

# Diminished Ratio of Estrogen Receptors to Progesterone Receptors in Breast Carcinomas of Women Who Have Had Multiple Miscarriages

STEVEN LEHRER, M.D., EVA LEVINE, M.S., PENNY SAVORETTI, R.N., JOAN CROPLEY, R.N., JACK DALTON, M.D., H. K. SONG, M.D., SWAN N. THUNG, M.D., JACK RABINOWITZ, M.D., AND LYNDA MANDELL, M.D.

## Abstract

We examined the relationship of a history of miscarriage to the ratio of tumor estrogen receptors to progesterone receptors in 74 women with breast carcinoma evaluated between 1988 and 1990. Only women who had been pregnant and whose tumor contained both estrogen and progesterone receptors were included. Women with breast carcinoma and a history of two to four miscarriages had significantly lower ratios ( $<1$ ) of tumor estrogen receptors to progesterone receptors than women with a history of zero or one miscarriage ( $>1$ ). This finding may be the result of a genetic anomaly in breast cancer patients that also affects the uterine environment during the reproductive years.

MANY STUDIES have shown that risk factors for the development of breast carcinoma affect tumor estrogen receptor (ER) levels. Among these factors are late age at first full-term pregnancy (1), history of benign breast disease (2), nulliparity (3), history of breast feeding (3), race (4), age at diagnosis (4-6), history of oophorectomy (7), use of oral contraceptives (7, 8), and body weight (9).

Pike et al. (10) and Hadjimichael et al. (11) have shown that abortion, whether spontaneous (miscarriage) or induced, poses a risk for the development of breast carcinoma. In addition, Brinton et al. (12) demonstrated that multiple miscarriages were also a risk factor.

In this study, we examined the relationship of a history of miscarriage to the ratio of tumor estrogen receptors to progesterone receptors in women with breast carcinoma.

## Materials and Methods

All the women in this study had been referred for therapy of a primary breast carcinoma. A registered nurse administered a questionnaire to the patients to obtain historical and clinical data. ER and progesterone receptor (PR) levels were determined with a commercially available dextran-coated charcoal assay kit (Rianen Assay System, Dupont Medical Products, N. Billerica, MA). The kit works by titrating binding sites in the tumor cytosol with increasing concentrations of tritiated estradiol or R5020, a synthetic progestin. Separation of the tightly bound receptor-hormone complexes from unbound steroid is achieved by adsorption of the free material onto dextran-coated charcoal. After centrifugation, the supernatant is decanted and counted. Scatchard plot analysis of the specific binding data is used to determine binding capacity and affinity.

The 74 women in this study were evaluated between 1988 and 1990. Only women who had been pregnant, and whose tumor contained both ER and PR, were included. Statistical analysis was performed with Student's *t*-test (pooled variance analysis) or Welch's *t*-test (separate variance analysis).

From the Department of Radiation Therapy and the Stratton-Popper Department of Pathology (SNT), Mount Sinai School of Medicine (CUNY), New York, NY. Address reprint requests to Steven Lehrer, M.D., Radiation Therapy Department, Box 1236, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

**Results**

Of the pregnancies in this study, 22% ended in miscarriage. There was a significantly lower tumor ER/PR ratio in breast cancer patients with a history of two to four miscarriages ( $p = 0.010$  two-tailed; see Fig. 1). There was, however, no difference in the levels of ER or PR alone (Fig. 2). We have analyzed square root (ER/PR) to normalize the distribution. Note that in breast cancer patients with a history of zero or one miscarriage, the ratio is greater than one, whereas in patients with a history of multiple miscarriages the ratio is less than one. This dichotomy was chosen because habitual abortion is broadly defined as the loss of two or more pregnancies before fetal viability (13).

Because ER/PR ratio is correlated with age (see Fig. 3), we examined the association of age of the breast cancer patients with multiple miscarriages. No relationship was found (Fig. 4).

**Discussion**

Miscarriage is common during pregnancy. Mills et al. found that recognized miscarriage occurs in 16% of normal pregnancies (14). Wilcox et al. found that recognized miscarriage occurs in 12% of normal pregnancies (15). But the 22% miscarriage rate we report here in women with breast cancer is relatively high compared with the normal rate.

Multiple studies have demonstrated a need for estrogen in early pregnancy. Ravindranath and Moudgal inhibited pregnancy in bonnet monkeys by administering tamoxifen, an antiestrogen, during the postovulatory period (16). Furr et al. (17) found that if tamoxifen was orally administered to rabbits on day 10 after implantation, fetal resorption resulted. Later tamoxifen treatment caused a significant reduction in the length of gestation and number of live young born. Because estrogen is necessary in early pregnancy,

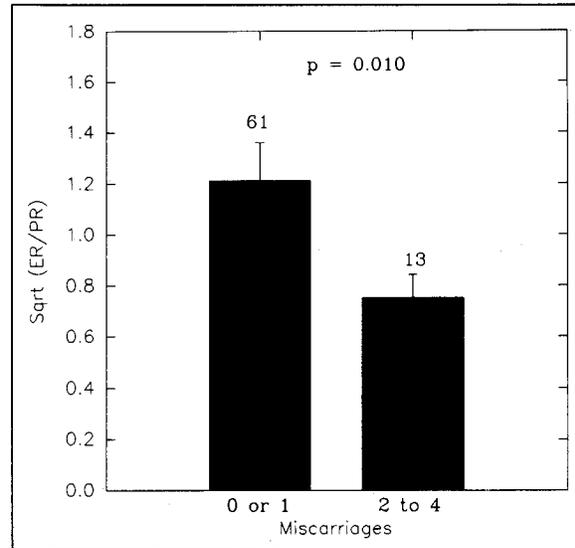


Fig. 1. Effect of miscarriage on square root of ratio of estrogen receptors to progesterone receptors (Sqrt [ER/PR]). Women with a history of 2 to 4 miscarriages had a lower Sqrt (ER/PR) than women with a history of 0 or 1 miscarriage (separate variance estimate) (mean  $\pm$  SEM).

