Genetic Polymorphisms in Catechol-O-Methyltransferase, Menopausal Status, and Breast Cancer Risk

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ABSTRACT

Polymorphic catechol-O-methyltransferase (COMT) catalyzes the O-methylation of estrogens. In a case-control study, we evaluated the association of the low-activity allele (COMTMet) with breast cancer risk. Compared to women with COMTVal/Val, COMTMetMet was associated with an increased risk among premenopausal women (odds ratio (OR), 2.1; confidence interval (CI), 1.4–4.3) but was inversely associated with postmenopausal risk (OR, 0.4; CI, 0.2–0.7). The association of risk with at least one low-activity COMT allele was strongest among the heaviest premenopausal women (OR, 5.7; CI, 1.1–30.1) and among the leanest postmenopausal women (OR, 0.3; CI, 0.1–0.7), suggesting that COMT, mediated by body mass index, may be playing differential roles in human breast carcinogenesis, dependent upon menopausal status.

INTRODUCTION

... This work was a collaborative effort by the Division of Molecular Epidemiology, National Cancer Institute, Bethesda, Maryland 20892, and the Laboratory of Human Carcinogenesis, National Cancer Institute. This work was supported, in part, by Grants CA11553, CA56295, and CA16363 from the National Cancer Institute and the National Institute for Environmental Health Sciences and USAMRICAMCNC17-94-J-4108. This work is solely the responsibility of the authors and does not necessarily represent the views of the National Cancer Institute.

RESULTS

Genotype data for COMT were available for 281 women with breast cancer and 289 community controls. For the most part, asso-
correlations between putative risk factors for breast cancer (i.e., those for which logistic models were adjusted) were similar within the larger data set and the subset for which COMT data were available. Values for cases and controls within each group, by menopausal status, are shown in Table 1. Results of the study of the association between COMT genotypes and breast cancer risk, evaluated by menopausal status, are shown in Table 2. Marked differences in the association of COMT genotypes with risk were noted between premenopausal and postmenopausal women. Premenopausal cases were less likely than controls to be homozygous for the high-activity COMT allele, 20% versus 36%, respectively. Heterozygosity was more frequent in the postmenopausal group. Premenopausal cases were more likely than controls to be heterozygous for the intermediate-activity phenotype, and COMT e' et with the low-activity phenotype.

In contrast to premenopausal women among whom the COMT low-activity allele was associated with increased risk, postmenopausal women with breast cancer were more likely than controls to be COMT Val/Val (29% versus 19%), and an inverse association was most pronounced among those who were COMT Met/Met (OR, 0.4; 95% CI, 0.3-0.9). When COMT Val/Val individuals were combined with the COMT Met/Met genotype, those with at least one low-activity allele showed significantly increased risk (OR, 2.4; CI, 1.4-4.3). This further supports arguments from a number of studies suggesting that breast cancer etiology may differ between premenopausal and postmenopausal women, warranting the careful classification and separation of women by menopausal status in studies of breast cancer risk factors. Lastly, it should be noted that no gene-dose effect was observed in these data. The lack of a gene-dose effect is common to these types of genotype-based studies that account for this lack of gene-dose effect, including the pharmacokinetic considerations that determine the rate-limiting steps in the metabolic pathway.

Table 2 COMT genetic polymorphisms and risk of breast cancer by menopausal status: Western New York Breast Cancer Study: 1986-1991

<table>
<thead>
<tr>
<th>COMT Val/Val</th>
<th>COMT Val/Met</th>
<th>COMT Met/Met</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td></td>
<td></td>
<td>28 (20)</td>
<td>48 (36)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>84 (60)</td>
<td>57 (42)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (20)</td>
<td>29 (22)</td>
<td>1.0 (0.8-3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 (20)</td>
<td>48 (36)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>113 (80)</td>
<td>86 (64)</td>
<td>2.2 (1.3-3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Postmenopausal |              |              | 41 (29)    | 30 (19)       | 1.0 |
|                | 75 (54)      | 82 (53)      | 0.7 (0.4-1.2) |
|                | 24 (17)      | 43 (28)      | 0.4 (0.2-0.8) |
|                | 41 (29)      | 30 (19)      | 1.0        |
|                | 99 (71)      | 125 (81)     | 0.6 (0.3-1.0) |

a ORs and 95% CIs calculated by unconditional logistic regression, adjusted for age and education.

DISCUSSION

In this study, we found that the genetic polymorphism in COMT associated with enzyme activity was differentially associated with breast cancer risk among premenopausal and postmenopausal women. Statistically significant increased risk was observed among premenopausal women with the low-activity allele, whereas there was decreased risk among postmenopausal women with this genotype. When stratified by BMI, the low-activity COMT allele was associated with significantly increased risk among the heaviest premenopausal women, which is the group thought to be at lowest risk, although the confidence interval was wide. Similarly, although there was an inverse relationship between COMT and postmenopausal breast cancer risk, this effect was attenuated in the heaviest postmenopausal women. We observed no association between COMT genotypes and breast cancer risk when premenopausal and postmenopausal women were combined (Table 4). This further supports arguments from a number of studies suggesting that breast cancer etiology may differ between premenopausal and postmenopausal women, warranting careful classification and separation of women by menopausal status in studies of breast cancer risk factors. Lastly, it should be noted that no gene-dose effect was observed in these data. The lack of a gene-dose effect is common to these types of genotype-based studies that serve as indicators of “lifetime” phenotype. Several mechanisms may account for this lack of gene-dose effect, including the pharmacokinetic considerations that determine the rate-limiting steps in the metabolic pathway.
COMT AND BREAST CANCER RISK

