Lack of Effect Modification between Estrogen Metabolism Genotypes and Combined Hormone Replacement Therapy in Postmenopausal Breast Cancer Risk

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Introduction

Postmenopausal use of combined hormone replacement therapy (CHRT) containing both estrogens and progestins has been associated with increased breast cancer risk (1, 2). There is also evidence that genetic variants in candidate estrogen metabolism genes influence the disposition of exogenous estrogen. The genes involved in the disposition of estrogen are well known, and include catechol-O-methyltransferase (COMT), the sulfotransferases SULT1A1 and SULT1E1, and members of the cytochrome P50 family including CYP1B1, CYP1A2, and CYP1A1. Functionally relevant genetic variants exist in each of these genes. However, it remains unclear whether these genes affect breast cancer risk (3-10), and there is even less information about whether these genes interact with relevant exposures to influence breast cancer etiology. Therefore, we evaluated whether there was evidence for modification of the effect of CHRT use by genes involved in the downstream metabolism of estrogens including COMT, CYP1A1, CYP1A2, CYP1B1, SULT1A1, and SULT1E1.

Materials and Methods

The Women’s Insights and Shared Experiences (WISE) study is a population-based case-control study that consisted of an efficient sampling design using shared controls to compare both breast cancer cases and endometrial cancer cases (11, 12). Incident breast cancer cases were identified through hospitals and the Pennsylvania State Cancer Registry, and frequency-matched controls were identified from the community using random-digit dialing. The source populations for this study were the three counties of Philadelphia (PA), Delaware (PA), and Camden (NJ). Potentially eligible cases were Caucasian women residing in these counties at the time of diagnosis who were ages 50 to 79 years old and were newly diagnosed with breast cancer between July 1, 1999 and June 30, 2002. Controls were selected from the same geographic regions as the cases, and were frequency-matched to the cases on age (in 5-year age groups) and calendar date of interview (within 3 months). The present analysis involved 677 breast cancer cases and 905 age-matched controls who met the abovementioned criteria. Genomic DNA was obtained from buccal swabs as previously described. Genetic variants in COMT, CYP1A1, CYP1A2, CYP1B1, SULT1A1, and SULT1E1 were assayed as previously described (13). Additional details of our study design, which included ascertainment of both breast and endometrial cancer cases and matched controls, have been previously reported (11-14).

Odds ratio (OR) estimates and 95% confidence intervals were calculated to evaluate the relationship between hormone metabolism genes and hormone use with breast cancer risk. Using multiple conditional logistic regression, we adjusted for (a) education (high school, high school graduate, more than high school but not a college graduate, college graduate or higher); (b) body mass index during the participant’s 40’s; (c) number of full-term pregnancies (0, 1, 2, 3+); (d) years of menses; (e) menopause type (known natural, assumed natural at reference age of 50 if menopausal status is unknown, and induced); (f) never/former/current smoker × years of smoking; and (g) oral contraceptive use (never, <3 years, 3 years or more). Adjustment for other covariates had no substantial effect on the ORs of interest. Two degrees of freedom χ² tests for interaction of genotype by CHRT use were computed.

Results and Discussion

As shown in Table 1, we identified no statistically significant modification of the effect of CHRT use and any genotype (Table 1). Statistically significant stratum-specific ORs were identified among never users of CHRT for carriers of CYP1A1*2C or SULT1A1*3 alleles. However, our a priori hypotheses specified that only statistically significant effect modification existed according to genotype with CHRT use. Thus, we did not consider stratum-specific OR effects as meaningful if no statistically significant interaction was observed. Similarly, no significant effect modification was observed for subgroups based on histology (ductal, lobular) or estrogen receptor or progesterone receptor status (results not shown). Therefore, the present results do not support the hypothesis that estrogen metabolism genotypes modify the effect of CHRT in breast cancer etiology among postmenopausal Caucasian women.

