Relationship between anthropometric factors and risk of second breast cancer events among Ductal Carcinoma In Situ survivors

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Abstract

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Introduction

There is currently a growing population of ductal carcinoma in situ (DCIS) survivors with considerable risk of second breast cancers in the United States. Although specific treatment factors have been shown to decrease this risk, there is little data regarding the impact of potentially modifiable lifestyle factors.

Methods

We conducted a population-based case-control study of DCIS survivors in Western Washington diagnosed between 1996 and 2013. We enrolled 347 patients diagnosed with an initial DCIS lesion and a second primary invasive or in situ breast cancer, and 587 matched controls diagnosed with only an initial DCIS. Associations between anthropometric factors and risk of an invasive or *in situ* second breast cancer events were evaluated using conditional logistic regression.

Results

Obese (≥30 kg/m^2) and underweight (<18.5 kg/m^2) BMI at initial DCIS diagnosis were associated with an elevated risk of invasive second breast cancers (odds ratio (OR)=2.1, 95% confidence interval (CI) 1.25 to 3.55; and OR=4.8, 95% CI 1.15 to 20.04, respectively). Compared to women with no change in BMI, those whose BMI increased ≥2 kg/m^2 between initial and second diagnosis (reference date for controls) had a 1.8-fold (95% CI 1.03 to 3.12) increased risk of invasive second breast cancer.

Discussion

This study adds to limited available literature and suggests that avoidance of weight gain may be an adjunct strategy to reduce the risk of second breast cancer events after DCIS. Given the overall scarcity of data on the influence of modifiable lifestyle factors on second breast cancers after DCIS, additional confirmatory studies are needed.

Introduction

Ductal carcinoma *in situ* (DCIS) is a non-obligate precursor for invasive breast cancer with heterogeneous potential for invasion and recurrence after treatment. The incidence of DCIS increased in parallel with the rise in screening mammography in the 1980s, and in 2013 DCIS was estimated to comprise nearly 30% of newly diagnosed breast cancer cases in the United States.[1,2] Although the 10-year breast cancer-specific mortality rate after treatment of DCIS is less than 2%,[3-5] approximately 4-30% of patients will experience a subsequent DCIS or invasive breast cancer event within 10 years of initial diagnosis.[3,6-12] For clinicians to make appropriate and individualized treatment recommendations to patients with a diagnosis of DCIS, it is imperative that they have the ability to stratify patients according to their risk of experiencing a second breast cancer event.[13]

Previous studies have identified factors associated with second breast cancer events after treatment of DCIS, including adjuvant radiation, endocrine therapy, age, race/ethnicity, margin width, mammographic breast density, degree of tumor differentiation and specific histologic subtypes.[3,7,10,12,14-23] Although it has been clearly demonstrated that radiation and adjuvant endocrine therapy decrease the risk of local recurrence and contralateral second breast cancer events after DCIS,[17,18] there is relatively little known about the impact of potentially modifiable lifestyle factors. In particular, the role of obesity in breast cancer is of increasing interest.[24] Obese patients with invasive cancer are more likely to experience a second breast cancer or die from breast cancer compared to women who are normal or underweight.[25-29] Three previous cohort studies have evaluated the association of BMI and second breast events in DCIS patients with inconsistent results.[30-32] One study demonstrated a 2-fold increase in risk of ipsilateral second breast cancer events in obese patients at initial diagnosis compared to patients in the lowest BMI group (<22 kg/m2);[32] another showed no overall association;[30] and a third found that the risk of second breast cancer events was modified by menopausal status.[31] In this study, obesity was associated with decreased risk of second breast cancer events in premenopausal women, and although there was a trend toward increased risk in postmenopausal women, the study was underpowered to detect this. Although study sizes were relatively large (480 to

1,925 patients) with 76 to 162 second breast cancer events, when stratified by pathology of the second breast cancer event (invasive versus *in situ*) and different categories of BMI to assess trends and associations, the number of events in each group was often too small to draw meaningful conclusions.

Given the growing population of DCIS survivors, the rising epidemic of obesity in the United States,[33] 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 population-based study of DCIS survivors. The identification of potentially modifiable lifestyle factors that impact this risk could guide and motivate changes in health behaviors among the growing population of DCIS survivors.

Methods

We conducted a population-based nested case-control study drawing participants from the underlying cohort of women aged 30-79 years who were diagnosed with DCIS in the Seattle-Puget Sound region between January 1, 1996 and December 31, 2013. Study participants were identified through the Seattle-Puget Sound Cancer Surveillance System (CSS), a population-based cancer registry serving 13 contiguous counties in western Washington State that has participated in the National Cancer Institute's SEER program since 1974. The Fred Hutchinson Cancer Research Center's institutional review board approved this study.

Study Population

CSS was used to identify patients with a second breast cancer event, either invasive or *in situ*, following an initial diagnosis of DCIS. Patients who underwent bilateral mastectomy for the initial DCIS lesion were excluded from the study because their risk of developing a second breast cancer is extremely low (<1%).[34,35] Women who developed non-breast cancers between initial DCIS diagnosis and second breast cancer events (cases)/reference date (controls) were also excluded because

treatment for interval cancers may impact the risk of subsequent DCIS or invasive breast cancer. Case patients were defined as women diagnosed with either an ipsilateral or contralateral second DCIS or local invasive breast cancer at least 6 months after the initial DCIS diagnosis. Control patients were those diagnosed with DCIS who did not have a second DCIS or invasive breast cancer event during the study period. They were matched 2:1 or 3:1 to cases by age and year of initial DCIS diagnosis, county of residence at diagnosis, surgical and radiation treatment, and histology and grade of initial DCIS lesion. A total of 347 cases and 587 controls were enrolled at the time of this analysis.

