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A retrospective review of the metabolic syndrome in women diagnosed with breast cancer and correlation with estrogen receptor

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Abstract

Women diagnosed with obesity and breast cancer have an increased risk of recurrence and death (Protani et al., Breast Cancer Res Treat 123:627–635, 1). Obesity is associated with the metabolic syndrome—a pathophysiologically distinct inflammatory process comprised of central obesity, insulin resistance, hypertension, and atherogenic dyslipidemia. The relationship of obesity as a risk factor for breast cancer is complex with a protective effect for younger women in contrast to a risk for older women (Kabat et al., Cancer Epidemiol Biomarkers Prev 18:2046–2053, 2; Ursin et al., Epidemiology 6:137–141, 3). The metabolic syndrome has been associated with the risk of cancer, and pro-inflammatory circulating factors may be associated with risk of more aggressive breast cancer (Capasso et al., Cancer Biol Ther 10:1240–1243, 4; Healy et al., Clin Oncol (R Coll Radiol) 22:281–288, 5; Laukkanen et al., Cancer Epidemiol Biomarkers Prev 13:1646–1650, 6). We conducted a retrospective review of 860 breast cancer patients to determine the relationship between estrogen receptor status and the metabolic syndrome. We collected the relevant metabolic diagnoses, medications, physical findings, and laboratory values and adapted the National Cholesterol Education Program criteria to define the metabolic syndrome retrospectively. No relationship was found between estrogen receptor status and the individual components of the metabolic syndrome. Based on findings in the medical records, 15% of the women with breast cancer had the metabolic syndrome, and 26% of the women were considered obese, 16% hyperglycemic, 54% hypertensive, and 30% dyslipidemic. The metabolic syndrome was associated with advanced age and African-American race ($P<0.001$). When adjusted for age, race, and stage, the metabolic syndrome was marginally associated with estrogen receptor-positive tumors ($P = 0.054$). Our findings do not support the concern that the metabolic syndrome may contribute to more biologically aggressive breast cancer.

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Keywords

Breast cancer; Metabolic syndrome; Comorbidities

Introduction

Breast cancer is second only to lung cancer as a cause of cancer deaths in women. During 2011, an estimated 200,000 women will be diagnosed with breast cancer and nearly 40,000 women will die of the disease [7]. Breast cancer subtypes differ most significantly by hormonal responsiveness and are identified as having estrogen receptors (ER+) or lacking estrogen receptors (ER−). The distribution of ER+ versus ER− differs by age, with ER− breast cancer occurring more commonly in younger women [8]. ER− breast tumors have a higher risk of recurrence and lower overall survival than ER+, which is partly attributable to a more advanced stage at presentation and a higher pathologic grade [8, 9]. Furthermore, therapeutic options available to women with ER− breast cancer are chemotherapy and biologics, which have significantly more side effects and potential for late effects than the hormonal therapy options available to women with ER+ breast cancer. The occurrence of ER− breast cancer in young women and especially among women from minority groups is a contributor to breast cancer disparities [10, 11]. Therefore, the identification of potential modifiable risk factors for ER− breast cancer may lead to significant reductions in morbidity and mortality from breast cancer.

As rates of obesity increase worldwide, and more rapidly among women from lower socioeconomic groups [12, 13], the contribution of obesity and related metabolic disorders may increase disparities in breast cancer mortality. Obesity is commonly associated with a constellation of metabolic disorders that comprise the metabolic syndrome. The metabolic syndrome is a pathophysiologically distinct inflammatory process comprised of central obesity, insulin resistance, hypertension, and atherogenic dyslipidemia [14] and is associated with a risk of cardiovascular disease, diabetes mellitus [15], and prostate cancer [6]. Individual components of the metabolic syndrome—obesity, elevated insulin levels, and insulin resistance—have been associated with risk for breast cancer [4, 5, 16]. The relationship of obesity as a risk factor for breast cancer is complex, with a protective effect in premenopausal women and a positive association among postmenopausal women [3, 17–19]. The obesity risk in older women has been associated with an increased production of estrogen due to increased adiposity with age [20]. Postmenopausal women have higher rates of hormonally responsive breast cancer (ER+). Furthermore, postmenopausal women have an increased risk of breast cancer once diagnosed with the metabolic syndrome [2, 21]. However, more recently there have been reports of an association of the metabolic syndrome with triple-negative breast cancer or tumors that are absent of ER, PR, and HER2—a small subset of all hormonally non-responsive breast cancer (ER−) [22]. We sought to further understand the relationship between obesity and the metabolic syndrome when tumors are classified as hormonally derived or ER+ versus ER−. In relation to triple-negative breast cancer, ER− breast cancer is more common and would include the more rare subtype of triple negative disease. The association of the metabolic syndrome with ER− breast cancer

