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The effect of modifiable risk factors on breast cancer aggressiveness among black and white women

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Abstract

Introduction: Although breast cancer incidence is higher among white women, black women are more likely to have aggressive tumors with less favorable histology, and to have a worse prognosis. Obesity and alcohol consumption have been identified as two modifiable risk factors for breast cancer, while physical activity may offer protection. Little however is known about the association of these factors with race on the severity of breast cancer.

Methods: Data collected as part of a large prospective study looking at insulin resistance and race among women with breast cancer was queried for patient characteristics, lifestyle factors and tumor characteristics. The association with Nottingham Prognostic Index (NPI) was assessed with different models using univariate and multivariate linear regression.

Results: Among 746 women in our cohort, 82% (n=615) were white and 18% (n=131) were black, mean age 58 years. Black patients were more likely to have high BMI (31.0 vs. 26.7, p<.0001), comorbidities (69% vs 55%, p=.01), self-reported poor diet (70% vs 42%, p<.001), be sedentary (56% vs 46%, p=.03) and were less likely to consume alcohol (8% vs 32%, p<.0001) compared to white patients. Overall, 137 (18%) of the patients had poorer prognosis (NPI > 4.4), which was significantly associated with younger age (55.6 vs 58.5 years, p=0.02), black race (27%

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vs 15%, p=.001), triple negative cancer (15% vs 6%, p=.003), and poor diet (54% vs 45%, p=.046) compared to patients with better prognosis (NPI ≤ 4.4).

On multivariate analysis, (model R^2=0.12; p<.001), age (β=−.011 per year, p=.002), healthy diet (β=−.195, p=.02), and exercise (β=−.004, p=.02) were associated with better prognosis, while black race (β=.247, p=.02) and triple negative cancer (β=.908, p<.0001) were associated with poor prognosis. Neither alcohol use nor BMI was significantly associated with NPI.

Conclusion: Among modifiable risk factors, diet and exercise are associated with NPI. Unmodifiable factors including race and biologic subtype remain the most important determinants of prognosis.

Introduction

(1) Although breast cancer is the second most common cause of cancer death among women in the United States, not all breast cancers behave similarly . Distinct molecular breast cancer subtypes based on gene expression profiling have been identified, and demonstrate predictable patterns of behavior and response to treatment.(2) More aggressive molecular subtypes are more likely to metastasize and/or recur even with standard treatment compared to others.(3-5)

Prognostic features such as age, stage at diagnosis, and hormone receptor status, are commonly used in the clinical setting to help guide patient education and physician decision making regarding treatment. While prior research has established modifiable risk factors, including obesity and alcohol consumption as risk factors for breast cancer,(6-11) their relationships to aggressive types of breast cancer are uncertain. Further, race is clearly a risk factor for aggressive types of breast cancer(12) but whether breast cancer prognosis is affected by other modifiable risk factors is unclear.(13)

The purpose of this study was to assess the relationship between modifiable risk factors and race on breast cancer aggressiveness.

Methods

Data was collected as part of a multi-center, prospective study looking at racial disparities in breast cancer aggressiveness with respect to insulin levels and insulin resistance (National Cancer Institute (NCI) grant 1R01CA17155801). Participants were recruited from multiple medical institutions in New York, New Jersey, Baltimore, and New Haven at the time of their breast cancer surgery. Inclusion criteria included women over the age of 21 with a primary diagnosis of incident, stage I-III breast cancer, who self-identified as Black or White. Women of Asian and white Hispanic descent were excluded, as they are more likely to have ER/PR negative tumors compared to non-Hispanic White women (26% vs. 19%, respectively), and could potentially attenuate the association between hormone receptor status and race. Women with a history of bariatric surgery for weight loss, a history of organ transplantation, a history of diabetes mellitus, and those with end stage renal disease or hepatic cirrhosis were excluded. We also excluded women who were taking oral or injected glucose-lowering medications, as these medications influence insulin levels, one of the

primary endpoints of the main study . IRB approval was obtained at all participating institutions and patients signed informed consent. Patients were given a $25 gift card for participation.

