RESEARCH ARTICLE

Lack of Associations of the COMT Val158Met Polymorphism with Risk of Endometrial and Ovarian Cancer: a Pooled Analysis of Case-control Studies

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Abstract

This meta-analysis was conducted to examine whether the genotype status of Val158Met polymorphism in catechol-O-methyltransferase (COMT) is associated with endometrial and ovarian cancer risk. Eligible studies were identified by searching several databases for relevant reports published before January 1, 2014. Pooled odds ratios (ORs) were appropriately derived from fixed-effects or random-effects models. In total, 15 studies (1,293 cases and 2,647 controls for ovarian cancer and 2,174 cases and 2,699 controls for endometrial cancer) were included in the present meta-analysis. When all studies were pooled into the meta-analysis, there was no evidence for significant association between COMT Val158Met polymorphism and ovarian cancer risk (Val/Met versus Val/Val: OR=0.91, 95% CI=0.76-1.08; Met/Met versus Val/Val: OR=0.90, 95% CI=0.73-1.10; dominant model: OR=0.90, 95% CI=0.77-1.06; recessive model: OR=0.95, 95% CI=0.80-1.13). Similarly, no associations were found in all comparisons for endometrial cancer (Val/Met versus Val/Val: OR 0.97, 95% CI=0.77-1.21; Met/Met versus Val/Val: OR=1.02, 95% CI=0.73-1.42; dominant model: OR=0.98, 95% CI=0.77-1.25; recessive model: OR=1.02, 95% CI=0.87-1.20). In the subgroup analyses by source of control and ethnicity, no significant associations were found in any subgroup of population. This meta-analysis strongly suggests that COMT Val158Met polymorphism is not associated with increased endometrial and ovarian cancer risk.

Keywords: COMT - endometrial cancer - ovarian cancer - risk - meta-analysis

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Introduction

Ovarian cancer is associated with the highest mortality rate among gynaecological malignancies (Hennessy et al., 2009). There are over 205, 000 new cases and 125, 000 deaths annually from ovarian cancer (Jemal et al., 2011). Endometrial cancer is the fourth most common cancer among women and the most common gynecological cancer in the USA (Jemal et al., 2009). Multiple lines of evidence support a central role of hormones in the etiology of endometrial and ovarian cancers (Lundin et al., 2012). Polymorphisms within genes responsible for estrogen catabolism could alter cellular levels of genotoxic 4-hydroxylated catechol estrogens and antiangiogenic 2-methoxyestradiol, thus influencing risk of developing endometrial and ovarian cancers.

Catechol-O-methyltransferase (COMT) catalyzes catechol estrogens to form methyl conjugates, a process that detoxifies the catechol estrogens and prevent them from forming depurinating adducts. In addition, the intermediate products of catechol estrogen metabolism, including 2- and 4-methoxyestradiol, may themselves have antiestrogenic properties and have been shown to inhibit tumor cell growth, stimulate apoptosis, and inhibit angiogenesis (Chang et al., 2012). The COMT gene is located on chromosome 22q11.2, consisting of six exons with exons 1 and 2 being noncoding (Park et al., 2009). Lachman et al. identified a functional polymorphism in the COMT gene, a G-A transition at codon 158 in exon 4, leading to a substitution of methionine for valine that result in a thermolabile enzyme with reduced activity (Lachman et al., 1996). It has been hypothesized that this COMT polymorphism (rs4680) may modulate risk of hormonally responsive cancers because of a decreased ability of COMT to methylate and thereby inactivate catechol estrogens, as well as through decreased production of the intermediate products of catechol estrogen metabolism (Lajin et al., 2013).

