Published in final edited form as:

Breast Cancer Res Treat. 2016 June ; 157(3): 597–603. doi:10.1007/s10549-016-3846-4.

Associations between metabolic syndrome, breast cancer recurrence, and the 21-gene recurrence score assay

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Abstract

PURPOSE—The 21-gene recurrence score (RS) assay is prognostic in estrogen receptor-positive (HR+), HER2 negative, node negative breast cancer (BC). The interaction between RS and host factors including metabolic syndrome (MS) is unclear. MS conditions such as obesity have been associated with worse BC prognosis. The aim of this study was to identify associations between presence of MS conditions and RS group or breast cancer recurrence.

METHODS—Demographic, pathologic and treatment data, MS criteria and menopausal status were abstracted from medical records of women with stage I–II, HR+, HER2 negative BC evaluated with the RS assay at a single institution since 2005. MS was defined as presence of ≥3 of the following within 2 years of diagnosis: body mass index ≥27.7 kg/m^2; hypertension; impaired fasting glucose; HDL <50mg/dL; hypertriglyceridemia.

RESULTS—Of 533 eligible women, 22% had MS. MS was more common in post- vs pre-menopausal women (30% vs 9%; p<0.0001). There was no significant association between RS group and overall MS status or any individual criterion, controlling for stage, and no association after stratification by menopausal status. Postmenopausal status was associated with higher RS group (p=0.039), independent of stage. With 4.2 year median follow-up, no association between disease recurrence and MS was identified.

CONCLUSIONS—Although MS has been associated with worse BC outcomes, we were unable to identify associations between RS group and MS criteria. Identification of prognostic factors other than RS that underlie this higher risk will be important for optimizing breast cancer treatment-decision making in patients with MS.

Keywords

recurrence score; metabolic syndrome; obesity; breast cancer

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CONFLICT OF INTEREST DISCLOSURES

No authors had any conflicts of interest to disclose.

INTRODUCTION

In early stage hormone receptor (HR) positive breast cancer, the benefit from chemotherapy in addition to endocrine therapy is uncertain. In addition to standard pathologic assessment, tumor gene expression is being increasingly used to better understand tumor biology. Integration of both anatomic and biologic tumor factors has allowed for improvement in the ability to predict recurrence and guide treatment decisions in early stage breast cancer. The 21-gene recurrence score (RS) assay (OncotypeDX) has been validated to be prognostic for breast cancer recurrence in HR positive, HER2 negative, node negative breast cancer [1–3]. Patients with low risk RS (0–17) are generally recommended to receive endocrine therapy with tamoxifen or an aromatase inhibitor without chemotherapy. Those with high RS (31–100) benefit from both chemotherapy and endocrine therapy. Intermediate risk patients (RS 18–30) are also recommended to have endocrine therapy but the additional benefit from chemotherapy is less clear. More recently the RS assay was evaluated retrospectively for use in patients with node positive breast cancer [4]. As with node negative breast cancer, those with node positive disease and low RS were found to have minimal benefit from chemotherapy, whereas those with high RS demonstrated significant reduction in risk of recurrence with chemotherapy.

Metabolic syndrome is a constellation of pathologic disorders involving energy metabolism. Metabolic syndrome and its comprising conditions of central obesity, diabetes, hyperlipidemia and hypertension (HTN) are rising epidemics in our society. While studies have associated obesity with increased incidence and poorer prognosis of breast cancer it is unclear how other MS conditions, individually and in combination, affect risk of BC development or prognosis. It is also uncertain whether the 21-gene RS assay accurately predicts recurrence in patients with metabolic syndrome. One study showed a higher risk of recurrence in metabolic syndrome within the low RS group [5]. It has been proposed that metabolic syndrome creates a complex biochemical milieu with increased levels of estrogen, adipokines and inflammatory cytokines IL-6 and TNFα, which have been implicated in tumorigenesis and metastasis.

For this study, we hypothesized that the 21-gene RS assay may not fully capture the proposed higher risk tumor microenvironment in metabolic syndrome and thus may underestimate the actual risk of breast cancer recurrence within this population. In order to investigate this hypothesis we performed a retrospective analysis of patients who underwent testing with the RS assay at a single institution since 2005. Our goal was to investigate the association between metabolic syndrome conditions, both individually and in combination, and the 21-gene RS, as well as the risk of breast cancer recurrence, metastasis and death.

