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No Association of Reproductive Risk Factors with Breast Cancer Tumor Grade

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Abstract

Histological tumor grade is a well-established marker of breast tumor aggressiveness and prognosis. A number of reproductive factors, including parity and age at first birth, have been shown to be related to breast cancer risk, but few studies have examined the association of these variables with breast cancer aggressiveness. In this study, 813 newly diagnosed breast cancer patients were surveyed for demographic and lifestyle characteristics. Tumor grade and other clinical variables were abstracted from medical records. Multivariate logistic regressions were conducted with each reproductive factor as the independent variable of interest. Regressions were also stratified on menopausal status, hormone therapy use and tumor receptor status. None of the reproductive factors examined including age of first period, number of pregnancies, number of births, and hormone usage was statistically significantly associated with tumor grade. Although more studies are needed to see if other factors unexplored in this study relate to tumor aggressiveness, our study indicates that these factors do not predict the aggressiveness breast cancers.

Keywords

breast cancer; grade; hormone

1. Introduction

In the United States, breast cancer is the second most common cause of cancer deaths and the most common cause of invasive cancer in women [1]. For 2015, the estimated annual incidence of breast cancer was over 230,000, and that same year, there were over 40,000 related deaths [1]. While the breast cancer survival rates are increasing due to improvements in diagnosis, management and therapy, some women develop more aggressive forms of breast cancer, which account for most of the breast cancer mortality [1].

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Histological tumor grade is used to characterize the proliferation of the tumor in order to indicate disease aggressiveness, determine prognosis, and predict survival [2, 3]. Indeed, the grade of a breast cancer tumor is considered to be an essential prognostic indicator [3], and provides physicians with a quick and accurate tool for assessing tumor aggressiveness to help guide the appropriate course of treatment [2]. Higher grade tumors are associated with more aggressive disease and higher rates of recurrence and metastasis [2].

A number of reproductive factors are established risk factors for developing breast cancer. There exists a well-established association of ovarian estrogen, non-ovarian estrogen, and estrogens of exogenous origin with increased risk of developing breast cancer [4], and are likely to play a potentially causative role in the etiology of breast cancer. Parity, age at first birth, breastfeeding and age at menarche are some of the most well established factors associated with risk of breast cancer.

However, the association of these factors with tumor aggressiveness has not been well studied. Indeed, factors associated with risk of breast cancer might overlap with those predicting for greater disease aggressiveness. Hormonal related factors are particularly of interest as it is known that estrogen driven breast cancers tend to express the Estrogen Receptor (ER) gene, and typically have a better prognosis [5], but the association of estrogen, or estrogen-related lifestyle variables, with tumor grade has not been fully explored. In an earlier study, we found that short sleep duration was associated with more aggressive and higher grade tumors [6, 7]. In this study, we will extend this and investigate the association of reproductive factors with breast cancer tumor grade.

2. Materials and Methods

Patient Population

Newly diagnosed cases of breast cancer patients at University Hospitals Case Medical Center (UHCMC) were recruited from January 2007 to July 2014 were approached for study participation via letter and then a phone call. Prior nonsurgical treatments for any cancer, other concurrent cancers, and/or known presence of a BRCA1 or BRCA2 mutation were the exclusion criteria. Our overall recruitment rate of eligible breast cancer patients was 82%. All participants provided informed consent that linked their survey responses to their medical records. The UHCMC institutional review board approved the study. From a total of 1,097 breast cancer patients participating in the study, the medical records for 118 patients could not be obtained. Two additional patients were excluded due to concurrent diagnoses of Paget's disease or Phyllodes tumor. The tumor grade for another 164 patients was unavailable, so they were excluded as well. The remaining 813 patients were included in this study.

Data Collection

The women enrolled in the study were asked about several lifestyle and demographic factors by phone survey based on the California Teacher's Study [8] baseline survey (<https://www.calteachersstudy.org/surveys.html>), and were asked to report on their lifestyle factors based on the two years prior to their diagnosis. The questions included self-reported race,

weight, height, family history of breast cancer, parity, breast cancer status, age, age of first period, age of first birth and use of hormone replacement therapy. Body mass index (BMI) was calculated from the self-reported weight and height prior to diagnosis. Physical activity was recorded as the self-reported average weekly hours of strenuous exercise and average weekly hours of moderate exercise. For each participant, medical records were reviewed in order to obtain tumor grade, ER, PR and HER2 status. If multiple concurrent tumors were present (N=3), the most advanced tumor was coded for this study.

