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Biologic features and prognosis of ductal carcinoma in situ are not adversely impacted by initial large body mass

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Abstract

Obesity is associated with adverse biologic features and poor outcome in patients with invasive breast cancer, yet this relationship has not been evaluated in patients with ductal carcinoma in situ (DCIS). From 1996 to 2009, body mass index (BMI) was recorded at initial diagnosis for 1,885 patients with DCIS treated at our institution. Patients were categorized as obese (BMI ≥ 30 kg/m^2), overweight (BMI 25 to<30 kg/m^2), or of normal weight or underweight (BMI <25 kg/m^2). Logistic regression was used to examine associations between BMI and patient, clinical, and pathologic features and treatment. Local–regional recurrence was calculated using the Kaplan–Meier method. All statistical tests were two-sided. Of the 1,885 patients, 514 (27.7%) were obese, 510 (27.5%) were overweight, and 831 (44.8%) were normal/underweight. In multivariate analysis, overweight and obese patients were significantly more likely to be African American (odds ratio [OR], 3.93; 95% confidence interval [CI], 2.66–5.80) or Hispanic (OR, 1.44; CI, 1.02–2.04), be postmenopausal (OR, 1.63; CI, 1.28–2.07), have diabetes (OR, 4.60; CI, 2.60–8.12), have estrogen-receptor-positive DCIS (OR, 1.39; CI, 1.00–192), and present with a radiologic abnormality rather than clinical symptoms (OR, 1.35; CI, 1.01–1.80). At a median follow-up time of 4.96 years (range, 1.0–14.34 years), no significant differences in local recurrence rates were detected based on patients' initial BMI category. Furthermore, there was no significant difference in risk of recurrence between diabetic patients receiving metformin or not. In conclusion, higher BMI is not associated with adverse biologic features or prognosis in patients with DCIS.

Keywords

DCIS; Obesity; Breast cancer; Body mass index; Metformin

Introduction

Obesity and breast cancer both represent major public health problems in developed countries. In the United States, 64.1% of women over the age of 20 years are overweight or obese [1]. Obesity is a risk factor for multiple chronic medical conditions, including diabetes, hypertension, hypercholesterolemia, cardiovascular disease, and arthritis, as well as for cancers of the colon, endometrium, and kidney and invasive breast cancer [2]. In the case of invasive breast cancer, there is an increasing body of literature showing that obese patients are more likely to present with advanced-stage disease, derive less benefit from adjuvant systemic therapy, are more likely to develop distant metastases, and die from breast cancer more often than normal weight or underweight patients [3–8].

Although there are increasing numbers of reports supporting a relationship between high body mass index (BMI) and worse prognosis in patients treated for invasive breast cancer, we are aware of no specific studies related to the effect of obesity on prognosis in patients with ductal carcinoma in situ (DCIS). Given that DCIS now accounts for approximately 20–25% of breast cancer diagnoses and given the high prevalence of obesity in the United States, understanding the effect of obesity on the presentation, treatment, and outcome of DCIS is essential. To elucidate these issues, we studied 1,855 patients with pure DCIS recently treated at The University of Texas MD Anderson Cancer Center. As diabetes is known to be associated with obesity and the antidiabetic metformin has been identified as a potential anticancer agent in preclinical, epidemiologic, and clinical breast cancer studies, the relationship between metformin use and clinical and pathologic presenting features of DCIS and outcome was also explored [9–11]. This is the first report to comprehensively describe the impact of initial BMI on the clinical presentation, clinicopathologic features, treatment received, and outcome in patients with DCIS.

Methods

Following approval from the Institutional Review Board of MD Anderson Cancer Center, we used the MD Anderson Breast Cancer Management System (BCMS) database to identify 1,855 patients with a diagnosis of pure DCIS who were treated with surgery and/or radiotherapy between January 1996 and July 2009, had a minimum follow-up time of 1 year, and had documentation of height and weight at initial diagnosis of DCIS. The BCMS database contains detailed information on demographic, diagnostic, clinical, pathologic, treatment, and follow-up data. The aforementioned variables were analyzed with respect to the patient's recorded BMI at initial diagnosis of DCIS, which was calculated as the prospectively recorded patient weight (kg) divided by the square of the patient height (m^2). Patients were categorized into three following groups as classified by the Centers of Disease Control and Prevention: obese (BMI ≥ 30 kg/ m^2); overweight (BMI 25 to ≤ 30 kg/m^2); and normal weight or underweight (BMI ≤ 25 kg/m^2) [5].

