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EPIDEMIOLOGY

Catechol-*O*-methyltransferase haplotypes and breast cancer among women on Long Island, New York

Mia M. Gaudet · Jeannette T. Bensen · Jane Schroeder · Andrew F. Olshan · Mary Beth Terry · Sybil M. Eng · Susan L. Teitelbaum · Julie A. Britton · Teresa A. Lehman · Alfred I. Neugut · Christine B. Ambrosone · Regina M. Santella · Marilie D. Gammon

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Abstract The gene encoding catechol-*O*-methyltransferase (*COMT*), critical to the inactivation of reactive catechol estrogens, has several single nucleotide polymorphisms (SNPs) that influence enzyme activity. A 3-SNP haplotype (IVS1+255 C > T; Ex4-12 G > A; 3′UTR-521 A > G), which has been shown to reduce COMT expression in the human brain, has been identified. To evaluate the influence of genetic variation of *COMT* on breast cancer risk, these 3-SNPs were genotyped in 1052 cases and 1098 controls. We estimated the associations between breast cancer and individual SNPs, as well as, multilocus haplotypes. We also examined surrogates of hormone exposure as potential modifiers of the putatively functional Ex4-12 SNP-breast cancer association. Odds ratios (OR) and 95% confidence intervals (CI) were based on age-adjusted unconditional logistic regression models. We found no association between the individual SNPs alone and breast cancer. When examining the association between breast cancer and the 3-SNP haplotypes, we observed a 19% increase in risk associated with each copy of the TGG haplotype (OR=1.19, 95% CI 0.96–1.49), relative to the common TAA haplotype, which was statistically significant when assuming a dominant model (OR=1.32, 95% CI 1.05–1.67, *p*-value=0.02). In this report of *COMT* haplotypes and breast cancer, we found some evidence that additional genetic variability beyond the Ex4-12 G > A SNP contributes to risk of breast cancer among a small subgroup of women; however, these results need to be replicated in additional studies.

Introduction

Catechol-*O*-methyltransferase (COMT) contains a common, functional variant (Ex4-12 G > A; rs4680), which causes a

M. M. Gaudet · J. T. Bensen · J. Schroeder · A. F. Olshan · M. D. Gammon
Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hil, NC 27516, USA

M. B. Terry · A. I. Neugut
Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032, USA

S. M. Eng
Global Epidemiology, Worldwide Safety and Risk Management, Pfizer, Inc., New York, NY 10017, USA

S. L. Teitelbaum · J. A. Britton
Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA

T. A. Lehman
BioServe Biotechnologies, Ltd., Laurel, MD 20707, USA

A. I. Neugut
Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

C. B. Ambrosone
Department of Epidemiology, Roswell Park Cancer Institute, Buffalo, NY 14222, USA

R. M. Santella
Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032, USA

M. M. Gaudet (✉)
Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., EPS/7055, Bethesda, MD 20852, USA
E-mail: gaudetm@mail.nih.gov
Fax: +1-301-402-0916

valine–methionine (Val158Met) substitution [1, 2], that has been associated with breast cancer risk in some, but not all, studies [3–16]. However, the Ex4-12 SNP alone may not entirely account for variability in disease risk [17, 18]. The combined effects (or haplotypes) of Ex4-12 and two additional SNPs, including a SNP within intron 1 (IVS1+255 C > T; rs737865) and a SNP in the 3′UTR (3′UTR-521 A > G; rs165599), are potentially of functional importance [17, 18]. The TAA haplotype, and in particular the 3′UTR-521 A-allele, were associated with higher levels of COMT mRNA [17].

We evaluated whether this putatively functional 3-SNP *COMT* haplotype (IVS1+255; Ex4-12; 3′UTR-521) altered breast cancer risk in a large population-based case–control study. Multiple locus haplotypes, in addition to individual SNPs, were evaluated to identify potential SNP–SNP interactions. We also examined surrogates of hormone exposure as potential modifiers of the putatively functional Ex4-12 SNP–breast cancer association.

Methods

Study population

The LIBCSP, a population-based case–control study, was conducted among women who were aged 20 years or older, English-speakers, and residents of Nassau and Suffolk counties, Long Island, New York [19]. Institutional Review Board approval was obtained from all participating institutions, and signed informed consent was obtained for all respondents. Cases were newly diagnosed with a first primary in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. Study personnel identified cases through rapid case ascertainment via active daily or weekly contact with local pathology departments. Each case's physician was contacted to verify the details of diagnosis and to obtain permission for patient contact. Of the 2,030 eligible cases, physician's consent was obtained for 1,837 (90.5%). For most cases, physician refusal was due to illness of the patient.

