postmenopausal women.

Materials and methods

Study population

The WECARE Study is a multi-center, population-based, case–control study where cases are women with asynchronous CBC and controls are women with UBC [19]. Subjects were

identified through five population-based cancer registries: Los Angeles County Cancer Surveillance Program; Cancer Surveillance System of the Fred Hutchinson Cancer Research Center (Seattle); State Health Registry of Iowa; and the Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control (Orange County/San Diego). These cancer registries all contribute to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program. The fifth registry from which subjects were recruited was the Danish Breast Cancer Cooperative Group Registry, supplemented by data from the Danish Cancer Registry.

Each eligible case met the following criteria: (a) was diagnosed between 1/1/1985 and 12/31/2000 with UBC followed by a second primary, in situ or invasive, breast cancer in the contralateral breast, diagnosed at least 1 year after the first diagnosis; (b) resided in the same study reporting area for both diagnoses; (c) had no previous or intervening cancer diagnosis; (d) was under age 55 years at the time of diagnosis of the first primary breast cancer; (e) was alive at the time of contact; and (f) was able to provide informed written consent, complete the interview, and provide a blood sample. For the purpose of this study the “at-risk” interval was defined as starting 1 year after the first diagnosis and ending at reference date: i.e., date of the second breast cancer diagnosis in cases or the corresponding date in matched controls.

Eligible WECARE Study controls were: (a) diagnosed between 1/1/1985 and 12/31/1999 with UBC while residing in one of the study reporting areas; (b) residing on the reference date (defined as 1 year after first diagnosis plus the at-risk interval of matched cases) in the same cancer reporting area as when first diagnosed with breast cancer; (c) never diagnosed with any other cancer; (d) under age 55 years at the time of diagnosis; (e) able to provide informed written consent, complete the interview, and provide a blood sample; and (f) without prophylactic mastectomy of the contralateral breast. Two controls were individually matched to each case on year of birth (in 5-year strata), year of diagnosis (in 4-year strata), registry region, and race/ethnicity. The majority of women (92%) were identified as Caucasian based on registry data. Additionally, to improve statistical efficiency, cases and controls were counter-matched on registry-reported radiation exposure such that two members of the case–control triad had received radiation therapy for their index breast cancer [19].

Across the five cancer registries, a total of 998 women with CBC and 2,112 women with UBC were identified as being eligible for the study as cases and controls, respectively. Of these, 708 cases (71%) and 1,399 controls (66%) completed the study interview and provided a blood sample. Reasons for non-participation of eligible women included, physician refusal (0.5% cases 1% controls), subject interview refusal (27% cases, 31% controls), and subject blood draw refusal (3% cases, 3% controls). The data collection protocol was approved by the institutional review board at each recruitment site and by the ethical committee system in Denmark.

Data collection

All participants in the WECARE Study were interviewed by telephone using a pre-tested, structured questionnaire. The questionnaire was designed to obtain information about events occurring before the diagnosis of the first primary breast cancer, as well as events that occurred within the at-risk period. The focus of the questionnaire was on known and suspected risk factors for breast cancer, including personal demographics, medical history, family and reproductive history, use of hormones, body size, smoking status, and alcohol intake. Additionally, medical records, pathology reports, and hospital charts were used to collect detailed treatment information (i.e., chemotherapy, hormonal therapy, and radiation therapy). Data on tumor characteristics of the first primary tumor (location in the breast,

stage at diagnosis, ER and PR status, and histology) were also collected from the medical records.

Body size measures reported through the interview included height and weight at age 18 years as well as weight at first breast cancer diagnosis and at reference date. Sixteen women (3 cases and 13 controls) were missing information for height and/or weight at age 18 years, 4 (1 case and 3 controls) at first diagnosis and 1 (control) at reference date, and were therefore excluded from the analysis. Additionally, women with an implausibly high (>53 kg/m^2) (1 control at first diagnosis, 1 case at reference date) or low (<16 kg/m^2) (12 cases and 23 controls at age 18 years, 3 cases and 2 controls at first diagnosis, and 2 cases at reference date) BMI were excluded. Four women (1 case and 3 controls) were excluded because of weight values that were outliers (<36.3 kg and >136 kg).

