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Obesity and Angiolymphatic Invasion in Primary Breast Cancer

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Abstract

Background—Obesity is associated with poorer breast cancer-specific survival. The purpose of this study was to investigate the relationships between obesity and the presence of angiolymphatic invasion as well as other features of invasive breast cancer, including stage at presentation, estrogen receptor (ER) status, the triple-negative phenotype, and tumor grade.

Methods—Detailed clinical and pathologic data were abstracted from the medical records of all 1,312 patients with Stage I – III primary breast cancer who had breast surgery at the University of Michigan Comprehensive Cancer Center between January 1, 2000 and December 31, 2006.

Bivariate and multivariate analyses were conducted to investigate the relationships between body mass index and tumor biologic features controlling for menopausal status, diabetes and hypertension, hormone replacement therapy before diagnosis, race, and ethnicity.

Results—In multivariate analyses, severe obesity was independently associated with the presence of angiolymphatic invasion (odds ratio, OR 1.80, 95% C.I. 1.08 to 2.99, joint test of significance, $p = 0.03$). Severe obesity was associated with a lower likelihood of triple-negative breast cancer (OR 0.39, 95% C.I. 0.16 to 0.96). Among premenopausal women with diabetes, ER-negative (OR 5.22, 95% C.I. 1.22 to 24.29) and triple-negative (OR 14.8, 95% C.I. 1.92 to 113.91) disease was significantly more common.

Discussion—In this large sample of invasive breast cancers, obesity was independently associated with the presence of angiolymphatic invasion. Higher rates of angiolymphatic invasion among obese women may account in part for the poorer outcomes among obese women with breast cancer.

Keywords

Obesity; breast cancer; triple-negative breast cancer; angiolymphatic invasion; diabetes

Introduction

Obesity is associated both with higher rates of breast cancer^{1–4} and with unfavorable breast cancer outcomes.^{5–9} Hazard ratios for long-term (ten or more years) breast cancer-specific mortality among obese women compared with healthy weight women range from 1.34 (95% confidence intervals, C.I. 1.09 to 1.65)⁸ to 2.1 (95% C.I. 1.5 to 2.9).¹⁰

Explanations for the poorer survival rates among obese women with breast cancer include more advanced disease at presentation^{11–13} (in part related to lower rates of screening mammography),¹⁴ systematic underdosing of adjuvant chemotherapy,^{15,16} and higher rates of diabetes and hypertension, each of which has been associated with unfavorable breast cancer outcomes.^{17,18}

Unfavorable tumor biology in obese women may also contribute to poorer outcomes. In a population-based study of 1177 women, obese women under the age of 45 were found to have higher histologic grade and a higher likelihood of estrogen receptor (ER)-negative tumors.¹⁰ Triple-negative breast cancers—negative for expression of ER, progesterone receptors (PR), and human epidermal growth factor-2 receptor (HER2)—are associated with a worse prognosis and have been shown in some^{19–21} but not all²² studies to be more prevalent among obese women. Finally, diabetes has been associated with a higher likelihood of ER-negative breast cancer; the higher rate of diabetes among obese women may thus contribute to differences in tumor biology among obese women compared with lean women.²³

Angiolymphatic invasion, defined as presence of tumor cells in peritumoral lymphatics or blood vessels and associated with a higher risk of breast cancer recurrence,^{24–27} may also be more common in the breast cancers of obese women. The adipocytokines, cytokines produced by adipose tissue, may have proangiogenic effects, promoting vascular proliferation.²⁸ In one study of 393 patients, the presence of angiolymphatic invasion was more often identified among women weighing over 80 kilograms. In logistic regression, angiolymphatic invasion was independently associated with nodal status, histologic grade,

weight, and height.²⁹ The investigators did not, however, control for other factors associated with tumor biology, such as estrogen receptor status or diabetes. Information on the presence or absence of angiolymphatic invasion is largely missing from studies of breast cancer prognosis in obese women. In a recent study of 26 patients, body mass index was similarly associated with angiolymphatic invasion.³⁰

The purpose of this study was to investigate the relationship between obesity status, measured as body mass index (BMI), and tumor biologic features among women with breast cancer. We sought to characterize the independent association of obesity with the presence of angiolymphatic invasion, hormone receptor (ER and PR) status, HER2 status, stage, and tumor grade, after controlling for age, menopausal status, use of hormone replacement therapy (HRT), and diabetes and hypertension. We were particularly interested in the relationship between obesity and the prevalence of angiolymphatic invasion in primary breast cancers.