may indicate that the inflammatory process is associated with the more biologically aggressive and hormonally independent breast cancer.

We conducted a retrospective review to determine whether the components of the metabolic syndrome occurred more commonly among women with more biologically aggressive (ER −) breast cancer.

Methods

All female breast cancer patients, diagnosed between 1999 and 2005, were identified through the Tumor Registry of the Comprehensive Cancer Center at Wake Forest University. Of the 1,533 women identified, 1,081 had estrogen receptor status recorded. From the tumor registry, we obtained the date of diagnosis, age, stage, progesterone receptor, and grade of the breast cancer. Race was obtained from the medical records. The electronic medical records (EMR) of Wake Forest University Baptist Medical Center were then queried for all the diagnoses and medications that were entered into the medical record within 2 years following the breast cancer diagnosis. To ensure that we captured all possible components of the metabolic syndrome, we obtained all available blood pressures, heights, weights, glucose values, triglyceride levels, and HDL levels for each woman for the same 2-year time period. In total, over 70,000 data points were gathered from the EMR. Patients were excluded from the analysis if they did not have at least one diagnosis, one medication, one systolic blood pressure (SBP), and one weight record, leaving 860 patients in the analysis.

The most widely used and clinically relevant guidelines defining the metabolic syndrome are those proposed by the adult treatment panel III set forth by the National Cholesterol Education Program (NCEP) [15, 23, 24]. The NCEP criteria state that a patient has the metabolic syndrome when three of the following five criteria are met: (1) waist circumference ≥35 inches; (2) SBP of ≥130 mmHg or a diastolic blood pressure ≥85 mmHg; (3) fasting glucose >100 mg/dl; (4) HDL <50 mg/dl; and (5) triglycerides ≥150 mg/dl. Because most EMR diagnoses blended the dyslipidemias and the same medications can be used to treat both elevated triglycerides and depressed HDL levels, we combined these two separate components into one dyslipidemia category. In addition, patients were assumed to have random glucose values, and waist circumference measurements were not readily available in the EMR. Therefore, we adapted the NCEP criteria for diagnosing the metabolic syndrome in a retrospective review. We defined a patient as having the metabolic syndrome when she met three of the following four criteria: (1) SBP ≥ 160 mmHg or on a medication for hypertension; (2) BMI ≥ 30 or weight > 200 lbs; (3) glucose ≥ 200 or on a medication for diabetes mellitus; and (4) either HDL < 50 mg/dl or triglyceride ≥ 150 mg/dl or on a medication for dyslipidemia. Patients with a diagnosis code for any of the above conditions were also considered to meet the criteria for diagnosis. Patients without measurements for a variable (e.g., trigylcerides) were considered to have normal levels for that variable.

Statistical analysis

Patients were required to have a least one diagnosis, medication, SBP, and weight record, but in most cases patients had multiple records of each type. If any diagnosis code matched the code for one of the metabolic conditions (e.g., diabetes), the patient was coded positive for that condition based on diagnosis. If any medication matched that of any medication used to treat one of the metabolic conditions (e.g., diabetes), the patient was coded positive for that condition based on medication. For the quantitative measures like weight and SBP, we took the mean across the multiple measurements, and if those means met the criteria defined above for one of the conditions, the patient was coded positive for that condition based on measurement. If a patient was coded positive for a condition based on either a diagnosis, medication, or measurement record, we assumed they had the condition; otherwise, we assumed they did not have the condition. Wilcoxon rank-sum and Chi-square tests were used to assess group (ER+ vs. ER−) differences in patient and tumor characteristics and to assess unadjusted group differences in the metabolic conditions. Logistic regression was used to assess group differences in the metabolic conditions after adjustment for age, race, stage, and tumor grade. Since tumor grade was missing on over 1/4 of the patients, models were run with and without that variable.

