

# Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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S Lehrer, J Rabin, T Kalir and BS Schachter

*Hypertension* 1993;21:439-441

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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## Estrogen Receptor Variant and Hypertension in Women

Steven Lehrer, Jill Rabin, Tamara Kalir, and Beth S. Schachter

Eighty-eight women visiting a gynecologist were tested for an estrogen receptor B-variant allele. The women were ethnically and racially homogeneous to a large degree. They were from a suburb of Long Island, and most were white. The 12% incidence of hypertension in women with the estrogen receptor wild-type allele is comparable to the 13–32% incidence in the general population of women aged 55–64 years. However, the 48% incidence of hypertension in women with the estrogen receptor B-variant allele is considerably higher than in the general population of women in this age group. We conclude that the presence of the estrogen receptor B-variant allele might have increased the prevalence of hypertension in the women in this study. (*Hypertension* 1993;21:439–441)

**KEY WORDS** • receptors, estrogen • hypertension, essential • polymorphism (genetics)

The prevalence of hypertension in men and women is different and depends on age. In subjects aged 25–54 years, hypertension is more prevalent in men; but in subjects older than 54 years, hypertension is more prevalent in women.<sup>1</sup> At least one gene has been implicated in the genesis of hypertension.<sup>2</sup>

We recently documented the existence of a variant allele of the human estrogen receptor (ER) gene. We reported that women with breast cancer and this variant allele had a high incidence of spontaneous abortion.<sup>3</sup>

The variant gene differs from the wild-type gene within the B domain.<sup>4</sup> A single point mutation, a guanine-to-cytosine transition at position 261, causes a silent mutation in codon 87.<sup>5,6</sup> Of interest is the fact that the unmutated sequence, GCG, codes least frequently for alanine in humans (7.1% of cases); the silently mutated codon GCC codes most frequently (29.5% of cases).<sup>7</sup> No doubt another mutation, segregating with the silent mutation, plays a role in producing the high incidence of spontaneous abortion.

We now report that the ER B-variant allele is associated with hypertension in women. Furthermore, women with the variant allele are significantly younger than those without the variant.

From the Department of Radiation Therapy (S.L.), Department of Pathology (T.K.), Department of Obstetrics, Gynecology, and Reproductive Science (B.S.S.), Department of Cell Biology and Anatomy (B.S.S.), Mount Sinai Medical Center, and the Department of Obstetrics and Gynecology (J.R.), Long Island Jewish Medical Center, New York.

Funded by grants CA 49506 and HD 27557 from the National Institutes of Health, Bethesda, Md., as well as a grant from the Edgar McCoubrey Foundation. Additional support provided by the Department of Obstetrics, Gynecology, and Reproductive Science and by the Department of Cell Biology and Anatomy, Mount Sinai School of Medicine, New York.

Address for reprints: Dr. Steven Lehrer, Radiation Therapy Department, Box 1236, Mount Sinai Medical Center, New York, NY 10029.

Received June 9, 1992; accepted in revised form November 19, 1992.

### Methods

To identify the B-variant, we used the polymerase chain reaction to amplify genomic DNA around the polymorphic region of the ER gene, followed by allele-specific oligonucleotide hybridization. This analysis used DNA obtained from blood lymphocytes of women, as we have described.<sup>8</sup> Both the wild-type and variant alleles were specifically identified in the genotyping.

Eighty-eight women of all ages visiting a gynecologist were studied. Women were excluded if they had cancer or other serious illness. A nurse or physician made a single measurement of blood pressure. The technicians genotyping the blood lymphocyte DNA were blinded as to the blood pressure status of the patients. The women were ethnically and racially homogeneous to a large degree. They were from a suburb of Long Island, and most were white. None of the women who were approached refused to participate in the study.

A woman was classified as hypertensive if she had a systolic blood pressure  $\geq 140$  mm Hg and a diastolic blood pressure  $\geq 90$  mm Hg or if she was being treated for hypertension with antihypertensive medications. She was classified as borderline (isolated systolic hypertension) if she had a systolic pressure  $\geq 140$  mm Hg and a diastolic pressure  $< 90$  mm Hg and was not receiving antihypertensive medications.