Controls with no history of breast cancer were randomly selected for recruitment by random digit dialing (for women under the age of 65 years at contact) and by Health Care Finance Administration rosters (for women 65 years or older). Controls were frequency matched to the expected age distribution of cases by 5-year age group.

Trained interviewers completed in-home interviews for 1,508 (82.1%) of eligible case women (235 with in situ breast cancer) and 1,556 (62.7%) eligible controls. Interview topics included lifetime reproductive history, physical activity, body size, alcohol use, active/passive cigarette smoke exposure, and exogenous hormone use (http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html). The medical records of case women were obtained and abstracted for breast cancer estrogen receptor (ER) status.

Laboratory methods

A total of 73% of cases and 73% of controls donated a blood sample. Venous blood was collected in EDTA-treated tubes and stored at room temperature. Samples were shipped overnight to a single laboratory at Columbia University. Samples arrived de-identified with bar-code labels that were preprinted with the subject's randomly selected study identification number. Processing for most blood samples occurred within 24 h of collection. All lab personnel were blinded to case–control status of the specimens [19].

Stored DNA samples were available for 70% of participating cases (n=1052) and 71% of participating controls (n=1098). Blood donation at interview was not associated with the Jewish faith or family history of breast cancer, but was associated with race, cigarette smoking, alcohol use, use of oral contraceptives and hormone replacement therapy, lactation, and mammography [19]. However, the risk factor profiles among the subset of women with blood were not materially different from those observed among all LIBCSP women (data not shown).

Genomic DNA was extracted from mononuclear cells in whole blood separated by Ficoll (Sigma Chemical Co., St. Louis, MO) and washed twice with PBS. Pelleted cells were frozen at −80°C until DNA isolation by standard phenol and chloroform/isoamyl alcohol extraction and RNase treatment [20]. BioServe Biotechnologies (Laurel, MD) conducted the genotyping using Sequenom's high-throughput matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. Primers were designed by SpectroDESIGNER and results were analyzed by SpectroTYPER. All genotyping calls were manually reviewed for quality control. Further details about the genotyping methods have been previously published [21]. SNP assays failed for 4% of cases and 2% of controls.

A total of 170 (8%) blinded replicates were included throughout the set of LIBCSP DNAs. Greater than 95% of the pairs were concordant (p-values < 0.05) based on the kappa statistic. Discordant genotypes appeared to occur at random. Allele frequencies for the three loci were in Hardy–Weinberg equilibrium among controls (p-value=0.85, 0.45, 0.54, respectively).

Statistical analyses

Unconditional logistic regression [22] was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between *COMT* variants and breast cancer, with adjustments made for the frequency matching factor, age at reference (date of diagnosis for cases and date

of identification for controls) using SAS, Version 8.1 [23]. To evaluate the breast cancer association with individual SNPs, we used the following common genotypes as the reference categories: T/T for *COMT* IVS1+255, G/G for *COMT* Ex4-12, and A/A for *COMT* 3′UTR-521 SNP. We had no a priori hypothesis whether the genotype data would best fit an additive (analogous to the *p*-value for linear trend), dominant, or recessive genetic model; therefore, we evaluated each model. Case groups were further defined by ER status (ER+, ER−) or stage of disease (invasive, in situ cancer) using polytomous regression.

To assess deviations from a multiplicative interaction model, we used the log likelihood ratio test to compare the fit of logistic models with and without the interaction term. Factors that are thought to affect breast cancer risk through a hormonal mechanism were considered potential effect modifiers using dichotomous and detailed categories of exposure, including: age at menarche, parity, age at first birth, oral contraceptive use, postmenopausal hormonal replacement therapy use, menopausal status (defined using information about last menstrual period, prior surgical information on hysterectomy or oophorectomies, current cigarette smoking status, and use of hormone replacements), lifetime average alcohol intake, participation in any physical activity on a regular basis for at least 1 h per week for 3 months or more in any year prior to reference date, average physical activity from menarche to reference, and body mass index at 1 year prior to reference date among postmenopausal women [24].

Potential confounders were risk factors that might be related to *COMT* genotype frequency (secondary to variation among ethnic groups that may be associated with genotype), including religion, alcohol use, active cigarette smoking, OC use, age at first birth, and number of pregnancies. Potential confounders did not meaningfully alter the effect estimates by more than 10%; therefore, final models include only age at reference.

Pairwise linkage disequilibrium (LD) was calculated between SNPs using r^2 [25, 26]. Genotyping data for the 3-SNPs under study (IVS1+255 C > T; Ex4-12 G > A; 3′UTR-521 A > G) was imported into HaploStats (Version 1.2.1), which employed the expectation–maximization (EM) algorithm to estimate haplotype frequencies and an iterative two-step EM model to estimate the association between individual and risk [27, 28]. The variance estimates are corrected for the error associated with estimating the haplotypes [29]. We had no a priori hypothesis of whether the data would best fit an additive, recessive, and dominant genetic model; therefore, we ran all models. Except where noted, results from the additive genetic model are shown. The global score statistic, adjusted for age, was used to evaluate the overall difference in haplotype frequencies between cases and controls [28].

