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ARTICLE

Relationship Between Anthropometric Factors and Risk of Second Breast Cancer Among Women With a History of Ductal Carcinoma In Situ

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Abstract

Background: Women with ductal carcinoma in situ (DCIS) have an elevated risk of a second breast cancer, but few data are available regarding the impact of modifiable lifestyle factors on this risk.
Methods: In a population-based case–control patient study of women with a history of DCIS in western Washington diagnosed between 1996 and 2013, 497 patients diagnosed with DCIS and a second ipsilateral or contralateral invasive or in situ breast cancer were enrolled. There were 965 matched control patients with one DCIS diagnosis. Associations between anthropometric factors and risk of an invasive or in situ second breast cancer event were evaluated using conditional logistic regression. Statistical tests were two-sided.
Results: Obesity (body mass index [BMI] $\geq$ 30 kg/m^2) at initial DCIS diagnosis was associated with a 1.6-fold (95% confidence interval [CI] = 1.2 to 2.2) increased risk of any second breast cancer and a 2.2-fold increased risk of a contralateral second breast cancer (95% CI = 1.4 to 3.3) compared with normal weight women (BMI $<$ 25 kg/m^2). BMI and weight, both at initial DCIS diagnosis and at the time of the second breast cancer diagnosis, were positively associated with risk of any second and second invasive breast cancers (odds ratio = 1.01–1.04, all $P \leq .03$).
Conclusions: Although additional confirmatory studies are needed, obesity appears to be an important contributor to the risk of second breast cancers within the growing population of women with DCIS. This has potential clinical relevance with respect to identifying which women with a history of DCIS may require more careful monitoring and who may benefit from lifestyle modifications.

The incidence of ductal carcinoma in situ (DCIS) has increased in parallel with the rise in screening mammography, such that nearly one-third of all newly diagnosed breast cancer case patients in the United States are DCIS (1,2). Although the 10-year breast cancer–specific mortality rate after treatment of DCIS is approximately 2%–3% (3,4), up to 30% of patients will experience a subsequent DCIS or invasive breast cancer event (5). For clinicians to provide individualized treatment recommendations, it is imperative to be able to stratify patients according to their risk of experiencing a second breast cancer event.

Previous studies have identified demographic, mammographic, treatment, and clinical/pathologic characteristics associated with second breast cancer events among women with a history of DCIS (6–16). Adjuvant radiation and endocrine therapy decrease the risk of local recurrence and contralateral second breast cancer events after DCIS by 50% (11,12,17,18), but relatively little is known about the impact of potentially modifiable lifestyle factors. In particular, the role of obesity in breast cancer is of increasing interest (19). Obese patients with invasive cancer are more likely to experience a second breast cancer

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or die from breast cancer compared with women who are normal or underweight (20–24). Three previous cohort studies have evaluated the association of body mass index (BMI) and second breast events in DCIS patients with inconsistent results (25–27). One study demonstrated increased risk of ipsilateral second breast cancer events in obese patients at initial diagnosis (27), another showed no overall association (25), and a third found that the relationship was modified by menopausal status (26). A key limitation of these three studies was small sample sizes, with the number of second breast cancer events ranging from 76 to 162.

Given the growing population of DCIS survivors, the rising epidemic of obesity in the United States (28), and the paucity of studies that have evaluated the relationship between anthropometric factors and risk of developing a second breast cancer, further investigation is warranted. We examined the relationship between BMI, height, and weight and the risk of second breast cancers in a large population-based study of women with a history of DCIS. The identification of potentially modifiable factors that impact this risk could guide and motivate changes in health behaviors.

Methods

Study Population

We conducted a population-based nested case–control patient study from an underlying cohort of 4157 women age 30–79 years diagnosed with DCIS in the Seattle–Puget Sound region between January 1, 1996, and June 30, 2013 (Supplementary Figure 1, available online). Study participants were identified through the Cancer Surveillance System, a cancer registry serving 13 counties in western Washington State. Patients who underwent bilateral mastectomy were excluded (29,30), as were women who developed nonbreast cancers as treatment could impact the risk of a second breast cancer event. Cases were classified as patients with a second invasive or in situ breast cancer event at least six months following initial diagnosis. Of the 705 eligible case patients, 497 were enrolled (70.5% response rate). Control patients were those diagnosed with DCIS who did not have a second breast cancer event during the study period. Controls were individually matched to case patients on age and year of initial diagnosis (+/-2 years), county of residence, surgical and radiation treatment, histology, grade, and disease-free survival time. All potentially eligible control patients who met matching criteria for a given case patient were assigned a random number and placed in numerical order. Proceeding down the list, two to three control patients per case patient were contacted. Of the 1695 eligible matched control patients, 965 were enrolled (57% response rate). Written, informed consent was obtained from study participants, and the study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Data Collection