Although this weight-for-height measure is widely accepted in clinical settings, it is important to note some limitations of BMI in the assessment of patients. It does not calculate the distribution of fat in the body or differentiate between fat mass and lean body mass [12]. Patient self-reported diagnosis of diabetes and use of diabetic drugs was also recorded [13].

Statistical analyses

The Chi-square test was used to compare BMI groups with respect to categorical variables. The Kruskal–Wallis test was used to compare BMI groups with respect to continuous variables. Associations between clinical factors at diagnosis and BMI were analyzed using multivariate logistic regression, with controlling for the potential confounding effect of patient factors, tumor factors, and treatment-related variables. Odds ratios (ORs) and 95% CIs were generated for demographic and clinical characteristics and treatment variables. Significant associations identified by univariate analyses were utilized in the multivariate logistic regression model. The Hosmer–Lemeshow goodness-of-fit statistic was assessed to insure the validity of the model.

Two primary outcomes of interest—local–regional recurrence and development of contralateral breast cancer (in both outcomes, the recurrence and contralateral rates included DCIS and invasive events)—were evaluated using the Kaplan–Meier product-limit method, and differences in these outcomes were compared between BMI groups with the log-rank test. Local–regional recurrence was defined as ipsilateral local or regional recurrence, and if the patient did not experience recurrence, cases were censored at the time of last follow-up or death from any cause. For development of contralateral breast cancer, if the patient did

not experience contralateral breast cancer, cases were censored at the time of last follow-up or death from any cause. Time to local or regional recurrence or development of contralateral breast cancer was defined from the date of surgery. All reported *P* values are two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using STATA/IC (release 11.1; StataCorp, College Station, TX) and STATISTICA (release 9.0; StatSoft, Inc., Tulsa, OK).

Results

Relationship between BMI and clinical and pathologic characteristics

Clinical, pathologic, and treatment characteristics of the 1,855 patients with DCIS are summarized in Table 1. Overall, 831 patients (44.8%) were of normal weight or underweight at diagnosis, and 1,024 patients (55.2%) were either overweight (*N* = 510, 27.5%) or obese (*N* = 514, 27.7%). African American patients were significantly more likely to be obese than were patients of other races ($P < 0.001$). Of the 203 African American patients, 55.2% (*N* = 112) were obese. Postmenopausal patients were significantly more likely to be overweight or obese than were premenopausal patients (59.4 vs. 44.2%; $P < 0.001$). In line with the findings regarding menopausal status, patients who were of normal weight or underweight were significantly younger (median age, 52 years) than overweight (median age, 55 years) and obese patients (median age, 57 years; $P < 0.001$). First-degree family history of breast and/or ovarian cancer, use of hormone replacement therapy, and the presence of bilateral breast cancer at diagnosis were not significantly correlated with BMI (all $P > 0.05$). Initial presentation was more likely to be a clinical symptom (mass or nipple discharge) rather than an imaging abnormality in patients who were of normal weight or underweight than in patients who were overweight or obese (17.3 vs. 11.9 vs. 13.6%, respectively, $P = 0.022$). The largest recorded mammographic DCIS dimension was similar among patients in the different BMI groups, but the largest recorded pathologic DCIS dimension was marginally higher among obese patients (median, 1.5 cm) than among normal/underweight (median, 1.2 cm) and overweight patients (median, 1.1 cm; $P = 0.05$). Patients who were of normal weight or underweight were significantly less likely than the combined group of overweight and obese patients to have grade I DCIS lesions (10.9 vs. 12.3%; $P = 0.043$). Obese patients were significantly more likely than normal/underweight patients to have necrosis (41.6 vs. 38.4%; $P = 0.035$). Normal/underweight patients were more likely than obese patients to have estrogen receptor (ER)-negative DCIS lesions (22.9 vs. 16.8%; $P = 0.035$).