Statistical Analysis

Tumor grade was treated as an ordinal variable (1, 2, or 3). Race, BMI, family history, parity, ER status, PR status, HER2 status, and hormone therapy were treated as categorical variables. Race was categorized into Caucasian, African American, and Other. BMI was categorized into <25.0, 25.0–29.9, and >29.9. Family history and parity were categorized into yes and no. ER, PR, and HER2 status were coded as positive or negative. The statistical significance of differences in demographic and clinical characteristics for each categorical variable by tumor grade was done using a chi-square test. Average weekly hours of moderate exercise, average weekly hours of strenuous exercise, average weekly hours of total exercise, BMI, age, age at first period, and age at first birth were treated as continuous variables. Mean values were calculated for each of these variables by tumor grade stratification, and the statistical significances of differences in means between the three tumor grades were calculated using a standard t-test. Additionally, the statistical differences in means were calculated using a standard t-test to compare Grades 1 and 2 (combined) against Grade 3 and Grade 1 against Grades 2 and 3 (combined). Missing data was treated as missing and subjects excluded from individual analyses. In order to assess the multivariate trend of increasing tumor grade with various demographic and clinical characteristics, we used a linear regression on tumor grade with all variables. Stepwise regression modeling was used to find the most parsimonious model.

It is well known that tumor grade varies by breast cancer subtype. Thus we repeated association analyses stratified by ER status as well as HER2 status. Further, given the well-documented differences in risk factors for pre- and post-menopausal breast cancers, we then repeated all statistical analyses stratified by menopausal status as well as hormone replacement therapy use. Associations were considered statistically significant if $p < 0.05$.

3. Results

Table 1 shows the characteristics of the study population overall and by tumor grade. As expected, there were a significant difference in tumor grade by ER status ($p < 0.0001$), PR status ($p < 0.0001$), HER2 status ($p < 0.0001$), race ($p = 0.01$), and age ($p < 0.0001$). Most participants in the study were white (84.2%) or African-American (14.2%). When we compared grades 1 and 2 (combined) against grade 3, there was a significant association between race and tumor grade ($p < 0.0001$) as well as age and tumor grade ($p < 0.0001$). When we compared grade 1 against grades 2 and 3 (combined), there was no significant association between race and tumor grade ($p = 0.08$), but there was a significant association

between age and tumor grade ($p<0.0001$). There were no differences in BMI, family history or exercise by tumor grade (Table 1).

We did not find any reproductive factors statistically significantly associated with tumor grade (Table 2). Similarly no statistically significant results were found when stratified by menopausal status (Supplemental Table 1), by post-menopausal hormonal therapy use (Supplemental Table 2), ER status (Supplemental Table 3) or HER2 status (Supplemental Table 4).

In multivariate modeling incorporating age, race, age of first period, BMI, family history, average weekly hours of moderate exercise, average weekly hours of strenuous exercise, average weekly hours of total exercise, average hours of sleep per night, number of births, number of pregnancies, and age of first birth, differences in tumor grade were statistically significant for age ($p<0.0001$), race ($p=0.033$), and sleep ($p=0.024$) only in the most parsimonious model. These three have been previously known to be associated with tumor grade, and further suggests no association of reproductive factors with tumor grade in our sample.

4. Discussion

Here we present results from the first study to look at the association between reproductive factors and breast cancer tumor grade. We did not find significant associations of tumor grade with any of the reproductive factors that we hypothesized might be associated with aggressiveness of tumors after adjusting for known associations. Other than our previous work on sleep duration and tumor grade, very few other studies have reported associations with tumor grade among breast cancer patients. A very recent study has shown that the 77 single nucleotide polymorphism polygenic risk score was associated with tumor grade, suggesting that genetics play a role in tumor aggressiveness [9].

Although not the focus of this study, it is interesting to note that we found the correlation of race and tumor grade to be strong in post-menopausal women but our data suggested no correlation of race and grade among pre-menopausal women. Similarly, there was a strong correlation of race and tumor grade in women who did not use hormone replacement therapy, but not in those who did use hormone replacement therapy. However, African-Americans have previously been shown to develop higher-grade tumors at all ages [3], and this is likely due to the small number of pre-menopausal African-Americans in our sample, since, as expected, African-Americans represent a higher proportion of the higher grade tumors even in the pre-menopausal subset.

Strengths of this study include the large sample size and fact that breast cancer patients were recruited soon after diagnosis to minimize recall bias. There are a few limitations that are present in this study. First, most of the data other than what was obtained from the patients' medical records is self-reported and is therefore prone to errors from recall or bias. Second, we did not investigate the association of all reproductive factors, such as breastfeeding, with tumor grade. Additionally, the racial distribution of the sample population is reflective of a

largely Caucasian population, and further research is needed in order to verify if similar associations are noted in larger African-American and other minority populations.

