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Triple-Negative Breast Cancer and Obesity in a Rural Appalachian Population

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Abstract

Background—Our objective was to determine the clinicopathologic features of triple-negative (estrogen receptor, progesterone receptor, and human epidermal growth factor-2 receptor negative) breast cancer and their relationship to obesity in women drawn from a population with one of the highest obesity rates in the United States.

Methods—This retrospective study involved 620 White patients with invasive breast cancer in West Virginia. Hospital tumor registry, charts, and pathology records provided age at diagnosis, tumor histologic type, size, nodal status, and receptor status. Body mass index was calculated and a value of ≥30 was considered indicative of obesity.

Results—Triple-negative tumors occurred in 117 (18.9%) of the 620 patients, most often in association with invasive ductal carcinomas. Patients with triple-negative tumors were younger than those with other receptor types, 44.5% and 26.7%, respectively, being diagnosed at age <50 years ($P = 0.0004$). The triple-negative tumors were larger ($P = 0.0003$), most notably in the younger women, but small tumors (<2.0 cm) were more often accompanied by lymph node metastases. Obesity was present in 49.6% of those with triple-negative tumors but in only 35.8% of those with non-triple-negative tumors ($P = 0.0098$). Lymph node metastases were more frequently associated with T_2 tumors in obese patients ($P = 0.032$) regardless of their receptor status.

Conclusions—Triple-negative breast cancers within a White, socioeconomically deprived, population occurred in younger women, with later stage at diagnosis, and in association with obesity, which itself has been associated with a poor prognosis in breast cancer.

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Introduction

Breast cancer comprises a heterogeneous group of tumors with specific biological characteristics that carry prognostic implications. Among these, the absence of estrogen receptor (ER) and progesterone receptor (PR) expression is both associated with larger tumor size (1, 2) and undifferentiated tumors (3) and predictive of a poor prognosis (4-7).

African American women have a lower breast cancer incidence rate but a higher mortality rate (8) and a greater frequency of ER-negative tumors (9) than their White counterparts. These latter features could be the result of an intrinsic, genetically determined, aggressive tumor phenotype (10-13) but may also be causally associated with the consequences of social deprivation (14-16). Obesity, which is more prevalent in African American than White women and which, regardless of race, is associated with low income and educational levels, is also related to more advanced disease at the time of diagnosis and a poor prognosis in premeno-pausal and postmenopausal breast cancer patients (17, 18).

Triple-negative breast cancers lack both ER and PR and human epidermal growth factor-2 receptor (HER-2) expression: they are particularly common in young African American women (13, 19-21), more likely to be of high histologic and nuclear grade (19, 22), have shorter relapse-free survival times than patients with other tumor receptor patterns, and are more likely to have distant, hematogenous, metastases (22, 23).

The purpose of the present study was to examine the clinical and pathologic features of triple-negative breast cancer in an area of the United States with a high level of social deprivation, and their relationships to obesity, without the potential for interactions with racially determined factors. To achieve this goal, the investigation was done in West Virginia, the only state, which is entirely in Appalachia, has a population that is 95% White and, for the years 2000/2001, ranked sixth highest in the United States for the percent of the population that was below the poverty line (24). Moreover, in 2001, West Virginia ranked fourth in the nation for the prevalence of obesity (25), which showed a strong inverse correlation with both annual income and educational achievement, two indicators of socioeconomic status. West Virginia women also show a similar pattern to African American in breast cancer incidence and mortality rates; for the years 1997 to 2001, West Virginia ranked 41st in the incidence rates for 45 individual states with available data and 16th in the mortality rates for the 50 states (26).

