A CYP1A1 Restriction Fragment Length Polymorphism Is Associated with Breast Cancer in African-American Women

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Abstract

We examined the role of CYP1A1 polymorphisms as potential molecular markers of breast cancer susceptibility in Caucasian and African-American women. The case-control study involved 51 women with breast cancer and 269 female controls. In African-Americans, the frequency of the homozygous MspI polymorphism was 3.5% in controls and 19% in breast cancer cases. The odds ratio of breast cancer with the MspI homozygous variant was 9.7 (95% confidence interval: 2.0–47.9). This association was not observed in Caucasian women. The exon 7 and AA polymorphisms were not associated with breast cancer in either group. The mechanism for the observed association between the MspI polymorphism and breast cancer is unclear. It is possible that the CYP1A1 MspI RFLP is linked with other polymorphisms in the African-American population, either in the CYP1A1 gene, which is involved in estrogen metabolism, or other genes related to risk of breast cancer.

Introduction

Three polymorphisms have been described in the human CYP1A1 gene: a MspI RFLP in the 3'-noncoding region (1), an adenine to guanine transition in the heme-binding domain of exon 7 (2), and an African-American-specific RFLP in intron 7 (3). The frequency of each of these polymorphisms varies as a function of race (4). The African-American-specific RFLP is associated with an increased risk of adenocarcinoma of the lung (5). Estrogens have been implicated in both initiation and promotion of breast cancer. Most of the known risk factors for breast cancer are linked to an increased lifetime exposure to endogenous and/or exogenous estrogens (6). The oxidative metabolism of estradiol follows two mutually exclusive pathways, 2 and 16 hydroxylation, with opposite biological properties. The 2-hydroxylated (C-2) metabolites are devoid of peripheral biological activity (7), and the 16-hydroxylated (C-16) metabolites are estrogen agonists (8). Estrogen metabolism is partially determined by cytochrome P450 activity and is under the genetic control of both the CYP1A1 and CYP1A2 genes. Polymorphisms in these genes may influence the degree of estrogen C-2 hydroxylation and therefore individual susceptibility to breast cancer. We decided to examine CYP1A1 polymorphisms as potential molecular markers of breast cancer susceptibility in Caucasian and African-American women.

Materials and Methods

Study Population. The case-control study involved 51 women with breast cancer (21 African-Americans, 30 Caucasians) identified through a cohort study of women attending a screening clinic in New York City (9). Two hundred sixty-nine female controls (86 African-Americans, 183 Caucasians) were identified from a pool of over 500 healthy volunteers, recruited from the community living in the eastern United States. All the women answered a brief, standardized, self-administered questionnaire and provided a 10-ml blood donation from a peripheral vein. Written informed consent was obtained for each participant at the time of blood donation. Random codes were assigned to the samples before delivery to the laboratory, and all genotype analyses were conducted double blind. The odds ratio and 95% confidence intervals were calculated as a measure of the association between CYP1A1 genotype and breast cancer. This analysis was conducted first for each polymorphism separately, without taking into consideration whether two or more polymorphisms might occur in a single individual, and then for all the possible combinations of the three polymorphisms. Complete genotype was available for 20 African-American cases and 81 African-American controls, and for 29 Caucasian cases and 175 Caucasian controls.

Laboratory Methods. High molecular weight genomic DNA was isolated from lymphocytes and blood clots. Peripheral blood lymphocytes were isolated, and DNA extracted as described previously (4). Genotyping by PCR was performed using primers and conditions as described previously (5).

Results and Discussion

The mean age of the cases was 54.9 ± 7.7 years (range, 20–69), of the controls 43.3 ± 13.4 years (range, 29–70). The prevalence of ever smokers was 45.1% among controls and 55.3% among cases. Smoking was more frequent among Caucasian (61%) than among African-American (47%) cases.

The frequency of the three polymorphisms among controls of both ethnic groups was similar to what was observed in a previous study including a larger population of healthy volunteers (10). The frequency of the homozygous MspI polymorphism was significantly associated with breast cancer in African-American (odds ratio: 9.7; 95% confidence interval: 2.0–47.9) but not in Caucasian women (Table 1). The other two polymorphisms (exon 7 and AA) were not associated with breast cancer in either group. There are many possible alleles of the CYP1A1 gene resulting from the three polymorphisms. The most frequent genotype among Caucasians (usually termed “wild-type”), is actually present in less than one-half of Asians (4) and African-Americans (Table 1). An alternative approach to the description of CYP1A1 genotypes as normal or mutant for 2 or 3 separate polymorphisms is to consider the composite genotype containing combinations of the 8 possible alleles resulting from the three possible polymorphisms. We assessed the impact of combinations of the three polymorphisms on breast cancer risk by evaluating the composite genotype of the CYP1A1 gene, as shown in Table 2. The homozygous variant Msp I RFLP, present alone, was significantly associated with breast cancer in African-American women. The association between breast cancer and the MspI polymorphism was not modified by smoking status.

The MspI polymorphism has been associated with lung cancer (1) and in situ colon cancer (11) in Japanese but not in Caucasian populations. A recent study including Caucasians only did not show any association between the MspI RFLP and breast cancer (12). In Asians and Caucasians, the MspI RFLP, which is located in the
3'-noncoding region of the gene, was found to be associated with the exon 7 polymorphism (13). We have demonstrated that the exon 7 polymorphism has a role in gene function (14) by increasing both enzyme activity and mRNA levels. However, in other work (10), we have found that in African-Americans, all of the CYPIAI polymorphisms occur independently, without any association between the MspI RFLP and the functional polymorphism in exon 7. Therefore, the mechanism for the observed association between the MspI polymorphism and breast cancer is unclear. It is possible that the CYPIAI MspI RFLP is linked with other polymorphisms in the African-American population in either CYPIAI or other genes related to risk for breast cancer.

The effect of this or any of the other CYPIAI polymorphisms on estrogen metabolism is not yet known. A large breast cancer case control study, including functional assessment of estrogen metabolism as a function of CYPIAI genotype in African-Americans, is warranted.

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References

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