Data collection

Patient demographic, epidemiologic and clinical data were collected from structured telephone interviews and detailed medical record reviews. In addition to CSS and interview-acquired data, medical records were sought from multiple sources, including oncology and primary care practices, to ensure complete data on clinical and pathologic tumor characteristics as well as treatment data. Treatment data included type of surgical procedure performed, receipt of radiation, and receipt of adjuvant hormonal or chemotherapy. Lifestyle factors such as tobacco consumption, reproductive factors, receipt of menopausal hormone therapy and family history of breast cancer were obtained via telephone interviews. The primary exposures of interest (height and weight) were also obtained via telephone questionnaire. Self-reported weight measurements were collected for multiple time points, including at age 18, at initial DCIS diagnosis, and at second breast cancer event (or reference date for controls). Height at initial DCIS diagnosis was also collected.

Characterization of Exposures and Covariates

Weight (kg) and BMI (kg/m^2) were missing at initial DCIS diagnosis and reference date for 9 (7 cases, 2 controls) and 6 (4 cases, 2 controls) participants, respectively. Weight (kg) at age 18 was missing for 3 participants (2 cases, 1 control). Height (cm) data was complete. Height and weight were evaluated as continuous variables and in quartiles for both the initial and second event (reference date for controls). Likewise, associations between BMI and cases/controls were evaluated for both time points. BMI was categorized as a continuous variable, and as a categorical variable according to

the modified Centers for Disease Control (CDC) classification: underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2). Weight at age 18 was evaluated as a continuous variable associated with the initial DCIS lesion. Changes in BMI and weight were calculated as the difference in BMI and weight between the first DCIS diagnosis and second breast cancer (reference date for controls). Differences were evaluated as continuous BMI intervals by 2 kg/m^2 change, and weight per 2 kg change. BMI and weight change were also considered as categorical variables by units of 2kg/m^2 (≥-2 to ≥2 change in BMI) and 2 kg (≥-4 kg to ≥4 kg).

Patient age at the time of initial DCIS diagnosis was modeled as a categorical variable consisting of 10 year age groups: 30-39 years, 40-49 years, 50-59 years, 60-69 years and 70-79 years. Year of initial DCIS diagnosis was categorized as 1996-2000, 2001-2007 and 2008-2013. Race was classified as Hispanic, Non-Hispanic White, Black, Asian/Pacific Islander and Native American. A first degree family history of breast cancer was considered present if a study participant's mother, sister or daughter had a history of invasive breast cancer. Reproductive characteristics were defined as follows: age at menarche (<13, ≥13 years), menopausal status at the time of the initial DCIS diagnosis (premenopausal, postmenopausal), pregnancy history (nulliparous, number of full term pregnancies 1 to 4+) and age at first live birth (<20, 20-24, 25-29, 30-34 and ≥35 years). Smoking status was categorized as never use, former use or current use at the time of diagnosis. Duration of menopausal hormone therapy was categorized as never user and <1, 1 to 5 and ≥5 years. Treatment was categorized by type of surgery and receipt of adjuvant radiation: biopsy only, radiation only, breast conservation surgery with radiation, breast conservation surgery without radiation and mastectomy. Use of adjuvant endocrine therapy was coded as binary variables reflecting never versus ever use. Because the number of patients who underwent mastectomy with radiation for DCIS was extremely low (n=3), all patients with mastectomy were included in one treatment category.

Statistical Analysis

For the primary analysis, controls were compared to three case groups (any second breast event, invasive second breast event, *in situ* second breast event) with respect to demographic and treatment

characteristics (Table 1). Frequency distributions were calculated for categorical covariates, and the Chi^2 test was used for univariate pairwise comparisons. Associations between BMI, height, weight and changes in these variables with any second breast event, invasive second breast event or *in situ* second breast event were estimated by conditional logistic regression for matched case-control studies.[36] Odds ratios (OR) and Wald-type 95% confidence intervals were calculated as estimates of relative risk. Effect modification by menopausal status and receipt of adjuvant endocrine therapy were assessed based on likelihood ratio testing. Because there were no statistically significant interactions between menopausal status or receipt of adjuvant endocrine therapy and any of the main effects assessed at the pre-specified $p<0.05$ level, no effect modifiers were included in the final models.

As a secondary analysis, associations between BMI at initial diagnosis with ipsilateral or contralateral second breast cancers (invasive and *in situ*) were estimated using conditional logistic regression. One patient with bilateral second breast cancers was excluded from this analysis. Additionally, for the analysis of ipsilateral breast cancer events, patients who underwent a unilateral mastectomy for their initial procedure were excluded (n=327).