Results

Among women with available DNA (1,052 cases and 1,098 controls), most women were between the ages of 45 and 64 years old (51.3%, 55.4%, respectively), white (94.1%, 92.4%), self-described as Catholic (56.5%, 60.7%), and determined to be postmenopausal (66% and 62%) [19]. Among the controls, frequencies of the common alleles for *COMT* IVS1+255 (T allele: 69%), *COMT* Ex4-12 (A allele: 50%), and *COMT* 3′UTR-521 (A allele: 64 %) were consistent with other published reports of European–American populations [5, 7, 15, 18]. We found little association between *COMT* SNPs and breast cancer among all women or women stratified by menopausal status (*p*-value for interaction = 0.68) (Table 1). Results were similar regardless of the genetic model assumed: additive (Table 1), dominant, or recessive (individual results not shown; all *p*-values greater than 0.24). The results for SNPs modeled simultaneously were similar to results for individual SNP models (results not shown). ORs from polytomous logistic regression models of *COMT* genotypes and breast cancer cases subtyped by ER or stage did not indicate clear differences in association between case subtypes (results not shown).

We hypothesized that women with the lower expression A/A genotype (also known as LL or Met/Met genotype) who also had factors that were associated with elevated estrogen levels would have the greatest risk of breast cancer. However, reproductive-related factors, alcohol intake, and physical activity (data not shown) did not modify the association between genotype and breast cancer risk in the expected direction. Further investigation of duration or average lifetime exposure did not alter our conclusions (results not shown).

The three *COMT* SNPs were not in perfect LD in our study (IVS1 – Ex4: r^2=0.26; IVS1 – 3′UTR: r^2=0.17; Ex4 – 3′UTR: r^2=0.04). Overall, we found no association between *COMT* haplotypes and breast cancer risk (global *p*-value=0.46) (Table 2). The ORs in Table 2 were calculated assuming an additive genetic model; therefore, the ORs represent the incremental odds associated with each copy of the haplotype shown relative to the odds associated with carrying the TAA haplotype, the most common haplotype in our data. Carrying the TGG haplotype was associated with a 19% increase in risk for each copy; though, results for the additive model were not statistically significant (Table 2). However, the association between this haplotype and breast cancer was statistically significant if a dominant model was assumed (OR=1.32, 95% CI 1.05–1.67, *p*-value=0.02). When we assumed a recessive model, our conclusions did not differ (data not shown). Exclusion of the small proportion of non-white women did not appreciably alter risk estimates (data not shown).

Table 1 Age-adjusted ORs[a] and 95% CI[a] for the association between *COMT* polymorphisms and risk of breast cancer, Long Island Breast Cancer Study Project, 1996–1997

	All women			Premenopausal women			Postmenopausal women		
	Cases n^b (%)	Controls n^b (%)	Age-adjusted OR (95% CI)	Cases n^b (%)	Controls n^b (%)	Age-adjusted OR (95% CI)	Cases n^b (%)	Controls n^b (%)	Age-adjusted OR (95% CI)
IVS1 +255 C > T									
T/T	505 (48.7)	535 (48.5)	1.00	161 (48.5)	182 (49.3)	1.00	334 (48.8)	318 (47.0)	1.00
T/C	431 (41.5)	457 (41.4)	0.97 (0.81, 1.16)	142 (42.8)	151 (40.9)	1.06 (0.78, 1.46)	280 (40.9)	287 (42.4)	0.91 (0.73, 1.15)
C/C	102 (9.8)	111 (10.0)	0.95 (0.71, 1.28)	29 (8.7)	36 (9.8)	0.84 (0.49, 1.45)	70 (10.2)	72 (10.6)	0.95 (0.66, 1.37)
p-value for additive model			0.68			0.81			0.55
Ex4-12G > A (Val158Met)									
G/G	287 (27.6)	277 (25.1)	1.00	88 (26.5)	91 (24.7)	1.00	192 (28.1)	176 (26.0)	1.00
G/A	521 (50.2)	549 (49.8)	0.92 (0.75, 1.13)	177 (53.3)	188 (50.9)	0.97 (0.67, 1.39)	331 (48.4)	335 (49.5)	0.90 (0.70, 1.17)
A/A	240 (23.1)	266 (24.1)	0.88 (0.69, 1.12)	70 (21.1)	90 (24.4)	0.80 (0.52, 1.23)	166 (24.3)	167 (24.7)	0.93 (0.69, 1.25)
p-value for additive model			0.29			0.31			0.61
3′UTR-521 A > G									
A/A	428 (41.2)	455 (41.3)	1.00	135 (40.7)	154 (41.7)	1.00	285 (41.7)	286 (42.2)	1.00
A/G	478 (46.1)	490 (44.4)	1.03 (0.86, 1.24)	149 (44.9)	170 (46.1)	1.01 (0.73, 1.40)	317 (46.3)	300 (44.3)	1.05 (0.84, 1.33)
G/G	135 (13.0)	143 (13.0)	1.02 (0.78, 1.34)	49 (14.8)	44 (11.9)	1.31 (0.82, 2.11)	83 (12.1)	89 (13.1)	0.95 (0.68, 1.34)
p-value for additive model			0.79			0.39			0.98

