Risk of Endometrial Cancer and Estrogen Replacement Therapy History by CYP17 Genotype

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Abstract

Common variants among genes coding for enzymes in sex steroid biosynthetic pathways may influence the risk of endometrial cancer. We examined the association between endometrial cancer risk and estrogen replacement therapy (ERT) by CYP17 genotype using 51 incident cases and 391 randomly selected controls from a multiethnic cohort in Hawaii and Los Angeles, California. The relative risk of endometrial cancer was calculated for ever use versus never use of ERT by CYP17 genotype (TT, TC, and CC). We found that women who reported ever taking ERT were more than twice as likely to develop endometrial cancer as women who never took ERT (odds ratio [OR], 2.24; 95% confidence interval [CI], 1.19–4.23). Among these women, the risk of endometrial cancer was higher for women homozygous for the CYP17 T allele (OR, 4.10; 95% CI, 1.64–10.3), but not for women with the C allele (OR, 1.31; 95% CI, 0.53–3.21). These preliminary findings suggest that CYP17 or other variants in estrogen biosynthesis or metabolism pathways may be potential markers of endometrial cancer susceptibility due to ERT.

Introduction

Endometrial cancer risk is influenced by factors that alter serum estrogen and progesterone levels. Specifically, risk increases after exposure of endometrial tissue to estrogen that is unopposed by progesterone (1, 2). Estrogen causes proliferation of epithelial cells, and this effect can occur due to endogenous or exogenous sources of exposure. ERT,3 in which estrogen is given to postmenopausal women without progestins, was first shown to increase endometrial cancer risk by epidemiological data in the United States in the 1970s. After 1976, progestins were increasingly added to ERT to reduce or possibly eliminate this risk (3). Other risk factors associated with excess endogenous production of estrogen and/or low progesterone (obesity, anovulatory cycles, and polycystic ovaries) have been repeatedly associated with increased risk of endometrial cancer (4). Consistent with these data, endometrial cancer cases have significantly higher levels of serum estrogens and lower levels of sex hormone-binding globulins than controls (5). Given the strong relationships between estrogen, progesterone, and endometrial cancer risk, we hypothesized that common variants among genes coding for enzymes in sex steroid biosynthetic pathways may increase risk of endometrial cancer.

One potential marker of endometrial cancer susceptibility is a common variant in cytochrome P450 (CYP17), a gene that codes for a key enzyme (cytochrome P450c17α) in a rate-limiting step of estrogen biosynthesis (6). A single-base polymorphism in the 5′ untranslated region of CYP17 (27 bp downstream from the transcription start site) has been used to identify two alleles, T (formerly designated as A1) and C (formerly designated as A2). Of relevance to endometrial cancer risk, at least two studies have found that the C allele is associated with elevated levels of circulating estrogens in pre- and postmenopausal women (7, 8). Furthermore, we found that CYP17 is closely associated with patterns of postmenopausal hormone replacement therapy, such that women who carry two copies of the C allele are about half as likely as women with the T allele to be current users of hormone replacement therapy (9).

In the current study, we examined the association between endometrial cancer risk and ERT (without progestins) by CYP17 genotype using cases and controls from a MEC in Hawaii and Los Angeles, California.

Materials and Methods

The participants included in these analyses were selected from a large, ongoing MEC study in Hawaii and Los Angeles initiated with emphasis on diet and lifestyle characteristics in the etiology of cancer. Details of the study have been published previously (10). Briefly, the cohort was developed beginning in 1993 from driver’s license files in Hawaii and Los Angeles. The cohort totals 215,251 men and women, ages 45–75 years at the time of enrollment, and includes primarily African-Americans, Japanese, Hawaiians, Latinos, and non-Latino whites. Baseline data were collected on all cohort members via a mailed questionnaire that contained five sections: (a) background, including medical history and family cancer history; (b) diet history; (c) medication use; (d) physical activity; and (e) female reproductive history, including the use of hormones.

This case cohort study included 51 incident cases of endometrial cancer and 391 randomly selected MEC controls who reported never taking ERT or exclusively taking estrogens without progestins (ERT). Both cases and controls were postmenopausal women ages 60 years and over at the time of blood draw from the four primary cohort racial/ethnic groups (African American, Japanese, Latina, and non-Latina white). Cases and potential controls were contacted by letter and phone call, followed by a home visit to collect a blood specimen. Blood draw was completed in the morning, typically at the person’s home, after informed consent was obtained. Participation rates for providing a blood sample on request were 74% for cancer cases and 66% for cohort controls. Case ascertainment was completed through the Surveillance, Epidemiology and End Results program in Los Angeles and Hawaii. Controls had no history of endometrial, breast, or ovarian cancer and reported no prior hysterectomy.