All models were implicitly adjusted for the case/control matching variables. All covariates in Table 1 were assessed for confounding, and those that produced a 10% change in the main effect estimate when added individually to the conditional logistic regression model were selected for inclusion.[37] These included menopausal status at initial DCIS diagnosis, receipt of adjuvant endocrine therapy and duration of menopausal hormone therapy. Because the time period between initial diagnosis and second event (reference date for controls) differed among case/control pairs, models for change in BMI were adjusted for number of months between initial diagnosis and second event (reference date for controls). STATA/SE 12.1 (StataCorp LP, College Station Texas) was used for all analyses.

Results

Of the 347 patients with a second breast cancer event, 224 (64.5%) were invasive and 123 (35.5%) were *in situ*. The mean time between initial DCIS and second breast cancer event (reference date for

controls) was shortest for *in situ* second events (mean 67.5 months, range 6-184 months) and longest for invasive second events (mean 75.7 months, range 6-208). Patient and treatment characteristics were compared between controls and each of the case groups (Table 1). With the exceptions of age at menarche and receipt of adjuvant endocrine therapy there were no significant differences comparing controls to each of the case groups. Younger age at menarche (<13 years) was more common among women with any second breast cancer event (48.7%) or *in situ* (50.4%) breast cancer compared to controls (41.2%). Receipt of adjuvant endocrine therapy was less common among any (28.8%) and invasive (26.8%) second breast cancers compared to controls (38.3%).

Associations of BMI, height and weight at initial diagnosis with risk of second breast cancer event differed by case type (Table 2). Patients with any second breast cancer or an invasive second breast cancer had higher mean BMI and weight at initial DCIS diagnosis compared to controls [(BMI: p=0.04 and p=0.01, respectively) and (weight: p=0.03 and p<0.001, respectively)]. In adjusted analyses, increasing BMI (continuous per 1 kg/m^2) and weight (continuous per 1 kg) at initial diagnosis were significantly associated with elevated risk of any and invasive second breast cancer. Obesity (≥30 kg/m^2) at initial DCIS diagnosis was also associated with a significantly elevated risk of any and invasive second breast cancers [(any: OR=1.64; 95% confidence interval (CI), 1.08 to 2.50) and (invasive: OR=2.11; 95% CI, 1.25 to 3.55)]. Compared to patients with normal BMI (19.5-24.9 kg/m^2), those who were underweight (<18.5 kg/m^2) at initial DCIS diagnosis had an even higher, approximately 4-fold, risk of any or invasive second breast cancer events. These estimates were based on 7 (3.2%) invasive breast cancer events with underweight BMI, which resulted in unstable confidence intervals. There were no significant associations between BMI or weight at initial DCIS diagnosis and risk of second *in situ* breast cancer events, although there was a non-significant trend toward increased risk associated with underweight BMI. Height and weight at age 18 were not associated with risk of any second breast cancer event.

With respect to BMI and weight at second diagnosis (reference date for controls), all associations and trends were similar to BMI and weight at initial diagnosis. There continued to be an elevated risk

of any or an invasive second breast cancer with increasing BMI (continuous per 1 kg/m^2) and weight (continuous per 1 kg) (Table 2). Obese patients had a 2.1-fold (95% CI, 1.28 to 3.40) increased risk of a second invasive breast cancer compared to those with normal BMI. There were some suggestion of increased risk of all second breast cancer events (any, invasive and in situ) with underweight BMI, though these were within the limits of chance.

Significant associations were observed with higher levels of BMI and weight gain and risk of any and invasive second breast cancer events (Table 3). Patients who gained ≥4 kg had an approximate 2-fold (OR=1.97; 95% CI, 1.19-3.25) elevated risk. No associations were noted among patients with a second *in situ* breast cancer. There were non-significant trends toward increased second cancer risk with BMI and weight reduction for all case types.

When examined by laterality, there was no association between initial BMI and ipsilateral second breast cancer events (Table 4). However, there was a 2.2-fold (95% CI, 1.25 to 3.99) increased risk of a contralateral second breast cancer associated with obese BMI. There was also a suggestion of elevated risk of contralateral breast cancer associated with underweight BMI (OR=2.08; 95% CI, 0.45 to 9.60), although this was within the limits of chance.

Discussion

The population of women with a history of DCIS continues to grow as incidence rates have risen steadily over the past several decades. These women have an elevated risk of developing a subsequent invasive breast cancer, but there remains relatively little 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 incidence and survivorship.[25-29] Our results indicate that the relationship between BMI and second primary breast events among DCIS survivors is complex, varying across levels of BMI and according to pathology and laterality of the second breast cancer event. We observed an elevated risk of any, invasive and contralateral second breast cancers associated with obesity at both initial DCIS

diagnosis and second diagnosis (reference date for controls), but also noted a significantly higher risk of any and invasive second breast cancers associated with underweight BMI at initial diagnosis. Furthermore, weight gain after initial DCIS diagnosis adversely influenced risk; increasing weight gain was associated with higher risk of invasive second breast cancers when compared to patients who maintained their weight.