Materials and Methods

Patient selection

All adult female patients 21 years of age and older who had surgery for a primary Stage I, II, or III breast cancer at the University of Michigan Comprehensive Cancer Center between January 1, 2000 and December 31, 2006 were eligible for inclusion. Pregnant women and women with an occult breast primary tumor, metaplastic carcinoma, or inflammatory breast cancer were excluded. After the sample was selected, we further excluded women who were on tamoxifen for breast cancer prevention at the time of diagnosis (n = 2), patients who had had more than one primary within the breast (n = 35), patients treated on an institutional protocol of cryoablation (n = 7), and patients treated with primary endocrine therapy (n = 5).

Data collection

Detailed medical record review was conducted to obtain information regarding age at diagnosis, race, ethnicity, menopausal status, the use of systemic hormone replacement therapy in the year(s) before the diagnosis of breast cancer, height and weight at the time of diagnosis, the presence of diabetes or hypertension, and tumor pathologic characteristics (tumor size, lymph node status, histologic grade, ER status, PR status, HER2 status, and presence of angiolymphatic invasion). For patients in whom menopausal status was unknown, age over 50 was used as a proxy for postmenopausal status. Height and weight, collected by a second abstractor who was blinded to tumor and clinical characteristics, was obtained from the electronic medical record. BMI was calculated using the Quetelet Index and categorized according to World Health Organization criteria as shown in Table 1.³¹ Continuous quality checks of the data were performed.

Analyses

Descriptive statistics were generated for each of the independent and dependent variables. Tumor size, and thus pathologic stage, was not determined for patients who received primary systemic chemotherapy therapy. Clinical and pathologic tumor features were compared between BMI categories using chi-squared tests. In patients who received primary

systemic chemotherapy (n = 199), we report the tumor characteristics of the core biopsy specimen.

Separate multivariate logistic analyses were performed to identify predictors of ER-negative disease, the triple-negative (ER-, PR-, and HER2-negative) phenotype, grade 3 histology, the presence of angiolymphatic invasion, and Stage III disease. The independent variables for each of these analyses were menopausal status, race, ethnicity, obesity status, diabetes, hypertension, and use of hormone replacement therapy. Age was collinear with menopausal status in preliminary analyses and was thus dropped in the multivariate analyses. Analyses were repeated according to menopausal status (pre/perimenopausal vs. postmenopausal). For obesity, joint tests of significance were performed across categories. If the value of the dependent variable was unknown, those tumors were dropped from that analysis but retained for other analyses. Thus, the sample size for each multivariate analysis did not always sum to 1,312.

The Institutional Review Board at the University of Michigan approved all study procedures.

Results

Sample characteristics

Our sample included 1,312 patients. Table 1 shows the sample characteristics for the entire sample and by obesity status. Most (88.3%) of the patients were non-Hispanic whites. The mean age was 55.3 years (SD 12.5). Diabetes was present in 7.7% of the sample, and 32.4% of the tumors developed in patients who carried a diagnosis of hypertension. Hypertension ($p < 0.001$) and diabetes ($p < 0.001$) were significantly associated with increasing BMI. Insulin use did not differ according to BMI category. For 44 tumors, patient menopausal status was unknown, and in those patients we used age over 50 years as a proxy for menopausal status as described above. Hormone replacement therapy (HRT) at the time of the diagnosis was documented in 34.8%, with no difference in rates of HRT use according to BMI category.

Obesity and Stage of Disease

The majority (79.0%) of the cancers were pathologic Stage I or II. As described above, patients who received primary systemic chemotherapy (n = 199) were excluded from this portion of the analysis because a pathologic tumor measurement before resection could not be determined. There was no association between stage and obesity status.

Obesity and Tumor Biology

In bivariate analyses (Table 2), obesity was not associated with hormone receptor status, HER2 status, triple-negative phenotype, or histologic grade. There was a significant association between obesity category and the presence of angiolymphatic invasion ($p = 0.03$), severely obese women being the most likely to have angiolymphatic invasion. When the analysis was repeated by menopausal status, the likelihood of angiolymphatic invasion in the tumors varied by obesity category ($p = 0.05$) with angiolymphatic invasion more likely in

severely obese (21.6%) compared with the tumors of healthy weight (14.8%) women (data not shown) among the pre- and perimenopausal women.