The Nottingham Prognostic Index (NPI) is a tool that combines nodal status, tumor size, and histologic grade, measuring the intrinsic biologic features of a tumor and the probability of metastasis. (14-17) The NPI score is calculated as [0.2 × tumor size (cm) + lymph node stage (1, node negative; 2, 1-3 positive lymph nodes; 3, ≥4 positive lymph nodes) + histological grade (1, well differentiated; 2, moderately differentiated; 3, poorly differentiated)]. Pathology reports were queried for this information and NPI was calculated for each participant. Based on previous studies, good prognosis was defined as an NPI score of ≤ 4.4 and poor prognosis an NPI score >4.4.(18, 19) Tumor characteristics were obtained from pathology reports from the specimen block used to assess receptor status.

Patients were surveyed with a short, validated questionnaire prior to surgery which asked questions about demographic characteristics, access to care, alcohol consumption, smoking, , diet, exercise, and lifestyle factors. (Appendix 1.) Physical activity was calculated using methods described in the 1989 Nurses' Health Study II and a subsequent validation study.(20) Given the urban setting of patient recruitment, our study questionnaire only included questions about intensity and time spent walking/hiking outdoors (including walking to work) and bicycling (including stationary machine). The intensity of each activity was multiplied by duration of the activity, then the sum score of walking and bicycling was used to measure moderate/vigorous physical activity. A score of 0 was considered as having no moderate/vigorous physical activity and sedentary, a score greater than 0 and less than 33 was considered moderately active, and a score greater or equal to 33 was considered as highly active. The continuous value of moderate/vigorous score was used in multivariate regression analysis.

Data was queried for patient and tumor characteristics, lifestyle factors and tumor characteristics. Bivariate analysis was used to determine the association between individual variables, race and NPI. T-test was used to compare continuous variables by race, χ^2 statistics, or Fisher's exact test was used to compare categorical variable by race. Pearson correlation coefficient was used to assess the correlation between continuous variables. The adjusted associations between risk factors and NPI were assessed using multivariate linear regression. We constructed separate models with different combinations of risk factors to predict the NPI score and check for confounding. Collinearity of correlated risk factors was tested in each model. None of the variance inflation factors were greater than 5. The highest variance inflation factor was for BMI (1.23) in the full model, Model 6. Hence multicollinearity was not identified. No apparent outlier was identified or excluded in the models. All analyses were performed using SAS 9.4 (SAS Institute. Cary, NC). Statistical significance level was set at 0.05.

Results

There were a total of 746 women in our cohort with newly diagnosed breast cancer; 82% (n=615) white and 18% (n=131) black, mean age 57.8 ± 12.8 and 58.0 ± 12.1 years

respectively, p=.94. (Table 1.) On bivariate analysis, while there was no statistically significant difference by race with respect to tumor size, white women were more likely to have stage I breast cancer compared to black women: stage I 65% vs. 53%, stage II 32% vs. 41%, and stage III 3% vs. 8 6%, p=.03. With regard to modifiable risk factors, black women were more likely to have a high BMI (31.0 vs. 26.7, p<.0001), and to be sedentary (56% vs 46%, p=.03). Black women were significantly less likely to consume alcohol (8% vs 32%, p<.0001) and not smoke (71% vs. 52%, p<.0001).

Overall, 137 (18%) of the patients had NPI > 4.4, which on bivariate analysis was significantly associated with younger age (55.6 vs 58.5 years, p=0.02), black race (27% vs 15%, p=.001), triple negative cancer (15% vs 6%, p=.003), and poor diet (54% vs 45%, p=.046). (Table 2.) Obesity, as defined by BMI ≥30, was not associated with high NPI.

In multivariate linear regression predicting NPI score, alcohol consumption and exercise were considered as continuous variables. (Table 3.) We observed that the strongest predictors, including triple negative disease (β=.896, p<.0001), black race (β=.2466, p=0.02), and younger age (β=−.011, p=0.001) were all associated with poor prognosis (higher NPI). Physical activity (β=−.004, p=0.02) and a self-reported healthy diet (β=−.193, p=0.02) were associated with lower NPI. Neither alcohol use (β=−.002, p=0.90), recent screening mammogram (β=.112, p=0.23), nor BMI (β=−.002, p=0.77) were significantly associated with NPI. No significant interactions were found between race and BMI, diet, smoking, exercise, screening and triple negative status.