[a]ORs, odds ratios; CI, confidence interval

[b] Due to missing values not all totals are equal

Discussion

Consistent with previously large studies of Ex4-12 SNP [5, 10, 11, 14], we did not observe an independent association between breast cancer risk and the variant Ex4-12 SNP. In addition, our examination of subgroups defined by hormonally-related factors did not reveal any further modification of risk. However, we did observe suggestive evidence of an increased risk associated with the TGG haplotype relative to the common TAA haplotype, assuming a dominant model. These two haplotypes differ at the Ex4-12 and 3′UTR loci, which were not independently associated with breast cancer.

The discrepancy between the individual SNP results and the haplotype results may suggest SNP–SNP interactions, or that the SNPs we genotyped mark other functional variants in *COMT*. We expected the *COMT* TAA haplotype (referred to as the AGG haplotype in the Shifman et al. (2002) paper), which was associated with decreased risk of schizophrenia [18] and increased mRNA levels [17], to be associated with lower risk of breast cancer; however, compared to the CGA or the CGG haplotype, no risk was

Table 2 Age-adjusted Ors[a] and 95% Cis[a] for the association between common (> 10%) *COMT* haplotypes and risk of breast cancer, Long Island Breast Cancer Study Project, 1996–1997

Haplotype name and loci			Haplotype frequencies		Age-adjusted OR (95% CI)[a, b]	*p*-value for additive model
IVS+255	Ex4-12	3′UTR -521	Cases	Controls		
T	A	A	0.3784	0.3905	1.00 (reference)	
C	G	G	0.1447	0.1520	0.98 (0.80, 1.19)	0.83
T	G	G	0.1536	0.1311	1.19 (0.96, 1.49)	0.08
C	G	A	0.1199	0.1234	1.00 (0.80, 1.25)	0.98
T	G	A	0.1050	0.0989	1.09 (0.86, 1.39)	0.48
T	A	G	0.0575	0.0688	0.88 (0.72, 1.07)	0.41
C	A	A	0.0375	0.0305	1.25 (0.82, 1.89)	0.30
C	A	G	0.0034	0.0049	0.70 (0.46, 1.06)	0.66
Global *p*-value=0.46						

[a]ORs, odds ratios; CI, confidence interval

[b]ORs were calculated assuming an additive model; therefore, the ORs represent the incremental odds associated with carrying a copy of the haplotype shown relative to carrying the TAA haplotype, the most common haplotype in our data

associated with the TAA haplotype. The CAA haplotype (referred to as the GGG haplotype in the Shifman et al. (2002) paper) associated with higher risk of schizophrenia [18] was associated with increased risk of breast cancer in our study, although the haplotype was infrequent in our population and results are imprecise.

Among other factors, selection bias may have influenced our results since not every woman donated blood and donation differed by race [19]. Although race was related to genotype frequency, the bias introduced by racial differences in blood donation was likely negligible from the small number of non-white women in our study. In addition, our allele frequencies were similar to published reports of European–Americans. Lastly, evidence from other study populations suggests that genotype frequencies are not related to study participation [30].

In the rapidly evolving field of haplotype association studies, several researchers have proposed statistical models for the unbiased estimation of haplotypes in case–control studies [31–33]. Performance appears to differ based on the magnitude of the relative risk and the complexity of the haplotype structure [31]. In our study, we hypothesized modest relative risks associated with our 3-SNP haplotype; under such circumstances, all methods perform similarly [31]. Therefore, we chose to estimate haplotypes using Schaid's HaploStats program [28, 33], because it adjusts variance estimates for the error associated with estimating haplotypes.

In summary, we found no association between the individual *COMT* SNPs and breast cancer in our large study. However, we did observe some suggestion of a positive association with the TGG *COMT* haplotype. While our study provides evidence for a modest role of COMT in breast cancer risk, a comprehensive survey of genetic variants in larger, well-characterized populations is needed to fully appreciate the influence of *COMT* on breast cancer risk.

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