In multivariate analyses (Table 3), obesity status was independently associated with the presence of angiolymphatic invasion (joint test of significance, $p = 0.03$) after controlling for menopausal status, use of hormone replacement therapy at the time of diagnosis, diabetes and hypertension, and tumor features, including grade, stage, estrogen receptor status, and HER2 status. Grade was also associated with angiolymphatic invasion (odds ratio, OR, for grade 2 was 5.12, 95% C.I. 2.61 to 10.04; OR for grade 3 8.98, 95% C.I. 4.38 to 18.43). Obesity was associated with lower odds of triple-negative disease (OR among severely obese women 0.39, 95% C.I. 0.16 to 0.96). Obesity was not associated with other tumor features, including HER2 status (not shown in table).

There were significant associations between diabetes and tumor biology in multivariate analyses restricted to tumors in pre- and perimenopausal women (Table 4). Diabetes was associated with ER-negative tumor status (OR 5.22, 95% C.I. 1.12 to 24.29) and with the triple-negative phenotype (OR 14.80, 95% C.I. 1.92 to 113.91).

Discussion

In summary, in this sample of 1,312 patients, severe obesity was associated with a higher likelihood of angiolymphatic invasion after controlling for stage, grade, menopausal status, diabetes and hypertension, and use of HRT at the time of diagnosis. In pre- and perimenopausal women, diabetes was also independently associated with ER-negative status.²³ Triple-negative tumors were less common among the severely obese women in our sample.

Our results are consistent with those of other investigators demonstrating higher rates of angiolymphatic invasion in the tumors of heavy women.^{29,30} In contrast to other studies demonstrating higher rates of triple-negative breast cancer,^{19–21} the heavy patients in our sample were less likely to have triple-negative tumors. Obese women in our sample, as in others,³² are more likely to have diabetes. The association we identified between diabetes and triple-negative breast cancer raises the possibility that it is not obesity but rather diabetes that contributes to higher rates of triple-negative breast cancer in obese women.

Our sample is limited by low numbers of minority women and the lack of data on socioeconomic status (SES). Black race³³ and lower SES³⁴ have all been associated with ER-negative disease. Furthermore, black race^{22,35,36} and Hispanic ethnicity³⁵ have been associated with a higher likelihood of triple-negative breast cancer regardless of obesity status. It remains unknown whether there is a relationship between race, ethnicity, and SES and angiolymphatic invasion. Investigations of these relationships should include consideration of comorbid diabetes. In addition, our study is limited by the absence of information on exercise and dietary patterns and by the absence of information on duration of obesity and history of obesity among the non-obese.

Both estrogen-dependent and estrogen-independent mechanisms have been proposed as mechanisms for the association between obesity and poorer outcome.³⁷ Higher body mass

index is associated with higher levels of bioavailable estradiol, which in turn facilitates tumor growth.^{38,39} Although not a finding in our study, obesity has been associated with a higher likelihood of ER-negative disease by some authors.¹⁰ In addition, higher fasting insulin levels among obese people may lead to higher proliferative rates due to the mitogenic effects of insulin.⁴⁰ Finally, adipocytokines (also referred to as adipokines), such as leptin, tumor necrosis factor-alpha and interleukin-6, are increased in obesity and are associated with increased cell proliferation and angiogenesis in animal models^{28,41,42} and in cell lines.⁴³ The independent association of severe obesity with the presence of angiolymphatic invasion in our sample supports the relationship between adipocytokines and angiolymphatic invasion in primary breast cancer.

Reductions in adiposity, whether achieved through diet,⁴⁴ exercise,⁴⁵ or gastric reduction surgery,^{46,47} have been shown to reduce leptin and other adipocytokines. Such interventions may reduce the risk of breast cancer overall and, specifically, breast cancer exhibiting angiolymphatic invasion. Although a direct relationship between these interventions and rates of angiolymphatic invasion has not been identified, it is possible that the reduction in cancer mortality among obese patients having bariatric surgery^{48,49} can be attributed in part to reductions in adipocytokines.

In conclusion, this study has identified the independent association between severe obesity and the presence of angiolymphatic invasion. These findings may help explain poorer outcomes among obese women with breast cancer. Furthermore, diabetes was identified as being independently associated with triple-negative breast cancer. Further study of the relationships between tumor biology, obesity, diabetes, race, ethnicity, and SES are warranted.

