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Aggressive estrogen-receptor-positive breast cancer arising in patients with elevated body mass index

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Abstract

Background—Obese women with estrogen receptor (ER)-positive breast cancer may experience worse disease-free and overall survival. We hypothesize that this observation is due to intrinsically aggressive disease and that obesity will be associated with higher histologic grade and Ki67.

Methods—A sequential cohort of women with breast cancer diagnosed over 2 years was assembled from institutional tumor registries. Patient and tumor characteristics were abstracted from medical records; those with noninvasive tumors, or lacking body mass index (BMI), Ki67 or histologic grade data, were excluded. Univariate and multivariate analysis was performed to investigate the relationship between markers of aggressive disease (grade and Ki67) and multiple variables associated with obesity. A subgroup analysis was performed to investigate further whether ER and menopausal status influenced associations between BMI and aggressive phenotypes.

Results—Of the 1007 patients initially identified, 668 (68 %) met the eligibility criteria. In univariate analysis, histologic grade and Ki67 were strongly associated with increased BMI, younger age, and African-American race, but less so with diabetes, hypertension, and hyperlipidemia. Multivariate analysis confirmed that higher histologic grade was associated with

increased BMI ($p = 0.02$), and that increased Ki67 was associated with younger age ($p = 0.0003$) and African-American race ($p = 0.002$). Additional analysis found that the association between increased BMI and higher-grade tumors was particularly significant in premenopausal women with ER-positive disease.

Conclusion—This study concludes that increased BMI is associated with aggressive-phenotype breast cancer and may be particularly relevant to ER-positive breast cancer developing in premenopausal African-American women.

Keywords

Breast cancer; Obesity; Aggressive phenotype; Histologic grade; Ki67

Introduction

Epidemiologic studies strongly suggest that obesity is a risk factor for many cancers, especially breast cancer [1, 2]. In breast cancer patients, obesity is associated with an increased risk of breast cancer-related death [hazard ratio (HR) 1.33; 95 % confidence interval (CI): 1.19, 1.50], and overall mortality (HR 1.33; 95 % CI: 1.21, 1.47), particularly in estrogen receptor (ER)-positive subtypes [2–4]. It is unknown whether this clinical observation is secondary to undertreatment or the intrinsic biology of breast tumors arising in obese women. Overweight and obese patients undergoing adjuvant chemotherapy are more likely to have intentional first-cycle dose reductions than their leaner counterparts, despite studies suggesting that obese patients tolerate chemotherapy as well as or better than lean patients [5–7]. Furthermore, obese patients treated with aromatase inhibitors may have higher circulating levels of plasma estradiol and estrone sulfate, which may suggest decreased drug efficacy [8]. While obesity has been linked to several biologic mechanisms associated with breast oncogenesis, including insulin resistance, inflammation, adipokine imbalance, and hyperestrogenemia, it is not well understood whether these mechanisms predict aggressive-phenotype disease [9, 10]. Recent data from a Japanese cohort suggested that in premenopausal women, increased body mass index (BMI) was associated with larger, lymph node-positive, high-grade tumors; however, this has not been confirmed in United States (US) cohorts [11]. The prevalence of obesity, a reversible disease, is increasing in the US and may be associated with inferior breast cancer outcomes; therefore, understanding the unique biology of breast cancers that develop in obese patients may help identify those most likely to benefit from weight loss interventions [12, 13].

Patients and methods

This research was reviewed and approved by the University of Texas Southwestern Medical Center Institutional Review Board. A cohort of 1,007 ethnically diverse women diagnosed with primary breast cancer in 2008 or 2009 was sequentially identified from the University of Texas Southwestern Medical Center Simmons Comprehensive Cancer Center and Parkland Memorial Hospital tumor registries. Clinical and pathologic information was obtained by chart review. Scoring of histologic grade and Ki67 was assessed by standard institutional protocols, using Elston scoring for the former. High tumor grade and increased proliferation (Ki67) were selected as the primary adverse pathologic features to assess. ER