We attempted to limit the potential for inferential errors by restricting our analyses to Caucasians, thus eliminating the majority of the variability that could lead to confounding by ethnicity, and can lead to either false-positive or false-negative associations (15). In all studies involving effect modification, power and sample size considerations are critical when evaluating the potential for type II error. Our
Table 1. Genes and alleles under study, with adjusted ORs (95% confidence intervals) for effect modification of genotypes and CHRT use on breast cancer risk in postmenopausal Caucasian women

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP variant nucleotide designation (rs number)</th>
<th>Genotyping method</th>
<th>Putative function of variant</th>
<th>Genotypes represented by the ORs</th>
<th>Adjusted OR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Never CHRT</strong></td>
</tr>
<tr>
<td>COMT</td>
<td>1947G&gt;A (rs4680)</td>
<td>Val&lt;sup&gt;158&lt;/sup&gt;Met, Val&lt;sup&gt;208&lt;/sup&gt;Met</td>
<td>Met alkylozyme has decreased activity</td>
<td>AG/AA (any Met)</td>
<td>0.76 (0.49-1.18)</td>
</tr>
<tr>
<td>CYPIA1</td>
<td>6750A&gt;G (rs1048943)</td>
<td>Ile&lt;sup&gt;462&lt;/sup&gt;Val, *2C, m2</td>
<td>Val alkylozyme has increased inducibility to produce 2OH-catecholestrogens</td>
<td>AG/GG (any *2C)</td>
<td>2.35 (1.20-4.58)</td>
</tr>
<tr>
<td>CYPIA2</td>
<td>734C&gt;A, -163C&gt;A (rs762551)</td>
<td>*1F</td>
<td>*1F has increased inducibility, ultrarapid activity to produce 2-OH catecholestrogens</td>
<td>AA/AC (any *1F)</td>
<td>0.51 (0.25-1.03)</td>
</tr>
<tr>
<td>CYPIB1</td>
<td>1294G&gt;C (rs1056836)</td>
<td>Leu&lt;sup&gt;343&lt;/sup&gt;Val, *3</td>
<td>Val alkylozyme has increased 4-OH activity, increased adduct formation</td>
<td>CC/GC (any *3)</td>
<td>1.43 (0.91-2.26)</td>
</tr>
<tr>
<td>CYPIB1</td>
<td>1358A&gt;G or 3290A&gt;G (rs1800440)</td>
<td>Asn&lt;sup&gt;452&lt;/sup&gt;Ser, *4</td>
<td>Ser alkylozyme associated with higher catalytic efficiency towards 4-OH-estradiol</td>
<td>AG/GG (any *4)</td>
<td>1.40 (0.94-2.10)</td>
</tr>
<tr>
<td>SULT1A1</td>
<td>636C&gt;A (rs922861)</td>
<td>Arg&lt;sup&gt;213&lt;/sup&gt;His, *2</td>
<td>*2 alkylozyme has lower thermostability, lower enzyme activity, and lower estrogen sulfation ability</td>
<td>AG/AA (any *2)</td>
<td>1.25 (0.84-1.87)</td>
</tr>
<tr>
<td>SULT1A1</td>
<td>667A&gt;G (rs1801030)</td>
<td>Met&lt;sup&gt;225&lt;/sup&gt;Val, *3</td>
<td>*3 alkylozyme has similar or lower activity, depending on substrate</td>
<td>AG/GG (any *3)</td>
<td>0.30 (0.09-0.97)</td>
</tr>
<tr>
<td>SULT1E1</td>
<td>-64G&gt;A (rs3736599)</td>
<td>Promoter variant</td>
<td>Unknown</td>
<td>AG/AA</td>
<td>1.58 (0.96-2.59)</td>
</tr>
</tbody>
</table>

NOTE: Estimated from conditional logistic regression matched on age, and adjusted for age at menarche, age at menopause, number of full-term pregnancies, body mass index, and duration of oral contraceptive use.

study was originally designed with sufficient statistical power to detect first-order interactions of the type evaluated here between genotypes and CHRT use. The study was originally designed to ascertain 564 postmenopausal Caucasian cases and 719 matched postmenopausal Caucasian controls, which would provide 80% power to detect a first-order interaction between genotype classes (e.g., carriage of any variant allele in homozygous or heterozygous form) with a frequency of 5% or greater and an exposure (e.g., CHRT) with an exposure frequency of 60% or greater to detect an interaction OR of 2.2, assuming α = 0.05. The final sample size used here was 677 postmenopausal Caucasian cases and 905 matched postmenopausal Caucasian controls. In addition, the frequency of genotypes was generally higher than originally planned. Therefore, the study had greater power than originally designed, and provides adequate power to detect clinically relevant interactions had they been observed here.

We report that the elevated breast cancer risk associated with CHRT use is unlikely to be influenced by functionally relevant variants in candidate estrogen metabolism genes. These results suggest that breast cancer risk in women who use CHRT does not depend on genetic factors involved in estrogen metabolism. Additional research is required to evaluate whether the metabolism of other compounds, including progestins, might explain the elevated breast cancer risk associated with CHRT use.

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References


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