Another important consideration is that grade is an overly simplified measure of tumor aggressiveness. That said, few other markers are as well established as tumor grade for association with prognosis. Future studies would benefit from additional analyses investigating these factors with regard to other markers of aggressiveness, such as OncotypeDX scores. In our study, we did not find an association of any of these variables with OncotypeDX score (data not shown). However, with OncotypeDX scores available on only 146 of these patients, we are underpowered to detect these associations and make strong conclusions. Further, this data does not alter the conclusions of our manuscript, so we chose not to present it here.

Although this study does not suggest that reproductive factors are associated with tumor grade, studies in other populations, as well as studies exploring other hormonal and reproductive factors, such as breast feeding, related to tumor grade are needed. It is also important to note the tumor grade is just one measure of tumor aggressiveness. However, it is the most widely accepted and utilized measure of aggressiveness. Further studies will need to be done to investigate the association of reproductive factors with other markers of aggressiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty & Impact Statement

This manuscript presents the results from the first study to investigate the association of reproductive factors with tumor grade in breast cancer patients. Although previous studies have well established reproductive factors as playing an important role in breast cancer risk, this is the first to study how they relate to breast cancer tumor grade.

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Table 1

Description of Study Population and Covariates

	Everyone	Grade 1	Grade 2	Grade 3	p-Value	p-Value (Grades 1+2 vs. 3)	p-Value (Grade 1 vs. 2+3)
Age (years), mean (SD)	59.6 (±11.6)	61.9 (± 11.1)	58.9 (± 11.6)	55.1 (± 11.0)	<0.0001*	<0.0001*	<0.0001*
Race, N (%)							
Caucasian	681 (84.2)	162 (89.5)	328 (86.3)	191 (77.0)	0.0053*	0.0010*	0.084
African American	115 (14.2)	17 (9.4)	47 (12.4)	51 (20.6)			
Other	13 (1.6)	2 (1.1)	5 (1.3)	6 (2.4)			
BMI, mean (SD)	28.5 (± 6.7)	28.0 (± 6.1)	28.4 (± 6.6)	28.5 (± 7.1)	0.43	0.56	0.47
Family History, N (%)							
Yes	244 (30.2)	58 (32.0)	104 (27.4)	82 (33.1)	0.26	0.23	0.53
No	565 (69.8)	123 (68.0)	276 (72.6)	166 (66.9)			
ER Status, N (%)							
Positive	895 (82.3)	169 (94.4)	336 (89.1)	134 (54.0)	<0.0001*	<0.0001*	<0.0001*
Negative	192 (17.7)	10 (5.6)	41 (10.9)	114 (46.0)			
PR Status, N (%)							
Positive	792 (73.3)	151 (85.8)	293 (77.7)	120 (48.4)	<0.0001*	<0.0001*	<0.0001*
Negative	289 (26.7)	25 (14.2)	84 (22.3)	128 (51.6)			
HER2 Status, N (%)							
Positive	153 (17.4)	9 (5.3)	54 (15.0)	67 (28.3)	<0.0001*	<0.0001*	<0.0001*
Negative	727 (82.6)	161 (94.7)	305 (85.0)	170 (71.7)			
Exercise (average hours per week), mean (SD)							
Moderate	2.5 (± 2.7)	2.4 (± 2.5)	2.6 (± 2.7)	2.5 (± 2.8)	0.77	0.90	0.41
Strenuous	1.0 (± 2.1)	1.0 (± 1.8)	1.2 (± 2.2)	1.0 (± 2.2)	0.81	0.64	0.45
Total	3.5 (± 3.7)	3.3 (± 3.5)	3.7 (± 3.8)	3.4 (± 3.9)	0.72	0.63	0.34
Sleep Duration (average hours), mean (SD)	7.0 (±1.2)	7.2 (±1.2)	7.0(±1.3)	6.9(±1.2)	0.070	0.18	0.026*

Table 2

Reproductive Factors by Tumor Grade

	Everyone (N=813)	Grade 1 (N=181)	Grade 2 (N=382)	Grade 3 (N=250)	p-Value	p-Value (Grades 1+2 vs. 3)	p-Value (Grade 1 vs. 2+3)
Parity, N (%)							
Yes	669 (82.7)	144 (79.6)	322 (84.7)	203 (81.9)	0.29	0.67	0.21
No	140 (17.3)	37 (20.4)	58 (15.3)	45 (18.1)			
Age at First Period (years), mean (SD)	12.6 ($\pm$ 1.6)	12.5 ($\pm$ 1.4)	12.6 ($\pm$ 1.6)	12.7 ($\pm$ 1.6)	0.22	0.33	0.27
Age at First Birth (years), mean (SD)	25.2 ($\pm$ 5.4)	24.5 ($\pm$ 5.1)	25.5 ($\pm$ 5.5)	25.2 ($\pm$ 5.4)	0.36	0.99	0.094