Few studies have evaluated the impact of anthropometric factors on second breast cancer events after DCIS, and these have yielded contradictory results with respect to the effect of obesity. In addition to inconsistent findings, dissimilar study designs make it challenging to compare results across studies. In a cohort study that included 480 patients with complete interview data from 1980 to 1992, Habel et al. evaluated the risk of ipsilateral second breast cancers (invasive and *in situ* combined) or metastasis outside the breast in women who underwent breast conservation surgery (BCS).[32] They found a 2-fold increased risk comparing obese women to those with BMI below 22 kg/m^2 based on 76 ipsilateral breast cancers. Kuerer et al. also combined invasive and in situ events, but presented associations stratified by laterality. In contrast to the findings of Habel et al. but consistent with our findings, Kuerer et al. found no significant differences in ipsilateral second breast cancers based on BMI at initial DCIS diagnosis in a large single-institution cohort study (n=1,885) with 40 ipsilateral second breast cancer events.[30] The contrasting findings may be attributable to treatments that were common at the time of each study. Receipt of radiation therapy is associated with decreased risk of ipsilateral second breast cancers;[38,39] only 40% of patients in Habel et al. received adjuvant radiation compared to 80% of patients in Kuerer et al. and 60% of patients in our study. Adjuvant tamoxifen therapy has also been shown to decrease the risk of second breast cancer events.[40,41] This was used by approximately one-third of patients in Kuerer et al. and our study, but was not routinely used during the timeframe of the study by Habel et al.

Although Kuerer et al. found no significant differences in the risk of ipsilateral second breast events according to BMI, a univariate analysis of their data revealed a non-significant (p=0.057) elevated risk of contralateral second breast cancers associated with overweight and obesity based on

64 contralateral second breast cancers. This was seen only among women who did not receive adjuvant tamoxifen therapy, and no multivariate analysis was presented. In our adjusted analysis based on 210 contralateral cases, we found a significantly elevated risk of contralateral second breast cancers associated with obesity regardless of adjuvant endocrine therapy use. Though the study by Kuerer et al. may have been underpowered to detect a true association, there are also likely differences in ascertainment and definition of adjuvant endocrine therapy use. Additionally, the study by Kuerer et al. was a single-institution cohort study, which is subject to a different set of biases and is potentially less generalizable than our population-based study.

In contrast to the two previously discussed studies, Hart McLaughlin et al. conducted the largest examination of BMI and second cancer events in a DCIS population, but without stratifying by laterality. Instead, they considered any or invasive second breast cancer events regardless of laterality, and found that menopausal status at initial diagnosis modified the effect of obesity on the risk of second breast cancer events.[31] Premenopausal women who were obese at diagnosis were 77% less likely to develop any second breast cancer compared to normal and underweight women, whereas a non-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, and it is unclear why our results differ so dramatically from those found by Hart McLaughlin et al. Patient and treatment characteristics were largely comparable between the two studies with the exception of menopausal hormone therapy use, which was more commonly used by patients in our study compared to those in Hart McLaughlin. Because neither study reported on specific hormone therapy type (estrogen versus combined estrogen and progesterone), and Hart McLaughlin did not account for duration of use, the magnitude or directionality of any biases based on this variable cannot be determined. Another important consideration is the relatively small number of second breast cancer events on which Hart McLaughlin et al. based their results. In their analysis of premenopausal women there were only 4 obese patients with second breast cancer events (compared to 19 in our study), making their findings relatively

statistically unstable. Given the disparate results seen in these studies, further investigation is needed.

One finding unique to this study was the association between increased risk of any and invasive second breast cancers with underweight BMI at initial diagnosis. None of the previously discussed studies evaluating the risk of second breast cancers after DCIS assessed low BMI as a potential risk factor. However, there have been several reports in invasive breast cancer suggesting that the association of BMI with breast cancer outcomes may be U- or J-shaped.[42-46] Mechanisms explaining associations between low BMI and second breast cancers are lacking, but may involve compromised tumor-immune system interactions accompanying chronic undernutrition[47] or dysfunctional mammary adipocytes.[48,49] Although we were unable to assess for estrogen receptor (ER) status in this study, Kuerer et al. found an increased proportion of ER-negative initial DCIS lesions among their reference group of normal and underweight compared to overweight and obese patients.[30] ER-negativity has been associated with DCIS recurrence in a number of studies,[50-52] and could have contributed to our findings if underweight women were more likely to have ER-negative DCIS. Because of the relatively small number of underweight women in this study (n=19), our estimates were relatively unstable and results should be interpreted with caution. However, given similar findings in the invasive breast cancer literature, future studies on the effect of BMI on second breast cancers after DCIS should attempt to separately examine associations for underweight patients.

Weight gain is common after a diagnosis of DCIS,[53] but only one previous study has evaluated this potential risk factor. In contrast to the lack of association between weight gain and risk of second events in the study by Hart McLaughlin et al.,[31] we found increasing risk with each subsequent 2 kg/m^2 increase in BMI compared to no change in BMI between initial DCIS diagnosis and second diagnosis (reference date for controls). Differences in findings may be reflective of small sample sizes and lack of statistical power to show differences in the Hart McLaughlin study. In contrast to the dearth of information about weight change after DCIS, a number of studies have investigated the relationship between weight gain after invasive cancer diagnosis and prognosis.[54-63] These studies

have shown conflicting results with several reporting increased risk of second breast cancers associated with weight gain,[57,61] others demonstrating no association,[55] and another offering evidence of a relationship between substantial weight loss and increased risk of second breast cancer.[63] The underlying basis for weight gain and the biologic effects of changes in weight after invasive breast cancer remain poorly understood,[64] and may be fundamentally different for patients with DCIS. Our results suggest that avoidance of weight gain subsequent to a diagnosis with DCIS diagnosis may be an additional approach to reduce the risk of second breast cancer events, but this requires additional study.