Statistical analysis

Rate ratios (RR) and 95% confidence intervals (CI) were used to assess the relationship between weight and BMI and risk of CBC. These were obtained using conditional logistic regression adjusting for known risk factors for breast cancer, including age at diagnosis (continuous), age at menarche (<13, ≥13), number of full-term pregnancies (nulliparous, 1–3, ≥4), family history (yes, no, adopted), histology (lobular, other), stage (local, regional), chemotherapy (yes, no), hormonal treatment (yes, no), and radiation therapy (yes, no). Hormonal breast cancer treatments included tamoxifen, raloxifene, toremifene citrate, anastrozole, letrozole, exemestane, aminoglutethimide, goserelin acetate, leuprorelin, fulvestrant, and megestrol acetate. A log-weight covariate was included in the model to account for the sampling probability of the counter-matching [19]. World Health Organization (WHO) categories of BMI were used to classify women as normal weight (BMI < 25 kg/m^2), overweight (25–30 kg/m^2) or obese (≥30 kg/m^2).

Based on the results of prior studies of first primary breast cancer, the analysis was stratified by menopausal status at the start of the at-risk period (1 year after first breast cancer diagnosis). Menopausal status was determined by comparing the date or age a women last reported menstruating to the date of first diagnosis. If a woman reported that she was still menstruating up to 1 year after first diagnosis (the start of the at-risk period) or was pregnant, she was classified as premenopausal. Women were also asked to indicate all reasons why they stopped menstruating, including natural menopause, surgery (bilateral oophorectomy and/or hysterectomy) or treatment (chemotherapy, radiation, and tamoxifen).

All analyses were conducted excluding women who had reported HT use any time before reference date (173 cases and 352 controls), and those with unknown menopausal status (1 case and 2 controls), leaving 1510 women (511 CBC cases and 999 UBC controls) for this analysis. Results are presented stratified by menopausal status and by ER-status of the first primary tumor with *P*-values for a linear trend across BMI categories.

Results

Table 1 shows selected characteristics of the eligible WECARE Study population. Cases and controls were similar on all matching characteristics with a median age at first diagnosis of 45 years and a median age at reference date (age at second breast cancer diagnosis in cases) of 49 years. The average at-risk period was 4 years. There were 852 women (56.4%) who reported that they were postmenopausal at the start of the at-risk period. Of these, 23.8% indicated that they had experienced natural menopause, 17.8% attributed menopause to surgeries (including bilateral oophorectomy and/or hysterectomy), and 57.7% attributed menopause to treatment (chemotherapy, radiation, tamoxifen, and aromatase inhibitor) of

their first breast cancer. Information on reason for menopause was missing for approximately 1% of women.

Overall, no association was observed between CBC risk and BMI at first diagnosis or weight-change between first diagnosis and reference date, for premenopausal or postmenopausal women (Table 2). There was also no association between BMI at age 18 years or at reference date (data not shown). Table 3 shows the relationship between BMI and CBC risk stratified by menopausal status and ER-status of the first primary tumor. Obese (BMI ≥ 30 kg/m^2) postmenopausal women with ER-negative first primary tumors had an over five-fold higher risk of developing a second primary in the contralateral breast compared with normal weight (BMI < 25 kg/m^2) women with ER-negative first tumors (RR = 5.64, 95% CI 1.76, 18.1). CBC risk was also elevated in obese premenopausal women with ER-negative first tumors, but this association did not reach statistical significance (RR = 2.68, 95% CI 0.79, 9.11). An increase in risk was also seen when pre- and post-menopausal women with ER-negative first primaries were combined (RR = 3.31, 95% CI 1.39, 7.86). In all instances, the trend across BMI categories was not statistically significant. No association between BMI and CBC risk was seen in women with ER-positive first tumors, regardless of menopausal status. Results did not differ when the 203 women who underwent natural menopause were excluded from the analysis (data not shown). We had an insufficient number of women to look at weight-change between first diagnosis and reference date stratified by both menopausal status and ER-status of the first tumor.

Although we were able to evaluate the impact of ER-status of the first tumor on the relationship between BMI and CBC risk, data on the ER-status of the second primary was insufficient for analysis. Of the 139 CBC cases diagnosed with ER-negative first tumors, information on the ER-status of the second primary was only available for 88 (63.3%) women. Of these women 52 (59.1%) were diagnosed with an ER-negative second primary. The ER-status of the second primary was available for 186 (76.2%) cases diagnosed with an ER-positive first tumor, of whom only 12.9% were diagnosed with ER-negative second primaries.