METHODS

Patients, Metabolic Syndrome Criteria Variables and Outcomes

We retrospectively reviewed data from 534 women with stage I-II, HR positive, HER2 negative breast cancer treated at the University of Michigan since 2005 and who had Oncotype DX testing performed. Data collected from the Michigan Breast Oncology Quality Initiative database and the University of Michigan Tumor Registry included demographic,

pathologic, Recurrence Score (RS) and treatment data. Metabolic syndrome criteria and menopausal status at the time of diagnosis were abstracted from the University of Michigan electronic medical records (MiChart and CareWeb) with the assistance of the EMERSE search engine [6]. Institutional Review Board approval was obtained for this analysis, including a waiver of informed consent.

Metabolic syndrome was defined, based on a modification of the Adult Treatment Panel III (ATPIII) criteria [7], as having any 3 or more of the following: body mass index (BMI) ≥ 27.7 kg/m^2; HTN ≥ 130/85 mmHg on at least 3 clinic visits or anti-hypertensive medication use; hemoglobin A1c>=5.7 or insulin, metformin or other hypoglycemic medication use; HDL < 50 mg/dL; triglycerides ≥ 150 mg/dL. Modifications from ATPIII include the use of BMI ≥ 27.7 as a surrogate for elevated waist circumference ≥ 88 cm and the use of hemoglobin A1c ≥ 5.7 as a surrogate for elevated fasting plasma glucose ≥ 100 mg/dl. The relevant laboratory and clinical data used to determine each MS criteria were limited to a window encompassing two years before and two years after breast cancer diagnosis date, and data available closest to diagnosis date was preferred and used for statistical analysis. BMI was obtained at the date of diagnosis. In cases without available data the corresponding metabolic syndrome criteria was counted as negative. Outcomes of interest were secondary breast cancer event (SBCE), including local recurrence, secondary breast cancer, or metastasis, or death from any cause. The follow-up time was time to SBCE, death, or last clinic visit at the University of Michigan.

Statistical Analysis

Associations between menopausal status and metabolic syndrome and the number of metabolic syndrome criteria and RS group were assessed using Chi-Square or Fisher's exact tests. Associations between RS group and other categorical variables were assessed univariably using Chi-Square or Fisher's exact tests and multivariably using multinomial logistic regression, controlling for stage of disease. Continuous RS were assessed by clinical and disease categorical characteristics using Wilcoxon rank sum tests. Time to a SBCE was compared by MS status using the Kaplan-Meier method and log-rank test and a Cox proportional hazards model controlling for age and stage.

RESULTS

Patients and Disease Characteristics

There were 534 women with stage I-II, HR+, HER2- breast cancer. One patient was excluded from analysis since she had bariatric surgery with substantial change in weight and resolution of diabetes, hypertension and hypertriglyceridemia just prior to diagnosis (Online Resource 1). At the time of diagnosis 74% of women had Stage I disease, 61% were postmenopausal, and the mean age was 56 years old (standard deviation (SD) 9.7 years) (Table 1).

Prevalence of Metabolic Syndrome Conditions

Of the metabolic syndrome conditions, elevated BMI was most commonly identified (43%), followed by hypertension (41%), hypertriglyceridemia (34%), impaired fasting glucose

(14%) and low HDL (13%). Metabolic syndrome, defined as three of more conditions, was seen in 22% of women. Postmenopausal women had a 4.1 greater odds of having MS than premenopausal women (95% confidence interval (CI) 2.4–7.0, P < 0.0001).

Association of Metabolic Syndrome with the 21- gene Recurrence Score

Most patients had low (55%) or intermediate (38%) recurrence scores, with a mean 21-gene recurrence score of 18 (SD 9.1). Controlling for stage, postmenopausal status was associated with a significantly higher RS group than premenopausal status (P = 0.039; odds ratio (OR) of high vs low RS 2.7, 95% CI 1.2–6.2 for postmenopausal vs premenopausal women; OR of intermediate vs low RS 1.3, 95% CI 0.9–1.8 for postmenopausal vs premenopausal women) (Table 2). There was no difference in the distribution of RS groups between women with versus without MS (low: 54% vs. 55%, intermediate: 41% vs. 37%, high 5% vs. 8%; P = 0.55) or based on any individual MS condition. When stratified by menopausal status there were also no significant associations between RS group and any MS criteria. An analysis of obesity without MS versus MS did not reveal any statistically significant associations (Online Resource 2).

