Null Results in Brief

Cytochrome *P*450 1B1 and Catechol-*O*-Methyltransferase Genetic Polymorphisms and Endometrial Cancer Risk in Chinese Women

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Introduction

Metabolic conversion of estrogen to hydroxyl estrogens has been postulated to be involved in the carcinogenesis of the endometrium. Highly expressed in endometrial tissue, cytochrome *P*450 1B1 (CYP1B1) catalyzes the hydroxylation of 17β-estradiol (E_2) to catechol estrogens 4-hydroxyestradiol (4-OH-E_2) and 2-hydroxyestradiol (2-OH-E_2; ref. 1). Administration of 4-OH-E_2 could induce DNA damage and endometrial adenocarcinoma in CD-1 mice (2). Five common polymorphisms with amino acid substitutions of the *CYP1B1* gene have been described; compared with the wild type, *CYP1B1* variants in codons 48 (Arg → Gly, rs10012), 119 (Ala → Ser, rs1056827), 432 (Leu → Val, rs1056836), and 453 (Asn → Ser, rs1800440) display 2.4- to 3.4-fold higher catalytic efficiency (1, 3-5). Catechol-*O*-methyltransferase (COMT) catalyzes *O*-methylation of catechol estrogens (2-OH-E_2 and 4-OH-E_2) to methoxy-catechol estrogens (2-MeO-E_2 and 4-MeO-E_2), which have no estrogenic activity. If the methylation step is incomplete, some of these catechol estrogens could induce DNA single-strand breaks, or initiate the carcinogenic process through reacting with DNA and forming depurinated adducts (6). A functional polymorphism in the *COMT* gene, a G-to-A transition at codon 108/158 in exon 4 (rs4680), has been reported to result in a 3- to 4-fold reduction in *COMT* activity (7, 8), although another study suggested that the difference in catalytic activity might be less significant (9). Given the importance of *CYP1B1* and *COMT* in estrogen metabolism, it is biologically possible that polymorphisms of these genes that lead to an increase in *CYP1B1* activity and a decrease in *COMT* activity may influence an individual's susceptibility to the risk of endometrial cancer.

We tested this hypothesis by examining five putative functional polymorphisms of the *CYP1B1* and *COMT* genes using data from a recently completed population-based case-control study of endometrial cancer conducted in Shanghai, China.

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Materials and Methods

Detailed study methods have been published previously (10). In brief, this study includes 1,204 incident cases who were between 30 and 69 years of age at diagnosis and 1,212 randomly selected, age-frequency matched population controls. All study participants were interviewed in person by trained interviewers using a standardized and structured questionnaire. The response rates were 82.8% for cases and 74.4% for controls. In addition to the in-person interview, 10-mL blood samples were obtained from 860 cases (71.4%) and 861 (71.0%) controls. The samples were collected in vacutainer tubes containing EDTA and processed typically within 6 hours of blood draw. The buffy coat (WBC) samples were distributed into 2-mL vials and stored at −70°C. For those who did not donate a blood sample at baseline, we collected a sample of exfoliated buccal cells using a modified mouthwash method (16.5% of cases and 16.7% of controls). All collected mouthrinse samples were processed within 6 hours of collection, and the cell pellet for each subject was stored in two 2-mL vials at −70°C. As such, a DNA sample was available for 86.5% of cases and 85.2% of controls.

The allelic discrimination of the *CYP1B1* and *COMT* polymorphisms were assessed with the ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Foster City, CA) using the Taqman genotyping assay with primers and probes obtained from ABI. The Taqman assay method has been described previously (11), and the assay IDs or primers/probes information are listed in Appendix A. The fluorescence level was measured with the ABI PRISM 7900HT sequence detector (Applied Biosystems). Allele frequencies were determined by ABI SDS software. The laboratory staff were blind to the identity of the subjects. Quality control samples were included in the genotyping assays. The concordance rates for the quality control samples were 97.4% (38 of 39) for COMT rs6269 and 100% for all other single nucleotide polymorphisms (SNP).

The χ^2 test was used to compare the distributions of *CYP1B1* and *COMT* alleles and genotypes in cases and controls. The exact χ^2 goodness-of-fit test was used to test Hardy-Weinberg equilibrium of the genotypes. Haplotypes were estimated using PHASE software via a Bayesian method (12). Unconditional logistic regression was employed to estimate the odds ratios and 95% confidence intervals for the associations of *CYP1B1* and *COMT* genotypes with endometrial cancer risk. Interactions between gene-gene and genotype-estrogen exposures were evaluated by constructing a multiplicative term in the logistic regression model. All the analyses were adjusted by age. Potential confounding effects from other demographic

factors and known endometrial cancer risk factors, such as educational level, body mass index, age at menarche, age at menopause, parity, and oral contraceptive use, were also examined, and no appreciable confounding was observed.