Materials and Methods

Study Patients

Women with breast cancer treated according to clinical protocols, conducted in the Breast Care Clinic of the Mary Babb Randolph Cancer Center between 1999 and 2004, comprised the study group for this West Virginia University Institutional Review Board-approved investigation. They were all patients attending West Virginia University Hospital in Morgantown, one of two tertiary care facilities in the state, which cares for a high percentage of the medically underserved. Our population is predominantly (95%) non-Hispanic White and rural. Patients were referred from family practitioners and other

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physicians from the surrounding medical community for primary surgical treatment in our comprehensive breast cancer program. Medical records and pathology reports on 712 breast cancer patients seen in the breast cancer program were retrospectively reviewed for inclusion in the study. The clinical presentation and pathologic features of 620 patients, ranging in age from 23 to 93 years, with invasive breast cancer of known ER, PR, and HER-2 status were determined: cases of carcinoma *in situ* were excluded from the study. In addition, 92 (12.9%) patients with incomplete biomarker status were excluded. The hospital's tumor registry, patient chart review, and examination of records from the service pathology laboratories were used to obtain the following variables: patient age at diagnosis, height and body weight, tumor size (maximum diameter in cm), histologic type and tumor grade, presence of pathologically involved axillary lymph nodes, and ER, PR, and HER-2 status. An age cutoff at 50 years was used as a surrogate for defining menopausal status, as a considerable number of the patient records lacked this piece of information, and even when available there was often uncertainty as to whether standard criteria had been applied.

The tumor size was expressed as the maximum diameter and was classified as T_1 (<2 cm), T_2 (2-5 cm), or T_3 (≥5 cm). The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. BMI categories were defined according to the WHO criteria: <25, normal or underweight (lean); 25 to 29.9, overweight; and ≥30, obese.

Receptor Assays

Immunohistochemical staining was done in the hospital clinical laboratory for ER, PR, and HER-2 expression. Between 1999 and June 2002, ER and PR were determined using the DAKO antibodies (Biogenix); stains were interpreted as positive when expression was detected in >5% to 10% of the tumor cells. HER-2 status was immunohistochemically assessed using DAKO antibody and manually interpreted using the manufacturer's scoring system (0+, 1+, 2+, 3+). Between July 2002 and 2004, ER (6F11) and PR (1A6) status were determined using antibodies from Ventana Medical Systems; the stains were interpreted as positive when expression was detected in >5% of the tumor cells. HER-2 status was assessed in the hospital cytogenics laboratory using the CB11 monoclonal antibody from Ventana and interpreted using ChromaVision image analysis to determine a colorimetric index (0.0-5.0) with validated correlations to the DAKO scoring system (0+, 1+, 2+, 3+). HER-2 positivity (a score of 3+) was defined as strong complete membrane staining being present in at least 10% of the tumor cells; scores of 0 and 1 were considered negative, and fluorescence *in situ* hybridization was done on all 2+ tumors using Vysis probes. For this study, 620 (87%) patients had sufficient details on hormone receptors and HER-2 for classification and were eligible for the study.

Statistical Analyses

All statistical analyses were done using JMP version 7.0 (SAS Institute). All univariate analyses used Student's *t* test, ANOVA, logistic regression, or χ^2 tests, as appropriate. When analyzing age, tumor size, or BMI as categorical variables, likelihood ratio tests were used for correlation with univariate analysis of discrete variables. Multivariable analyses, by logistic regression, were done to evaluate factors associated with tumor size and nodal

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metastases. Post-test analyses was done using Tukey-Kramer on multiple comparisons or by least significant difference test for preplan comparison. Two-tailed tests were used at all times, and statistical significance was set *a priori* at $P < 0.05$. Mean ± SE are reported.

Results

Receptor Status, Histologic Type, and Age

There were 73.7% of women with ER-positive tumors and 67.7% with PR-positive tumors. Based on ER, PR, and HER-2 assay results, 117 of the 620 (18.9%) breast cancer patients available for study were classified as triple negative (Table 1). The histologic type was known for all 620 patients: 433 (69.8%) were invasive ductal carcinomas, 55 (8.9%) were purely lobular, 84 (13.5%) had both lobular and ductal elements, and 48 (7.8%) comprised other categories, including mucinous, tubular, and medullary carcinomas. Significantly more of the ductal carcinomas were ER and PR negative compared with the pure lobular and mixed lobular/ductal tumors ($P < 0.001$; Table 1); furthermore, 23.1% of the ductal carcinomas but only 5.5% and 7.1%, respectively, of the lobular and mixed lobular/ductal carcinomas were triple-negative tumors.

