

*RE: "RISK OF MISCARRIAGE AND A COMMON VARIANT OF THE ESTROGEN RECEPTOR GENE"*

Drawing upon reports from our laboratory, the study by Taylor et al. (1) formally tested the hypothesis that a silent polymorphism in the estrogen receptor (ER) gene is associated with a high risk of miscarriage. As they noted, in their small sample, they saw a weak association between the polymorphism and miscarriage (odds ratio = 1.8). Therefore, they concluded that this genetic marker is not associated with miscarriage risk and hence "provides little reason for further investigation" (1, p. 1361).

Our original report associating a history of miscarriage with the ER polymorphism dealt only with women who had ER-positive breast cancer (2). After setting up a polymerase chain reaction-based assay, we extended our studies to include women with ER-negative breast cancer and older women without cancer (3). In 1991 we reported, in both meeting abstract form and an oral presentation (and communicated to Dr. Taylor in several telephone conversations), that the observed association between the ER polymorphism and a history of miscarriage was restricted to women with ER-positive breast cancer (4). A more complete presentation of that finding has now been published (5); regrettably, its publication was delayed by the untimely death of the journal's Editor-in-Chief.

Our findings led us to conclude that the ER variant allele must be interacting with a variant allele of a second polymorphic gene, since we saw no evidence for an association between the ER polymorphism and miscarriage in women with ER-negative breast cancer or in older women without breast cancer (table 1). Thanks to the efforts of Dr. Taylor and his colleagues, we learned that our original report of two mutations was an error, and that, indeed, we were dealing with a silent mutation (6, 7). However, this genetic marker, together with a history of miscarriage, appears to identify a specific subgroup of women with breast cancer. Therefore, we suggest that future studies on breast cancer risk make use of this information.

REFERENCES

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**TABLE 1. Pregnancies and miscarriages as a function of estrogen receptor (ER) B genotype† in control women without breast cancer, estrogen receptor-positive (ER+) breast cancer patients, and estrogen receptor-negative (ER-) breast cancer patients, all of whom had been pregnant at least once‡**

Group	No. of subjects	No. of pregnancies	No. of miscarriages	% of pregnancies ending in miscarriage
Control BB	138	405	82	20.2
Control BB'	14	44	6	13.6
ER- BB	15	56	9	16.1
ER- BB'	14	41	4	9.8
ER+ BB	67	206	32	15.5
ER+ BB* <sup>*</sup>	20	77	27	35.1
Total	268	829	160	

\* This group differed significantly from the other five groups (at the 0.05 level) by the Tukey B multiple range test.

† BB', heterozygous for polymorphism; BB, homozygous wild type.

‡ The percentage of pregnancies ending in miscarriage was highest among women with the polymorphism (BB') with ER-positive tumors ( $p = 0.0035$  by Kruskal-Wallis one-way analysis of variance, corrected for ties). Adapted from Lehrer et al. (5).

human estrogen receptor (ER) gene is associated with a history of spontaneous abortion in women with ER positive breast cancer but not in women with ER negative breast cancer or women without breast cancer. In: Program and Abstracts of the 73rd Annual Meeting of the Endocrine Society, June 1991. Washington, DC: Endocrine Society, 1991:29.

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*THE FIRST TWO AUTHORS REPLY*

We appreciate the confirmation by Drs. Schachter and Lehrer (1) of our finding that the "silent" estrogen receptor (ER) polymorphism at codon 87 does not appear to increase overall risk of miscarriage (2). The data they present in table 1 for control and ER-negative breast cancer certainly support this lack of association—in fact, patients with the silent variant had lower rates of miscarriage. Taken as a whole, the data suggest that women who carry the variant are not at increased risk of miscarriage or of developing either ER-positive or ER-negative breast cancer.

Whether polymorphisms of the ER gene have other biologic effects is, of course, an intriguing and important question. The unequal risks of miscarriage across gene and disease categories in table 1 may be real, or they may be a consequence of the imprecision and bias that so easily

distort data on miscarriage risk. Until there is some replication of the association in other populations, we remain skeptical about the likelihood of a genetic basis for the observed difference in history of miscarriage among women with ER-positive breast cancer.

## REFERENCES

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