Results

The distributions of selected demographic characteristics and major risk factors of endometrial cancer among cases and controls have been reported elsewhere (10). Briefly, cases and controls had similar age distribution. Compared with controls, cases had an earlier age at menarche, later age at menopause, and longer duration of menstruation. Cases were more likely to have a higher educational level and a higher body mass index or waist-hip ratio; to have a family history of colorectal, endometrial, or breast cancer among first-degree relatives; to be nulliparous; and to have never used oral contraceptives. Subjects with genotyping data were representative of all participants in the study with regard to the distribution of major demographic and risk factors.

The frequencies of alleles and common haplotypes of *CYP1B1* and *COMT* polymorphisms among cases and controls are shown in Table 1. All *CYP1B1* and *COMT* SNPs were in Hardy-Weinberg equilibrium among both cases and controls. The common alleles in *CYP1B1* among controls were 81.7% for rs10012, 87.9% for rs1056836, and 87.9% for rs1056837. Variant alleles at rs1056836 and rs1056837 were in strong linkage disequilibrium (Lewontin's $D' = 1.00$; correlation, $r = 0.99$). Among controls, the frequencies of common *COMT* alleles were 72.8% for rs4680 and 64.1% for rs6269. The most common haplotype for *CYP1B1* rs10012, rs1056836, and rs1056837 was C-C-C with the estimated frequencies of 70.5% among cases and 71.5% among controls. Overall, the frequency differences of *CYP1B1* and *COMT* polymorphism and *CYP1B1* haplotype between cases and controls were not statistically significant.

We did not find significant associations of *CYP1B1* and *COMT* genotypes with endometrial cancer risk (Table 2). Analyses stratified by menopausal status showed similar results, and no interaction between menopausal status and genotype was evident (all *P*s for interaction tests were > 0.05). We also examined the interaction of *CYP1B1* and *COMT* genotypes with estrogen-related factors, such as body mass index, waist-hip ratio, years of menstruation, and oral contraceptive use, and found no significant interaction (data not shown).

The likelihood ratio test was done to explore the relationship between common *CYP1B1* haplotypes and endometrial cancer risk, pooling all haplotypes with frequencies <5% into a single category. Using the most common haplotype, which contains wild alleles at rs1002, rs1056836, and rs1056837 as the reference group, we did not find an association between *CYP1B1* haplotypes and endometrial cancer (data not shown).

We further explored the joint effect of two SNPs of the *COMT* gene on endometrial cancer risk. Comparing genotype AA with the GG/AG genotypes for SNP rs4680 among subjects carrying none or one variant allele in rs6269, the odds ratio (95% confidence interval) was 1.29 (0.92-1.82). Among women with none or one variant allele in rs4680, the odds ratio (95% confidence interval) was 1.05 (0.81-1.27) for the GG genotype in SNP rs6269 compared with the AA/AG genotypes. Similarly, using women carrying none or one variant allele in *CYP1B1* SNPs rs10012, rs1056836, and rs1056837 as the reference group, odds ratios (95% confidence interval) were 0.77 (0.48-1.23) for women carrying any one of the homozygous variant-type alleles of *CYP1B1* SNPs and 0.50 (0.24-1.03) for women carrying any two of the homozygous variant-type alleles. Finally, we examined the potential interactive effect between *CYP1B1* and *COMT* genotypes and no significant interaction was observed.

Discussion

Laboratory studies have shown that both *CYP1B1* and *COMT* are expressed in the endometrium (1, 7, 13). *CYP1B1* and *COMT* are involved in the hydroxylation and conjugation of estradiol and thus may be important factors contributing to host susceptibility to endometrial cancer. *CYP1B1* variants are more efficient than wild types in the conversion and accumulation of carcinogenic catechol estrogens (1). The *COMT* variants, on the other hand, are associated with a reduction of inactivating catechol estrogens to nongenotoxic methylethers (7, 8). Therefore, it is biologically possible that women with the variant genotypes of *CYP1B1* and *COMT* may have a greater risk of endometrial cancer.