The characteristics of the patients with triple-negative and other breast cancers are compared in Table 2. The patients with triple-negative tumors were younger than women with other combinations of ER, PR, and HER-2 status. The mean age at diagnosis was 51.7 versus 58.2 years, respectively ($P < 0.001$); a difference that was most apparent for those who were diagnosed at age <50 years, such that 44.5% with triple-negative tumors were diagnosed at age <50 years compared with only 26.7% of those with other forms of breast cancer ($P = 0.0004$).

Tumor Size and Nodal Status

The triple-negative tumors were larger than those in the other receptor categories. Mean tumor size of the triple-negative group was 3.01 ± 0.17 cm compared with 2.27 ± 0.08 cm for the non-triple-negative group ($P < 0.001$). Similarly, in Table 2, only 34 of 110 (30.9%) of the triple-negative tumors but 245 of 469 (52.2%) of the non-triple-negative tumors were designated T_1, being <2 cm in maximal diameter ($P = 0.0002$). Furthermore, patients ages <50 years, most of whom would have been premenopausal, had a higher frequency of triple-negative tumors of relatively large size.

The nodal status was known for 426 patients, 146 (34.3%) of whom had axillary lymph node involvement. These node-positive patients had larger tumors than those without lymph node involvement, 3.36 ± 0.15 versus 1.67 ± 0.07 cm, respectively ($P < 0.001$; Table 3). There was no difference in the prevalence of node-positive breast cancers between the two receptor groups (Table 2). Patients in the triple-negative group were more likely to have grade III tumors (80.5% versus 48.6%, respectively; $P < 0.001$). There was no significant relationship between tumor size and histologic subtype or BMI.

In the non-triple-negative group, there was a clear increase in node positivity as tumor size increased; 14.5% of women with T_1 tumors had positive nodes compared with 70.8% of women with T_3 tumors ($P < 0.0001$; Table 4). After stratification by tumor size, the numbers

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of observations in the triple-negative group were small, but the occurrence of nodal involvement was noticeably higher (22.2%) among these patients with T_1 tumors compared with 14.5% of the women in the non-triple-negative group ($P = 0.0464$; Table 4).

BMI and Obesity

Overall, 199 of the 512 (38.9%) breast cancer patients for whom height and body weight measurements were available were obese (BMI ≥ 30). Table 2 shows that the distribution of BMI values in the triple-negative patients was shifted to produce an increase in the obesity subgroup. For the purpose of statistical comparisons, the lean (BMI < 25) and overweight (BMI = 25-29.9) categories were combined into a single subgroup (BMI < 30). Triple-negative tumors were significantly more common in those patients who were classified as obese, 49.6% versus 35.8%, respectively ($P = 0.0098$; Table 2). Without consideration of the receptor status, however, there was no relationship between obesity and tumor size ($P = 0.8030$; Table 3).

Factors associated with BMI as a continuous variable are shown in Table 5. Higher BMI was associated with invasive ductal carcinomas and particularly with triple-negative receptor status. The mean BMI for patients with triple-negative tumors was 30.49 ± 0.67 compared with 28.81 ± 0.41 for the non-triple-negative receptor group ($P = 0.0157$). Obesity was also associated with T_2 ($P = 0.0368$) but not T_3 tumors perhaps because of weight loss associated with advanced disease. There was no significant relationship between BMI and nodal status or tumor grade. However, although the trend for lymph node metastases to occur more frequently in the obese women did not achieve statistical significance ($P = 0.233$; Table 5), when tumor size was taken into account, there was a clear trend between obesity and nodal involvement in T_2 tumors. In obese women with triple-negative T_2 tumors, 35% had node involvement compared with 61.5% who were non-triple-negative. Independent of triple-negative status, obese women with T_2 tumors were more likely to have nodal involvement (odds ratio, 1.77; 95% confidence interval, 0.9-3.4; $P = 0.032$; Table 6).

Discussion

Breast cancers in young women are more likely to be ER and PR negative, to have high cell proliferation rates and tumor grade, and to be associated with a poor prognosis; all these features occur more frequently in African American compared with White women (reviewed in 9). In a study of 1,016 African American breast cancer patients by Elledge et al. (10), 31.1% were diagnosed when ages <50 years compared with only 21.1% of 4,885 White patients, results that were similar to the 32.2% and 22.2%, respectively, reported by Simon and Severson (27).