One of the strengths of this study is its nested case-control design, which is an ideal study type for rare diseases such as second cancer events that often require many years of follow-up for detection. This is only the fourth study to assess the relationship between BMI and risk of second breast cancer events after a diagnosis of DCIS. Because there are more second breast cancer events than any of the other studies, we had additional statistical power to detect associations with smaller effect sizes. Additionally, the three previous studies assessed slightly different outcomes making it difficult to interpret inconsistent results. In order to facilitate better comparisons, we conducted multiple exploratory analyses and evaluated second breast cancer events by both pathology (invasive versus in situ) and laterality (ipsilateral versus contralateral).

However, there are also limitations associated with case-control studies, such as recall bias. Although we used medical record data where possible, self-reported height and weight were used to assess exposure status. Previous studies using self-reported BMI have demonstrated 75% agreement (k=0.63) between self-reported and medical record-based BMI data that did not differ by case/control status.[28] Subject participation was required for inclusion in the study, and no data exists on the exposure characteristics of patients who refused to participate. The directionality and extent of recall bias and participation bias are unknown. Because full medical record review is still in progress, histopathologic characteristics were unavailable and not assessed as potential confounders. One particularly important histologic characteristic that was missing for this analysis was ER status. In

studies of invasive breast cancer, the relation between body weight and breast cancer risk has been shown to be dependent on tumor ER/PR status, and we would expect to see similar associations with DCIS patients.[65]

Few studies have evaluated the influence of potentially modifiable lifestyle factors on the risk of second breast cancers among DCIS survivors. Second breast cancers are an important outcome for this population as they have a 2 to 4 times greater risk of developing a second breast cancer than women in the general population have of developing a first breast cancer.[23,66,67] Our findings reflect a potentially U- or J-shaped relationship between BMI and risk of second breast cancer events; both underweight and obesity were associated with increased risk in our study. Additionally, we found that weight gain after initial diagnosis was also associated with risk of second breast cancer events. However, given the heterogeneity of findings across this and the three other studies investigating modifiable risk factors and second breast cancer events, there remains a need for confirmatory studies that can stratify by both pathology and laterality of second events.

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

Patient characteristics At initial diagnosis	Controls (n=587) N (%)	Any second breast cancer (n=347) N (%)	Invasive (n=224) N (%)	*In situ* (n=123) N (%)
Age, years				
Median years [IQR][a]	52 [47-59]	52 [46-59]	53 [46-60]	51 [44-57]
30-39	23 (3.9)	17 (4.9)	9 (4.0)	8 (6.5)
40-49	212 (36.1)	117 (33.7)	74 (33.0)	43 (35.0)
50-59	215 (36.6)	131 (37.8)	79 (35.3)	52 (42.3)
60-69	111 (18.9)	64 (18.4)	50 (22.3)	14 (11.4)
70+	26 (4.4)	18 (5.2)	12 (5.4)	6 (4.9)
Year of diagnosis				
1995-2001	273 (46.5)	171 (49.3)	113 (50.4)	58 (47.2)
2002-2007	243 (41.4)	135 (38.9)	87 (38.8)	48 (39.0)
2008-2013	71 (12.1)	41 (11.8)	24 (10.7)	17 (13.8)
Race/ethnicity				
Hispanic	10 (1.7)	10 (2.9)	7 (3.1)	3 (2.4)
Non-Hispanic White	532 (90.6)	309 (89.3)	203 (91.0)	106 (86.2)
Black	9 (1.5)	7 (2.0)	4 (1.8)	3 (2.4)
Asian/Pacific Islander	28 (4.8)	14 (4.1)	4 (1.8)	10 (8.1)
Native American	8 (1.4)	6 (1.7)	5 (2.2)	1 (0.8)
Unknown	0	1	1	0
First degree family history				
No	416 (72.2)	232 (69.3)	152 (70.0)	80 (67.8)
Yes	160 (27.8)	103 (30.7)	65 (30.0)	38 (32.2)
Unknown	11	12	7	5
Age at menarche, years				
<13	242 (41.3)	169 (49.0)	107 (48.0)	62 (50.8)
≥13	344 (58.7)	176 (51.0)	116 (52.0)	60 (49.2)
Unknown	1	2	1	1
Menopausal status				
Premenopausal	232 (40.0)	137 (40.2)	81 (36.8)	56 (46.3)
Postmenopausal	348 (60.0)	204 (59.8)	139 (63.2)	65 (53.7)
Unknown	7	6	4	2
Age at first live birth, years[b]				
<20	55 (12.1)	37 (14.2)	28 (16.4)	9 (10.1)
20-24	172 (37.8)	97 (37.3)	65 (38.0)	32 (36.0)
25-29	132 (29.0)	68 (26.2)	41 (24.0)	27 (30.3)
30-34	69 (15.2)	40 (15.4)	25 (14.6)	15 (16.9)
≥35	27 (5.9)	18 (6.9)	12 (7.0)	6 (6.7)

Table 1 (continued). Patient and treatment characteristics of women with and without a second breast cancer event after initial ductal carcinoma *in situ* diagnosis.