Clinical and pathologic characteristics that were associated (significant or non-significant) of being overweight or obese on multivariate logistic regression are shown in Table 2. Of these characteristics, race [African American (OR = 3.93; CI = 2.66–5.80) or Hispanic (OR = 1.44, CI = 1.02–2.04)], post-menopausal status (OR = 1.63, CI = 1.28–2.07), diagnosis of diabetes (OR = 4.60, CI = 2.60–8.12), presentation with a radiographic abnormality versus a clinical symptom (OR = 1.35, CI = 1.01–1.80), and ER-positive DCIS (OR = 1.39, CI = 1.00–1.92) were independent predictors of being overweight or obese.

Relationship between BMI and Treatments for DCIS

The combined groups of obese and overweight patients were more likely than normal/underweight patients to undergo breast-conserving surgery (BCS) (60.6 vs. 56.0%; $P = 0.042$, Table 1). Among patients who underwent BCS, the use of adjuvant radiotherapy was significantly more common among obese patients than normal/underweight patients (82.2 vs. 75.6%; $P = 0.029$) and the combined group of overweight and obese patients than normal/underweight patients (81.3 vs. 75.6%; $P = 0.022$). Among patients who underwent mastectomy, the use of immediate breast reconstruction was significantly more common in

normal/underweight patients (73.0%) than in overweight (62.6%) and obese patients (52.5%; P <0.001). Contralateral prophylactic mastectomy was more likely in normal/underweight patients (9.3%) than in obese patients (6.0%) and the combination of overweight and obese patients (6.5%, P = 0.029). There were no significant differences in the use of adjuvant tamoxifen by BMI group. On multivariate logistic regression, the only treatment characteristic that was an independent predictor of being overweight or obese was immediate breast reconstruction (OR = 1.58; P = 0.007; Table 2).

Relationship between BMI and risk of local–regional recurrence or development of contralateral breast cancer

At a median follow-up of 4.96 years (range, 1.0–14.34), 45 patients (4.1%) had had a local–regional recurrence following BCS, for an overall 5-year local–regional recurrence rate of 4.14%. Among the 45 patients with local–regional recurrence, the recurrence was DCIS in 27 patients (60%) and invasive disease in 13 patients (40%) (Table 3). The 5-year rates of local–regional recurrence among patients in the 3 BMI categories by type of adjuvant therapy received are shown in Table 3. Within subgroups of patients treated with identical adjuvant therapies, no significant differences were observed in local–regional recurrence rates by BMI category (Table 3). Logistic regression analysis was also conducted to identify risks of recurrence for being overweight/obese compared to normal weight/underweight, and there were no significant differences found between BMI categories after adjusting for race, menopausal status, age, pathologic size, grade, necrosis, surgical procedure, and use of adjuvant therapy (OR, 1.87; 95% CI, 0.43–8.18; P = 0.47).

A total of 64 patients (3.5%) developed contralateral breast cancer during the study period, for an overall 5-year rate of contralateral breast cancer development of 3.9% (Table 3). Among the 64 patients who developed contra-lateral breast cancer, the contralateral cancer was DCIS in 32 patients (50%) and invasive cancer in 32 patients (50%). No significant differences were detected in the rate of contralateral breast cancer development based on BMI category or if the patient received adjuvant tamoxifen (Table 3). There was, however, a trend toward a higher 5-year rate of contralateral breast cancer development among overweight (5.7%) and obese patients (5.1%) not taking tamoxifen compared with normal/underweight patients not taking tamoxifen (2.8%; P = 0.057). This trend was not seen among patients taking tamoxifen (P = 0.588).