Discussion

In this study evaluating modifiable risk factors and breast cancer aggressiveness, we observed that neither alcohol consumption nor BMI were associated with differences in NPI between black and white women. Diet and exercise had a small but significant impact on breast cancer severity, where both were associated with a lower NPI score. The most important determinants of prognosis were nonmodifiable risk factors, including race, age and biologic subtype.

Disparities in breast cancer incidence and prognosis between black and white women have been well documented. Although Black women have a lower incidence of breast cancer than White women, they have higher overall mortality.(21, 22) These disparities have been described with respect to age, stage at diagnosis, molecular subtype, and response to treatment, among others. Whereas white women are more likely to be diagnosed at an older age and to have hormone receptor positive disease, black women are more frequently diagnosed at younger ages and with more aggressive subtypes, such as triple negative breast cancer. The reasons for these disparities are multiple and complex, and include numerous biologic and socio-demographic factors. For example, several studies have demonstrated an increased risk of developing breast cancer and higher breast cancer mortality among women with obesity and type 2 diabetes.(23-29) However, there is little data evaluating racial disparities with respect to these risk factors on the severity of breast cancer.

Our data support the fact that black women are more likely than white women to present with tumors displaying features indicative of a poorer prognosis, including higher grade, and negative hormone receptors. Prior studies have demonstrated rates of triple negative breast cancer among black women that are twice as high as the rate for whites.(30-32) In this largely urban population, we observed a rate that was nearly threefold. Our study had few stage III patients overall, and more white patients with stage I disease, consistent with historically known racial differences in screening.(33, 34) As expected, in our adjusted model, the variable “screening mammogram within 2 years of diagnosis” was not significantly associated with higher NPI, which is likely due to the fact that many aggressive cancers present not during the time of screening, but rather as interval cancers, between the time from one normal mammogram to the next.

The reasons why black women are more likely to be diagnosed with aggressive types of breast cancer are complex and incompletely understood. As the causes of aggressive breast cancer continue to be investigated with respect to biologic and environmental/socioeconomic factors, a useful paradigm in which to frame the question is by whether they are nonmodifiable, such as age, and race,. or modifiable including body mass index (BMI), and diet. Certainly, there is an argument to be made that factors such as diet, which is dependent upon income and availability of nutritious foods, parity which may be dependent upon access to family planning and healthcare services,. might not simply be classified as “modifiable”, but for the purpose of this study we chose to separate these risk factors accordingly. We observed similar rates of breast cancer screening between black and white women, supporting the data that neither differences in the established risk factors for breast cancer nor in screening or treatment can explain these disparities. Because the overall number of black women in our study was low, we were not able to analyze each of the risk factors and the association with NPI by race. We did however find that race was a significant predictor of high NPI in the multivariable regression analysis, .

Alcohol consumption is a known risk factor for breast cancer. (35, 36) There is emerging data suggesting that alcohol consumption may promote the growth and spread of breast cancer through multiple mechanisms, including stimulation of EGFR, oxidative stress, and by stimulating tumor angiogenesis, among others.(37, 38) While a known risk factor, data looking at the effect of alcohol consumption on the risk of death from breast cancer, is mixed. (39, 40) Prior work suggests increased incidence particularly among post-menopausal white women of hormone receptor positive disease, (41) and data looking at risks specifically for black women are sparse. A notable exception from the Carolina Breast Cancer Study found a nearly two-fold increased risk of triple negative breast cancer among black women who consumed more than 7 drinks per week.(13) Our findings support prior work demonstrating lower alcohol consumption among black women compared to white women. (42, 43) Our findings also showed that alcohol had no effect on the severity of breast cancer, and is the first study that we are aware of to examine the effect of alcohol consumption on NPI. Our study is limited however, by the fact that we do not have data on the duration of alcohol exposure.

Obesity at the time of diagnosis, another risk factor for breast cancer,(44) particularly among postmenopausal women, has also been studied extensively, but the findings are mixed.