Association of Metabolic Syndrome with Outcomes

Women were followed for a mean of 4.4 years (SD 2.3). During this time within our 533 patient cohort there were a total of 24 events. There were 20 secondary breast cancer events (SBCE), which included 5 ductal carcinoma in situ, 3 local recurrences, 1 second primary breast cancer and 11 distant recurrences. There were 7 deaths from any cause, 3 of which were preceded by a SBCE. There was no significant difference between the time to SBCE based on MS status univariably (hazard ratio 0.6, 95% CI 0.2–1.7; P = 0.30) or multivariably (hazard ratio 0.5, 95% CI 0.2–1.7; P = 0.30), controlling for age and stage (Figure 1).

DISCUSSION

While several studies have demonstrated that obesity and other metabolic syndrome conditions are associated with an increased incidence of breast cancer [8–19], few studies have explored the associations with risk of breast cancer recurrence. In our study, we demonstrated a fairly high prevalence of MS in our cohort of patients with breast cancer, as well as an association between MS status and menopausal status.

We were unable to identify an association between risk of recurrence as determined by RS and the presence of MS. Other reports have similarly demonstrated a lack of association between RS and both obesity [20] and overall MS status, however our study is the first to show this for all individual MS conditions.

Despite prior studies showing worse breast cancer prognosis with metabolic syndrome, our study was unable to demonstrate a significant difference in incidence of or time to SBCE or mortality based on MS status or individual criteria. This is in contrast to a previously reported study which demonstrated an association between increased incidence of SBCE and metabolic syndrome status specifically in the low RS risk group. Our inability to demonstrate a similar association between recurrence events and the presence of MS may be due to the overall low events in the relatively short follow-up time. Further validation studies

to assess a difference in recurrence and survival among those with MS conditions based on RS group could have important prognostic and treatment implications.

Strengths of our study include analysis of a large cohort of patients with a high prevalence of MS followed for up to 10 years, including the collection of data on individual conditions comprising metabolic syndrome in addition to metabolic syndrome as a whole. Additionally, the classification of patients as having individual metabolic syndrome conditions was made thorough a detailed chart review including clinical notes, laboratory studies and medication use at the time of diagnosis rather than relying solely on medical record billing code diagnoses, which may lead to under-reporting of diagnoses.

Even though we examined a cohort of patients with a mean follow-up of 4.4 years and a prevalence of metabolic syndrome of 22%, our study was limited by the low overall event rate of 20 SBCE and 7 deaths (of which 3 were preceded by breast cancer recurrence). The excellent prognosis of this cohort of women with hormone sensitive, HER2 negative breast cancer and primarily node-negative disease is superior to the 89% 5-year recurrence rate reported by the Oxford Overview for patients with ER-positive, node negative disease [21].

Our study is also limited by the definition of metabolic syndrome, which is an issue that affects all retrospective studies examining metabolic syndrome factors [22, 23]. We used a modification of the established Adult Treatment Panel III criteria for metabolic syndrome [7] which may result in incorrect categorization of some patients. Laboratory and clinical data used to determine MS criteria were obtained closest to diagnosis date, however data did span a window within two years of diagnosis date based on limitations in availability in our retrospective review of the electronic medical record. Thus we are unable to determine whether all components of MS were present at the exact time of diagnosis. In addition, we were unable to take into account variation in the status of patients' metabolic syndrome criteria over the study period. There may be important effects of adjuvant therapy or alternative medication or lifestyle changes that altered MS criteria following diagnosis that were not captured in our study. Changes in MS conditions may play an important role in their proposed mechanism of interaction with the tumor microenvironment. It is hypothesized that metabolic syndrome invokes a pro-inflammatory state that may alter tumor aggressiveness or metastatic potential. Thus it will be important to consider the effect of medications or lifestyle changes which may also alter cytokine stimulation, inflammation and insulin resistance. For example, we were unable to account for potential differences between patients with well-controlled versus poorly managed hypertension or diabetes mellitus during the follow-up period. In addition, there are emerging data on the anti-inflammatory effects of medications including metformin and aspirin that suggest they may result in reduction in breast cancer recurrence [24, 25]; the effect of metformin is currently being prospectively evaluated [25, 26]. Another area of investigation is the impact of dietary and weight loss interventions on reducing BC recurrence [27–30].

It is unclear whether the presence of MS impacts BC recurrence directly and/or via response to therapy. Some studies have suggested that obesity negatively impacts endocrine therapy or chemotherapy response due to underdosing [8]. Additionally patients with MS may have associated comorbidities such as renal dysfunction or cardiovascular complications; these

comorbidities may impact the decision to pursue chemotherapy as opposed to endocrine therapy alone, the duration of treatment, tolerability and overall outcomes. However these factors this would only impact the minority of patients with intermediate or high risk RS who would typically be considered for chemotherapy.