DCIS among diabetic patients with and without metformin use

As type II diabetes is known to be strongly associated with obesity, clinical and pathologic characteristics and outcome were evaluated with respect to the presence or absence of diabetes at diagnosis of DCIS. There were 118 patients (6%) in the study who were diabetic. Compared to the patients without diabetes, the diabetic patients were significantly older; were more likely to be obese, of African American descent, and postmenopausal; had larger pathologic tumor size; and were more likely to be treated with adjuvant radiotherapy (all P <0.05; Table 4). No differences were noted in patients with and without diabetes with respect to nuclear grade, presence of necrosis, ER status, or use of adjuvant tamoxifen therapy (all P >0.05). Four diabetic patients developed a local–regional recurrence or contralateral breast cancer during follow-up. No significant differences were detected in local–regional recurrences or contralateral breast cancer development between patients with and without diabetes (P >0.05).

The relationship between metformin use and clinical and pathologic characteristics and outcome was also explored [9–11]. Of the 118 patients with diabetes, 62 (53%) were taking metformin at diagnosis of DCIS, and 56 (48%) were not (Table 4). No significant differences were noted with respect to clinical and pathologic features, local–regional

recurrence, and development of contralateral breast cancer between patients with DCIS taking and not taking metformin ($P > 0.05$).

Discussion

Multiple published studies have documented overall worse biologic features, prognosis, and response to therapy for women with large body size (those who are overweight or obese) than for women with lean body size (those who are of normal weight or underweight) among patients with invasive breast cancer. Our study was undertaken to explore whether large body size was associated with similar effects in women with DCIS, a nonobligate precursor of invasive breast cancer and/or a marker for increased risk of development of invasive disease. In this cohort study of 1,855 women diagnosed with pure DCIS, 55.2% of patients had large body size, and large body size was independently associated with African American or Hispanic race, post-menopausal status, a diagnosis of diabetes, presentation of disease by radiologic abnormality as opposed to clinical findings, and having ER-positive disease. Large body size was not, however, associated with known adverse features of DCIS, including larger tumor size, higher nuclear grade, or the presence of necrosis. The 5-year local–regional recurrence rate was not significantly higher among women with large body size after stratification for type of therapy received. However, among women not taking tamoxifen, there was a trend toward increased rates of development of contralateral breast cancer among women with large body size compared with women of lean body size, an effect that has previously been demonstrated among patients with invasive breast cancer [14].

Our finding of an increased hazard of developing ER-positive DCIS among women with large body size is likely attributable to increased circulating estrogens related to an increased mass of adipose tissue and upregulation of aromatase seen in obese women [15, 16]. The same mechanism may also underlie the trend toward an increased risk of development of contralateral breast cancer among patients not taking tamoxifen in this study. Why then did we not see an increased rate of local–regional recurrence among patients with large body size compared with patients with lean body size? This may be because the overwhelming majority of patients presented with early, mammographically detected disease that was completely excised. Furthermore, tamoxifen and radiotherapy were utilized in a large proportion of patients. The use of adjuvant tamoxifen in patients with DCIS has a small protective effect against ipsilateral breast cancer recurrence and contralateral breast cancer [17]. However, the potential therapeutic benefit of tamoxifen use in women with large body size and DCIS must be carefully weighed against the potential risks, including thromboembolic events and endometrial carcinoma, which occur more commonly in obese women [14]. In the current study, rates of use of tamoxifen following surgery for DCIS were nearly identical among the different BMI categories. Although aromatase inhibitors are not currently being utilized in the management of DCIS as trials evaluating the efficacy of this intervention have yet to be analyzed and published, there is now evidence that anastrozole is less effective than tamoxifen in preventing reoccurrences in obese women with invasive breast cancer [18].

In addition to being the first report to assess the relationship between BMI and clinical and pathologic factors in patients with DCIS, this is also to our knowledge the first report to evaluate the relationship between BMI and type of surgery utilized for DCIS. Patients with large body size were significantly less likely to undergo mastectomy, immediate breast reconstruction following mastectomy, and contralateral prophylactic mastectomy. Although surgical decision-making and postoperative complications were not evaluated in the present study, obesity has been shown to be an independent predictor of wound and flap complications after breast surgery in general and specifically after immediate breast

reconstruction and therefore may have played a role in procedure selection [19–21]. Nevertheless, even though the rate of immediate reconstruction was significantly lower in women of large body size (57.6%) than in women of lean body size, the rate was substantially higher than the overall rates of immediate reconstruction in the United States, which have been reported to be as low as 15% [22].

