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Past Pregnancy Is Associated With Axillary Node Involvement in Women With Breast Cancer

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In 186 women with breast cancer, there was a progressive increase in the proportion of axillary nodal involvement as the number of pregnancies increased from zero to two or more ($P = 0.026$). Logistic regression analysis demonstrated that this effect was independent of the known relationship of age and tumor size to nodal involvement. Race and history of breast feeding had no influence on nodal involvement. *Cancer* 1992; 69: 981–983.

In women with invasive breast carcinoma, the presence or absence of metastases in axillary nodes is of paramount prognostic importance.[1] If there is no nodal involvement, the average 10-year survival rate is 74%. If there is nodal involvement, the 10-year survival rate drops to 30%.

There is a direct relationship between tumor size and the probability of axillary node involvement. When tumors are 1.0 cm or smaller in diameter, 26% of patients will have node involvement, whereas 80% of patients will have involved nodes for tumors larger than 10 cm.[2]

Age also is related to axillary node involvement.[3] Older women have fewer axillary node metastases. Of patients younger than 40 years of age, 49% have axillary node involvement, whereas only 42% of patients 70 years of age and older have tumor in their axillary nodes.[2]

In this report, a history of pregnancy is independently associated with axillary node involvement. The probability of involvement increases with the number of pregnancies.

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Methods

One hundred eighty-six women who received radiation therapy for breast cancer were examined between 1988 and 1991. Most of the women had early stage disease. Information on age, race, and number of pregnancies was obtained by questionnaire as part of a larger study. A registered nurse administered the questionnaires and clarified any questions that the patients did not understand. Tumor size was obtained from the surgical pathology report.

A patient was considered to have no axillary node involvement if the axilla was clinically negative (physical examination showed a false-negative rate of 27% to 32%)[4] or if an histologic examination showed no node involvement after axillary dissection.

The axillary nodes were considered to be involved only if demonstrated as such on histopathologic examination.

Results

There was a progressive increase in the proportion of women with axillary node involvement as the number of pregnancies increased from zero to two or more ($P = 0.026$) (Fig. 1).

To exclude the confounding effect that tumor size or age might have on node involvement, a logistic regression analysis was performed.[5] Number of pregnancies, tumor size, and age were the three independent variables. The results are shown in Table 1. The number of pregnancies had a significant effect on node involvement ($P = 0.026$) that was independent of tumor size and age.

There was no significant difference in the incidence of node involvement in white, black, or Hispanic women in this study (chi-square test = 1.084; $P = 0.6$). There was no significant difference in the incidence of

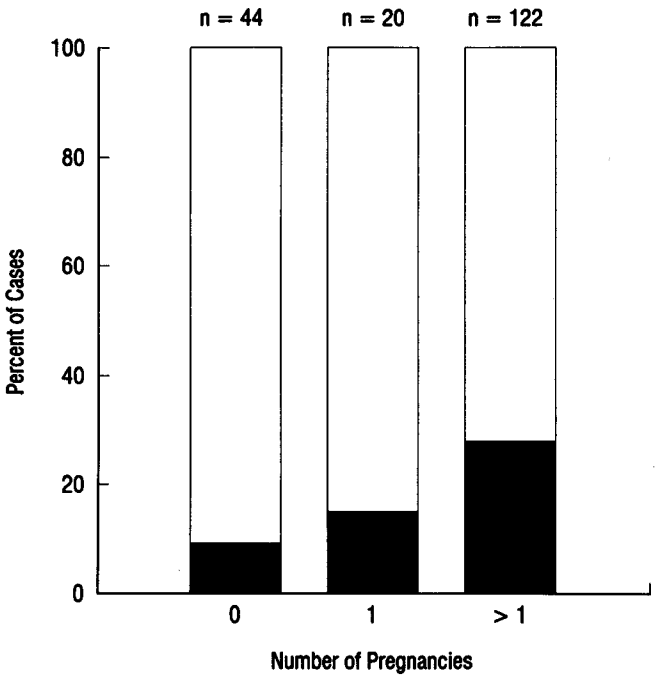

Figure 1. Percent of women with axillary node involvement *versus* number of pregnancies. Notice that a higher proportion of women had nodal involvement as the number of pregnancies increased. ■: Nodal involvement; □: no nodal involvement. Chi-square test = 7.28; $P = 0.026$.

node involvement in women who had or had not breast fed (chi-square test = 0.053; $P = 0.817$). In addition, parity was not significantly associated with node involvement (chi-square test = 2.1 with Yates correction; $P = 0.14$).