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Synopsis

This study demonstrates that severe obesity is independently associated with the presence of angiolymphatic invasion after controlling for other clinical and pathologic factors.

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Sample Characteristics

Table 1

	All		Healthy Weight (BMI <25)		Overweight (BMI 25 – 29.9)		Obese (BMI 30 – 34.9)		Severely Obese (BMI 35)		p-value
	N = 1,312		N = 502		N = 404		N = 232		N = 174		
Mean age, years (SD)	55.3 (12.5)		52.8 (12.9)		55.9 (12.7)		58.5 (11.5)		56.4 (10.8)		<0.001
	N	%	N	%	N	%	N	%	N	%	
Race											<0.001
White	1,158	88.3	443	88.3	365	90.4	210	90.5	140	80.5	
Black	77	5.9	14	2.8	21	5.2	18	7.8	24	13.8	
Asian/Pacific Islander	45	3.4	34	6.8	8	2.0	1	0.4	2.0	1.2	
Multiracial	3	0.2	1	0.2	1	0.3	0	0	1	0.6	
Unknown	29	2.2	10	2.0	9	2.2	3	1.3	7	4.0	
Ethnicity											0.22
Hispanic	25	1.9	7	1.4	11	2.7	6	2.6	1	0.6	
Non-Hispanic	1,287	98.1	495	98.6	393	97.3	226	97.4	173	99.4	
Menopausal status*											<0.001
Pre/perimenopausal	533	40.6	257	51.2	161	39.9	64	27.6	51	29.3	
Postmenopausal	779	59.4	245	48.8	243	60.2	168	72.4	123	70.7	
Comorbidity											
Hypertension	425	32.4	87	17.3	121	30.0	108	46.6	109	62.6	<0.001
Diabetes mellitus	101	7.7	11	2.2	21	5.2	29	12.5	40	23.0	<0.001
Type 1	9	8.9	2	18.2	1	4.8	2	6.9	4	10.0	0.61
Type 2	92	91.1	9	81.8	20	95.2	27	93.1	36	90.0	
Insulin	20	21.7	1	11.1	2	10.0	5	18.5	12	33.3	0.16
HRT	457	34.8	162	32.3	141	34.9	88	37.9	66	37.9	0.37
Primary systemic therapy											
Chemotherapy	199	15.2	70	13.9	73	18.1	35	15.1	21	12.1	0.15

* 44 patients menopausal status unknown; age used for assignment of menopausal status (see text)

p values are chi-square tests except for weight, which is an F-test from ANOVA

HRT, hormone replacement therapy

Table 2

Stage and Tumor Biologic Characteristics, N = 1312

	Normal Weight N = 502		Overweight N = 404		Obese N = 232		Severely Obese N = 174		p value
	N	%	N	%	N	%	N	%	
AJCC 2003 Stage									0.58
I	268	53.4	206	51.0	128	55.2	90	51.7	
II	138	27.5	104	25.7	56	24.1	47	27.0	
III	21	4.2	16	4.0	12	5.2	13	7.5	
Unknown	10	2.0	10	2.5	3	1.3	5	2.9	
Clinical Stage II–III [†]	65	13.0	68	16.8	33	14.2	19	10.9	
Mean tumor size (SD) ^{††}	1.5 cm (1.1)		1.6 cm (1.1)		1.5 cm (1.3)		1.7 cm (1.5)		0.35
ER status									0.70
Positive	351	69.9	291	72.0	165	71.1	132	75.9	
Negative	132	26.3	102	25.3	62	26.7	37	21.3	
Unknown	19	3.8	11	2.7	5	2.2	5	2.9	
PR status									0.24
Positive	263	52.4	236	58.4	129	55.6	110	63.2	
Negative	219	43.6	157	38.9	96	41.4	60	34.5	
Unknown	20	4.0	11	2.7	7	3.0	4	2.3	
HER2 status									0.48
Positive	87	17.3	76	18.8	36	15.5	21	12.1	
Negative	392	78.1	312	77.2	189	81.5	145	83.3	
Unknown	23	4.6	16	4.0	7	3.0	8	4.6	
Triple negative									0.20
Yes	42	8.4	24	5.9	12	5.2	7	4.0	
Unknown	28	5.6	18	4.5	7	3.0	10	5.8	
Angiolymphatic invasion									
Yes	69	13.8	71	17.6	26	11.2	36	20.7	0.03
No	433	86.3	333	82.4	206	88.8	138	79.3	
Grade									0.75