Patient demographic, epidemiologic, and clinical data were collected from structured telephone interviews and detailed medical record review. Tumor and treatment data were obtained via medical records. Lifestyle factors such as tobacco and alcohol consumption, reproductive factors, menopausal status, and family history were obtained via interview. Data on weight were collected at initial diagnosis and date of second breast cancer diagnosis for case patients; for control patients, this was the date corresponding to the interval between the first DCIS and second breast cancer diagnosis of the case patient they were matched to. Height was collected at the same time points. Data from medical record review were used as the primary source for anthropometric measures, and when unavailable, interview-based data were used (24%).

Characterization of Exposures

The 49 case patients and 103 control patients with missing BMI (kg/m^2) data were excluded, leaving a final analytic data set consisting of 448 case patients and 862 control patients. Results from this case patient–complete analysis were not appreciably different from those completed on the entire study population. Height and weight were evaluated as continuous variables. BMI was categorized as a continuous variable and as a categorical variable using the modified Centers for Disease Control (CDC) classification system (underweight and normal [<25 kg/m^2], overweight [25 to 29.9 kg/m^2], and obese [≥ 30 kg/m^2]). Changes in BMI and weight between the initial DCIS diagnosis and reference date were also evaluated.

Statistical Analysis

For the primary analysis, control patients were compared with three case patient groups: any second breast event, invasive second breast event, in situ second breast event. Associations between anthropometric factors and these outcomes were estimated using conditional logistic regression given our use of a matched case–control patient design (31). Odds ratios (ORs) and Wald-type 95% confidence intervals were calculated as estimates of relative risks. Effect modification by menopausal status at initial diagnosis, change in menopausal status between initial diagnosis and second breast event/reference date, and receipt of adjuvant endocrine therapy were assessed based on likelihood ratio testing. Because there were no statistically significant interactions with any of the main effects assessed at the prespecified P value of less than .1, no effect modifiers were included in the final models.

Associations between BMI at initial diagnosis with ipsilateral or contralateral second breast cancers were examined in a secondary analysis. One patient with bilateral second breast cancers was excluded. For the analysis of ipsilateral events, patients who underwent a unilateral mastectomy for their initial procedure were excluded.

A sensitivity analysis was performed to assess for significant differences in risk estimates using data from medical record review and interview-based data for our primary exposures. Risk estimates changed less than 10% when analyses were restricted to participants with medical record data, and thus in our final models we included all participants with available data, prioritizing medical record over interview data for anthropomorphic variables.

All models were implicitly adjusted for the case/control patient matching variables given our use of conditional logistic regression. Additionally, we adjusted for menopausal status at initial diagnosis and receipt of adjuvant endocrine therapy as these have been shown to be potential confounders in previous literature (25,26,32). The time period between initial diagnosis and second event (or reference date) varied among some case/control patient pairs (case patients: median = 61 months; control patients: median = 58 months). Consequently, models for

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Table 1. Patient, pathology, and treatment characteristics of women with and without a second breast cancer event after initial ductal carcinoma in situ diagnosis