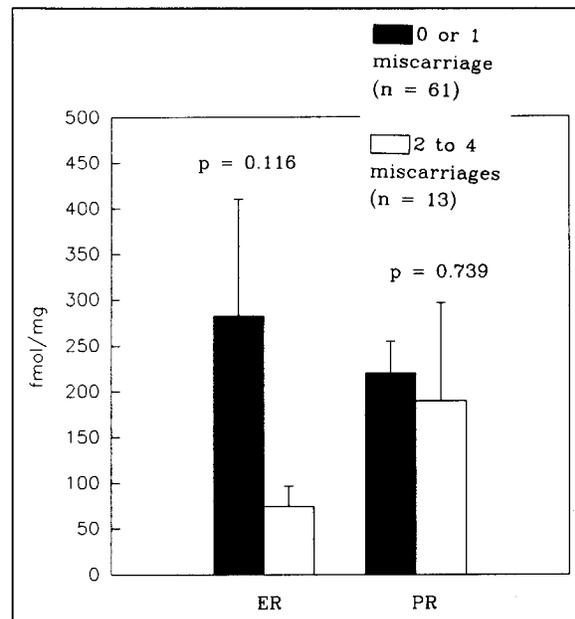


Fig. 2. Effect of history of miscarriage on ER or PR levels alone (Student's *t*-test) (mean  $\pm$  SEM).

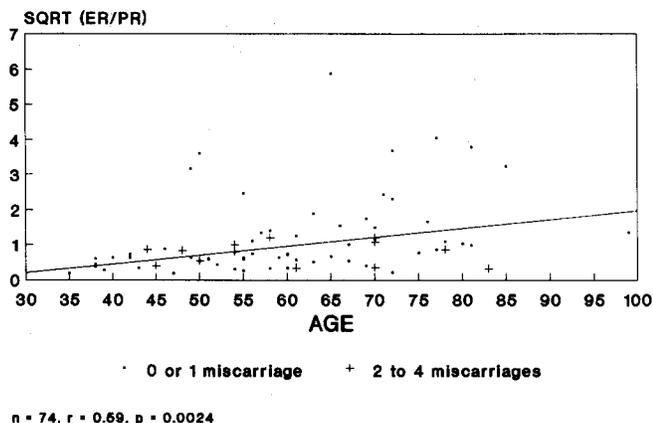


Fig. 3. Effect of age on ratio of estrogen receptors to progesterone receptors in breast cancer. Sqrt (ER/PR) measured in breast cancers increases with age.

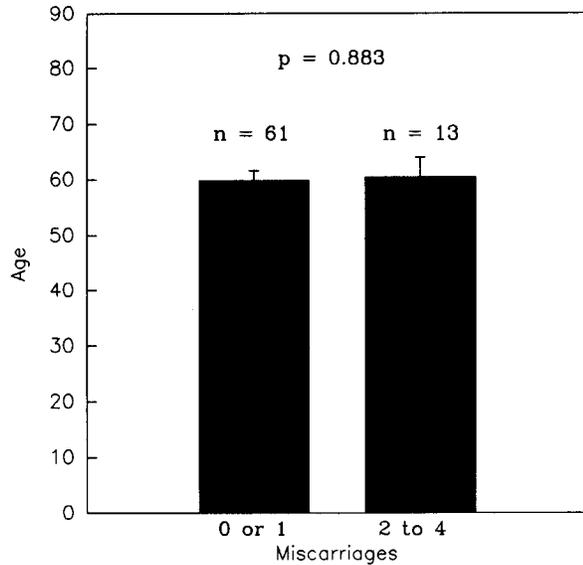


Fig. 4. Influence of history of miscarriage on age of breast cancer patients (Student's *t*-test) (mean  $\pm$  SEM).

the ER, too, must play an important role in pregnancy maintenance.

There is evidence that naturally occurring variations in the structure of the ER gene can affect its function. Hill et al. (18) examined a single, two-allele restriction fragment length ER polymorphism in human breast carcinoma cell lines and human breast tumor biopsy specimens. Their studies showed an association between absence of one allele and absence of ER expression.

There is a high incidence of miscarriage in women with breast carcinoma (10–12). Moreover, our finding of diminished ER/PR ratio in the breast carcinomas of women with a history of two to four miscarriages suggests that an ER anomaly might be responsible for the diminished ER/PR ratio and the miscarriages, since the synthesis of PR is controlled by ER (19). One such anomaly has already been identified (20).

The findings in this study suggest that the ER/PR ratio in the breast tumors reflects the uterine environment. This is not surprising because the same genes control synthesis of both uterine and breast tumor ER and PR. Furthermore, our findings imply that PR level, in addition to being controlled by ER, is regulated by a feedback mechanism. Some breast cancer patients have a genetic change that resets this mechanism and diminishes the ER/PR ratio, thus predisposing to miscarriage during the reproductive years and to breast cancer later.

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