Discussion

Pregnancy, and especially early age at first full-term pregnancy, reduces the relative risk of breast cancer development. The relative risk is 1.98 for full-term delivery at 40 years of age *versus* 0.4 for full-term delivery at 15 years of age.[6]

However, in this study we found that there is a higher incidence of positive nodes in patients with prior pregnancies who have breast cancer. Moreover, the risk increases with the number of pregnancies.

Although the explanation for this phenomenon is not obvious, pregnancy does cause changes in the breast that might predispose to tumors of increased malignant potential. At the beginning of pregnancy, there is heightened vascularity and rapid growth and branching of mammary tissue.[7] Moreover, the mammary tissue is exposed to high levels of many hormones during pregnancy, among them prolactin, that may have a role in the genesis of breast cancer.[6]

Past pregnancy also might predispose to node metastasis because of the association of lactational mastitis, a common complication of nursing.[2] The resulting abscesses and node enlargement might create pathways in the breast favoring the spread of tumor to the axillary nodes. However, the fact that there was no difference in the incidence of node involvement in women who had and had not breast fed argues against this mechanism.

One might postulate that poor women, especially black women, tend to have more pregnancies. Also, black women usually are seen later and therefore tend to have larger breast tumors than white women. Based on these assumptions, women with more pregnancies would have larger primary tumors and more node involvement. However, according to the results of the logistic regression analysis, the effect of the number of pregnancies is independent of the primary tumor size. Furthermore, there was no significant difference in the incidence of nodal involvement among the white, black, and Hispanic women in this study.

A potential source of weakness in our study is the lack of histologic confirmation in all cases with no axillary node involvement. However, the results of the logistic regression analysis strongly confirm the well-documented effects of age and tumor size on node involvement. Therefore, it is reasonable to assume that the methods used to determine axillary node involvement were reliable.

Table 1. Maximum Likelihood of Fit of a Binary Logistic Regression Model to Node Involvement in 186 Women With Breast Cancer

Factor	Logistic coefficient	Standard error	Significance (*P* value)	Odds ratio
No. of pregnancies	0.622	0.2793	0.026*	1.8627
Tumor size	0.4497	0.1394	0.0013	1.5679
Age	−0.0323†	0.0155	0.0378	0.9682

* Notice that the effect of pregnancy was significant ($P = 0.026$) and independent of the effects of tumor size and age.

† The negative coefficient for age (−0.0323) indicates that the incidence of nodal involvement goes down as age increases.

Multiple risk factors are known to predispose women to breast cancer: early menarche, late menopause, nulliparity, no lactation, gain in adult body mass, family history of breast cancer, and age.[6,8] Of these, body mass and age also are known to be prognostic factors.[9–11] And, although cigarette smoking is not a risk factor,[12] it is associated with node involvement.[3]

An additional prognostic factor is parity. Nulliparity is strongly associated with a poorer 5-year survival rate, but only in Stage III disease.[13] Nulliparity is not related to survival in early stage disease.

There is great interest in identifying other prognostic factors for breast cancer.[14] Among these factors are cathepsin D,[15] Neu-protein overexpression,[16] tumor progesterone receptor level, haptoglobin-related protein,[17] aneuploidy and percent S-phase,[18] and tumor epidermal growth factor receptors.[19]

The results presented here suggest that the number of pregnancies may affect the risk of node involvement. Thus, it should be determined whether there is any correlation with the number of pregnancies and the above biochemical and cellular phenomena. Moreover, the prognostic significance of the other risk factors cited above should be studied further because these also may be predictive of outcome and could be much more easily and economically assessed than the biochemical prognostic factors now receiving so much attention.

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