Patient characteristics at initial diagnosis	Controls (n=587) N (%)	Any second breast cancer (n=347) N (%)	Invasive (n=224) N (%)	*In situ* (n=123) N (%)
Number of full term pregnancies				
Nulliparous	131 (22.4)	86 (24.9)	52 (23.3)	34 (27.6)
1	90 (15.4)	61 (17.6)	35 (15.7)	26 (21.1)
2	212 (36.2)	106 (30.6)	73 (32.7)	33 (26.8)
3	103 (17.6)	61 (17.6)	36 (16.1)	25 (20.3)
4+	50 (8.5)	32 (9.2)	27 (12.1)	5 (4.1)
Unknown	1	1	1	0
Duration of menopausal hormone therapy				
0	319 (56.8)	194 (58.3)	125 (57.9)	
<1	37 (6.6)	21 (6.3)	16 (7.4)	
1 to 5	74 (13.2)	41 (12.3)	28 (13.0)	
≥5	132 (23.5)	77 (23.1	47 (21.8)	
Unknown	25	14	8	
Smoking status at initial diagnosis				
Never	358 (61.0)	195 (56.2)	122 (54.5)	73 (59.3)
Former	175 (29.8)	106 (30.5)	71 (31.7)	35 (28.5)
Current	54 (9.2)	46 (13.3)	31 (13.8)	15 (12.2)
Treatment for initial DCIS				
Biopsy only	0	2 (0.6)	2 (0.9)	0
Radiation only	1 (0.2)	0	0	0
BCS[a] without radiation	127 (21.6)	73 (21.0)	55 (24.6)	18 (14.6)
BCS with radiation	346 (58.9)	202 (58.2)	127 (56.7)	75 (61.0)
Mastectomy	113 (19.3)	70 (20.2)	40 (17.9)	30 (24.4)
Adjuvant endocrine therapy				
No	358 (61.4)	247 (71.2)	164 (73.2)	83 (67.5)
Yes	225 (38.6)	100 (28.8)	60 (26.8)	40 (32.5)
Unknown	4	0	0	0

[a] BCS, breast conservation surgery; IQR, interquartile range
[b] Excludes nulliparous patients (n=219)

Table 2. Relationship of body mass index, height and weight at initial ductal carcinoma *in situ* diagnosis and second breast cancer (reference date for controls) with risk of second breast event.

	Controls (n=587)	**Any second breast cancer**[a] (n=347)		**Invasive**[a] (n=224)		***In situ***[a] (n=123)	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Initial diagnosis							
BMI[b] (kg/m^2), mean(sd)	24.5 (4.95)	25.3 (5.91)	**1.03 (1.00-1.06)**[†]	25.7 (6.29)	**1.05 (1.01-1.08)**[†]	24.5 (5.08)	0.99 (0.94-1.04)
P trend (per 1 kg/m^2)			**0.046**		**0.008**		0.59
BMI categories (kg/m^2)[a]							
<18.5	9 (1.5)	10 (2.9)	**3.93 (1.15-13.45)**[†]	7 (3.2)	**4.80 (1.15-20.04)**[†]	3 (2.5)	3.00 (0.25-35.53)
18.5-24.9	352 (60.2)	182 (53.5)	1.0 (*ref*)	113 (51.6)	1.0 (*ref*)	69 (57.0)	1.0 (*ref*)
25-29.9	145 (24.8)	85 (25.0)	1.20 (0.84-1.72)	54 (24.7)	1.39 (0.88-2.20)	31 (25.6)	0.92 (0.50-1.70)
≥30	79 (13.5)	63 (18.5)	**1.64 (1.08-2.50)**[†]	45 (20.5)	**2.11 (1.25-3.55)**[†]	18 (14.9)	1.00 (0.48-2.07)
BMI quartiles (kg/m^2)							
I – 16.93-21.69	159 (27.2)	81 (23.8)	1.08 (0.71-1.64)	49 (22.4)	1.03 (0.61-1.77)	32 (26.4)	1.22 (0.62-2.42)
II – 21.70-24.11	155 (26.5)	78 (22.9)	1.0 (*ref*)	48 (21.9)	1.0 (*ref*)	30 (24.8)	1.0 (*ref*)
III – 24.14-27.49	142 (24.3)	81 (23.8)	1.27 (0.84-1.92)	52 (23.7)	1.45 (0.85-2.46)	29 (24.0)	1.06 (0.54-2.11)
IV – 27.6-53.37	129 (22.1)	100 (29.4)	**1.60 (1.07-2.39)**[†]	70 (32.0)	**1.93 (1.15-3.23)**[†]	30 (24.8)	1.17 (0.61-2.23)
Height (cm), mean(sd)	165 (6.43)	165 (6.98)	1.01 (0.98-1.03)	165 (6.97)	1.01 (0.98-1.03)	165 (7.03)	1.00 (0.97-1.04)
Ptrend (per 1cm)			0.64		0.61		0.94
Height quartiles (cm)							
I – 147.32-160.02	159 (27.1)	104 (30.0)	1.16 (0.80-1.69)	68 (30.4)	1.22 (0.75-1.98)	36 (29.3)	1.07 (0.58-1.99)
II – 162.56-165.10	193 (32.9)	99 (28.5)	1.0 (*ref*)	61 (27.2)	1.0 (*ref*)	38 (30.9)	1.0 (*ref*)
III – 167.64-170.18	137 (23.3)	73 (21.0)	0.96 (0.64-1.43)	50 (22.3)	0.93 90.56-1.54)	23 (18.7)	1.02 (0.52-2.00)
IV – 172.72-187.96	98 (16.7)	71 (20.5)	1.37 (0.90-2.09)	45 (20.1)	1.53 (0.89-2.63)	26 (21.1)	1.15 (0.58-2.26)
Weight (kg), mean(sd)	67.6 (13.9)	69.7 (15.9)	**1.01 (1.00-1.02)**[†]	71.0 (16.6)	**1.01 (1.00-1.02)**[†]	67.5 (14.3)	1.00 (0.98-1.01)
P trend (per 1kg)			**0.04**		**0.008**		0.66
Weight quartiles (kg)							
I – 45.36-58.97	180 (30.8)	96 (28.2)	1.02 (0.68-1.52)	54 (24.7)	1.03 (0.61-1.73)	42 (34.7)	1.01 (0.53-1.94)
II – 59.87-65.77	149 (25.5)	77 (22.6)	1.0 (*ref*)	50 (22.8)	1.0 (*ref*)	27 (22.3)	1.0 (*ref*)
III – 67.13-74.84	127 (21.7)	73 (21.5)	1.23 (0.80-1.90)	47 (21.5)	1.48 (0.86-2.56)	26 (21.5)	0.95 (0.46-1.98)
IV – 75.30-131.54	129 (22.1)	94 (27.6)	1.36 (0.89-2.07)	68 (31.1)	**1.90 (1.12-3.21)**[†]	26 (21.5)	0.71 (0.35-1.48)