Current evidence has associated metabolic syndrome and comprising conditions with increased risk of breast cancer recurrence. Our study adds to the suggestion that the increased risk of disease recurrence associated with metabolic syndrome may not be adequately captured by the 21-gene RS. This highlights the importance of considering host factors including metabolic syndrome along with tumor gene expression when determining BC prognosis and for making treatment decisions.

Studies are beginning to reveal the complex biochemical interplay involving insulin resistance and associated inflammatory cytokines, which has led to clinical trials examining pharmacologic or non-pharmacologic interventions. Understanding more about the modifiable risk factors for breast cancer recurrence may lead to improvements in patient management following diagnosis. Lifestyle interventions targeting weight loss and glycemic control as well as optimization of cholesterol profiles and blood pressure may prove to be important and previously underappreciated adjuncts to our endocrine and chemotherapies in breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NLH was supported in part by a National Cancer Institute Clinical Cancer Investigator Team Leadership Award (supplement to 3-P30-CA046592, PI M Wicha).

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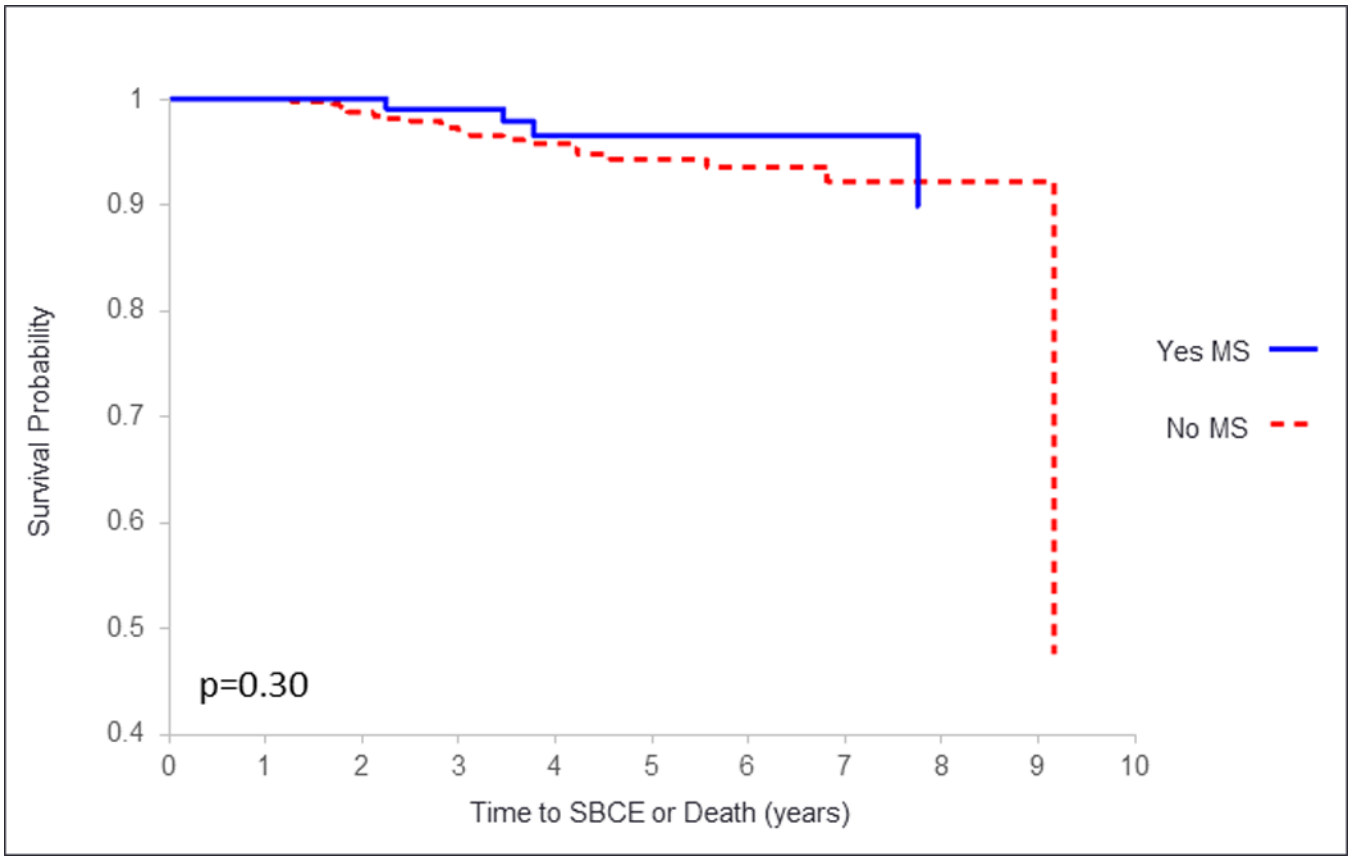

Figure 1. Survival based on metabolic syndrome (MS) status

Time to second breast cancer event (SBCE) or death is given on the x axis. The solid line represents survival of those with MS, and the dashed line represents survival of those without MS.