Approximately 10% of large-size women in this study also had diabetes. There is a complex relationship between obesity, insulin and insulin resistance, IGF-1, and potential adverse effects on cellular proliferation and angiogenesis that may impact carcinogenesis and progression of disease through direct pathways and cross-talk with estrogenic and altered adipokine and cytokine pathways [23]. The relationship between metformin use and clinical and pathologic characteristics of DCIS and outcome of DCIS was explored as metformin has been shown to be a potential anticancer agent in preclinical, epidemiologic, and clinical breast cancer studies [9–11]. No differences in adverse features of DCIS or risk of local–regional recurrence were noted between diabetic patients taking and not taking metformin. The lack of association between metformin and adverse features and prognosis of DCIS may be due to the relatively small sample size, or the drug may have no detectable efficacy in DCIS. In this regard, it is important to note that different associations of metformin with cancer may exist in nondiabetic subjects who have not had similar long-term exposure to hyperinsulinemia [10]. Metformin as a potential chemopreventive agent or as an adjuvant treatment for breast cancer may prove to be of more value in nondiabetic women, although this is yet to be proven [9, 10].

The use of BMI in clinical settings is ubiquitous; however, there are several limitations that clinicians need to be aware of. BMI is commonly used to measure adiposity; however, it does not accurately calculate the distribution of fat in the body or differentiate between fat mass and lean body mass. There are other established methods used by investigators to address this concern. Waist-to-height ratio (WHtR) and waist-to-hip ratio (WHR) are commonly used to assess the body fat distribution and distinguish between both fat mass and muscle mass [24]. However, despite the many different methods available, there has been no consensus in the field that measure adiposity accurately [25]. Because of the nature of our study, we were unable to collect WHtR and WHR at the initial diagnosis of DCIS. A number of recent studies in the field have elucidated the role of weight loss after diagnosis of invasive breast cancer, suggesting an advantage of losing weight and leading to being disease-free and global survival [26–28]. The potential impact of weight loss on local recurrence following a diagnosis of DCIS is yet to be studied.

There may be fundamental differences in DCIS and invasive breast cancer that account for the finding that large body size does not adversely affect biologic features or prognosis of patients with DCIS. In this regard, it is interesting that large body size does not appear to be related to an increased risk of development of in situ cancers, regardless of menopausal status, but shows an unambiguous relationship with increased risk of development of postmenopausal invasive breast cancer [29–31]. It is possible that a larger sample size or much longer follow-up times may be needed to demonstrate that large body size is an independent adverse prognostic feature in DCIS. The present study has several strengths, including prospective recording of BMI at diagnosis of DCIS, the large dataset, and treatment of all patients at a single institution using standardized diagnostic imaging, pathology, and multidisciplinary clinical practice protocols. Considered in light of these strengths, the findings of this study suggest that large body size is unlikely to have a significant independent prognostic impact on present-day patients with imaging-detected DCIS.

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Table 1

Clinical, pathologic, and treatment characteristics by BMI group at DCIS diagnosis (N = 1,855; univariate analyses)