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	Normal Weight N = 502		Overweight N = 404		Obese N = 232		Severely Obese N = 174		p value
	N	%	N	%	N	%	N	%	
Grade I	110	21.9	66	16.3	43	18.5	37	21.3	
Grade II	215	42.8	194	48	101	43.5	76	43.7	
Grade III	130	25.9	106	26.2	65	28	46	26.4	
Unknown	47	9.4	38	9.4	23	9.9	15	8.6	

[‡]Treated with primary systemic chemotherapy, n = 199

[‡]Excludes women treated with primary systemic chemotherapy, n = 199

Table 3

Multivariate analyses

	Stage III n = 1247	Grade III n = 1189	ER-negative 1272	Triple-negative n = 979	Angiolymphatic Invasion n = 1312
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Menopausal status					
Pre/peri	Referent	Referent	Referent	Referent	Referent
Post	0.84 (0.44 – 1.60)	0.80 (0.55 – 1.17)	0.97 (0.67 – 1.41)	1.24 (0.70 – 2.22)	0.80 (0.54 – 1.18)
Race					
White	Referent	Referent	Referent	Referent	Referent
Black	0.91 (0.31 – 2.69)	2.55 (1.40 – 4.66)	0.90 (0.49 – 1.65)	0.46 (0.14 – 1.57)	1.20 (0.64 – 2.25)
Asian/Pacific Islander	1.43 (0.42 – 4.93)	0.94 (0.40 – 2.19)	0.62 (0.25 – 1.52)	0.82 (0.23 – 2.86)	1.23 (0.54 – 2.78)
Unknown	2.62 (0.86 – 7.94)	1.14 (0.46 – 2.82)	1.31 (0.54 – 3.22)	2.22 (0.76 – 6.46)	2.18 (0.97 – 4.88)
Ethnicity					
Hispanic	(Dropped)	0.96 (0.31 – 2.94)	1.24 (0.44 – 3.52)	(Dropped)	0.52 (0.12 – 2.31)
Non-Hispanic	Referent	Referent	Referent	Referent	Referent
Obesity status					
Normal weight	Referent	Referent	Referent	Referent	Referent
Overweight	0.99 (0.50 – 1.95)	1.12 (.77 – 1.61)	0.89 (0.62 – 1.27)	0.62 (0.36 – 1.08)	1.36 (0.93 – 1.99)
Obese	1.36 (0.63 – 2.93)	1.28 (0.82 – 1.99)	0.97 (0.63 – 1.50)	0.51 (0.25 – 1.03)	0.84 (0.51 – 1.40)
Severely obese	1.85 (0.83 – 4.11)	1.26 (0.76 – 2.09)	0.75 (0.44 – 1.26)	0.39 (0.16 – 0.96)	1.80 (1.08 – 2.99)
Joint test for significance for obesity category test for trend	p = 0.40	p = 0.69	p = 0.70	p = 0.08	p = 0.03
Diabetes	p = 0.12	p = 0.25	p = 0.39	p = 0.02	p = 0.14
Hypertension	1.46 (0.59 – 3.61)	0.67 (0.36 – 1.23)	1.16 (0.63 – 2.12)	2.03 (0.85 – 4.86)	1.27 (0.69 – 2.32)
HRT	0.85 (0.44 – 1.65)	1.01 (0.70 – 1.46)	0.68 (0.47 – 0.98)	0.82 (0.45 – 1.50)	0.75 (0.50 – 1.12)
ER status	0.73 (0.37 – 1.43)	0.82 (0.56 – 1.18)	1.12 (0.78 – 1.62)	0.96 (0.54 – 1.69)	0.98 (0.66 – 1.45)
ER status					
Positive	Referent	Referent			Referent
Negative	0.66 (0.33 – 1.31)	13.15 (9.63 – 17.96)			0.80 (0.54 – 1.29)
Unknown	(Dropped)	2.09 (0.54 – 8.13)			0.26 (0.03 – 2.06)
Grade					