### Results

There was a significantly increased incidence of hypertension (including borderline) in women with the ER B-variant allele (Figure 1). The 12% incidence of hypertension in women with the ER wild-type allele is comparable to the 13–32% incidence in the general population of women aged 55–64 years.<sup>1</sup> However, the 48% incidence of hypertension in women with the ER B-variant allele is considerably higher than in the general population of women in this age group.<sup>1</sup> Five women were receiving estrogen replacement therapy, but only one of these women was hypertensive. In addition, women with the ER B-variant were signifi-

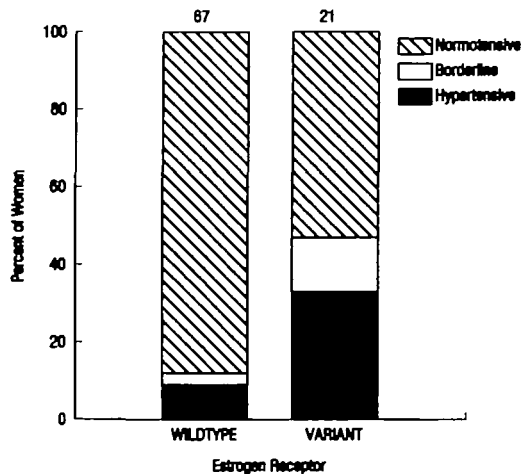


FIGURE 1. Bar graph shows incidence of hypertension in 67 women with the estrogen receptor (ER) wild-type allele and 21 women with the ER B-variant allele. Note that the incidence of hypertension is significantly higher in women with the ER B-variant than in women with the wild-type allele ( $\chi^2=12.6$ ,  $p=0.002$ ).

cantly younger than women with the wild-type allele, although there was no significant difference in body mass index of the two groups (Figure 2). All women carrying the ER variant allele were heterozygous for it.

Hypertension is influenced by race, with more hypertension being found in blacks.<sup>1</sup> However, race did not significantly affect the elevated blood pressures of the ER variant women in the present study. Only one of the ER variant women with borderline hypertension was black. None of the ER variant women with nonborderline hypertension was black.

Analysis of the data in Figure 1<sup>9</sup> indicates that presence of the ER B-variant allele increases the risk of hypertension in women, including borderline (odds ratio, 6.7; 95% confidence interval, 2.3–22;  $p=0.001$ ).

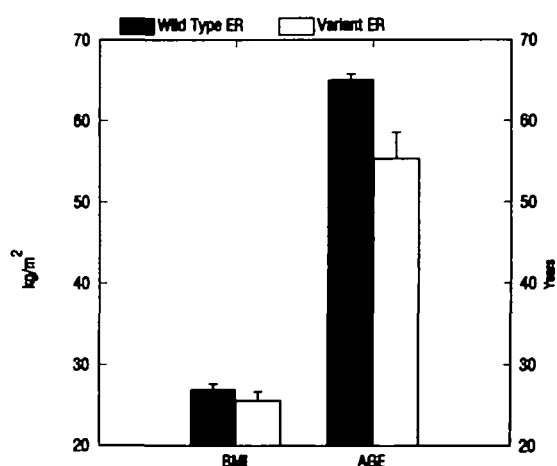


FIGURE 2. Bar graph shows mean (SEM) age and body mass index (BMI) of 67 women with the wild-type estrogen receptor (ER) allele and 21 women with the variant allele. Note that women with the variant allele were significantly younger than those with the wild-type allele ( $t=2.81$ ,  $p=0.01$ , separate variance estimate). There was no significant difference in BMI in the two groups ( $p=0.15$ ).

## Discussion

Hypertension in women and the cardiovascular disease to which it contributes are major health problems. Men aged 35–84 years have approximately twice the incidence of heart disease as women. This sex gap tends to diminish at the upper end of the age range because of a precipitous rise in the incidence of heart disease in women after age 45. In addition, there is a higher death rate in women than men after a myocardial infarct (32% versus 27%).<sup>10</sup> Although factors such as high serum lipid levels, diabetes, and obesity contribute to the death rate, hypertension is a very important component.<sup>11</sup>

The silent ER variant described in this article might cosegregate with a second ER mutation associated with hypertension. The association would not be surprising because oral contraceptive use is linked to elevated blood pressure.<sup>12</sup> Furthermore, the hypertension, and perhaps other associated problems, could be responsible for the diminished mean age of the women with the silent ER polymorphism. In other words, the second mutation might confer a survival disadvantage.

The results of this investigation could be strengthened by additional studies. For example, another genetic allele in the population might be analyzed to be certain that it also did not associate with hypertension. ABO blood group would be a good candidate because it is not known to be linked with hypertension.

A second, more racially homogeneous population might also be studied because the observed age difference in women with and without the B-variant allele might be explained by population stratification; that is, the younger women with hypertension and the variant allele might be from a different ethnic background and display different gene frequencies than the older women without the allele. Moreover, the ER B-variant allele and hypertension might be analyzed by linkage analysis in families to confirm the specificity of the association.

Finally, locating and characterizing the second mutation would be a worthwhile endeavor. The characterization could lead to a better understanding of hypertension in women and perhaps to better forms of therapy.

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