	Normal or underweight (BMI <25 kg/m^2) Group 1	**Overweight (BMI 25 to <30 kg/m^2) Group 2**	**Obese (BMI ≥ 30 kg/m^2) Group 3**	***P*, all groups**	***P*, group 1 versus groups 2 and 3**	***P*, group 1 versus group 3**
Number of patients	831 (44.8)	510 (27.5)	514 (27.7)			
Race						
White	661 (79.5)	382 (74.9)	329 (64.0)			
African American	36 (4.3)	55 (10.1)	112 (21.8)			
Hispanic	62 (7.5)	41 (8.0)	59 (11.5)			
Asian/Pacific Islander	65 (7.8)	27 (5.3)	7 (1.4)			
Other	7 (0.8)	5 (1.0)	7 (1.4)	0.001	0.001	0.001
Menopausal status[a]						
Premenopausal	293 (35.3)	117 (23.0)	115 (22.5)			
Postmenopausal	538 (64.7)	392 (77.0)	397 (77.5)	<0.001	<0.001	0.001
Hormone replacement therapy	259 (31.2)	164 (32.2)	153 (29.8)	0.707	0.922	0.588
Age						
Median (range)	52 years (18–89)	55 years (29–88)	57 years (31–82)	<0.001	<0.001	<0.001[b]
≤40 years	94 (11.3)	32 (6.3)	32 (6.2)			
41–50 years	270 (32.5)	138 (27.1)	119 (23.2)			
51–60 years	255 (30.7)	166 (32.6)	176 (34.2)			
61–70 years	133 (16.0)	112 (22.0)	132 (25.7)			
>70 years	79 (9.5)	62 (12.2)	55 (10.7)	<0.001	<0.001	<0.001
First-degree family history of breast and/or ovarian cancer	172 (20.7)	102 (20.0)	125 (24.3)	0.181	0.444	0.120
Diabetic at diagnosis	15 (1.8)	27 (5.3)	76 (14.8)	0.001	<0.001	<0.001
Receiving metformin	5 (33.3)	12 (44.4)	45 (59.2)	0.117	0.111	0.066
Presence of bilateral breast cancer at diagnosis	61 (7.3)	42 (8.2)	36 (7.0)	0.737	0.822	0.817
Initial presenting signs[c]						
Clinical	139 (17.3)	59 (11.9)	68 (13.6)			
Radiologic	667 (82.8)	436 (88.1)	431 (86.4)	0.022	0.008	0.082

	Normal or underweight (BMI <25 kg/m^2) Group 1	Overweight (BMI 25 to <30 kg/m^2) Group 2	Obese (BMI ≥ 30 kg/m^2) Group 3	*P*, all groups	*P*, group 1 versus groups 2 and 3	*P*, group 1 versus group 3
Largest recorded mammographic dimension,[d] median (range)	2.0 cm (0.05–14)	2.0 cm (0.01–18)	2.5 cm (0.3–10)	0.641	0.591	0.380[b]
Largest recorded pathologic dimension,[e] median (range)	1.2 cm (0.03–19)	1.1 cm (0.01–12)	1.5 cm (0.05–18)	0.05	0.724	0.099[b]
Nuclear grade[f]						
I	66 (8.1)	57 (11.3)	53 (10.6)			
II or III	747 (91.9)	448 (88.7)	447 (89.4)	0.120	0.043	0.128
Necrosis present	319 (38.4)	190 (37.3)	214 (41.6)	0.319	0.640	0.035
ER status[g]						
Positive	356 (77.1)	250 (81.7)	272 (83.2)			
Negative	106 (22.9)	56 (18.3)	55 (16.8)	0.077	0.027	0.035
Surgery						
BCS	465 (56.0)	307 (60.2)	314 (61.1)			
Mastectomy	366 (44.0)	203 (39.8)	200 (38.9)	0.120	0.042	0.064
Immediate breast reconstruction (in patients who underwent mastectomy)	267 (73.0)	127 (62.6)	105 (52.5)	<0.001	<0.001	<0.001
Contralateral prophylactic mastectomy	77 (9.3)	36 (7.1)	31 (6.0)	0.077	0.029	0.034
Adjuvant tamoxifen (in all patients)	298 (35.9)	189 (37.1)	192 (37.4)	0.832	0.549	0.580
Adjuvant tamoxifen (in patients who underwent BCS)	208 (44.7)	134 (43.6)	138 (44.0)	0.968	0.808	0.871
Adjuvant tamoxifen (in patients who underwent mastectomy)	90 (24.6)	55 (27.1)	54 (27.0)	0.764	0.464	0.553
Adjuvant radiotherapy (in patients who underwent BCS)	353 (75.9)	247 (80.5)	258 (82.2)	0.063	0.022	0.029
Adjuvant tamoxifen and radiotherapy (in patients who underwent BCS)	173 (68.7)	118 (72.8)	125 (74.4)	0.398	0.187	0.203

P values are from the Chi-square test unless otherwise indicated

ER estrogen receptor, *BCS* breast-conserving surgery

[a] Two patients were perimenopausal; menopausal status was not available for one patient