positivity was defined as 1 % of cells staining positive for ER by immunohistochemistry. Human epidermal growth factor 2 (HER2) positivity was defined as an immunohistochemical score greater than 2, or, if equal to 2, a fluorescent in situ hybridization (FISH) ratio greater than 2.2. BMI was treated both as a continuous variable and categorically according to World Health Organization (WHO) classifications. Univariate analysis was performed to investigate the relationship between adverse pathologic features (defined by histologic grade and Ki67) and parameters of excess energy states (including BMI, diabetes, hypertension, and hyperlipidemia) and other demographic variables using chi-squared, Student's *t* test, ANOVA, or linear regressions as appropriate [14, 15]. Multivariate regression analysis, using a backward model selection method, was then performed to identify variables independently predicting increasing histologic grade or Ki67. The entering criterion for the multivariate model was a *p* value less than 0.15 by univariate analysis; however, the final model only kept those variables with a two-sided *p* value less than 0.05. Given the small number of covariates, multiple comparisons were not adjusted for. Data were collected and verified using Microsoft Excel and all statistical analyses were performed using SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). An exploratory subgroup analysis was performed to investigate the relationship of BMI with histologic grade and Ki67 in ER-positive versus ER-negative tumors, further subdivided by menopausal status, using chi-squared, Student's *t* test, ANOVA, or linear regressions as appropriate.

Results

From the initial cohort of 1,007 patients, BMI, histologic grade, and Ki67 were available for 668 (66 %) with invasive breast cancer, which defined the study population. The characteristics of the study population are shown in Table 1. The mean age of diagnosis was 55.3 years, 68 % were postmenopausal, 72 % were overweight or obese, and 92 % had stage I–III breast cancer, which is similar to previous cohorts and the nationwide prevalence [16, 17]. Tumors in our cohort tended to have high histologic grade (81 % had grade 2 or 3), the median Ki67 was 33.9, 76 % of tumors were ER-positive, 18 % were HER2-positive, and the most common histology seen was invasive ductal carcinoma (74 %). Compared to national averages, our cohort had a higher prevalence of diabetes (DM; 16 % compared to 8.3 %) and hypertension (HTN; 44 % compared to 21 %), but a lower prevalence of hyperlipidemia (HLD; 21 % compared to 33.5 %) [18–20]. Only 46 % of the cohort was free of any of the aforementioned metabolic diseases.

Univariate analysis established that increasing BMI, treated as a continuous variable, was strongly associated with higher histologic grade ($p < 0.0001$) and increasing Ki67 ($p < 0.0001$). This association was also observed when analyzing BMI by WHO category. ER-negative and HER2-positive tumors, younger age, premenopausal status, and African-American race were also found to be associated with higher histologic grade and Ki67. Of the metabolic diseases, only hyperlipidemia was associated with increased Ki67 (Table 2). As expected, Ki67 and histologic grade were closely associated with each other ($p < 0.0001$). Additional analysis of the entire cohort evaluating BMI with stage, ER and HER2 status did not reveal any significant associations.

Multivariate analysis was then performed to verify whether these variables independently were associated with higher histologic grade or increased Ki67. Increased BMI was found to predict breast cancers of higher histologic grade, but not increased Ki67. Conversely, younger age and African-American race were associated with high Ki67, but not histologic grade. ER-negative tumors were more likely to have higher grade and Ki67, and HER2-positive tumors were more likely to be higher grade. Metabolic diseases including DM, HTN, or HLD were not associated with either histologic grade or Ki67 (Table 3).

As an internal validation of our data quality we checked to see whether BMI also correlated with metabolic conditions such as DM, HTN, and HLD. The associations were significant, as would be predicted for DM, HTN ($p < 0.0001$), and HLD ($p = 0.018$).

An exploratory subgroup analysis was performed to determine whether the association between BMI and aggressive phenotypes varied by ER status. BMI was most strongly associated with increased Ki67 and higher grade for ER-positive tumors. When the data was further subdivided by menopausal status, increased BMI was associated with higher-grade ER-positive tumors in premenopausal women. Additionally, BMI was associated with postmenopausal women with ER-negative tumors (Table 4).

