Comparative Analysis of SNP in Estrogen-metabolizing Enzymes for Ovarian, Endometrial, and Breast Cancers in Novosibirsk, Russia

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Summary We estimated the frequency of CYP1A1, CYP1A2, CYP1B1, CYP19, and SULT1A1 allelic variants in a female population of the Novosibirsk district and their association with the elevated risk of breast (BC), ovarian (OC), and endometrial (EC) cancers. Significant differences (OR = 2.34, \( p = 0.0002 \)) in the allele distributions for CYP1A1 M1 polymorphism between patients with BC (\( n = 118 \)) and controls (\( n = 180 \)) were found. No significant difference in both genotype and allele distributions for CYP1A1 polymorphisms in patients with OC (\( n = 96 \)) and EC (\( n = 154 \)) was observed. Remarkable differences in the allele and genotype distributions for CYP1A2*1F polymorphism in patients with BC or OC were found (OR = 0.26, \( p = 0.0000005 \) and OR = 0.34, \( p = 0.00000002 \)). There were no differences for this polymorphism in women with EC. In patients with BC no significant differences were found in genotype and allele distributions for R264C polymorphism in the CYP19 gene. The frequency of a mutant CYP19 heterozygote genotype C/T was higher in patients with OC and EC compared with healthy women (OR = 3.87, \( p = 0.001 \) and OR = 3.73, \( p = 0.0004 \), respectively). Comparison of allele frequencies revealed a deficiency of an allele A of SULT1A1*2 in patients with OC (OR = 0.64, \( p = 0.019 \)) compared with controls. No differences were found in the genotype and allele distributions for SULT1A1 polymorphism between patients with BC and EC and controls. In addition, there were no difference in allele and genotype distributions for CYP1B1 119G→T polymorphism between BC and control. In conclusion, these results support the hypothesis that susceptibility gene alleles of estrogen-metabolizing enzymes may differentially influence risk for woman hormone-dependent cancers.

Introduction

Hormone-dependent cancer such as breast, ovarian, and endometrial cancers (BC, EC, and OC) shows a growing incidence rate all over the world including Russia. In the city of Novosibirsk, the incidence of BC, EC, and OC is approximately 80, 25, and 12/100 000 women. Currently, a common strategy to study mechanisms of hormone-dependent cancer is impairment of estrogen metabolism in general and
17β-estradiol (E$_2$) in particular, resulting in enhanced circulating hormone levels in blood or at local target tissues. At the present time, the ability of estrogens to stimulate the growth of a number of endocrine cancers is well established (1, 2). In most of human BC, OC, and ECs, estrogens, especially E$_2$, have been shown to contribute greatly to the growth and development of these tumors and some of these cancers require estrogen for their continued growth (3, 4). Excessive exposure to endogenous and exogenous estrogens increases cell division that increases cancer risk (5). Estrogens are produced by conversion of androgens after a series of complex biochemical reactions. The key role in these reactions belongs to the aromatase enzyme CYP19 (6). Estrogens are metabolized by several enzymes, including cytochrome P450s. The role of such P450 isozymes such as CYP1A1, CYP1A2, and CYP1B1 is to oxidize estrogens resulting in the formation of substrates for phase II metabolism of xenobiotics (7). Further utilization of hormone metabolites is carried out via sulfotransferase (8). Any breach in any of these systems may lead to significant changes in estrogen levels that may result in the development of malignant tumors.

A crucial mechanism for the development of all above mentioned cancers is excessive production of E$_2$. However, the development of BC, EC, or OC may occur by different mechanisms. One of which may be impairment of a a particular metabolite that may promote the preferential appearance of a hormone-dependent cancer. To prove this hypothesis, we studied genetic polymorphism present in several estrogen-metabolizing enzymes: CYP1A1, CYP1A2, CYP1B1, CYP19, and SULT1A in a woman population of the Novosibirsk region (Russia) aged 45 ± 17 years with BC, OC, and EC (n = 358). As a control group, women of the same age group without gynecological diseases (n = 180) were also studied. Clinical diagnosis was provided by board-certified gynecologists–oncologists from the Regional Clinical Oncological Hospital of Novosibirsk. Prior to enrollment for the study, its aims were fully explained and informed consent was obtained from each patient. The study protocol was reviewed and approved by the appropriate Institutional Review Boards.

Results

For detection of germ line mutations in estrogen-metabolizing enzymes, the PCR-RFLP method was used. The following functional polymorphisms were studied: the amino acid substitution Ile→Val increasing the enzyme activity of CYP1A1 by a few times (9); the substitution C→A in the 734 position for CYP1A2 gene resulting in significant decrease in the protein activity (10); the functional polymorphism G→T in the codon 119 for the CYP1B1 gene associated with BC risk (11) and a nucleotide substitution G638→A resulting in the Arg213His substitution for the SULT1A1 sulfotransferase leading to significant decrease (as high as 85%) of enzyme activity (12); the substitution C→A in the 264 codon for CYP19 gene (Arg264Cys polymorphism) changing the enzyme stability (13). All polymorphisms