	Controls (n = 862) No. (%)	Any second breast cancer (n = 448) No. (%)	Invasive* (n = 303) No. (%)	In situ† (n = 145) No. (%)
Patient demographics				
Age at initial diagnosis, y				
Median (IQR)	53 (47–61)	53 (47–61)	54 (47–63)	52 (47–59)
30–39	29 (3.4)	20 (4.5)	13 (4.3)	7 (4.8)
40–49	274 (31.8)	138 (30.8)	92 (30.4)	46 (31.7)
50–59	307 (35.6)	156 (34.8)	97 (32.0)	59 (40.7)
60–69	186 (21.6)	95 (21.2)	75 (24.8)	20 (13.8)
70+	66 (7.7)	39 (8.7)	26 (8.6)	13 (9.0)
Year of diagnosis				
1995–2001	448 (52.0)	448 (52.0)	167 (55.1)	70 (48.3)
2002–2007	358 (41.5)	358 (41.5)	119 (39.3)	62 (42.8)
2008–2013	56 (6.5)	56 (6.5)	17 (5.6)	13 (9.0)
Race/ethnicity				
Hispanic	15 (1.7)	11 (2.5)	8 (2.6)	3 (2.1)
Non-Hispanic white	772 (89.6)	389 (86.8)	267 (88.1)	122 (84.1)
Black	17 (2.0)	12 (2.7)	8 (2.6)	4 (2.8)
Asian/Pacific Islander	45 (5.2)	26 (5.8)	12 (4.0)	14 (9.7)
Native American	13 (1.5)	9 (2.0)	7 (2.3)	2 (1.4)
Unknown	0	1 (0.2)	1 (0.3)	0 (0)
First-degree family history				
No	620 (73.5)	300 (68.6)	202 (68.2)	98 (69.5)
Yes	223 (26.5)	137 (31.4)	94 (31.8)	43 (30.5)
Unknown	19	11	7	4
Reproductive characteristics				
No. of full-term pregnancies				
Nulliparous	179 (20.9)	101 (22.6)	66 (21.9)	35 (24.1)
Parous	677 (79.1)	346 (77.4)	236 (78.1)	110 (75.9)
Unknown	6	1	1	0
Age at first live birth‡, y				
<20	87 (10.5)	50 (14.9)	38 (16.5)	12 (11.4)
20–24	257 (30.9)	133 (39.6)	94 (40.7)	39 (37.1)
25–29	185 (22.2)	85 (25.3)	54 (23.4)	31 (29.5)
30–34	84 (10.1)	47 (24.0)	31 (13.4)	16 (15.2)
≥35	40 (4.8)	21 (6.3)	14 (6.1)	7 (6.1)
Unknown	24	10	5	5
Menopausal status at initial DCIS diagnosis				
Pre- or perimenopausal	340 (40.8)	180 (41.3)	115 (39.1)	65 (45.8)
Postmenopausal	493 (59.2)	256 (58.7)	179 (60.9)	77 (54.2)
Unknown	29	12	9	3
Menopausal hormone replacement therapy				
Never	492 (57.4)	492 (57.4)	190 (63.1)	87 (60.0)
Former (any type)	29 (3.4)	29 (3.4)	18 (6.0)	5 (3.4)
Current estrogen only	182 (21.2)	182 (21.2)	56 (18.6)	29 (20.0)
Current estrogen and progesterone	154 (18.0)	154 (18)	37 (12.3)	24 (16.6)
Unknown	5	2	2	0
Tumor characteristics				
Histology of initial DCIS*				
Mixed	339 (39.3)	155 (34.6)	103 (34.0)	52 (35.9)
NOS	210 (24.4)	88 (19.6)	63 (20.8)	25 (17.2)
Comedo	104 (12.1)	67 (15.0)	47 (15.5)	20 (13.8)
Cribriform	100 (11.6)	58 (12.9)	41 (13.5)	17 (11.7)
Solid	73 (8.5)	55 (12.3)	35 (11.6)	20 (13.8)
Other	36 (4.2)	25 (5.6)	14 (4.6)	11 (7.6)
Grade of initial DCIS				
1	20 (2.8)	20 (2.8)	13 (5.3)	4 (3.4)
2	210 (29.4)	210 (29.4)	63 (25.6)	30 (25.6)
3	223 (31.3)	223 (31.3)	70 (28.5)	41 (35.0)
4	259 (36.4)	259 (36.4)	100 (40.7)	42 (35.9)
Unknown	150	85	57	28

(continued)

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Table 1. (continued)

	Controls (n = 862) No. (%)	Any second breast cancer (n = 448) No. (%)	Invasive* (n = 303) No. (%)	In situ† (n = 145) No. (%)
Size of initial DCIS, cm				
<2	541 (79.7)	541 (79.7)	197 (81.4)	83 (75.5)
2.1–5	116 (17.1)	116 (17.1)	32 (13.2)	20 (18.2)
>5	22 (3.2)	22 (3.2)	13 (5.4)	7 (6.4)
Unknown	183	96	61	35
Treatment characteristics				
Treatment for initial DCIS				
Biopsy only	7 (0.8)	6 (1.3)	4 (1.3)	2 (1.4)
BCS with radiation	465 (53.9)	242 (54.0)	161 (53.1)	81 (55.9)
BCS without radiation	203 (23.5)	105 (23.4)	79 (26.1)	26 (17.9)
Mastectomy	187 (21.7)	95 (21.2)	59 (19.5)	36 (24.8)
Adjuvant endocrine therapy				
No	542 (63)	321 (71.7)	218 (71.9)	103 (71)
Yes	318 (37)	127 (28.3)	85 (28.1)	42 (29)
Unknown	2	0	0	0

*Classified according to ICD-O-3 codes for invasive carcinomas: 8000/3, 8010/3, 8050/3, 8140/3, 8201/3, 8211/3, 8230/3, 8401/3, 8480/3, 8490/3, 8500/3, 8501/3, 8503/3, 8504/3, 8507/3, 8520/3, 8522/3, 8523/3, 8524/3, 8530/3, 8540/3, 8541/3, 8543/3, 8575/3. BCS = breast conservation surgery; DCIS = ductal carcinoma in situ; IQR = interquartile range; NOS = not otherwise specified.

