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Does Nulliparity Influence Estrogen Receptor Status Among Women with Breast Cancer? A North Carolina Pilot Study

by

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ABSTRACT

Objectives: There is epidemiological evidence that reproductive factors and reproductive hormones are important in the incidence of breast cancer. Previous research has yielded consistent results on the effects of parity (previous births) and estrogen receptor (ER) status on women developing breast cancer. The aim of this study is to investigate the feasibility and utility of a larger study with North Carolina Central Cancer Registry patients to examine the association between parity and ER status among breast cancer patients. We did not examine the prognosis or survival of ER-positive versus ER-negative women.

Methods: This study employed convenience sampling techniques and examined the influence of parity on ER values among 1995 North Carolina breast cancer patients. Subjects included 103 women ages 32 to 87 years, living in three different regions of the state, who received treatment in 1995 in hospitals with cancer registries. Two groups were compared for statistically significant differences. The first group consisted of breast cancer patients who had one or more full-term pregnancies; the comparison group was composed of women with breast cancer who had not carried a pregnancy to full term. Our hypothesis was that positive ER status would be higher in the group with no full-term pregnancies, since they would have had uninterrupted ovulatory cycles and therefore more estrogen stimulation of their breast tissue, potentially leading to cancer. Measuring and comparing ER status in the two groups was a preliminary approach to test this hypothesis.

Results: The results suggest that, when women's age and stage of disease are controlled, there is a link between parity and ER status among North Carolina women with breast cancer.

Conclusion: We recommend another study with more subjects to further investigate the association found here between parity and ER status.

Introduction

The World Health Organization recently reported that breast cancer, a disease almost exclusive to females, has become the most frequently occurring cancer in women throughout the world.[1] This is also the case for both the United States and North Carolina. The North Carolina Central Cancer Registry estimates 5,660 new breast cancer cases occurred among North Carolina women in 1999. There were 1,163 deaths from breast cancer among North Carolinians in 1998. Breast cancer was the second major cause of cancer death among women, accounting for 7.6 percent of the state's cancer deaths and 1.7 percent of all deaths. North Carolina data from 1990 to 1997 indicate that about 65 percent of breast cancers were diagnosed at the in-situ or local stages.[2] Twenty-three percent of North Carolina women are Black. While breast cancer incidence rates are lower in this race group, the mortality rates are higher.[3]

Several risk factors for breast cancer have been identified. A family history of breast cancer is one of the strongest risk factors. Breast cancer risk increases with age, with rates greatest for women over the age of 50. Histories of ovarian or endometrial cancer are also known to be associated with increased breast cancer risk. Obesity, alcohol use, high-fat diets, and estrogen replacement therapy have been suggested as possible risk factors for breast cancer. Estrogen exposure is also a major risk factor for breast cancer. Increased estrogen responsiveness of breast tissue may enhance this effect.[4] The estrogen-associated risk factors include: early menarche or onset of menses (periods); late menopause; and nulliparity, or never having given birth.[5] Many women have one or more of these risk factors for breast cancer.

Estrogen helps women get pregnant and have babies. On the other hand, it is associated with breast cancer risk. The hormone's ability to cause cells to divide gives breast tissue more opportunity for genetic mutation. Therefore, estrogen can become a problem because it promotes cell growth and increases women's chances of acquiring further damage to cells. Studies of nulliparous women, who never carried a pregnancy to full term, showed increased breast cancer risk.[5] Pregnancy doesn't stop all estrogen production, but for most of the pregnancy estrogen levels are below what a menstruating woman would experience. It is thought that this results in a lower lifetime estrogen exposure for women who have had one or more full-term pregnancies than for those who have had none.[6] Women who had one or more full-term pregnancies would have had interruptions in their hormone cycles, leading to decreased estrogen stimulation. Therefore, their breast cancers may have arisen from a mechanism other than estrogen stimulation of breast tissue.