Table 2 (continued). Relationship of body mass index, height and weight at initial ductal carcinoma *in situ* diagnosis and second breast cancer/reference date with risk of second breast event.

	Controls (n=587)	**Any second breast cancer**[a] (n=347)		**Invasive**[a] (n=224)		***In situ***[a] (n=123)	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Initial diagnosis							
Weight at age 18 (kg)	55.9 (7.93)	56.1 (8.65)	1.01 (0.99-1.02)	56.1 (8.19)	1.01 (0.99-1.04)	56.1 (9.5)	1.00 (0.97-1.03)
P trend (per 1kg)			0.44		0.24		0.90
Second Breast Cancer/Reference Date							
BMI (kg/m^2), mean(sd)	25.1 (5.25)	26.1 (6.09)	**1.03 (1.00-1.06)**[†]	26.6 (6.03)	**1.05 (1.02-1.09)**[†]	25.3 (6.13)	0.99 (0.95-1.04)
P trend (per 1 kg/m^2)			**0.02**		**0.003**		0.82
BMI categories (kg/m^2)							
<18.5	11 (1.9)	10 (2.9)	3.07 (0.99-9.54)	7 (3.2)	3.40 (0.95-12.20)	3 (2.5)	2.60 (0.22-31.53)
18.5-24.9	310 (53.0)	156 (45.5)	1.0 (*ref*)	91 (41.0)	1.0 (*ref*)	65 (53.7)	1.0 (*ref*)
25-29.9	166 (28.4)	96 (28.0)	1.27 (0.90-1.80)	65 (29.3)	**1.60 (1.03-2.50)**[†]	31 (25.6)	0.87 (0.50-1.53)
≥30	98 (16.8)	81 (23.6)	**1.60 (1.08-2.38)**[†]	59 (26.6)	**2.08 (1.28-3.40)**[†]	22 (18.2)	0.99 (0.50-1.94)
BMI quartiles (kg/m^2)							
I – 15.36-21.98	151 (25.8)	82 (23.9)	1.23 (0.81-1.88)	45 (20.3)	0.91 90.53-1.56)	37 (30.6)	1.99 (1.00-3.97)
II – 21.99-24.84	157 (26.8)	75 (21.9)	1.0 (*ref*)	49 (22.1)	1.0 (*ref*)	26 (21.5)	1.0 (*ref*)
III – 24.91-28.79	150 (25.6)	86 (25.1)	1.45 (0.96-2.19)	55 (24.8)	1.46 (0.86-2.46)	31 (25.6)	1.45 (0.73-2.88)
IV – 28.88-51.04	127 (21.7)	100 (29.2)	**1.64 (1.09-2.47)**[†]	73 (32.9)	**1.91 (1.15-3.17)**[†]	27 (22.3)	1.19 (0.58-2.43)
Weight (kg), mean(sd)	69.2 (15.0)	72.2 (16.8)	**1.01 (1.00-1.02)**[†]	73.5 (16.8)	**1.02 (1.01-1.03)**[†]	69.8 (16.5)	1.00 (0.98-1.01)
P trend (per 1kg)			**0.02**		**0.002**		0.78
Weight quartiles (kg)							
I – 40.82-58.97	160 (27.4)	85 (24.8)	0.96 (0.65-1.42)	46 (20.7)	0.75 (0.45-1.27)	39 (32.2)	1.33 (0.72-2.45)
II – 59.87-68.04	191 (32.6)	96 (28.0)	1.0 (*ref*)	62 (27.9)	1.0 (*ref*)	34 (28.1)	1.0 (*ref*)
III – 68.49-79.38	118 (20.2)	68 (19.8)	1.26 (0.84-1.89)	48 (21.6)	1.34 (0.80-2.24)	20 (16.5)	1.05 (0.52-2.13)
IV – 79.83-136.08	116 (19.8)	94 (27.4)	1.38 (0.93-2.07)	66 (29.7)	**1.66 (1.01-2.73)**[†]	28 (23.1)	0.92 (0.46-1.85)