†Classified according to ICD-O-3 codes for subtypes of ductal carcinoma in situ: 8201/2, 8230/2, 8500/2, 8501/2, 8503/2, 8507/2, 8522/2, 8523/2.

‡Excludes nulliparous patients (n = 280).

change in BMI were adjusted for number of months between initial diagnosis and reference date. All other covariates in Table 1 were assessed as potential confounders. None were found to change odds ratios more than 10% for continuous or categorical weight, height, or BMI variables, so they were not added to the final multivariable models. To quantify the magnitude of the case patient–case differences, we calculated two-sided $P_{heterogeneity}$ values by excluding control patients and comparing different case patient groups. STATA/SE 12.1 (StataCorp LP, College Station, TX) was used for all analyses.

Results

Of the 448 case patients with a second breast cancer event, 303 (67.6%) were invasive and 145 (32.4%) were in situ. The median time between initial DCIS and second breast cancer event (range) was 68 (6–208) months for invasive and 49 (6–213) months for in situ events. Case and control patients groups had similar distributions of age, diagnosis year, race, parity, and menopausal status (Table 1). Patients with invasive second breast cancer events were more likely to have used menopausal hormone therapy before initial diagnosis. Patients with any or an invasive second breast cancer event were less likely to have received adjuvant endocrine therapy after their initial diagnosis.

Body weight and BMI, both at the time of initial diagnosis and at second diagnosis/reference date, were positively associated with risk of a second breast cancer event (odds ratio = 1.01–1.04, all $P \leq .03$) (Table 2). For each 1 mg/kg^2 increase in BMI at initial DCIS diagnosis, there was a 3% increase in the odds of any second breast cancer event (OR = 1.03, 95% confidence interval [CI] = 1.01 to 1.05). Women who were obese at initial diagnosis had a 1.6-fold (95% CI = 1.2 to 2.2) higher risk of developing a second breast cancer compared with women with a normal BMI. Similar odds were seen for BMI at second diagnosis (OR = 1.01 to 1.04, all $P \leq .03$). These risks were more pronounced for invasive vs in situ second breast cancers; however, the differences were not statistically significantly different (initial: $P_{heterogeneity} = .61$; second: $P_{heterogeneity} = .38$). Height was not related to risk of second breast cancer.

There were no statistically significant associations observed with gain or loss of BMI and second breast cancer event (Table 3). There was a suggestion of increased risk with BMI loss of –3 kg/m^2 or more for any, invasive, and in situ second breast events, but this was not significant.

After exclusion of four unilateral mastectomy patients and one bilateral recurrence, there were 173 ipsilateral (39.0%) and 270 contralateral (60.8%) second breast cancers. Most ipsilateral (74.0%) and contralateral (63.3%) second breast events were invasive. There was no association between initial BMI and ipsilateral second breast cancer events among all women (Table 4), or those with invasive second breast cancer events (data not shown). However, there was a 2.2-fold (95% CI = 1.4 to 3.3) increased risk of a contralateral second breast cancer associated with obese BMI at initial diagnosis, and there was increased risk associated with both overweight and obese BMI at the second breast cancer event (overweight: OR = 1.6, 95% CI = 1.1 to 2.4; obese: OR = 1.9, 95% CI = 1.3 to 2.8). There was a statistically significantly elevated risk of a contralateral breast cancer event associated with a decrease in BMI of 3 kg/m^2 or more (OR = 2.0, 95% CI = 1.1 to 3.6), which was the only statistically significant risk difference between ipsilateral and contralateral case patients ($P_{heterogeneity} = .01$). Among women with invasive contralateral second breast cancer events, there was an approximately twofold increased risk associated with obesity at both the first and second events, as well as with a BMI loss of 3 kg/m^2 or more (data not shown).