In the present study, we found the age relationship to breast cancer was closer to that reported in African American than it was to the later age at presentation seen in White women; 32.9% of the West Virginian White women were diagnosed with breast cancer when they were ages <50 years, and triple-negative breast cancers occurred preferentially in younger, largely premeno-pausal, women; 44.5% were ages <50 years and 20.0% were ages <40 years compared with only 26.7% and 9.4%, respectively, of those with non-triple-

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negative tumors. This high frequency of triple- negative tumors is also seen in young, premenopausal, African American (13, 19-21) and British Black (28) women.

In our study, 69.8% of the tumors were invasive ductal, and only 8.9% were pure invasive lobular carcinomas. It was reported previously that invasive lobular carcinomas represent ∼5% to 15% of all breast cancers (29, 30), are more likely to be ER-positive (31, 32), and are associated with a lower mortality rate (30) than invasive ductal carcinomas. Consistent with these different characteristics, we found that not only were significantly more of our ductal carcinomas ER and PR negative but also 23.1% of the ductal but only 5.5% of the pure lobular and 7.1% of the lobular/ductal were triple-negative; those with the ductal histologic subtype of breast cancer were more often obese compared with all others, suggesting a link between obesity and invasive ductal carcinoma.

In agreement with earlier publications (20, 22, 23), we found that the mean size of the triple-negative tumors was greater than that of the non-triple-negative group, but as reported by Carey et al. (19) and Haffty et al. (23) and in contrast to the results obtained by Dent et al. (22), there was no greater involvement of the axillary lymph nodes. However, Dent et al. (22) also observed that a positive correlation existed between tumor size and the presence of nodal involvement only in the non-triple-negative group, an indication that metastasis was taking place earlier from the triple-negative tumors, and a similar relationship was seen in our study.

There is a global epidemic of obesity, which in the United States and elsewhere is frequently associated with social deprivation (33). This is a particularly serious problem in West Virginia, which ranked fourth among the states in both the occurrence of obesity among women ages ≥20 years in 2001 and the prevalence of poverty (25, 34). Bauer et al. (20) reported that, in their study of data from the California Cancer Registry, triple-negative tumors occurred more frequently in women from areas of low socioeconomic status, and Lund et al. (35) found a high prevalence of triple-negative breast cancer in a multiracial, but largely African American, low socioeconomic, urban population in Atlanta, GA. The majority of the studies done in North America and Europe found that the prevalence of triple-negative tumors in White women ranged from ∼10% to 13% (13, 20, 22, 36, 37), which contrasts with the 18.9% seen in the West Virginian patients. Although we did not evaluate the individual socioeconomic status of the patients in our study, the background of severe social deprivation that exists in West Virginia may well have been a contributing factor for the relatively high prevalence of triple-negative tumors. Furthermore, in our study, more of the patients with triple-negative tumors were also obese, so there also exists the potential for an interaction between obesity and triple-negative receptor status in influencing the risk of recurrence and the likelihood of a poor outcome.

As with any study, our study had certain limitations. First, within the period during which the breast cancer patients in this hospital series were diagnosed, the obesity prevalence among women in West Virginia was 25% (25). Although one can geographically define a hospital service area, it is not possible to determine precisely the rural Appalachian population at risk, as hospital-based studies do not define populations in the same way that true population-based studies do. However, the strengths of our study lie in the fact that our

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cohort of patients is largely racially homogeneous, rural, and obese. Second, this study was restricted to using immunostaining methodology to identify triple-negative breast cancer. Inherent in this is the possibility of a certain degree of misclassification of tumor type when using negative markers for identifying hormone receptor status and grade as biomarkers of prognosis.