Methods

The research question is: "Does nulliparity influence estrogen receptor (ER) status among women with breast cancer?" Estrogen receptors are specific areas on a cell membrane that recognize the hormone. Estrogen receptor tests help physicians learn more about the cancer. Positive test results mean hormones help the cancer grow.[7] We hypothesize that women who have delivered children are less likely to have positive ER status, since a high number of full-term pregnancies has a demonstrated protective effect on breast cancer.[5]

Ten cancer registry hospitals (clusters) were selected for this study. A convenience sample of hospitals was chosen from a list of registry hospitals, depending on their ability to provide the required data. Patients were then randomly selected from each hospital, using a table of random numbers. Eligible subjects were defined as North Carolina registry hospital patients who were diagnosed with a histologically confirmed breast cancer in 1995. Clinical data (ER status, defined as positive or negative) and pregnancy data (parity) on the subjects were obtained from medical records.

Data for 175 patients were requested, and 155 reports were received from ten registry hospitals in the state. Fifty records were removed from the list for having incomplete clinical or pregnancy data before matching with the 1995 North Carolina Central Cancer Registry data. Matching of the 1995 breast cancer incidence patients and the 105 hospital reports was done using a SAS program, with matching on Social Security numbers and last names. After the matching process, two records were removed because they were duplicate cases.

The association between parity and ER status was examined overall, and after controlling separately for age, race, and stage of disease. There were 5,225 women diagnosed with breast cancer in North Carolina in 1995. About 25 percent of these cases involved women under

50 years age, in whom the disease tends to be more aggressive.[8] Since criteria of menopausal status vary widely, we used age 50 years and above as a definition of postmenopausal and under age 50 as a definition of premenopausal. There were 31 younger (premenopausal) women and 72 older (postmenopausal) women with known ER status in the study.

The hypothesis was tested at α=0.05 level using the SAS Cochran-Mantel-Haenszel test and one-sided significance level. With the reduced sample size of 103, the test had 67 percent power to detect the difference between a group 1 proportion of 0.500 and a group 2 proportion of 0.700.[9]

Results

The 103 subjects included 88 (85 percent) White women and 15 (15 percent) minority women – 14 of whom were Black. This is similar to the distribution of 84 percent White and 16 percent minority among all North Carolina breast cancer cases. The women ranged in age from 32 to 87 years, with a median age of 59. Thirty-one of the total 103 patients reported by various registry hospitals in North Carolina were under age 50. Seventy-two (70 percent) of the 103 women had positive ER status, 19 of whom had no children. Of the 103 selected women, 12 percent came from the Coastal region, 63 percent from the Piedmont, and 25 percent from the Mountain region of the state. The distribution of all breast cancer patients from the three regions is as follows: 24 percent Coastal, 52 percent Piedmont, and 24 percent Mountain. Statewide, 75 percent of the Central Cancer Registry's cases come from large hospitals (over 50 cases per year). Since registry hospitals were chosen according to their ability to provide the required data, 87 percent of the hospitals in the study had more than 50 breast cancer patients a year.

Table 1 shows the distribution of parity and ER results. The percentages with positive ER values for nulliparous (no full-term pregnancies) and parous (with pregnancies carried to full term) subjects are 86.4 and 65.4, respectively. Despite having a large percentage difference and a large odds ratio (OR=3.3, 95 percent Confidence Interval (CI)=0.96,11.72, p=0.059), the resulting p-value indicates that there is no statistically significant association between parity and ER results.

Table 1. Frequencies of 103 subjects according to parity and ER status

Estrogen Receptor Status	Parity	
	With Children	No Children
Negative ER	28	3
Positive ER	53	19
Percent Positive ER	65.4	86.4

A secondary analysis was performed after grouping patients by age and using age as a control for ER results. Table 2 shows the ER distribution for the subjects under 50 years old and ages 50 and over. Sixty-seven percent of the nulliparous women under 50 had positive ER values, whereas 64 percent of parous women in this age group had positive ER values. In the 50-and-over age group, the nulliparous women had 100 percent ER positivity and parous women had only 66 percent. A significant association between parity and ER status of the subjects was found when controlled for age (OR=3.8, 95 percent CI=1.02,14.27, p=0.047).