Polymorphisms of *CYP1B1* have been investigated in relation to breast, ovarian, and endometrial cancers with conflicting results (3, 8, 9, 14, 15). In our large-scale, case-control study conducted in Shanghai, we found that *CYP1B1* SNPs in codons 48, 119, and 432 were not associated with breast cancer risk (15). Four epidemiologic studies, mostly conducted in Caucasians, which have investigated *CYP1B1* gene polymorphisms in relation to endometrial cancer risk in recent years have resulted in mixed findings (16-19). Rylander-Rudqvist et al. found no overall association between the *CYP1B1* codon 48, 119, and 453 genotypes and endometrial cancer risk (16). Similarly, Doherty et al. reported no strong alteration in risk among women with the *CYP1B1* codon 432 variant alleles (17). However, in a nested case-control study, McGrath et al. reported that a decreased risk of endometrial cancer was associated with the *CYP1B1* codon 453 variant allele (odds ratio, 0.62; 95% confidence interval, 0.42-0.91; ref. 18) but not with the *CYP1B1* codon 432 polymorphism. A case-control study that included 113 Japanese endometrial cancer patients and 100 healthy female controls observed a

Table 1. Allele frequencies (%) of the *CYP1B1* and *COMT* genes and haplotype distribution of CYP1B1 polymorphisms, the Shanghai Endometrial Cancer Study

Alleles		Cases (%)	Controls (%)	*P*
CYP1B1				
rs10012	C	81.2	81.7	0.68
	G	18.8	18.3	
P (HWE)		0.11	0.25	
rs1056836	C	87.6	87.9	0.73
	G	12.4	12.1	
P (HWE)		0.39	0.06	
rs1056837	C	87.9	87.9	0.99
	T	12.1	12.1	
P (HWE)		0.22	0.05	
COMT				
rs4680	G	73.2	72.8	0.76
	A	26.8	27.2	
P (HWE)		0.09	0.16	
rs6269	A	64.3	64.1	0.87
	G	35.7	35.9	
P (HWE)		0.62	0.31	

Estimated frequency of CYP1B1 haplotypes (in the order of SNP 1-2-3 based on their chromosome positions)

	Cases	Controls
C-C-C	70.5	71.5
C-G-C	0.4	0.1
C-G-T	10.3	10.0
G-C-C	17.0	16.3
G-G-T	1.8	1.9
Overall χ^2 test		$P = 0.38$

NOTE: The number of participants does not add up to the total number of women because of missing data on genotypes for some participants. SNP1, rs10012; SNP2, rs1056836; SNP3, rs1056837.
Abbreviation: HWE, Hardy-Weinberg equilibrium.

Table 2. Associations between CYP1B1 and COMT genotypes and endometrial cancer risk

	All subjects			Premenopausal women			Postmenopausal women		
	Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)
CYP1B1									
rs10012									
C/C	676	693	1.0	287	252	1.0	389	441	1.0
C/G	333	298	1.16 (0.97-1.39)	146	127	0.99 (0.74-1.33)	187	171	1.24 (0.97-1.59)
G/G	29	40	0.75 (0.46-1.22)	17	16	0.95 (0.47-1.93)	12	24	0.57 (0.28-1.15)
P_{trend}			0.69			0.91			0.63
C/C+C/G	1,009	991	1.0	433	379	1.0	576	612	1.0
G/G	29	40	0.71 (0.44-1.15)	17	16	0.95 (0.47-1.92)	12	24	0.53 (0.26-1.07)
$P_{interaction}$ = 0.27									
rs1056836									
C/C	792	806	1.0	351	299	1.0	441	507	1.0
C/G	232	206	1.16 (0.94-1.42)	93	90	0.87 (0.63-1.21)	139	116	1.38 (1.05-1.82)
G/G	13	22	0.61 (0.30-1.21)	6	7	0.64 (0.21-1.94)	7	15	0.54 (0.22-1.33)
P_{trend}			0.73			0.28			0.23
C/C+C/G	1,024	1,012	1.0	444	389	1.0	580	623	1.0
G/G	13	22	0.59 (0.29-1.17)	6	7	0.66 (0.22-2.00)	7	15	0.50 (0.20-1.24)
$P_{interaction}$ = 0.62									
rs1056837									
C/C	797	803	1.0	353	297	1.0	444	506	1.0
C/T	229	205	1.14 (0.93-1.41)	94	91	0.86 (0.62-1.20)	135	114	1.35 (1.02-1.79)
T/T	11	22	0.51 (0.25-1.06)	4	7	0.42 (0.12-1.45)	7	15	0.53 (0.22-1.32)
P_{trend}			0.99			0.16			0.30
C/C+C/T	1,026	1,008	1.0	447	388	1.0	579	620	1.0
T/T	11	22	0.49 (0.24-1.02)	4	7	0.43 (0.13-1.50)	7	15	0.50 (0.20-1.24)
$P_{interaction}$ = 0.94									
COMT									
rs4680									
G/G	563	534	1.0	229	204	1.0	334	330	1.0
A/G	383	425	0.88 (0.74-1.05)	176	160	0.97 (0.73-1.29)	207	265	0.77 (0.61-0.98)
A/A	85	67	1.24 (0.89-1.74)	42	30	1.24 (0.75-2.06)	43	37	1.15 (0.72-1.83)
P_{trend}			0.76			0.64			0.33
G/G+A/G	946	959	1.0	405	364	1.0	541	595	1.0
A/A	85	67	1.29 (0.92-1.79)	42	30	1.25 (0.77-2.05)	43	37	1.28 (0.81-2.01)
$P_{interaction}$ = 0.99									
rs6269									
A/A	420	414	1.0	194	161	1.0	226	253	1.0
A/G	478	489	0.98 (0.82-1.16)	204	178	0.94 (0.70-1.26)	274	311	0.99 (0.78-1.26)
G/G	127	125	1.01 (0.77-1.33)	48	54	0.74 (0.47-1.15)	79	71	1.24 (0.86-1.80)
P_{trend}			0.87			0.22			0.39
A/A+A/G	898	903	1.0	398	339	1.0	500	564	1.0
G/G	127	125	1.02 (0.79-1.33)	48	54	0.76 (0.50-1.15)	79	71	1.26 (0.89-1.77)
$P_{interaction}$ = 0.07									