Discussion

These data suggest that increased BMI is associated with aggressive breast cancer phenotypes, particularly tumors of higher histologic grade. This may be especially true in premenopausal women with ER-positive tumors, and postmenopausal women with ER-negative tumors. Younger age and African-American race were additionally found to be associated with increased Ki67, consistent with other studies [21, 22].

Though grade and proliferation are highly correlated with one another, multivariate analysis demonstrated that higher BMI was associated with higher histologic grade, but not Ki67. Conversely, while younger age and African-American race was associated with increased Ki67, it was not associated with histologic grade. A similar discordance between histologic grade and Ki67 had previously been observed in a Japanese cohort investigating tumor features and elevated BMI [11]. Though related, Ki67 and histologic grade may be surrogates for different biologies. Ki67 is strictly a marker of proliferation, whereas histologic grade considers not only proliferation, through pathologic mitotic count, but also nuclear pleomorphism and tubule formation [23]. While Ki67 and histologic grade reflect different biologies, they tend to trend together, as they did in our study ($p < 0.0001$). It is unclear whether the small sample size contributed to these discordant findings or if obesity truly affects these markers differently.

There are important strengths and limitations to consider when interpreting these results. These data were obtained by retrospective chart review, and interpretation is limited by this design. Investigating biomarkers of aggressive disease as part of prospective studies could validate these findings. BMI may not be the most accurate surrogate of energy excess states, particularly in African-American patients [24]. Waist circumference is thought to be a more accurate surrogate, especially among different ethnic groups, although abnormal BMI and

waist circumference tend to trend together [25]. Following National Institute of Health recommendations, waist circumference should be included in future studies in addition to BMI when evaluating energy excess states [26]. Another consideration is that histologic grade and Ki67 have limited inter-laboratory reproducibility [27, 28]. All pathologic analysis in our study, however, was reviewed by pathologists within the same institution, and intra-laboratory correlation has previously been shown to be good for these markers, particularly Ki67 [inter-class correlation coefficient (ICC) = 0.94; 95 % CI = 0.93–0.97] [27]. Another strength of this study is that the cohort is ethnically diverse, and the relationships demonstrated may be applicable to both Caucasians and African-Americans.

While our results confirmed that increased BMI is associated with metabolic diseases such as DM, HTN, and HLD, these metabolic diseases were not associated with either high histologic grade or Ki67. Although numerous clinical and preclinical studies have found that insulin resistance is associated with important pro-neoplastic pathways, we found that DM and other metabolic diseases commonly associated with insulin resistance were not associated with aggressive-phenotype breast cancer, suggesting that other mechanisms may be involved. Inflammatory pathways have been shown to mediate various oncogenic pathways and are frequently upregulated in energy excess states [29]. This relationship supports our findings that increased BMI was associated with post-menopausal women with ER-negative tumors. Obesity is also associated with hyperestrogenemia, which is a known risk factor for ER-positive breast cancers, and may explain our findings in premenopausal women with ER-positive tumors [30]. Inflammatory cytokines may also contribute to hyperestrogenemia, as they have also been found to upregulate aromatase expression in breast tissue, which may contribute to the relationship between obesity and ER-positive tumors [31]. Furthermore, adipokines, such as leptin, have been shown to promote oncogenesis, and have been linked to inferior breast cancer outcomes in ER-positive tumors [13, 32]. Understanding the biologic pathways influenced by excess energy states relevant to specific breast cancers subtypes may inform the development of future pharmacologic targeting of these pathways.

In summary, these results confirm that in an ethnically diverse US cohort, similar to previous data from Japanese cohorts, BMI is associated with aggressive-phenotype breast cancers [11]. These data may in part explain the worse clinical prognosis experienced by women with ER-positive breast cancer who have an increased BMI, adding additional evidence that these tumors are particularly sensitive to the biologic effects of obesity. Identifying tumor and patient characteristics relevant to breast cancers arising in excess energy states may inform future studies targeting excess energy pathways including weight loss interventions.