Table 1

Summary of baseline patient demographic, pathologic and metabolic syndrome criteria.

Characteristic	*N*	*%*
Age, mean (SD)	55.9 (9.7)	
Height (centimeters), mean (SD)	163.0 (7.0)	
Weight at diagnosis (kilograms), mean (SD)	75.3 (18.2)	
Body mass index, mean (SD)	28.5 (7.0)	
21- gene Recurrence Score, mean (SD)	17.9 (9.1)	
Follow-up Time (years), mean (SD)	4.4 (2.3)	
Stage		
I	392	73.5
II	141	26.5
Estrogen Receptor Status		
Positive	531	99.6
Negative	2	0.4
Progesterone Receptor Status		
Positive	481	90.2
Negative	50	9.4
Unknown	2	0.4
Menopausal Status		
Pre	204	38.3
Post	324	60.8
Unknown	5	0.9
Charlson Comorbidity Index		
1	499	93.6
2	21	3.9
3	12	2.3
Unknown	1	0.2
Path Stage T		
T1a	10	1.9
T1b	127	23.8
T1c	292	54.8
T2	104	19.5
Path Stage N		
N0	477	89.5
N1	55	10.3
Unknown	1	0.2
Body Mass Index Criteria		
No	303	56.8
Yes	230	43.2

Characteristic	*N*	*%*
Hypertension Criteria		
No	312	58.5
Yes	221	41.5
Triglycerides Criteria		
No	350	65.7
Yes	183	34.3
HDL Criteria		
No	463	86.9
Yes	70	13.1
Diabetes or Impaired Glucose Tolerance Criteria		
No	458	85.9
Yes	75	14.1
Metabolic Syndrome (≥3 of 5 criteria)		
No	416	78.0
Yes	117	22.0
Number of Metabolic Syndrome Criteria		
0	164	30.8
1	146	27.4
2	106	19.9
3	67	12.6
4	30	5.6
5	20	3.8
Chemotherapy		
No	391	73.4
Yes	142	26.6
Endocrine Therapy		
No	27	5.1
Yes	506	94.9

Abbreviations: HDL, high density lipoprotein, SD, standard deviation

Table 2

Associations between Recurrence Score group and individual metabolic syndrome (MS) conditions.

	Recurrence Score Group						
Variable	***Low (N=292)***		***Intermediate (N=203)***		***High (N=38)***		***P value***
Number of MS Criteria	***N***	***%***	***N***	***%***	***N***	***%***	
0	99	33.9	52	25.6	13	34.2	0.66
1	74	25.3	60	29.6	12	31.6	
2	56	19.2	43	21.2	7	18.4	
3	33	11.3	29	14.3	5	13.2	
4	19	6.5	11	5.4	0	0	
5	11	3.8	8	3.9	1	2.6	
BMI Criteria							
No	167	57.2	112	55.2	24	63.2	0.65
Yes	125	42.8	91	44.8	14	36.8	
Hypertension Criteria							
No	179	61.3	109	53.7	24	63.2	0.20
Yes	113	38.7	94	46.3	14	36.8	
Triglycerides Criteria							
No	189	64.7	133	65.5	28	73.7	0.55
Yes	103	35.3	70	34.5	10	26.3	
HDL Criteria							
No	260	89.0	169	83.3	34	89.5	0.15
Yes	32	11.0	34	16.7	4	10.5	
Diabetes or Impaired Glucose Criteria							
No	249	85.3	175	86.2	34	89.5	0.77
Yes	43	14.7	28	13.8	4	10.5	
Metabolic Syndrome (≥3 criteria)							
No	229	78.4	155	76.4	32	84.2	0.55
Yes	63	21.6	48	23.6	6	15.8	

	Recurrence Score Group						P value
Variable	Low (N=292)		Intermediate (N=203)		High (N=38)		
	N	%	N	%	N	%	
Number of MS Criteria							
Menopausal Status*							
Pre	122	41.8	74	36.5	8	21.1	0.033
Post	167	57.2	127	62.6	30	78.9	

Abbreviations: BMI, body mass index; HDL, high density lipoprotein.

*5 missing menopausal status, n=528