NOTE: The number of participants does not add up to the total number of women because of missing data on genotypes for some participants.
*Unconditional logistic model adjusted for age.

significantly increased risk of endometrial cancer associated with the *CYP1B1* codon 119 and 432 polymorphisms (19). Although our results differ from the findings of the small-scale Japanese study (19), our results are consistent with most previous studies (16-18), depicting no association of endometrial cancer risk with *CYP1B1* genotypes.

We did not find any association between *COMT* rs4680 and rs6269 genotypes and the risk of endometrial cancer. Previous studies investigating the relationship of *COMT* rs4680 genotype and hormone-related cancers have had inconsistent results (9, 15, 17, 18, 20). McGrath et al. did not observe an association between the *COMT* rs4680 genotype and endometrial cancer (18), whereas Doherty et al. reported that the low-activity allele was associated with a slightly decreased risk of endometrial cancer (17). The inconsistency in study findings may result from the ethnic differences of the study populations and the limitations of the study designs. One recent study also suggested that other functional variations, especially regulatory variations, might exist and that *COMT* haplotypes could be used to ascertain the effect of *COMT* on disease etiology (21). Results from another study showed that CpG hypermethylation could selectively inactivate *COMT*, leading to the accumulation of catechol estrogens and promotion of endometrial carcinogenesis (22).

Chinese women typically have a low level of circulating estrogen (23), which might mask the effect of estrogen metabolic gene polymorphisms. We conducted analyses among women with conditions related to a high level or long period of estrogen exposure, such as women with high body mass index/waist-hip ratio and longer durations of menstruation. However, we failed to find any gene-environment interactions with the above factors.

Strengths of this study include the population-based study design and large sample size, which minimized selection bias and led to relatively stable risk estimation. The detailed exposure information enabled an evaluation of gene-environment interactions. Nevertheless, the statistical power in subgroups of our study remained limited due to the low frequencies of variant alleles, which prevented our ability to identify weak associations. The study applied the candidate gene approach, which primarily focuses on the potential function of common genetic variants (>5%) and SNPs with amino acid changes. However, we cannot rule out the possibility that SNPs of *CYP1B1* and *COMT* other than those included in our study may be related to the risk of endometrial cancer. Given that multiple genes are involved in estrogen biosynthesis and metabolism (24, 25), the confounding and/or modifying effects of other genes also cannot be excluded.

Appendix A. Summary of the genotyping assays of CYP1B1 and COMT polymorphisms

Gene	SNP	Primer sequence (5′-3′)	Probe sequence (5′-3′)
CYP1B1	R48G (rs10012)	F, GCTGCTGAGGCAACGGA	VIC, CAGCTCCGGTCCGC
		R, CAGTGGCCACGCAAACG	FAM, AGCTCGGGTCCGC
	V432L (rs1056836)	F, GATCAAAGTTCTCCGGGTTAGG	VIC, ATGACCCACTGAAGTG
		R, TTTGTCAACCAGTGGTCTGTGAAT	FAM, ATGACCCAGTGAAGTG
COMT	*D449D* (rs1056837)	ABI Assay ID: C_3099975_20	ABI Assay ID: C_3099975_20
	V158M (rs4680)	F, CCCAGCGGATGGTGGAT	VIC, TTCGCTGGCATGAAG
		R, CAGGCATGCACACCTTGTC	FAM, TCGCTGGCGTGAAG
	rs6259	ABI Assay ID: C_2538746_1_	ABI Assay ID: C_2538746_1_

Abbreviations: F: forward; R: reverse.

In summary, we found no strong evidence that common polymorphisms of the *CYP1B1* and *COMT* genes play a major role in the development of endometrial cancer among Chinese women.

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