Several studies have demonstrated that weight gain during treatment increases the risk of breast cancer death, (45, 46) while others have shown no difference.(24) Our study showed no effect of BMI on the aggressiveness of breast cancer at diagnosis, which may be partially explained by the higher incidence of ER positive, postmenopausal breast cancers in our study. The effect of diet on breast cancer outcomes, a related but distinct risk factor to BMI, also demonstrate mixed results. A study by Chlebowski, et al demonstrated a lower risk of breast cancer related death among patients who adopted a low-fat diet (HR 0.82; 95%C.I. 0.70 to 0.96)(47). We found that a self-reported healthy diet was associated with lower NPI. We acknowledge that these findings may be influenced by the fact that dietary data was subjective, and there may be cultural and ethnic differences in what constitutes a “healthy” diet and weight.(48) In contrast, Kwan et al. showed no difference in breast cancer recurrence or death from breast cancer between early stage patients who consumed a diet with high intake of fruits, vegetables, whole grains and lean protein compared to those who consumed aa Western diet with higher amounts of processed meats and refined carbohydrates.(49) Furthermore the authors did not observe in changes in on the risk of breast cancer recurrence or breast cancer death with exercise, BMI, or smoking for either those on the prudent diet or the Western diet.

Our findings support the extensive literature demonstrating that black women with breast cancer are more likely to be obese, have a poor diet, and be sedentary compared to white women. In addition, our study demonstrates an association between these risk factors and breast cancer severity, as measured by NPI. These findings are important, as modifiable risk factors may have a small but real impact on breast cancer aggressiveness, particularly where effective systemic treatment options are suboptimal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix 1.

Prognosis by NPI score

NPI Score	Cancer-specific ten-year survival	All-cause ten-year survival
I (Excellent) ≤2.4	96%	88%
II (Good) >2.4 and ≤3.4	93%	86%
III (Moderate) >3.4 and ≤5.4	78%	74%
IV (Poor) >5.4	44%	42%

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Black breast cancer patients more likely to have high BMI, and be sedentary.

Poorer breast cancer prognosis associated with poor diet.

Neither alcohol use nor BMI associated with prognosis.

Among modifiable risk factors, diet and exercise are associated with NPI.

Table 1.

Patient and tumor characteristics by race

	Total N=746	**White N=615 (82%)**	**Black N=131 (18%)**	**P value**
Age, mean (SD) years	57.9 (12.2)	58.0 (12.1)	57.9 (12.8)	0.94
BC Stage				0.03
I	466 (63%)	397 (65%)	131 (53%)	
II	251 (34%)	197 (32%)	54 (41%)	
III	29 (4%)	21 (3%)	8 (6%)	
Tumor Size, mean (SD) cm	1.6 (1.2)	1.5 (1.1)	1.8 (1.4)	0.10
Tumor grade				0.0003
I (Well differentiated)	168 (23%)	150 (24%)	18 (14%)	
II (Moderately differentiated)	370 (50%)	311 (51%)	59 (45%)	
III (Poorly differentiated)	208 (28%)	154 (25%)	54 (41%)	
ER/PR+ †	590 (83%)	500 (85%)	90 (73%)	0.002
Triple negative †	53 (8%)	35 (6%)	18 (15%)	0.0007
NPI				0.0013
≤4.4	609 (82%)	515 (84%)	94 (72%)	
>4.4	137 (18%)	100 (16%)	37 (28%)	
BMI †				<.0001
BMI 18-24	384 (52%)	357 (59%)	27 (21%)	
BMI 25-29	167 (23%)	119 (20%)	48 (37%)	
BMI >=30	182 (25%)	126 (21%)	56 (43%)	
Alcohol consumption (drinks/week) †				<.0001
0	220 (29%)	151 (25%)	69 (53%)	
1-4	416 (56%)	359 (58%)	57 (44%)	
≥ 5	110 (15%)	105 (17%)	5 (4%)	
Physical Activity †				0.08
Sedentary	348 (48%)	274 (46%)	74 (56%)	
Moderate Active	198 (27%)	167 (28%)	31 (24%)	

	Total N=746	**White N=615 (82%)**	**Black N=131 (18%)**	**P value**
Highly Active	182 (25%)	156 (26%)	26 (20%)	
Diet[†]				<.0001
Very good/Excellent	395 (53%)	356 (58%)	39 (30%)	
Good/Fair/Poor	346 (47%)	256 (42%)	90 (70%)	
Smoking[†]				0.0005
non-smoker	402 (55%)	313 (52%)	89 (71%)	
former smoker	296 (41%)	264 (44%)	32 (25%)	
current smoker	30 (4%)	25 (4%)	5 (4%)	
Mammogram ≤ 2 years[†]	579 (79%)	472 (78%)	107 (82%)	0.29

[†]Numbers may not add up to total due to missing data.