Since this was an analysis on data collected retrospectively from EMRs and not an analysis on data collected from a prospectively planned clinical trial using standardized protocols, we performed sensitivity analyses to assess the impact our definitions and inclusion criteria had on estimates of the metabolic syndrome and their associations with ER status. We varied the number of records of each type required for inclusion from 0 to 5 and used means and maximums over the multiple records per person. The univariate analyses just described were repeated for each subset of data to determine if estimates and associations changed depending on our definitions and criteria.

Results

Of the 860 women identified between 1999 and 2005 with ER status and sufficient clinical data available, 28% were less than 50-year old at the time of diagnosis, 15% were African-American or Hispanic, and 25% had ER− tumors. Patient characteristics are shown in Table 1. Patients with ER− tumors were younger (median = 54 vs. 59 years, $P < 0.001$) and were more likely to be African-American (24 vs. 12%, $P < 0.001$). In addition, patients with ER− cancer were more likely to present at a later stage (60 vs. 48% stage 2 or greater, $P = 0.002$) and have poorly differentiated tumors (72 vs. 19%, $P < 0.001$).

The frequency of the conditions of the metabolic syndrome found in the breast cancer study group is summarized in Table 2. Based on findings in the medical records, overall, 26% of the women were considered obese, 16% hyperglycemic, 54% hypertensive, and 30% dyslipidemic. These conditions did not differ by receptor group. The occurrence of three or more metabolic conditions consistent with the metabolic syndrome occurred in 15% of the patients with ER− disease and 16% of patients with ER+ disease.

Results of the multivariable logistic models are shown in Table 3. Older age was significantly associated with the prevalence of hypertension, dyslipidemia, and having the metabolic syndrome. African-American women had a significantly increased risk of each metabolic condition and of having the metabolic syndrome. Stage was significantly associated with the conditions of obesity, hypertension, and hyperglycemia; women with stage 0–1 cancers were less likely to have each condition compared to women with stage 3–4 cancer. Women with PR− tumors were more likely to have dyslipidemia. ER status was not significantly associated with any of the metabolic conditions; however, women with ER − tumors were borderline significantly less likely to have three or more of the metabolic conditions. Separate models were run to include tumor grade, classified as well-differentiated versus other, due to the missing data for that variable on 227 individuals. Grade was not significantly associated with any of the metabolic conditions, after adjustment for the other covariates.

To assess the impact of our criteria for defining the metabolic conditions, we varied the number of required records (of specific types as defined previously) from 0 to 5 and used the mean and the maximum values across the multiple records for a given patient. Results are summarized in Table 4. Using the mean of the quantitative measurements and varying the number of required records from 0 to 5, we found that the estimates varied as follows: obesity 22–30%, hypertension 47–60%, diabetes 14–21%, dyslipidemia 26–37%, and the metabolic syndrome 12–20%. Using the maximum instead of the mean further increased the estimates by 4–7% for obesity, 10–11% for hypertension, 6–8% for diabetes, 0–1% for dyslipidemia, and 3–5% for the metabolic syndrome. In no case was there a significant association between any metabolic condition and estrogen receptor status.

Discussion

Our retrospective review of 860 women diagnosed with breast cancer did not find a correlation between the metabolic syndrome or any of the metabolic conditions and estrogen receptor status. Although, ER− breast cancer and the individual metabolic conditions occurred more commonly among African-American women, the metabolic syndrome does not account for the more common occurrence of ER− breast cancer in that ethnic group. We did find that 15% of the women with breast cancer had conditions that would suggest the metabolic syndrome and that individual components of the metabolic syndrome occurred at high rates: for example, 54% of women had hypertension. The prevalence of the comorbidities at the time of diagnosis of breast cancer is significant to a potential risk of breast cancer treatment on cardiovascular mortality.