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Table 1

Cohort characteristics

Characteristic	Number (%)
Total cohort	668
Age, years (mean, range)	55.3 (25-93)
Body mass index	
<25 kg/m ²	192 (29)
25-29.9 kg/m ²	191 (29)
>30 kg/m ²	285 (43)
Menopausal status	
Premenopausal	197 (29)
Postmenopausal	452 (68)
Unknown	19 (3)
Race	
Caucasian	347 (52)
African-American	232 (35)
Other	89 (13)
Ethnicity	
Non-hispanic	605 (91)
Hispanic	58 (9)
Unknown	5 (< 1)
Hypertension	
Yes	293 (44)
No	351 (52)
Unknown	24 (4)
Diabetes	
Yes	110 (16)
No	533 (80)
Unknown	25 (4)
Hyperlipidemia	
Yes	137 (20)
No	506 (76)
Unknown	25 (4)
Grade	
1	129 (19)
2	299 (45)
3	240 (36)
Ki67 (mean, standard deviation)	33.9 (29.8)
ER	
Positive	510 (76)
Negative	155 (23)
Unknown	3 (< 1)

Characteristic	Number (%)
HER2	
Positive	123 (18)
Negative	538 (81)
Unknown	7 (1)
Stage	
1	142 (21)
2	341 (51)
3	135 (20)
4	30 (5)
Unknown	20 (3)
Histology	
Invasive ductal	491 (74)
Invasive lobular	65 (10)
Mixed histology	36 (5)
Other	76 (11)

Table 2

Univariate analysis identifying additional covariates predicting tumor grade and Ki67

Characteristic	Histologic grade				Ki67	
	1	2	3	<i>p</i> value	Mean Ki67 ± standard deviation	<i>p</i> value
Age, years (mean ± standard deviation)	59.3 ± 11.9	56.4 ± 13.3	51.9 ± 12.4	<0.0001	−0.559 ± 0.086 ^a	<0.0001
BMI, kg/m ² (mean ± standard deviation)	27.3 ± 5.5	29.7 ± 7.23	30.9 ± 8.0	<0.0001	0.632 ± 0.156	<0.0001
Menopausal status, <i>n</i> (%)						
Pre	26 (4)	82 (13)	89 (14)	0.002	40.8 ± 31.4	<0.0001
Post	102 (16)	205 (31)	145 (22)		30.7 ± 28.7	
Race, <i>n</i> (%)						
White	84 (13)	157 (24)	106 (16)	<0.0001	28.4 ± 27.0	<0.0001
African-American	28 (4)	95 (14)	109 (16)		43.2 ± 32.0	
Other	17 (3)	47 (7)	25 (4)		31.1 ± 28.3	
Diabetes, <i>n</i> (%)						
Yes	17 (3)	60 (9)	33 (5)	0.077	32.8 ± 29.6	0.645
No	108 (16)	228 (34)	197 (29)		34.3 ± 30.1	
Hypertension, <i>n</i> (%)						
Yes	63 (9)	122 (18)	108 (16)	0.293	34.1 ± 30.2	0.966
No	62 (9)	166 (25)	124 (19)		34.0 ± 29.7	
Hyperlipidemia, <i>n</i> (%)						
Yes	31 (5)	67 (10)	39 (6)	0.118	28.5 ± 27.4	0.016
No	94 (14)	221 (33)	192 (29)		35.5 ± 30.5	
ER, <i>n</i> (%)						
Positive	125 (19)	262 (39)	123 (19)	<0.0001	25.2 ± 24.0	<0.0001
Negative	4 (1)	35 (5)	116 (17)		62.7 ± 28.9	
HER2, <i>n</i> (%)						
Positive	10 (2)	46 (7)	67 (10)	<0.0001	43.7 ± 25.9	<0.0001
Negative	115 (17)	250 (38)	173 (26)		32.0 ± 30.3	