Discussion

BMI at age 18 years, first diagnosis, and reference date (date of second breast cancer diagnosis for cases and corresponding date in controls) was not associated with CBC risk in this population of young breast cancer survivors. Weight-change between first diagnosis and reference date also was not associated with risk, although the majority of women in our study maintained a relatively stable weight between first diagnosis and reference date. On average this time period was 5 years long, but could have been as short as 1 year, limiting our ability to fully examine the relationship between weight-change and CBC risk.

A small group of obese, postmenopausal women with ER-negative first primary tumors was found to have more than a five-fold greater risk of developing a second primary in the contralateral breast, than normal weight women with ER-negative first tumors (RR = 5.6). However, the trend across BMI categories was not statistically significant. CBC risk was also elevated (RR = 2.7) in obese premenopausal women with ER-negative first tumors, although the association was not statistically significant. When pre- and post-menopausal women with ER-negative first primaries were combined, again a significant increase in risk was seen in obese women (RR = 3.3). No association between BMI and CBC risk was seen in premenopausal or postmenopausal women with ER-positive first primaries. We were unable to investigate the relationship between BMI and CBC risk by the ER-status of the second primary because, as a result of missing information on receptor status, the sample size was too small for analysis.

Few studies have explored the association between BMI and CBC risk and the results have been inconsistent [11–18, 20]. Even fewer studies have examined whether hormone receptor status of the first primary tumor influenced this relationship [15, 16, 18]. Our results for ER-negative first breast cancers are consistent with those from the National Surgical Adjuvant Breast and Bowel Project B-14 Trial, which found that among women with node-negative ER-negative first tumors, those women who were obese and postmenopausal had a two-fold greater risk of CBC than normal weight postmenopausal women [16]. Unlike the results of this study, they also found an association between BMI and CBC risk in premenopausal women [16]. Their results for ER-positive first breast cancers also differed from ours. They found that both premenopausal and postmenopausal obese women with node-negative ER-positive first tumors had a greater risk of CBC than normal weight women (HR = 1.58, 95% CI 1.10, 2.25) [15]. In another population-based case–control study of women with an ER-positive first tumor, obese women had a higher risk of CBC than normal weight women (OR = 1.5, 95% CI 1.0, 2.1) [18].

Some studies have suggested that the impact of BMI on postmenopausal first primary breast cancer risk maybe limited to ER-positive tumors [5–7, 21]. This has largely been attributed to the positive association between endogenous estrogen levels and BMI [9]. Estrogens play a central role in breast cancer etiology and elevated levels of circulating estrogens are associated with increased breast cancer risk in postmenopausal women [22]. Conversion of androgens (testosterone and androstenedione) to estrogens (estradiol (E2) and estrone (E1), respectively) by aromatase in peripheral adipose tissues is the primary source of estrogens in postmenopausal women.

Unlike other studies [15, 18], we did not find an association between BMI and CBC risk in women with ER-positive first tumors. If the impact of BMI on CBC risk is mediated through its effects on endogenous hormones, it may be attenuated by the use of hormonal treatments (tamoxifen and aromatase inhibitors) for ER-positive first primaries, as tamoxifen is known to be associated with a lower risk of developing CBC [23]. Thus the strong impact of tamoxifen on subsequent CBC risk may overshadow any adverse effect that BMI may have on risk in these women. Although we adjusted for hormonal treatments in this analysis, we were unable to conduct the analysis excluding women who had received tamoxifen treatment due to sample size limitations.

The strengths of this study include the population-based design, large study population, detailed questionnaire data, and confirmation of interview data, where possible, by medical records. Limitations include the lack of data on physical activity, limited number of women with ER-negative first breast cancers, incomplete data on ER-status of the second primary breast cancer in cases, and insufficient sample size to examine the relationship between BMI and CBC risk after excluding women who received hormonal treatment. The short interval between first diagnosis and CBC prevented assessing the impact of long-term weight-change on risk or of evaluating whether BMI might affect CBC risk at longer intervals as found by Majed et al. [20].

In this population of young breast cancer survivors, BMI at first diagnosis did not influence CBC risk overall. Our finding of an over five-fold higher risk of CBC in obese postmenopausal women with an ER-negative first primary breast cancer is based on small numbers and requires confirmation in other studies. The potential benefit of weight-loss on CBC risk in women with ER-negative first tumors is yet to be established. These results add to the limited body of literature describing non-treatment related risk factors for CBC. If our result for ER-negative breast cancer is confirmed, it would have important implications for the clinical management of ER-negative breast cancers.