Obesity is related to a poor prognosis in breast cancer patients regardless of their menopausal status (17, 18, 38). It has also been associated with larger tumor size, a higher incidence of lymph node metastases and high tumor grade (17, 18, 38-42), and, of particular interest in the context of triple-negative tumors, an increased risk of recurrence at distant sites (42). Daling et al. (38) obtained direct evidence that the larger tumor size in obese women is the result of growth stimulation: they were more likely than tumors of the same size from nonobese women to have high Ki-67 antigen expression and high mitotic cell counts and S-phase fractions. In postmeno-pausal women, the responsible mechanisms most likely involve increased synthesis of estrogens in adipose tissue, but in the premenopausal women studied by Daling et al. (38), the estrogen levels secreted by the ovaries would greatly exceed extraglandular production and not be enhanced by adiposity: here, nonsteroidal hormones and growth factors are likely to be involved, including insulin and the adipokines such as leptin (18).

Overall, obese patients were shown to have an unusually high frequency of ER- and PR-positive breast cancers, which is consistent with the proposed stimulation of tumor cell growth, invasion, and metastasis by adipose tissue-derived estrogens (reviewed in ref. 18). However, in their study of premenopausal women, all of whom had invasive ductal carcinomas, Daling et al. (38) found that obesity in combination with ER-negative tumors, some of which may, in fact, have been triple-negative, predicted a particularly poor prognosis. We have suggested elsewhere that the adipokines, which include leptin and vascular endothelial growth factor, and heparin-binding epidermal growth factor-like growth factor, exert a stimulatory effect on ER-negative breast cancers, where estrogen action is not a factor, by hormonal, paracrine, and autocrine mechanisms (43). Such a proposal does not, of course, imply that obesity is directly responsible for the loss of ER, PR, and HER-2 expression by breast cancer cells.

Leptin, the production of which is increased in obesity, exerts stimulatory effects on breast cancer cell proliferation and invasion, but also possesses angiogenic activity, both directly and by way of induction of vascular endothelial growth factor expression, which, in turn, could be responsible for promoting blood-borne distant metastases. Ishikawa et al. (44) found that high leptin and leptin receptor expression in breast cancer tissue was associated with distant metastases, and Liu et al. (45) reported that serum leptin concentrations were higher in patients with high-grade tumors and that a polymorphism in the leptin receptor gene at codon 109 (LEPRO-109RR genotype) was more frequent in patients who were overweight. Among patients with the LEPRO-109RR phenotype, higher serum leptin concentrations were present in those with triple-negative cancers.

Consistent with these data, which may be interpreted as suggesting an interaction among obesity, adipokines, triple-negative tumors, and systemic metastasis, several studies found

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that patients with triple-negative breast cancer have an increased likelihood of early, distant, recurrences and death compared with other types of breast cancer (22, 23, 46). In particular, Rakha et al. (46) observed a specific pattern, with a high frequency of metastases to the central nervous system, liver, and lungs, sites that typically have been associated with an extremely poor prognosis. Clearly, the relationships between outcome and obesity in triple-negative breast cancer are an important topic for further study.

Acknowledgments

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Table 1

Univariate analysis of ER, PR, and HER-2 status of patients with ductal, lobular, and mixed ductal/lobular histologic types

	Ductal, *n* (%)	Lobular, *n* (%)	Mixed lobular/ductal, *n* (%)	Other,* *n* (%)	Total population	*P*
ER+	307 (70.9)	48 (87.3)	68 (81.0)	34 (70.8)	457/620	0.0153
ER−	126 (29.1)	7 (12.7)	16 (19.0)	14 (29.2)	163/620	
PR+	283 (65.5)	46 (86.8)	63 (75.9)	28 (59.6)	420/620†	0.0015
PR−	149 (34.5)	7 (13.2)	20 (24.1)	19 (40.4)	195/620	
HER+	67 (22.6)	5 (16.7)	19 (36.5)	12 (35.3)	103/620†	0.0511
HER−	229 (77.4)	25 (83.3)	33 (63.5)	22 (64.7)	309/620	
Triple-negative	100 (23.1)	3 (5.5)	6 (7.1)	8 (16.7)	117/620	<0.0001
Non-triple-negative	333 (76.9)	52 (94.5)	78 (92.9)	40 (83.3)	503/620	

*Mucinous, tubular, and medullary carcinomas.

†Some tissues were not tested for all characteristics.