Genotyping. DNA was purified from buffy coats of peripheral blood samples. The CYP17 assay has been described previously (11). A PCR fragment containing the bp change was generated using the following primers: CYP-1, 5-CATTCGCACTCTGGAGTC-3; and CYP-2, 5-AGGCTCTTGGGTACTTGG-3. PCR reactions were carried out in 25-μl aliquots containing about 50 ng of genomic DNA, 50 pmol of each primer, 1× reaction buffer, 100 μM deoxynucleotide triphosphates, and 1 unit of Taq polymerase (Pharmacia). The amplification was performed for 30 cycles of denaturation at 94°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 1 min. An initial denaturation step of 5 min at 94°C and a final extension at 72°C for 5 min were used. The PCR products were digested for 3 h at 37°C using MspAI, separated by agarose gel electrophoresis, and stained with ethidium bromide to identify the bp change.

Statistical Analysis. The relative risk of endometrial cancer was calculated for ever use versus never use of ERT by CYP17 genotype (TT, TC, and CC). Logistic regression, conditional on CYP17 genotype, was used to calculate
The risk of endometrial cancer in women taking estrogen replacement therapy (ERT) is an area of ongoing research. Women with a specific genotype, namely the CC allele of the CYP17 gene, were found to have a higher risk of developing endometrial cancer with ERT use than those without the CC allele. The CC genotype was associated with a significant increase in the risk of endometrial cancer, with an odds ratio (OR) of 4.10 (95% CI: 1.64–10.27, p = 0.003) compared to women without the CC allele. This relationship was observed even after adjusting for age (quartiles) and controls. The OR for the CC genotype was 2.24 (95% CI: 1.19–4.23, p = 0.013) for women taking ERT compared to women who never took ERT.

Discussion

The positive association between postmenopausal use of ERT and endometrial cancer risk found in this study has been described in previous publications. The risk of endometrial cancer was much higher for women homozygous for the CYP17 T allele, but not for women with the C allele. The small changes in premenopausal E1, estradiol, and possibly progesterone levels due to CYP17 may not significantly alter endometrial cancer risk as long as progesterone levels are high enough to induce epithelial shedding in each menstrual cycle. One potential explanation for the difference in risk for endometrial cancer by CYP17 genotype for postmenopausal ERT users may be due to individual differences in estrogen binding and metabolism, such as the T allele of the T27C marker may distinguish women whose estrogen biosynthetic and metabolism systems are down-regulated or up-regulated for the C allele. Based on normal, circulating estrogen levels by CYP17 genotype (7, 8), women with the T allele may bind and eliminate circulating estrogens less efficiently than women with the C allele. If the efficiency of a woman’s metabolic system to process E2 differs according to normal Endogenous E2 production levels, the addition of a similar dose of postmenopausal ERT may have a greater effect on women with the T allele (who would normally transport and metabolize relatively low endogenous levels of E2) compared with women with the C variant. However, to accurately interpret these findings, more testing on circulating levels of endogenous estrogens is necessary to see whether estrogen levels are correlated with CYP17 genotype among women taking a standard dose of ERT.

The relationship between risk of endometrial cancer and use of estrogen and progesterin replacement therapy is extremely important, given findings that estrogen and progesterin replacement therapy is protective for endometrial cancer risk but may increase a woman’s risk of breast cancer (13). The risks and benefits of prescribing unopposed estrogen or estrogens in combination with progestins for women in relation to their risk for endometrial and breast cancer would be better clarified if markers of disease and individual responsiveness to exogenous hormones were available. The current findings suggest that CYP17 or other variants in the estrogen biosynthesis or metabolism pathway may be potential markers of endometrial cancer susceptibility due to ERT. The current findings are based on small numbers and need to be replicated in larger epidemiological studies. Although the functional relevance of the CYP17 gene is still unknown, these preliminary data suggest that CYP17 could be a marker of up-regulated estrogen biosynthesis and metabolism that may be of utility in studies of endometrial cancer risk.

References

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