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Appendix: The WECARE Study Collaborative Group

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Abbreviations

BMI	Body mass index
CBC	Contralateral breast cancer
CI	Confidence interval
E1	Estrone
E2	Estradiol
ER	Estrogen receptor
HR	Hazard ratio
HT	Postmenopausal hormone therapy
OR	Odds ratio
PR	Progesterone receptor
RR	Rate ratio
SEER	Surveillance, Epidemiology and End Results program
UBC	Unilateral breast cancer
WECARE	Women's Environmental Cancer and Radiation Epidemiology
WHO	World Health Organization

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Table 1

Characteristics of cases (women with asynchronous contralateral breast cancer) and controls (women with unilateral breast cancer only) from the WECARE Study population

Variable	Median (range)	Cases (CBC) median (range)	Controls (UBC) median (range)
Age at first diagnosis (years)	45 (23–55)	44 (24–55)	45 (23–55)
Age at reference date (years)	49 (27–71)	49 (27–71)	49 (27–69)
Length of at-risk period[a] (years)	4.2 (1.0–15.6)	4.2 (1.0–15.6)	4.3 (1.0–15.6)

Variable	Level	Cases (CBC)		Controls (UBC)	
		N	%	*N*	%
Center	Iowa	83	16.2	162	16.2
	UC Irvine	86	16.8	148	14.8
	Los Angeles	145	28.4	277	27.7
	Seattle	65	12.7	133	13.3
	Denmark	132	25.8	279	27.9
Year at first diagnosis	1985–1988	183	35.8	345	34.5
	1989–1992	176	34.4	355	35.5
	1993–1996	122	23.9	237	23.7
	1997+	30	5.9	62	6.2
Chemotherapy	No	253	49.5	416	41.6
	Yes	258	50.5	583	58.4
Hormone treatment[b]	No	382	74.8	686	68.7
	Yes	129	25.2	312	31.2
	Unknown	0	0	1	0.1
Radiation treatment	Never	266	52.1	187	18.7
	Ever	245	47.9	812	81.3
Histology of first breast cancer	Lobular	61	11.9	92	9.2
	Other	450	88.1	907	90.8
Stage of first breast cancer	Localized	355	69.5	631	63.2
	Regional	156	30.5	368	36.8
ER Status of first breast cancer[c]	Positive	244	47.7	509	51

Variable	Level	Cases (CBC)		Controls (UBC)	
		N	%	*N*	%
	Negative	139	27.2	252	25.2
	Other	128	25	238	23.8
PR Status of first breast cancer[c]	Positive	211	41.3	423	42.3
	Negative	120	23.5	232	23.2
	Other	180	35.2	344	34.4
Age at menarche (years)	8–13	239	46.8	435	43.5
	13–19	272	53.2	564	56.5
Number of full-term pregnancies	None	102	20	170	17
	1–3	375	73.4	729	73
	4–14	34	6.7	100	10
Menopausal status/age at menopause at start of at-risk period[d]	Premenopausal	247	48.3	411	41.1
	Postmenopausal age <45	109	21.3	249	24.9
	Postmenopausal age 45+	155	30.3	339	33.9
	Unknown	0	0	0	0
Family history of breast cancer	None	342	66.9	781	78.2
	1+	161	31.5	201	20.1
	Adopted	8	1.6	17	1.7

Excludes women with missing height and/or weight (n = 21), those who were outliers for BMI (n = 44) or weight (n = 4) at either age 18, first diagnosis or reference date, women who reported use of postmenopausal hormone therapy at any time prior to reference date (n = 525) and women with missing information on menopausal status (n = 3). This left 511 CBC cases and 999 UBC controls for this analysis

CBC asynchronous contralateral breast cancer, *UBC* unilateral breast cancer, *ER* estrogen receptor, *PR* progesterone receptor

[a] Beginning 1 year after first diagnosis extending to the reference date (date of second diagnosis in cases)

[b] Hormone therapy includes all hormonal breast cancer treatments including: tamoxifen, raloxifene, toremifene citrate, anastrozole, letrozole, exemestane, aminoglutethimide, goserelin acetate, leuprorelin, fulvestrant and megestrol acetate

[c] Refers to receptor status of the first primary breast cancer. The ‘Other’ category consists of women where no lab test was given, the test was given and the results are unknown or the test was given and the results were borderline

[d] Defined as menopausal status as of 1 year after first diagnosis (the start of the at-risk period). If a woman reported that she was still menstruating up to 1 year after first diagnosis or was pregnant, she was classified as premenopausal