Our study is one of the larger retrospective reviews of women with breast cancer that comprehensively evaluated the individual components of the metabolic syndrome. Studies have evaluated the smaller subset of triple-negative breast cancer and found an association with the metabolic syndrome [22]. Triple-negative breast cancer as determined from routine immunohistochemistry and fluorescence in situ hybridization analyses is loosely representative of the basal-like breast cancer described by Sorlie et al. [25]; however, the triple-negative breast cancer group is clearly heterogeneous [26]. Likewise, the hormonal

receptor status indicates a heterogeneous group but a more fundamental difference in tumor type of hormonal responsiveness.

Obesity is emerging as an important concern for women with breast cancer with an increased risk of recurrence and death in women who have diagnoses of both obesity and breast cancer [27–30]. The inherent question to that finding is, does the obesity contribute to the biologic aggressiveness of the cancer? Many of the pro-inflammatory processes of the metabolic syndrome have been associated with a risk of breast cancer so the question of whether the pro-inflammatory condition contributes to a poor prognosis is plausible. Mechanisms include increased levels of inflammatory markers such as leptin, tumor necrosis factor-alpha, insulin-like growth factor-1, and decreased adiponectin [31–33]. Adiponectin is an anti-inflammatory protein that has been correlated with the metabolic syndrome, and decreased adiponectin is associated with a risk of ER− breast tumors [34, 35]. However, our finding that the metabolic syndrome is not associated with greater rates of hormonally independent breast cancer suggests that the impact of obesity and the metabolic syndrome on breast cancer prognosis is independent of the circulating factors.

A major limitation of this study is that it is a retrospective review through an EMR system with various amounts of data collected using various methods. It is not a prospective clinical trial using standardized protocols. To be conservative, we chose to adapt more stringent criteria for the metabolic conditions and only consider physical findings and laboratory values that were most consistent with a concern such as a SBP ≥ 160 mm/Hg rather than 130 mm/Hg and a random glucose value of ≥200 g/dl. Most of the qualifying findings that led to a classification of one component of the metabolic syndrome were based on a diagnosis code and/or medication prescribed rather than a random physical finding or laboratory value. For example, of the patients that were classified as hyperglycemic, only 4% were based on a glucose reading alone (≥200 mg/dl). The remainder of those who were classified as diabetic (96%), were based on a diagnosis code and/or a medication for glucose control. The sensitivity and specificity of our criteria using medical record data are unknown, and these results should be confirmed in a prospective study.

Waist-hip ratio and BMI are both indicators of obesity although waist-hip ratio has evolved in recent years as a better indicator of the metabolic syndrome [15]. As the availability of waist circumference is limited in the EMRs, BMI has served as a substitute in the diabetes literature and in other cancer reviews that rely on billing codes [36, 37]. Another limitation of this study is that the data come from a single institution. The population served by the Comprehensive Cancer Center of Wake Forest University covers a broad geographic area with a relatively large rural representation. Among this group, 54% were considered hypertensive, 26% obese, 16% hyperglycemic, and 30% dyslipidemic. Fifteen percent of the women had three or more metabolic conditions consistent with the metabolic syndrome. An important finding from our study is the high rates of the metabolic syndrome and the individual components of the metabolic syndrome that were found in our breast cancer population. The significance of a high prevalence of the metabolic syndrome and the individual components is that hypertension and diabetes are associated with an increase in cardiovascular complications of therapy [38, 39]. As less than 10% of the women with breast cancer in the U.S. participate in a clinical trial, the quantification of late effects of

novel therapies will lag behind the translation of those findings to the larger breast cancer community [40].