^aSlope (per year) ± standard error

Table 3

Multivariate analysis of variables predicting histologic grade and Ki67

Characteristic	Histologic grade			Ki67		
	OR (95 % CI)	p value	Overall p value	Correlation coefficient (95 % CI)	p value	Overall p value
BMI (per unit)	1.039 (1.014-1.066)	0.0024	0.0024	0.149 (−0.114 to 0.411)	0.2675	0.2675
Age (per year)	0.991 (0.976-1.005)	0.2004	0.2004	−0.288 (−0.439 to 0.137)	0.0002	0.0002
Race						
White	Reference		0.5664	Reference		0.006
Black	1.207 (0.805-1.808)	0.3625		6.379 (2.391-10.368)	0.0018	
Other	0.928 (0.556-1.547)	0.7735		0.675 (−4.610 to 5.961)	0.8020	
ER						
Positive	Reference		<0.0001	Reference		<0.0001
Negative	3.779 (2.284-6.252)	<0.0001		23.062 (18.466-27.657)	<0.0001	
HER2						
Positive	1.555 (0.996-2.429)	0.0521	−0.0521	−3.106 (−7.766 to 1.555)	0.1912	0.1912
Negative	Reference			Reference		
Diabetes	1.031 (0.637-1.668)	0.9014	0.9014	1.196 (−3.822 to 6.214)	0.6399	0.6399
Hypertension	0.791 (0.541-1.156)	0.2260	0.2260	0.104 (−3.823 to 4.031)	0.9587	0.9587
Hyperlipidemia	1.070 (0.695-1.649)	0.7577	0.7577	−0.317 (−4.917 to 4.283)	0.8924	0.8924

Variables included in the model investigating histologic grade were: BMI, age, menopausal status, race, Ki67, and ER and HER2 status; since menopausal status was not significant, it was removed in the final model shown below. Variables included in the model investigating Ki67 were: BMI, age, menopausal status, race, histologic grade, and ER and HER2 status

BMI body mass index, OR odds ratio, CI confidence interval

Table 4

Association of BMI with histologic grade and Ki67 by estrogen receptor and menopausal status using chi-squared analysis

	Estrogen receptor negative (<i>n</i> = 155)				Estrogen receptor positive (<i>n</i> = 510)			
	BMI <25 kg/m ²	BMI 25-29.9 kg/m ²	BMI >30 kg/m ²	<i>p</i> value	BMI <25 kg/m ²	BMI 25-29.9 kg/m ²	BMI >30 kg/m ²	<i>p</i> value
All	41	48	66		150	142	218	
Grade								
1	1	3	0	0.264	48	35	42	0.042
2	10	12	13		70	78	114	
3	30	33	53		32	29	62	
Ki67								
%	61.1 ± 30.9	55.4 ± 29.2	68.9 ± 26.5	0.043	21.0 ± 22.5	24.9 ± 22.4	28.2 ± 25.7	0.019
Premenopausal (ER-, <i>n</i> = 52; ER+, <i>n</i> = 145)	12	20	20		45	36	64	
Grade								
1	0	0	0	0.701	14	8	4	0.005
2	2	5	3		17	21	34	
3	10	15	17		14	7	26	
Ki67								
%	62.6 ± 30.2	63.0 ± 29.9	70.0 ± 31.5	0.714	26.8 ± 27.3	32.5 ± 24.7	35.0 ± 27.2	0.280
Postmenopausal (ER-, <i>n</i> = 99; ER+, <i>n</i> = 351)	27	27	45		98	103	150	
Grade								
1	1	3	0	0.197	33	27	38	0.583
2	8	6	10		48	55	77	
3	18	18	35		17	21	35	
Ki67								
%	58.6 ± 31.9	49.6 ± 28.4	68.6 ± 24.7	0.021	19.0 ± 20.3	21.8 ± 21.2	24.7 ± 24.5	0.143