Table 2.

Patient and tumor characteristics by NPI score

	Total N=746	**Good prognosis N=509 (82%)**	**Poor prognosis N=137 (18%)**	**P value**
Age, mean (SD) years		58.5 (12.1)	55.6 (12.7)	0.02
Race				0.001
White	615	615 (82%)	100 (73%)	
Black	131	94 (15%)	37 (27%)	
Stage				<.0001
I	466	466 (77%)	0	
II	251	142 (23%)	109 (80%)	
III	29	1 (0.2%)	28 (20%)	
Tumor size, mean (sd), cm		1.3 (0.9)	2.8 (1.6)	<.0001
Tumor grade				<.001
I (Well differentiated)	168	166 (27%)	2 (1%)	
II (Moderately differentiated)	370	325 (53%)	45 (33%)	
III (Poorly differentiated)	208	118 (19%)	90(66%)	
ER/PR+ †	590	489 (84%)	101 (77%)	0.01
Triple negative †	53	33 (6%)	20 (15%)	0.003
BMI, mean (sd) †	27.5 (6.5)	27.5 (6.7)	27.1 (5.6)	0.5
BMI 18-24	384	311 (52%)	73 (54%)	
BMI 25-29	167	139 (23%)	28 (21%)	
BMI >30	182	147 (25%)	35 (26%)	
Alcohol consumption (drinks/week) †				0.4
0	220	177 (29%)	43 (31%)	
1-4	416	337 (55%)	79 (58%)	
≥ 5	110	95 (16%)	15 (11%)	
Physical Activity †				0.3

	Total N=746	Good prognosis N=509 (82%)	Poor prognosis N=137 (18%)	P value
Sedentary	348	277 (47%)	71 (53%)	
Moderately active	198	161 (27%)	37 (27%)	
Highly active	182	155 (26%)	27 (20%)	
Diet†				0.046
Very good/Excellent	395	334 (55%)	61 (46%)	
Good/Fair/Poor	346	273 (45%)	73 (54%)	
Smoking†				0.8
non-smoker	402	327 (55%)	75 (57%)	
past smoker	296	243 (41%)	53 (40%)	
current smoker	30	26 (4%)	4 (3%)	
Mammogram ≤ 2 years†	579	479 (80%)	100 (14%)	0.1

†Numbers may not add up to total due to missing data.

Table 3.

Multivariate regression analyses of risk factors on NPI score for black and white women

β p-value	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Age	−0.0097 p=0.001	−0.0123 p<.0001	−0.0085 p=0.0032	−0.0082 p=0.0038	−0.0105 p=0.0005	−0.0106 p=0.0012
Triple neg	---	---	0.9294 p<.0001	0.8921 p<.0001	0.8635 p<.0001	0.8963 <.0001
Good diet	---	---	−0.2576 p=0.002	−0.2377 p=0.0063	−0.2089 p=0.018	−0.1932 p=0.0197
Black race	---	---	---	0.2382 p=0.018	0.2396 p=0.0196	0.2459 p=0.0207
BMI	0.0105 p=0.1	0.0063 p=0.4	0.0054 p=0.4	0.0023 p=0.8	−0.0012 p=0.8	−0.0019 p=0.8
# drinks/wk	−0.0291 p=0.6	−0.0215 p=0.2	−0.0103 p=0.5	−0.0054 p=0.7	−0.0016 p=0.9	−0.0021 p=0.9
Physical activity	---	−0.0053 p=0.001	---	---	−0.0040 p=0.0177	−0.0040 p=0.02
No Mammography screening within the past 2 years						0.1122 p=0.2