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Table 1

Summary of patient characteristics

Characteristics	ER− *N*(%)	ER+ *N* (%)	*P* value
Total	219 (100)	641 (100)	
Age			< 0.001
Median (range)	54.0 (27–88)	59.0 (27–97)	
Age ≥ 50	144 (66)	474 (74)	
Race			< 0.001
Black	52 (24)	80 (12)	
Hispanic	3 (1)	3 (<1)	
White	163 (74)	557 (87)	
Other	1 (<1)	1 (<1)	
TNM stage			0.025
0	9 (4)	28 (4)	
1	78 (36)	305 (48)	
2	96 (44)	231 (36)	
3	27 (12)	63 (10)	
4	9 (4)	14 (2)	
Tumor grade			< 0.001
Well-differentiated	13 (8)	154 (33)	
Moderately differentiated	29 (17)	209 (45)	
Poorly differentiated	123 (72)	90 (19)	
Undifferentiated	6 (4)	9 (2)	
Progesterone status			< 0.001
Negative	199 (91)	135 (21)	
Positive	20 (9)	506 (79)	

Table 2

Metabolic conditions by estrogen receptor status

Condition	ER− *N* (%)	ER+ *N* (%)	*P* value
Total	219 (100)	641 (100)	
Obese	57 (26)	163 (25)	0.861
Hyperglycemia	28 (13)	110 (17)	0.128
Hypertension	116 (53)	346 (54)	0.796
Dyslipidemia	61 (28)	197 (31)	0.422
Number of conditions			0.566
0	72 (33)	195 (30)	
1	76 (35)	205 (32)	
2	39 (18)	141 (22)	
3	20 (9)	71 (11)	
4	12 (5)	29 (5)	

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Table 3

Characteristics associated with metabolic conditions

Characteristic	Obese	HTN	Hyperglycemia	Dyslipidemia	Metabolic syndrome*
Age	0.995**	< 0.001	0.274	< 0.001	< 0.001
< 50	1.00 (0.72–1.40)	0.19 (0.14–0.27)	0.81 (0.56–1.18)	0.24 (0.16–0.37)	0.33 (0.19–0.56)
≥50	Ref	Ref	Ref	Ref	Ref
Race	< 0.001	< 0.001	< 0.001	0.021	< 0.001
Black	2.88 (1.95–4.26)	3.30 (2.01–5.42)	2.60 (1.72–3.92)	1.79 (1.17–2.72)	3.10 (1.95–4.92)
Other	2.88 (0.70–11.8)	1.20 (0.26–5.46)	0.69 (0.08–5.77)	0.57 (0.07–4.93)	1.49 (0.17–12.9)
White	Ref	Ref	Ref	Ref	Ref
TNM stage	0.008	0.048	< 0.001	0.070	0.558
0–1	0.57 (0.36–0.90)	0.55 (0.33–0.90)	0.38 (0.24–0.61)	1.67 (1.01–2.77)	0.84 (0.46–1.53)
2	0.90 (0.57–1.42)	0.68 (0.41–1.14)	0.57 (0.35–0.90)	1.26 (0.75–2.13)	1.05 (0.57–1.93)
3–4	Ref	Ref	Ref	Ref	Ref
PR	0.485	0.318	0.228	0.038	0.087
Negative	1.15 (0.78–1.71)	1.23 (0.82–1.84)	1.30 (0.85–1.98)	1.52 (1.02–2.24)	1.52 (0.94–2.46)
Positive	Ref	Ref	Ref	Ref	Ref
ER	0.321	0.525	0.086	0.070	0.054
Negative	0.80 (0.51–1.25)	0.86 (0.55–1.36)	0.65 (0.40–1.06)	0.66 (0.42–1.04)	0.57 (0.32–1.01)
Positive	Ref	Ref	Ref	Ref	Ref

*3+ Conditions

***P* value on *top row*, odds ratios and 95% confidence intervals on *subsequent rows*

Table 4

Estimated percentages of patients with each component of the metabolic syndrome by the amount of data required and the method of summarizing multiple readings

	Number of records of each type required*											
	0+		1+		2+		3+		4+		5+	
Condition	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**
Obesity	22	26	26	30	27	32	27	33	29	35	30	37
HTN	47	57	54	64	56	67	57	68	59	70	60	71
Diabetes	14	22	16	23	18	24	19	25	20	27	21	28
Lipids	26	26	30	30	32	32	35	35	36	37	37	37
Metabolic Syndrome	13	16	15	19	17	21	18	23	20	24	20	25

*Diagnosis, medication, SBP, and weight records