	Stage III n = 1247	Grade III n = 1189	ER-negative 1272	Triple-negative n = 979	Angiolymphatic Invasion n = 1312
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Grade 1	Referent		Referent	(Dropped)	Referent
Grade 2	1.37 (0.63 – 2.97)		4.89 (2.41 – 9.92)	Referent	5.12 (2.61 – 10.04)
Grade 3	2.39 (1.00 – 5.68)		47.15 23.28 – 95.50	3.64 (2.25 – 5.88)	8.98 (4.38 – 18.43)
Unknown	0.32 (0.04 – 2.59)		8.88 (3.91 – 20.13)	0.22 (0.03 – 1.61)	1.02 (0.31 – 3.37)

HRT, hormone replacement therapy

Table 4

Multivariate analyses, premenopausal only

	Stage III N=463	Grade III N=478	ER-negative N=515	Triple-negative N=418	Angiolymphatic Invasion N=521
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Race					
White	Referent	Referent	Referent	Referent	Referent
Black	0.52 (0.06 – 4.45)	2.17 (0.76 – 6.25)	1.44 (0.49 – 4.24)	0.33 (0.03 – 3.49)	2.33 (0.89 – 6.13)
Asian/Pacific Islander	0.70 (0.09 – 5.60)	0.22 (0.06 – 0.86)	1.49 (0.49 – 4.52)	1.11 (0.21 – 5.87)	0.96 (0.31 – 3.03)
Unknown	2.28 (0.42 – 12.52)	1.20 (0.27 – 5.30)	2.58 (0.57 – 11.64)	5.29 (0.82 – 33.94)	3.11 (0.83 – 11.59)
Ethnicity					
Hispanic	Dropped	0.80 (0.14 – 4.39)	2.80 (0.67 – 11.61)	Dropped	Dropped
Non-Hispanic		Referent	Referent		
Obesity Status					
Normal weight	Referent	Referent	Referent	Referent	Referent
Overweight	0.80 (0.30 – 2.09)	0.88 (0.52 – 1.51)	1.16 (0.69 – 1.95)	0.63 (0.27 – 1.43)	1.76 (1.04 – 2.99)
Obese	0.56 (0.12 – 2.63)	1.27 (0.61 – 2.62)	0.94 (0.45 – 1.98)	0.38 (0.10 – 1.50)	0.73 (0.31 – 1.75)
Severely obese	2.68 (0.88 – 8.12)	0.99 (0.41 – 2.38)	0.53 (0.20 – 1.37)	0.09 (0.01 – 0.97)	1.61 (0.69 – 3.76)
Joint test for significance for obesity category test for trend	p=0.15	p=0.84	p=0.46	p=0.15	p=0.08
Diabetes	p=0.27	p=0.82	p=0.36	p=0.02	p=0.45
Hypertension	1.29 (0.12 – 13.65)	0.08 (0.01 – 0.95)	5.22 (1.12 – 24.29)	14.80 (1.92 – 113.91)	0.54 (0.06 – 5.14)
HRT	1.29 (0.40 – 4.16)	1.00 (0.47 – 2.14)	0.46 (0.20 – 1.05)	1.44 (0.42 – 4.97)	0.70 (0.31 – 1.57)
ER status	1.42 (0.30 – 6.67)	2.40 (0.87 – 6.64)	0.83 (0.31 – 2.21)	0.45 (0.06 – 3.58)	0.54 (0.15 – 1.90)
ER status					
Positive	Referent	Referent			Referent
Negative	1.23 (0.47 – 3.23)	13.65 (8.32 – 22.39)			1.18 (0.66 – 2.10)
Unknown	Dropped	2.53 (0.45 – 14.30)			0.65 (0.07 – 5.75)
Grade					
Grade 1	Referent		Referent	Dropped	Referent
Grade 2	1.09 (0.33 – 3.55)		5.06 (1.48 – 17.31)	Referent	6.43 (1.93 – 21.49)
Grade 3	1.50 (0.41 – 5.59)		51.71 (15.19 – 176.02)	3.64 (1.67 – 7.95)	8.43 (2.38 – 29.84)

	Stage III N=463	Grade III N=478	ER-negative N=515	Triple-negative N=418	Angiolymphatic Invasion N=521
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Unknown	Dropped		13.66 (3.56 – 52.41)	0.45 (0.05 – 3.84)	0.53 (0.05 – 5.45)

HRT, hormone replacement therapy