Table 2. Frequencies of subjects according to parity and ER status controlled for age

Estrogen Receptor Status	Parity	
	With Children	No Children
Under Age 50		
Negative	8	3
Positive	14	6
Percent Positive ER	63.6	66.7
Age 50 and over		
Negative	20	0
Positive	39	13
Percent Positive ER	66.1	100.0

Next, analysis was performed for two racial groups, White and Black. The justification for this grouping is that Black patients have been found to have lower hormone receptor levels than White patients.[10] There were 88 White and 14 Black women with known ER status. The distribution in Table 3 shows parity and ER values for White and Black women. Our analysis shows no statistically significant association between parity and ER status when controlled for race. The

proportion of subjects with positive ER status is considerably larger for subjects with no children in both racial groups; however, the results were not quite statistically significant (OR=3.3, 95 percent CI= 0.91, 11.65, p=0.068).

Table 3. Frequencies of subjects according to parity and ER status controlled for race

Estrogen Receptor Status	Parity	
	With Children	No Children
White		
Negative	24	3
Positive	45	16
Percent Positive ER	65.2	84.2
Black		
Negative	3	0
Positive	8	3
Percent Positive ER	72.7	100.0

Finally, we performed analysis after grouping patients by the stage of disease at diagnosis. There are four main stages of disease: in-situ, localized, regional, and metastasis. The four stages of disease were regrouped into two groups: early stage, including 7 in-situ and 77 localized cases; and late stage, including 10 regional and 7 metastasis cases. These two groups were used as a control to analyze ER results to see if there were ER status differences by stage. Table 4 shows the relationship between parity and ER for the two different stage groups

Table 4. Frequencies of subjects according to parity and ER status controlled for stage of disease

Estrogen Receptor Status	Parity	
	With Children	No Children
Early Stages		
Negative	23	1
Positive	44	16
Percent Positive ER	65.7	94.1
Late Stages		
Negative	5	2
Positive	7	3
Percent Positive ER	58.3	60.0

(early and late). When the test was controlled for stage of disease, the result showed a significant association between parity and ER (OR=3.9, 95 percent CI=1.05, 14.53, p=0.042).

Discussion

In this study, we performed simple statistical analyses to investigate the possible association between parity and ER status of breast cancer patients in North Carolina. While the data collected for this study failed to show an overall statistically significant association between parity and ER status, it was nearly significant and with more cases it may have been statistically significant.

A significant association between parity and estrogen receptivity was found among breast cancer patients when the study was controlled for age. Older women with no full-term pregnancies were at higher risk of having a positive ER status. Another statistically significant association was observed between parity and ER status of breast cancer patients when controlled for stage of disease, with a large difference occurring in women with early-stage disease. A previous study concluded that nulliparous women have a significantly increased risk of being diagnosed with an advanced breast tumor compared with parous women. This warrants increased efforts to achieve earlier diagnosis among nulliparous women with the hope of improving their prognosis.[11]

There was a modest but not statistically significant relationship between parity and ER status when controlled for race, with an odds ratio of 3.3 (95 percent CI=0.91,11.65). This is probably due to the small number of Black cases included in this study. Subjects with unknown ER status were not included in the study, further reducing the power of the statistical tests performed. These results may have been significant if we had had a larger group to study.

Estrogen receptor status has been linked with a woman's social class. In general, lower social class has been related to a higher intake of fat, and greater weight in both childhood and adulthood. A diet high in fat has been implicated in increased levels of estrogen along with other sex hormones, which is thought to contribute to the incidence of estrogen receptor tumors.[12]

Our results showed a statistically significant association between parity and ER status after controlling for age and stage of disease. However, the odds ratios were relatively large (>3) and consistent in size across all of the

analyses, suggesting a substantial association. Limitations of this study include the small sample size and lack of random sampling of the hospitals. We recommend performing another study using more subjects to investigate the association between parity and ER status. If there is a strong association, then further studies of estrogen suppression as a preventive measure for women at high risk for breast cancer would be warranted.

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