Reprinted from CANCER, Vol. 76, No. 3, August 1, 1995
Published by Lippincott–Raven Publishers Printed in U.S.A.

Reproductive History and Prognosis in Patients with Operable Breast Cancer

Recently, Korzeniowski and Dyba[1] reported that pregnancy has an adverse effect on breast cancer prognosis. Further, pregnancy is associated with a poor prognosis in women with breast cancer, even years after the pregnancy has occurred.[2] In addition, we have reported that a history of pregnancy is independently associated with axillary lymph node involvement.[3] Our finding has recently been corroborated twice[4,5] and not confirmed once.[6] Moreover, others have found an increased incidence of lymph node involvement in pregnant women with breast cancer.[7]

A circulating tumor marker, lipid-associated sialic acid in plasma (LASA-P), is abnormally increased in plasma and serum of patients with gynecologic malignancies, including breast cancer.[8–10] LASA-P levels reflect alteration in the surface membrane of tumor cells. The LASA-P assay measures total gangliosides and glycoproteins.[9]

We measured LASA-P in a group of women with benign and malignant breast tumors. We now report that LASA-P is increased in the plasma of women with breast tumors who have been pregnant. Our finding confirms the findings of Korzeniowski and Dyba,[1] and suggests that pregnancy may alter the surface membranes of neoplastic cells, increasing their malignant potential.

We studied 207 women with benign and malignant breast tumors operated in Mount Sinai Medical Center between 1991 and 1994. Cases were selected for study if the number of pregnancies was known and LASA-P had been measured.

Plasma specimens to be assayed for LASA-P were collected in tubes containing ethylenediamine tetraacetic acid and frozen until tested. Lipid-associated sialic acid in plasma was determined by the procedure of Katopodis and Stock.[11] Dianon Systems (Stratford, Connecticut) performed all assays. Statistical analysis was done with the SPSS System.[12]

The average age of the 207 women studied was 48.5. The youngest woman was 16, and the oldest was 84. The average number of pregnancies was 2.4; the minimum number of pregnancies was 0 and the maximum was 10.

The concentration of LASA-P rose with the number of pregnancies in women with both benign and malignant tumors ($P = 0.0046$, one way ANOVA; Fig. 1). The mean age also varied in the patient groups. Women with benign breast tumors tended to be younger. Because LASA-P levels rise with age, we analyzed our data using multiple linear regression. Benign versus malignant, number of pregnancies, and age were the three independent variables (Table 1). Pregnancy had a significant effect on LASA-P levels ($P = 0.015$) that was independent of the effects of age ($P = 0.008$) and benign versus malignant ($P = 0.31$).

Pregnancy causes changes in the breast that might predispose to tumors of increased malignancy. At the beginning of pregnancy, there is heightened vascularity, as well as rapid growth and branching of mammary tissue.[13] Moreover, the mammary tissue is exposed to high levels of many hormones

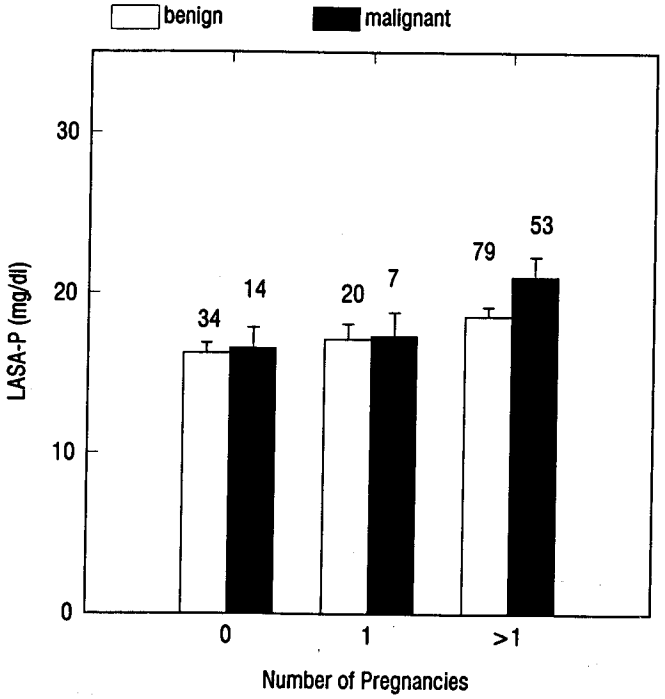

Figure 1. The number of pregnancies and LASA-P levels (mean + SEM) in women with benign and malignant breast tumors. The number of women in each group is indicated above the corresponding error bar.

during pregnancy, among them prolactin, which may have a role in the genesis of breast cancer.[13]

We hypothesize that the increased malignancy of breast cancers associated with pregnancy is due, at least in part, to changes in the tumor surface membranes resulting from high hormone exposure, reflected by the increase in circulating LASA-P. Indeed, the epidermal growth factor receptor, a powerful prognostic factor in breast cancer, is a specific cell membrane receptor.[14] Also, vasoactive intestinal peptide and somatostatin, which have a wide range of biologic activities, bind to tumor cell membrane receptors.[15] Further study may lead to characterization of the exact nature of the cell membrane changes associated with pregnancy, and perhaps to better methods of breast cancer prevention and treatment.

Table 1. Multiple Linear Regression Analysis of the Effect of the Number of Pregnancies on Lipid-Associated Sialic Acid in Plasma, Controlling for the Effects of Age and Histology

Variable*	Regression coefficient	Standard error	*t* test	*P* value
Pregnancy†	1.26	0.513	2.46	0.015
Histology‡	0.96	0.93	1.02	0.31
Age	0.09	0.033	2.70	<0.0001

* The variables had a significant effect overall ($F = 7.61$, $P = 0.0001$).
† Number of pregnancies: 0, 1, or <1.
‡ Benign versus malignant.

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