[†] Bold indicates p<0.05

[a] Adjusted for menopausal status at initial DCIS diagnosis, use of hormone replacement therapy, use of adjuvant endocrine therapy and initial DCIS treatment

[b] BMI, body mass index

Table 3. Relationship of changes in body mass index and weight between initial ductal carcinoma *in situ* diagnosis and second breast cancer (reference date for controls) with risk of second breast event.

	Controls (n=587)	**Any second breast cancer**[a] (n=347)		**Invasive**[a] (n=224)		***In situ***[a] (n=123)	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Change in BMI[b] (kg/m^2)							
BMI loss ≥2	30 (5.1)	23 (6.8)	1.90 (0.98-3.68)	13 (6.0)	1.74 (0.73-4.14)	10 (8.3)	2.25 (0.79-6.43)
BMI loss 0-2	75 (12.8)	38 (11.2)	1.15 (0.70-1.89)	21 (9.6)	0.93 (0.50-1.76)	17 (14.2)	1.69 (0.73-3.93)
No change in BMI	232 (39.7)	104 (30.8)	1.0 (*ref*)	68 (31.2)	1.0 (*ref*)	36 (30.0)	1.0 (*ref*)
BMI gain 0-2	157 (26.9)	101 (29.9)	**1.51 (1.02-2.23)**	66 (30.3)	**1.65 (1.00[c]-2.72)**[†]	35 (29.2)	1.33 (0.70-2.53)
BMI gain ≥2	90 (15.4)	72 (21.3)	**1.70 (1.07-2.71)**[†]	50 (22.9)	**1.79 (1.03-3.12)**[†]	22 (18.3)	1.58 (0.66-3.76)
P trend (2 kg/m^2)			0.25		0.08		0.73
Change in weight (kg)							
Loss ≥4	51 (8.7)	35 (10.4)	1.63 (0.94-2.83)	21 (9.6)	1.44 (0.72-2.86)	14 (11.7)	2.12 (0.83-5.42)
Loss 0-4	54 (9.2)	26 (7.7)	1.07 (0.60-1.92)	13 (6.0)	0.80 (0.37-1.74)	13 (10.8)	1.63 (0.65-4.11)
No change in weight	232 (39.7)	104 (30.8)	1.0 (*ref*)	68 (31.2)	1.0 (*ref*)	36 (30.0)	1.0 (*ref*)
Gain 0-4	117 (20.0)	68 (20.1)	1.34 (0.87-2.07)	44 (20.2)	1.33 (0.76-2.33)	24 (20.0)	1.33 (0.65-2.71)
Gain ≥4	130 (22.3)	105 (31.1)	**1.76 (1.17-2.65)**[†]	72 (33.0)	**1.97 (1.19-3.25)**[†]	33 (27.5)	1.45 (0.71-2.96)
P trend (2 kg)			0.21		0.06		0.77

[†] Bold indicates p<0.05

[a] Adjusted for menopausal status at initial DCIS diagnosis, use of hormone replacement therapy, use of adjuvant endocrine therapy and initial DCIS treatment

[b] BMI, body mass index

[c] Lower confidence interval of 1.00 was rounded from 0.999, and does not include 1.0

Table 4. Relationship of body mass index at initial ductal *carcinoma in situ* diagnosis and second breast cancer (reference date for controls) with risk of ipsilateral versus contralateral second breast cancer event.

	Ipsilateral[a]			**Contralateral**		
	Controls (n=474)	**Cases** (n=132)		**Controls** (n=587)	**Cases** (n=210)	
	N (%)	N (%)	OR[b] (95% CI)	N (%)	N (%)	OR[b] (95% CI)
BMI[c] categories (kg/m^2)						
<18.5	7 (1.5)	4 (3.1)	8.58 (0.91-81.21)	9 (1.5)	6 (2.9)	2.08 (0.45-9.60)
18.5-24.9	264 (55.9)	71 (54.6)	1.0 (*ref*)	352 (60.2)	108 (52.4)	1.0 (*ref*)
25-29.9	128 (27.1)	34 926.2)	0.85 (0.48-1.51)	145 (24.8)	50 (24.3)	1.38 (0.82-2.32)
≥30	73 (15.5)	21 (16.2)	0.88 (0.44-1.77)	79 (13.5)	42 (20.4)	**2.23 (1.25-3.99)**[†]
P trend (per 1 kg/m^2)			0.534			**0.04**[†]

[†] Bold indicates p<0.05

[a] Excludes patients with previous unilateral mastectomy

[b] Adjusted for menopausal status at initial DCIS diagnosis, use of hormone replacement therapy, use of adjuvant endocrine therapy and initial DCIS treatment

[c] BMI, body mass index

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