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Table 2
Univariate analysis of triple-negative status

	Triple-negative, *n* (%)	on-triple-negative, *n* (%)	*P*
Age at diagnosis (y)			
<40	22 (20.0)	41 (9.4)	0.0004
40-49	27 (24.5)	76 (17.3)	
50-59	33 (30.0)	128 (29.2)	
60-69	18 (16.4)	95 (21.7)	
>70	10 (9.1)	98 (22.4)	
BMI (kg/m^2)			
<25	28 (24.8)	104 (26.1)	0.0098
25-29.9	29 (25.7)	152 (38.1)	
≥30	56 (49.6)	143 (35.8)	
Tumor size			
T_1 (<2 cm)	34 (30.9)	245 (52.2)	0.0002
T_2 (2-5 cm)	58 (52.7)	179 (38.2)	
T_3 (>5 cm)	18 (16.4)	45 (9.6)	
Tumor grade			
1	2 (1.9)	63 (14.5)	<0.0001
2	19 (17.6)	161 (36.9)	
3	87 (80.5)	212 (48.6)	
Nodal status			
Negative	54 (67.5)	277 (69.8)	0.6886
Positive	26 (32.5)	120 (30.2)	

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Table 3
Multivariate analysis of presentation factors associated with tumor size

Variable	*n*	Tumor size ± SE (cm)	*P*
Ductal	404	2.37 ± 0.09	0.4263
Nonductal	175	2.22 ± 0.14	
Triple-negative	110	3.01 ± 0.17	0.0003
Non-triple-negative	469	2.27 ± 0.08	
Lymph node-negative	325	1.67 ± 0.07	<0.0001
Lymph node-positive	137	3.36 ± 0.15	
Age group (y)			
<40	60	2.99 ± 0.24	0.0064
40-49	96	2.83 ± 0.19	
50-59	152	2.49 ± 0.15	
60-69	103	2.09 ± 0.18	
≥70	104	2.18 ± 0.18	
BMI (kg/m^2)			
<30	328	2.49 ± 0.11	0.8030
≥30	199	2.51 ± 0.14	

NOTE: Excludes patients in whom no receptor status or pathologic axillary node staging was done. Numbers with different superscripts are significantly different.

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Table 4

Tumor size by nodal status in the triple-negative and non-triple-negative groups

Tumor size	Lymph node positive, *n* (%)	
	Triple-negative (*n* = 77)	Non-triple-negative (*n* = 385)
T_1 (<2 cm)	6/27 (22.2)	32/221 (14.5)
T_2 (2-5 cm)	14/45 (31.1)	64/140 (45.7)
T_3 (>5 cm)	4/5 (80.0)	17/24 (70.8)
	$P = 0.0464$*	$P < 0.0001$*

* *P* value was calculated by ordinal logistic regression.

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Table 5
Univariate analysis of BMI as a continuous variable

Category	BMI ± SE (kg/m^2)	*P*
Histologic subtype		
Ductal	29.60 ± 0.35	0.0192
Nonductal	28.12 ± 0.80	
Receptor status		
Triple-negative	30.49 ± 0.67	0.0157
Non-triple-negative	28.81 ± 0.41	
Tumor size		
T_1 (<2 cm)	28.66 ± 0.50	0.0368
T_2 (2-5 cm)	30.01 ± 0.61*	
T_3 (>5 cm)	27.95 ± 1.07	
Node status		
Negative	28.61 ± 0.49	0.2334
Positive	29.42 ± 1.64	
Histologic grade		
1	28.65 ± 0.47	0.1215
2	29.97 ± 0.72	
3	28.78 ± 2.63	
4	26.19 ± 2.85	

*Mean for T_2 is significantly higher than the means for T_1 and T_3.

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Table 6
Multivariate analysis of presentation factors associated with lymph node metastases

Variable	Odds ratio (95% confidence interval)	*P*
Histologic subtype		
Ductal vs nonductal	0.87 (0.56-1.3)	0.767
Triple-negative vs non-triple-negative	0.89 (0.53-1.5)	0.561
Age, <50 vs ≥50 y	0.84 (0.56-1.3)	0.111
BMI (kg/m^2)	1.77 (0.94-3.4)	0.032

NOTE: Excludes patients in whom no receptor status or pathologic axillary node staging was done.