[b] Calculated using the Kruskal–Wallis test

[c] Initial presenting signs were not determined in 55 patients; clinical refers to presentation with a mass or nipple discharge

[d] Largest mammographic dimension recorded in 870 patients

[e] Largest pathologic size recorded in 1,442 patients

[f] Nuclear grade not available for 37 patients

[g] ER status determined in 1,095 patients

Table 2

Multivariate logistic regression model of clinical, pathologic, and treatment characteristics associated with being overweight or obese at DCIS diagnosis (N = 1,855)

Variable	OR	95% CI	*P*
Race			
White	1.00 (reference)		
African American	3.93	2.66–5.80	<0.001
Hispanic	1.44	1.02–2.04	0.039
Asian/Pacific islander	0.54	0.36–0.80	0.003
Menopausal status			
Premenopausal	1.00 (reference)		
Postmenopausal	1.63	1.28–2.07	<0.001
Age, years			
<40	1.00 (reference)		
40–70	1.27	0.83–1.95	0.273
>70	1.16	0.67–1.98	0.600
Diabetic at diagnosis			
No	1.00 (reference)		
Yes	4.60	2.60–8.12	<0.001
Initial presenting signs			
Clinical	1.00 (reference)		
Radiologic	1.35	1.01–1.80	0.040
Largest recorded pathologic dimension (cm)			
<1	1.00 (reference)		
≥1	0.95	0.74–1.21	0.657
Nuclear grade			
I	1.00 (reference)		
II or III	0.72	0.51–1.02	0.067
Necrosis			
Present	1.00 (reference)		
Absent	0.88	0.71–1.09	0.257
ER status			
Negative	1.00 (reference)		
Positive	1.39	1.00–1.92	0.042
Immediate breast reconstruction (in patients with mastectomy)			
Yes	1.00 (reference)		
No	1.58	1.13–2.20	0.007
Contralateral prophylactic mastectomy			
Yes	1.00 (reference)		
No	1.06	0.73–1.55	0.764
Adjuvant radiotherapy (in patients who underwent BCS)			
Yes	1.00 (reference)		

Variable	OR	95% CI	*P*
No	0.78	0.58–1.05	0.102

OR odds ratio, *BMI* body mass index, *ER* estrogen receptor

Table 3

Local–regional recurrence and development of contralateral breast cancer by BMI group at DCIS diagnosis

	Normal or Underweight (BMI <25 kg/m^2); Group 1	**Overweight (BMI 25 to <30 kg/m^2); Group 2**	**Obese (BMI ≥ 30 kg/m^2); Group 3**	***P*, All Groups**	***P*, Group 1 versus Groups 2 and 3**	***P*, Group 1 versus Group 3**
LRR, no. of patients (%)						
Total	18 (3.9)	12 (3.9)	15 (4.8)			
DCIS	12 (66.7)	8 (66.7)	7 (46.7)			
Invasive	6 (33.3)	4 (33.3)	8 (53.3)	0.435	0.456	0.247
5-year LRR rate						
BCS with radiotherapy (*n* = 858)	2.2%	2.1%	3.2%	0.395	0.417	0.218
BCS without radiotherapy (*n* = 230)	6.1%	11.6%	9.7%	0.648	0.377	0.601
BCS without radiotherapy without tamoxifen (*n* = 166)	8.7%	12.9%	2.9%	0.658	0.857	0.626
BCS with radiotherapy without tamoxifen (*n* = 442)	3.7%	3.2%	3.7%	0.376	0.388	0.205
BCS with radiotherapy with tamoxifen (*n* = 416)	0.6%	1.0%	2.8%	0.997	0.964	0.954
Development of contralateral breast cancer, no. of patients (%)[a]						
Total	25 (3.7)	16 (3.9)	23 (5.4)			
DCIS	15 (57.7)	7 (43.8)	10 (43.5)			
Invasive	11 (42.3)	9 (56.2)	13 (56.5)	0.538	0.265	0.321
5-year rate of development of contralateral breast cancer[a]						
Overall	3.2%	4.0%	5.0%	0.213	0.186	0.084
In patients taking tamoxifen (*n* = 566)	3.8%	1.2%	5.0%	0.111	0.588	0.545
In patients not taking tamoxifen (*n* = 945)	2.8%	5.7%	5.1%	0.162	0.057	0.086