Discussion

The population of women with a history of DCIS has grown as incidence rates have risen steadily over the past several

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Table 2. Risk of second breast cancer event in relation to anthropometric factors at initial ductal carcinoma in situ diagnosis and reference date

	Controls (n = 862) No. (%)	Any second breast cancer* (n = 448)		Invasive* (n = 303)		In situ* (n = 145)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Initial diagnosis							
BMI, mean (SD), kg/m^2	26.1 (6.13)	27.1 (6.49)	1.03 (1.01 to 1.1)†	27.2 (6.41)	1.04 (1.01 to 1.1)†	26.8 (6.69)	1.01 (0.9 to 1.05)
P_{trend} (per 1 kg/m^2)			.007		.005		.491
BMI categories, kg/m^2							
<25.0	417 (48.4)	186 (41.5)	1.0 (ref)	124 (40.9)	1.0 (ref)	62 (42.8)	1.0 (ref)
25.0–29.9	255 (29.6)	133 (29.7)	1.2 (0.9 to 1.6)	89 (29.4)	1.3 (0.9 to 1.9)	44 (30.3)	0.9 (0.6 to 1.6)
≥30.0	190 (22.0)	129 (28.8)	1.6 (1.2 to 2.2)†	90 (29.7)	1.8 (1.2 to 2.6)†	39 (26.9)	1.3 (0.8 to 2.3)
Height, mean (SD), cm	164 (6.8)	165 (6.8)	1.0 (0.9 to 1.03)	165 (6.8)	1.0 (0.9 to 1.04)	164 (7.0)	1.0 (0.9 to 1.1)
P_{trend} (per 1 cm)			.123		.202		.389
Height, quartiles, m							
130–160	278 (32.3)	139 (31)	1.0 (ref)	91 (30)	1.0 (ref)	48 (33.1)	1.0 (ref)
161–164	179 (20.8)	88 (19.6)	1.0 (0.7 to 1.4)	61 (20.1)	1.0 (0.7 to 1.5)	27 (18.6)	0.9 (0.5 to 1.7)
165–168	213 (24.7)	98 (21.9)	0.9 (0.7 to 1.3)	67 (22.1)	1.0 (0.6 to 1.5)	31 (21.4)	0.8 (0.5 to 1.5)
169–188	192 (22.3)	123 (27.5)	1.3 (0.9 to 1.9)	84 (27.7)	1.4 (0.9 to 2.1)	39 (26.9)	1.2 (0.7 to 2.2)
Weight, mean (SD), kg	70.9 (16.7)	74.2 (18.2)	1.01 (1.00 to 1.02)†	74.5 (17.6)	1.01 (1.01 to 1.02)†	73.4 (19.5)	1.01 (0.99 to 1.02)
P_{trend} (per 1 kg)			.002		.002		.349
Weight, quartiles, kg							
37.2–59.9	231 (26.8)	96 (21.4)	1.0 (ref)	58 (19.1)	1.0 (ref)	38 (26.2)	1.0 (ref)
60.0–68.9	239 (27.7)	119 (26.6)	1.1 (0.8 to 1.6)	82 (27.1)	1.3 (0.9 to 2.0)	37 (25.5)	0.8 (0.5 to 1.4)
69.0–80.9	201 (23.3)	94 (21.0)	1.2 (0.8 to 1.7)	63 (20.8)	1.3 (0.8 to 2.1)	31 (21.4)	0.9 (0.5 to 1.8)
81.0–168.3	191 (22.2)	139 (31.0)	1.8 (1.3 to 2.6)†	100 (33.0)	2.2 (1.4 to 3.4)†	39 (26.9)	1.1 (0.6 to 2.1)
Second breast event/reference date							
BMI, mean (SD), kg/m^2	26.5 (6.3)	27.4 (6.4)	1.03 (1.00 to 1.04)†	27.6 (6.3)	1.03 (1.01 to 1.06)†	27.1 (6.5)	1.01 (0.97 to 1.05)
P_{trend} (per 1 kg/m^2)			.028		.017		.698
BMI categories, kg/m^2							
<25.0	388 (45.0)	162 (36.2)	1.0 (ref)	106 (35.0)	1.0 (ref)	56 (38.6)	1.0 (ref)
25.0–29.9	263 (30.5)	154 (34.4)	1.4 (1.1 to 1.9)†	106 (35.0)	1.8 (1.3 to 2.7)†	48 (33.1)	0.9 (0.6 to 1.5)
≥30.0	211 (24.5)	132 (29.5)	1.5 (1.1 to 2.1)†	91 (30.0)	1.6 (1.1 to 2.3)†	41 (28.3)	1.3 (0.8 to 2.3)
Weight, mean (SD), kg							
P_{trend} (per 1 kg)	71.9 (17.5)	74.9 (17.8)	1.01 (1.00 to 1.02)†	75.4 (17.4)	1.01 (1.00 to 1.02)†	74.0 (18.7)	1.00 (0.90 to 1.02)
Weight quartiles, kg			.008		.006		.509
42.0–60.9	212 (24.6)	103 (23.0)	1.0 (ref)	63 (20.8)	1.0 (ref)	40 (27.6)	1.0 (ref)
61.0–69.0	248 (28.8)	87 (19.4)	0.7 (0.5 to 1.02)	57 (18.8)	0.8 (0.5 to 1.2)	30 (20.7)	0.6 (0.4 to 1.2)
69.1–81.9	211 (24.5)	126 (28.1)	1.3 (0.9 to 1.9)	93 (30.7)	1.7 (1.1 to 2.8)†	33 (22.8)	0.8 (0.4 to 1.4)
82.0–172.8	191 (22.2)	132 (29.5)	1.4 (0.9 to 2.0)	90 (29.7)	1.6 (1.04 to 2.6)†	42 (29.0)	1.1 (0.6 to 1.9)