Table 2

Relative risk and 95% confidence intervals for BMI and CBC risk stratified by menopausal status/age at menopause

BMI (kg/m^2) at first diagnosis	Cases (CBC)		Controls (UBC)		RR[a]	95% CI	*P* for trend[b]
	N	%	*N*	%			
Premenopausal[c]							
<25	190	76.9	300	73.0	1.00		0.79
25 to <30	36	14.6	80	19.5	0.77	0.45, 1.31	
≥30	21	8.5	31	7.5	1.12	0.56, 2.23	
Postmenopausal[d]							
<25	184	69.7	405	68.9	1.00		0.87
25 to <30	49	18.6	138	23.5	0.69	0.43, 1.11	
≥30	31	11.7	45	7.7	1.59	0.79, 3.17	
Postmenopausal (age <45 years at menopause)							
<25	76	69.7	177	71.1	1.00		0.71
25 to <30	20	18.3	52	20.9	0.69	0.35, 1.39	
≥30	13	11.9	20	8.0	1.39	0.56, 3.48	
Postmenopausal (age 45+ years at menopause)							
<25	108	69.7	228	67.3	1.00		0.88
25 to <30	29	18.7	86	25.4	0.69	0.37, 1.28	
≥30	18	11.6	25	7.4	1.85	0.69, 4.97	
Weight change between first diagnosis to reference date Premenopausal							
> 5 kg loss	7	2.8	15	3.6	0.43	0.14, 1.30	
–5 to <5 kg change	179	72.5	293	71.3	1.00		
5 to <10 kg gain	39	15.8	59	14.4	1.19	0.67, 2.11	
≥10 kg gain	22	8.9	44	10.7	0.63	0.32, 1.24	
Postmenopausal							
>5 kg loss	8	3.0	21	3.6	0.49	0.15, 1.61	
–5 to <5 kg change	169	64.0	381	64.8	1.00		
5 to <10 kg gain	49	18.6	111	18.9	0.86	0.53, 1.40	
≥10 kg gain	38	14.4	75	12.8	1.33	0.73, 2.42	

CBC asynchronous contralateral breast cancer, *UBC* unilateral breast cancer, *BMI* body mass index (kg/m^2), *RR* rate ratio, *CI* confidence interval

[a] Adjusted for age at first diagnosis, age at menarche, number of pregnancies, family history, histology, stage, chemotherapy, hormonal therapy and radiation treatment

[b] *P*-value for a linear trend across BMI categories, no trend is given for weight change

[c] Median (range) BMI in premenopausal women at first diagnosis was 22.3 kg/m^2 (16.2–42.5) in cases and 22.5 kg/m^2 (16.1–40.4) in controls

[d] Median (range) BMI in postmenopausal women at first diagnosis was 22.7 kg/m^2 (17.2–45.5) in cases and 22.9 kg/m^2 (16.9–45.7) in controls

Table 3

Rate ratios and 95% confidence intervals for BMI and CBC risk stratified by menopausal status and ER status of the first primary tumor

	Cases (CBC)		Controls (UBC)		RR[a]	95% CI	*P* for trend[b]
	N	%	*N*	%			
Premenopausal							
ER positive							
<25	86	79.6	147	76.6	1.00		0.85
25 to <30	15	13.9	30	15.6	0.86	0.41, 1.82	
≥30	7	6.5	15	7.8	0.86	0.29, 2.58	
ER negative							
<25	43	64.2	71	66.4	1.00		0.26
25 to <30	14	20.9	29	27.1	1.02	0.44, 2.35	
≥30	10	14.9	7	6.5	2.68	0.79, 9.11	
Postmenopausal							
ER positive							
<25	94	69.1	206	65.0	1.00		0.40
25 to <30	25	18.4	80	25.2	0.71	0.38, 1.32	
≥30	17	12.5	31	9.8	0.94	0.39, 2.30	
ER negative							
<25	43	59.7	98	67.6	1.00		0.30
25 to <30	17	23.6	38	26.2	0.51	0.22, 1.17	
≥30	12	16.7	9	6.2	5.64	1.76, 18.13	

CBC asynchronous contralateral breast cancer, *UBC* unilateral breast cancer, *BMI* body mass index (kg/m^2), *RR* rate ratio, *CI* confidence interval, *ER* estrogen receptor

[a] Adjusted for age at first diagnosis, age at menarche, number of pregnancies, family history, histology, stage, chemotherapy, hormonal treatment, and radiation treatment

[b] *P*-value for a linear trend across BMI categories