BCS breast-conserving surgery

[a]Excludes patients who had contralateral prophylactic mastectomy, bilateral breast cancer at diagnosis, and history of contralateral breast cancer

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Table 4

Characteristics and outcomes of patients with DCIS by diabetes status and metformin use status at DCIS diagnosis

	Without diabetes	With diabetes, receiving metformin	With diabetes, Not receiving metformin	*P*, without versus with diabetes	*P*, receiving metformin versus not
Number of patients	1,737 (93.6)	62 (3.3)	56 (3.0)		
BMI					
Normal or underweight (BMI <25 kg/m^2)	816 (47.0)	5 (8.1)	10 (17.9)		
Overweight (BMI 25 to <30 kg/m^2)	483 (27.8)	12 (19.4)	15 (26.8)		
Obese (BMI ≥ 30 kg/m^2)	438 (25.2)	45 (72.6)	31 (55.4)	<0.001	0.117
Race					
White	1,310 (75.4)	30 (48.4)	32 (57.1)		
African American	171 (9.8)	19 (30.7)	13 (23.2)		
Hispanic	147 (8.5)	9 (14.5)	6 (10.7)		
Asian/Pacific Islander	90 (5.2)	4 (6.5)	5 (8.9)		
Other	19 (1.0)	0 (0)	0 (0)	<0.001	0.659
Menopausal status					
Premenopausal	510 (29.4)	8 (12.9)	7 (12.5)		
Postmenopausal	1,224 (70.6)	54 (87.1)	49 (87.5)	<0.001	0.948
Hormonal replacement therapy use	539 (31.0)	18 (29.0)	19 (33.9)	0.941	0.567
Age, median (range)	54 years (18–89)	61 years (37–79)	58.5 years (11–82)	<0.001	0.736
Largest recorded mammographic dimension, median (range)	2.5 cm (0.05–18)	2.4 cm (0.3–11)	2.1 cm (0.07–10)	0.804	0.901
Largest recorded pathologic size, median (range)	1.2 cm (0.01–19)	1.5 cm (0.09–17)	1.7 cm (0.05–12)	0.012	0.342
Nuclear grade					
I	163 (9.6)	6 (10.0)	7 (13.0)		
II or III	1,541 (90.4)	54 (90.0)	47 (87.0)	0.521	0.619
Necrosis present	672 (38.7)	30 (48.4)	21 (37.5)	0.329	0.233
ER status					
Positive	814 (80.0)	35 (85.4)	29 (80.6)		
Negative	204 (20.0)	6 (14.6)	7 (19.4)	0.503	0.574
Adjuvant tamoxifen (in all patients)	631 (36.3)	28 (45.2)	20 (35.7)	0.342	0.297
Adjuvant radiotherapy (in patients who underwent BCS)	799 (78.2)	33 (89.2)	26 (89.7)	0.031	0.951

	Without diabetes	With diabetes, receiving metformin	With diabetes, Not receiving metformin	*P*, without versus with diabetes	*P*, receiving metformin versus not
Local–regional recurrence (in patients who underwent BCS)					
Total	44 (4.3)	1 (2.7)	0 (0)	0.605	0.376
DCIS	26 (59.1)	1 (100.0)	0 (0)		
Invasive	18 (40.9)	0 (0)	0 (0)		
Development of contralateral breast cancer[a]					
Total	61 (4.3)	0 (0)	3 (6.0)	0.856	0.145
DCIS	30 (48.4)	0 (0)	2 (66.7)		
Invasive	32 (51.6)	0 (0)	1 (33.3)		

NA not applicable (a test was not possible because no failures occurred), *BCS* breast-conserving surgery

[a]Excludes patients who had contralateral prophylactic mastectomy, bilateral breast cancer at diagnosis, and history of contralateral breast cancer