*Odds ratios and 95% confidence intervals were estimated using conditional logistic regression and were implicitly adjusted for matching variables (age and year of the initial DCIS diagnosis, county, histology, grade of initial DCIS lesion, surgical and radiation treatment, and survival time). All models were additionally adjusted for menopausal status at initial DCIS diagnosis and use of adjuvant endocrine therapy. BMI = body mass index; CI = confidence interval; OR = odds ratio.
†$P < .05$.

decades. These women have an elevated risk of developing a subsequent breast cancer, but relatively little is known regarding how modifiable lifestyle factors influence this risk. Of particular importance is obesity given the continued rise in obesity rates and previously established links between obesity and invasive breast cancer (20–24). Our results indicate that the relationship between BMI and second primary breast events among DCIS survivors is complex, with variation across levels of BMI and possibly according to stage and laterality.

Few studies have evaluated the impact of anthropometric factors on second breast cancer events after DCIS, and they had inconsistent results. In a population-based cohort study including 480 patients from 1980 to 1992, Habel et al. evaluated the risk of invasive or in situ ipsilateral second breast cancers or metastases among breast conservation patients (27). Based on 76 ipsilateral events, obesity was associated with a twofold increased risk of ipsilateral second breast cancer compared with women with a BMI of less than 22 kg/m^2. Kuerer et al. also combined invasive and in situ events, but presented associations stratified by laterality. Consistent with our findings, but contrasting those of Habel et al., they found no association with risk of an ipsilateral second breast cancer in a single-institution cohort study (n = 1885) with 40 ipsilateral events (25). A potential explanation for these differences is variation in DCIS treatment. Receipt of radiation therapy is associated with decreased risk of ipsilateral second breast cancers (5). In the Kuerer et al. study, 80% of patients received adjuvant radiation compared with 55% in our study and 40% in Habel et al. Adjuvant tamoxifen therapy also decreases the risk of second breast cancer events (17,33). This was used by approximately one-third of patients in Kuerer et al. and our study but was not routinely used during the time frame of Habel et al.

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Table 3. Risk of second breast cancer event in relation to changes in body mass index and weight between initial ductal carcinoma in situ diagnosis and reference date

	Controls (n = 862)	Any second breast cancer* (n = 448)		Invasive* (n = 303)		In situ* (n = 145)	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Change in BMI, kg/m^2							
BMI loss ≥3	56 (6.5)	42 (9.4)	1.5 (0.95 to 2.4)	26 (8.6)	1.4 (0.8 to 2.5)	16 (11.0)	1.7 (0.8 to 3.8)
BMI loss >1–<3	122 (14.2)	59 (13.2)	1.0 (0.6 to 1.4)	38 (12.5)	0.8 (0.5 to 1.4)	21 (14.5)	1.3 (0.6 to 2.5)
BMI change +/- 1	389 (45.1)	193 (43.1)	1.0 (ref)	124 (40.9)	1.0 (ref)	69 (47.6)	1.0 (ref)
BMI gain >1–<3	203 (23.5)	103 (23.0)	1.0 (0.7 to 1.4)	80 (26.4)	1.1 (0.8 to 1.7)	23 (15.9)	0.7 (0.4 to 1.3)
BMI gain ≥3	92 (10.7)	51 (11.4)	1.1 (0.7 to 1.6)	35 (11.6)	1.0 (0.6 to 1.7)	16 (11.0)	1.2 (0.5 to 2.5)
P_{trend} (2 kg/m^2)			.302		.572		.326
Change in weight, kg							
Loss ≥6	95 (11.0)	68 (15.2)	1.3 (0.9 to 2.0)	43 (14.2)	1.3 (0.8 to 2.1)	25 (17.2)	1.4 (0.7 to 2.8)
Loss >2–5.9	146 (16.9)	67 (15.0)	0.9 (0.6 to 1.3)	47 (15.5)	0.9 (0.5 to 1.4)	20 (13.8)	0.9 (0.5 to 1.9)
Gain or loss within 2	242 (28.1)	120 (26.8)	1.0 (ref)	79 (26.1)	1.0 (ref)	41 (28.3)	1.0 (ref)
Gain >2–5.9	236 (27.4)	111 (24.8)	0.9 (0.6 to 1.2)	75 (24.8)	1.0 (0.6 to 1.5)	36 (24.8)	0.7 (0.4 to 1.3)
Gain ≥6	143 (16.6)	82 (18.3)	1.0 (0.7 to 1.5)	59 (19.5)	1.1 (0.7 to 1.8)	23 (15.9)	0.8 (0.4 to 1.7)
P_{trend} (2 kg)			.321		.477		.481