Table 3 Effect of COMT genotype on risk, within tertiles of BMI: Western New York Breast Cancer Study, 1986–1991

<table>
<thead>
<tr>
<th>BMI COMT genotype</th>
<th>23-27</th>
<th>&gt;27</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI)</td>
<td>OR (CI)</td>
</tr>
<tr>
<td>COMT Val/Val</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>COMT Val/Met and COMT Met/Met</td>
<td>3.3 (1.1–9.8)</td>
<td>5.7 (1.1–30.1)</td>
</tr>
</tbody>
</table>

Table 4 COMT genetic polymorphisms and risk of breast cancer among premenopausal and postmenopausal women combined: Western New York Breast Cancer Study: 1986–1991

<table>
<thead>
<tr>
<th>COMT genotype</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val/Val</td>
<td>19/18</td>
<td>8/16</td>
<td>1.0</td>
</tr>
<tr>
<td>Val/Met</td>
<td>55/34</td>
<td>29/22</td>
<td>1.8 (0.8–4.1)</td>
</tr>
<tr>
<td>Met/Met</td>
<td>19/11</td>
<td>8/7</td>
<td>3.3 (1.1–9.8)</td>
</tr>
<tr>
<td>Val/Val</td>
<td>31/50</td>
<td>42/43</td>
<td>0.5 (0.1–1.6)</td>
</tr>
</tbody>
</table>

a ORs and 95% CIs calculated by unconditional logistic regression, adjusted for age, education, age at menarche, age at first pregnancy, BMI, and family history of breast cancer.

...genotype distribution in these and other similar data sets (15, 20, 25–27).

Because our results were so similar to those of Lavigne et al. (23), except that associations were flipped by menopausal status, we also considered the possibility that there were errors in classification or coding. A thorough review of the original gels, the coding of genotypes within the database, and other variables that could affect results was performed, and this possibility was ruled out. Clearly, there is a need for this hypothesis to be evaluated in other study populations, so that a preponderance of data can further direct research as well as identify subgroups who may be at higher risk and thus, need to be targeted for preventive strategies.

Although the mechanisms are not elucidated, these data suggest that the COMT genotypes associated with high, intermediate, and low enzyme activity may contribute to breast cancer etiology. Furthermore, these data indicate that there may be an interaction between BMI, COMT, and menopausal status in breast cancer risk. The mechanism of this interaction may be an opposing role of catechol estrogen metabolism in breast cancer etiology, depending on the hormonal environment. We suggest that the differing biological effects of the catechols estrogens reported in the literature (i.e., DNA damaging versus growth inhibiting) may be dependent on the levels of circulating estrogens. Therefore, in a high estrogen environment such as in the premenopausal and to some extent in the heaviest postmenopausal women, the presence of higher circulating levels of the catechol compounds (2-OH and 4-OH) of estradiol generated in a low COMT environment may result in higher circulating levels of potentially mutagenic compounds (5, 7, 9). Conversely, low COMT activity may be associated with lower circulating levels of the putative anticarcinogen, 2-methoxyestradiol (28, 29). In a low-estrogen environment, as in leaner postmenopausal women, higher circulating levels of the unmethylated catechols in a low COMT background may elevate the levels of the putative anticarcinogenic 2-hydroxy estrone (3). It is of interest to note that in leaner postmenopausal women, colorectal cancer risk is reduced by HRT (30) and that HRT appears to maintain the age-related decline in DNA repair capacity (31). The fact that the leanest women appear to benefit more from higher circulating levels of estrogen and estrogen catechols might suggest that some exposure to estrogen postmenopausally is beneficial, but that too little or too much estrogen exposure, as in the premenopausal women, places an individual at increased risk for cancer of the breast and perhaps the colon, the mechanisms of which remain unclear.

In addition to its role in conjugation of estrogenic compounds, COMT acts on a number of other compounds thought to modify cancer risk, including ascorbic acid and certain flavonoids (14, 15, 32). The impact of COMT on breast cancer risk in premenopausal and...
postmenopausal women may be reflective of differing etiological events that encompass both endogenous and exogenous exposures.

As discussed above, results from these analyses may be affected by sources of bias that are common to case-control studies. Low participation rates may produce results that are not generalizable to all women. Although it is possible that body mass could differ between those who participated and those who did not, it is unlikely that selection bias would affect overall associations between genetic polymorphisms and breast cancer risk. Of more concern, however, are the relatively small sample numbers in this study, particularly when women were stratified by BMI. Resulting estimates of risk may be unstable, as evidenced by wide CI, due to chance alone. Nonetheless, these data are consistent with biologically plausible interactions and merit further investigation of the associations between hormonal/postmenopausal status, variability in metabolism of estrogens, and breast cancer risk.

REFERENCES


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