*Odds ratios and 95% confidence intervals were estimated using conditional logistic regression and were implicitly adjusted for matching variables (age and year of the initial ductal carcinoma in situ [DCIS] diagnosis, county, histology, grade of initial DCIS lesion, surgical and radiation treatment, and survival time). All models were additionally adjusted for menopausal status at initial DCIS diagnosis and use of adjuvant endocrine therapy. BMI = body mass index; CI = confidence interval; OR = odds ratio.

Table 4. Relationship of second breast cancer laterality and body mass index at initial ductal carcinoma in situ diagnosis, second breast cancer/reference date, and change in BMI

	Ipsilateral*			Contralateral		
	Controls (n = 336)	Cases (n = 173) No. (%)	OR† (95% CI)	Controls (n = 513) No. (%)	Cases (n = 270) No. (%)	OR† (95% CI)
Initial diagnosis						
BMI categories, kg/m^2						
<25.0	165 (49.1)	77 (44.5)	1.0 (ref)	246 (48.0)	106 (39.3)	1.0 (ref)
25.0–29.9	93 (27.7)	52 (30.1)	1.2 (0.7 to 1.9)	158 (30.8)	79 (29.3)	1.2 (0.8 to 1.8)
≥30.0	78 (23.2)	44 (25.4)	1.1 (0.7 to 1.8)	109 (21.2)	85 (31.5)	2.2 (1.4 to 3.3)‡
P_{trend} (per 1 kg/m^2)			.466			.008
Second breast event/reference date						
BMI categories, kg/m^2						
<25.0	146 (43.5)	66 (38.2)	1.0 (ref)	237 (46.2)	94 (34.8)	1.0 (ref)
25.0–29.9	100 (29.8)	57 (32.9)	1.6 (0.9 to 2.8)	157 (30.6)	94 (34.8)	1.6 (1.1 to 2.4)‡
≥30.0	90 (26.8)	50 (28.9)	1.1 (0.6 to 2.1)	119 (23.2)	82 (30.4)	1.9 (1.3 to 2.8)‡
P_{trend} (per 1 kg/m^2)			.572			.027
Change in exposure status						
Change in BMI, kg/m^2						
BMI loss ≥3	24 (7.1)	9 (5.2)	0.8 (0.4 to 1.9)	32 (6.2)	33 (12.2)	2.0 (1.1 to 3.6)‡
BMI loss >1–<3	44 (13.1)	24 (13.9)	1.1 (0.6 to 2.1)	76 (14.8)	34 (12.6)	0.8 (0.5 to 1.4)
BMI change +/- 1	145 (43.2)	74 (42.8)	1.0 (ref)	237 (46.2)	117 (43.3)	1.0 (ref)
BMI gain >1–<3	83 (24.7)	41 (23.7)	1.0 (0.6 to 1.7)	117 (22.8)	61 (22.6)	1.0 (0.7 to 1.6)
BMI gain ≥3	40 (11.9)	25 (14.5)	1.3 (0.7 to 2.4)	51 (9.9)	25 (9.3)	0.9 (0.5 to 1.6)
P_{trend} (2 kg/m^2)			.991			.198

*Excludes patients with previous unilateral mastectomy. BMI = body mass index; CI = confidence interval; OR = odds ratio.
†Odds ratios and 95% confidence intervals were estimated using conditional logistic regression and were implicitly adjusted for matching variables (age and year of the initial ductal carcinoma in situ [DCIS] diagnosis, county, histology, grade of initial DCIS lesion, surgical and radiation treatment, and survival time). All models were additionally adjusted for menopausal status at initial DCIS diagnosis and use of adjuvant endocrine therapy.
‡$P < .05$.

Although Kuerer et al. found no statistically significant differences in the risk of ipsilateral second breast events according to BMI, a univariate analysis of their data revealed a borderline significantly ($P = .06$) elevated risk of contralateral second breast cancers associated with overweight/obesity among women who did not receive adjuvant tamoxifen therapy. No multivariable analysis was presented. In our analysis adjusted for adjuvant endocrine therapy, there were no statistically significant

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differences in risk of ipsilateral or contralateral second breast cancers; however, there was a suggestion of increased contralateral risk associated with obesity at both initial and second diagnosis. Both studies were likely underpowered to detect statistically significant associations, and further studies with longer follow-up and larger numbers of contralateral breast cancers are needed to confirm our finding of a possible association between obesity and contralateral breast cancer risk.

McLaughlin et al. conducted the largest examination of BMI and second breast cancer events in a DCIS population (n = 1925). In contrast to our study, they did not observe increased risk of second breast cancer events associated with increasing BMI before initial diagnosis (HR = 0.99, 95% CI = 0.96 to 1.02) or between initial and subsequent diagnosis (HR = 1.03, 95% CI = 0.97 to 1.10) in the overall cohort. However, they found that menopausal status at initial diagnosis modified the effect of obesity on the risk of second breast cancer events (26). Premenopausal women who were obese at diagnosis were 77% less likely to develop any second breast cancer compared with normal and underweight women, whereas a non-statistically significant trend toward increased risk associated with overweight and obesity was seen in postmenopausal women. We did not find evidence of effect modification according to menopausal status in our study, but in their analysis of premenopausal women, there were only four obese patients with second breast cancer events (compared with 39 in our study), limiting the statistical power and generalizability of their findings.

One finding unique to our study was the increased risk of a contralateral second breast cancer event associated with a substantial loss of BMI after initial diagnosis, but no increased risk associated with weight gain. McLaughlin et al. evaluated change in weight, and also did not observe an association between weight gain and risk of second breast cancer events (26). In contrast to our study, they also found no association with loss of BMI. Although there is a dearth of information about weight change after DCIS, a number of studies have investigated this relationship after an invasive cancer diagnosis (34–43). These studies have shown conflicting results, with several reporting an increased risk of second breast cancers associated with weight gain (37,41), others demonstrating no association (35), and another offering evidence of a relationship between substantial weight loss and increased risk of second breast cancer (43). Mechanisms explaining associations between weight loss and second breast cancers are lacking but may involve compromised tumor–immune system interactions accompanying chronic undernutrition (44) or dysfunctional mammary adipocytes (45,46). Whether our results suggest that avoidance of major weight loss subsequent to a DCIS diagnosis may be an additional approach to reduce the risk of second breast cancer events or if this is merely a reflection of cachexia associated with a second breast cancer event is unclear and requires additional study.

One of the strengths of our study is its population-based nested case–control patient design, which is well suited to studying rare diseases such as second cancer events that require many years of follow-up for detection. This is only the fourth published study to assess the relationship between BMI and risk of second breast cancer events after a diagnosis of DCIS, and our sample size is appreciably larger than any of the prior studies. Further, the population-based nature of our study makes it potentially more generalizable than single-institution series.

The primary potential limitation of our study is recall bias. However, data for our primary exposures of interest were largely abstracted from medical records and not subject to recall bias. For those patients missing BMI data, there may be bias that we cannot account for in our models. There was no difference with respect to patient demographic, lifestyle, and tumor characteristics compared with patients without missing data, and the degree and direction of bias are unknown. An additional limitation is lack of data on other modifiable risk factors, particularly physical activity. However, data on this subject in DCIS are lacking. However, data from a large meta-analysis including 11 cohort and eight case–control patient studies found no differential effects of physical activity on invasive breast cancer risk according to BMI (47). Therefore, we would not expect physical activity to significantly confound or modify our findings. Participation bias is another potential concern, but we did achieve reasonable response rates for a study of this type, which limits the impact of this bias. During the time frame including many of the initial DCIS diagnoses, hormone receptors were not routinely tested. Therefore, there is a substantial amount of missing data for this variable, and we were unable to include this as a matching variable, effect modifier, or confounder. Finally, although our results suggest that there may be increased risk of invasive and contralateral second breast cancer events associated with increasing BMI, the study lacked power to show significant heterogeneity. Larger studies are needed to confirm our findings.

Few studies have evaluated the influence of potentially modifiable lifestyle factors on the risk of subsequent breast cancers among women with DCIS. Second breast cancers are an important outcome for this population, as women with DCIS have a two to four times greater risk of developing a second breast cancer than women in the general population have of developing a first breast cancer. Additionally, a second invasive event is associated with a 1.75-fold increased mortality risk (12). Our findings suggest that obesity is positively related to second breast cancer events, and possibly more strongly with invasive and contralateral second cancers. Efforts to maintain a normal weight have well-known health benefits for a variety of diseases, and this may also extend to lowering risk of a second breast cancer among women diagnosed with DCIS. Further research is needed on the types of exercise/dietary interventions that could be effective among DCIS survivors.

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