To data, several epidemiologic studies have investigated the relationship between the COMT polymorphism and predisposition to endometrial and ovarian cancer (Goodman et al., 2000; Goodman et al., 2001; Garner et al.,

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2002; McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Sellers et al., 2005; Tao et al., 2006; Holt et al., 2007; Szyllo et al., 2007; Wang et al., 2007; Zhao et al., 2007; Delort et al., 2008; Hirata et al., 2008; Jakubowska et al., 2010). Although it is an appealing hypothesis that genes affecting the production or metabolism of estrogen may affect the risk of hormonally related cancers, the evidence from the literature is inconsistent. Individual studies may have been underpowered to detect the effect of this COMT polymorphism on the susceptibility of endometrial and ovarian cancer. Therefore we performed this meta-analysis of all eligible studies to derive a more precise estimation of the association of COMT Val158Met with the endometrial and ovarian cancer risk.

Materials and Methods

Identification and Eligibility of Relevant Studies

A comprehensive literature search was performed using the PubMed and Medline database for relevant articles published (the last search update was January 1, 2014) with the following key words "polymorphism", "COMT", "cancer" and "endometrial" or "ovarian". The search was limited to human studies. We included all the case-control studies and cohort studies that investigated the association between COMT polymorphism and endometrial and ovarian cancer risk with genotyping data for Val158Met polymorphism. All eligible studies were examined carefully, and their bibliographies were checked for other relevant publications.

Inclusion Criteria

All eligible studies were included if they met the following criteria: (1) evaluate the association between COMT Val158Met polymorphism and the risk of endometrial and ovarian cancer; (2) studies with full-text article; and (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were as follows: (1) not for endometrial and ovarian cancer research; (2) the Val158Met polymorphism distribution missing; and (3) duplicate of previous publication.

Data Extraction

Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria listed above. Reviews, non-original articles and studies on endometrial and ovarian cancer cell lines and animal models were excluded from the meta-analysis. The following data were collected from each study: first author's name, year of publication, ethnicity, polymorphism variant, source of controls, total numbers of cases and controls, and genotyping methods.

Statistical Methods

We performed a meta-analysis to estimate the risk (ORs) of endometrial and ovarian cancer associated with COMT Val158Met polymorphism. The risks (ORs) of endometrial and ovarian cancers associated with the COMT Val158Met polymorphism were estimated for each study. The pooled ORs were performed for co-dominant model (Val/Met versus Val/Val, Met/Met versus Val/Val), dominant model (Val/Met+Met/Met versus Val/Val), and recessive model (Met/Met versus Val/Met+Val/Val), respectively. In addition to the comparison among all subjects, we also performed stratification analyses by ethnicity and source of controls. Heterogeneity among studies was checked by the random-effects model (the DerSimonian and Laird method) if there was significant heterogeneity. A P value of more than the level of 0.05 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of the fixed-effects model (the Mantel-Haenszel method). The publication bias was diagnosed by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was assessed by the method of Egger's linear regression test. The significance of the intercept was determined by the t test suggested by Egger (p<0.05 was considered representative of statistically significant publication bias). All the statistical tests were performed with SPSS version 13.0 and STATA version10.0 (Stata Corporation, College Station, TX, USA).

Results

Eligible Studies and Meta-analysis Databases

A total of 15 studies with full-text articles examined the association of COMT Val158Met polymorphism with endometrial and ovarian cancer were found (Goodman et al., 2000; Goodman et al., 2001; Garner et al., 2002; McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Sellers et al., 2005; Tao et al., 2006; Holt et al.,

Table 1. Main Characteristics of All Studies Included in the Meta-Analysis

First author	Year	Cancer type	Genotyping method	Case.(age)	Control.(age)	Design of experiment
JE.Goodman	2000	Ovarian cancer	PCR-RFLP	108 (58.9±13.1)	106 (51.0±14.8)	HB
MT.Goodman	2001	Ovarian cancer	PCR-RFLP	125 (18-84 years)	144 (age-matched)	PB
EI.Garner	2002	Ovarian cancer	PCR-RFLP	210 (NA)	225 (age-matched)	PB
M.McGrath	2004	Endometrial cancer	PCR-RFLP	215 (59.0±7.8)	641 (59.0±7.6)	PB
TS.Zimarina	2004	Endometrial cancer	PCR-RFLP	124 (59.0±8.4)	140 (63.0±5.7)	HB
JA.Doherty	2005	Endometrial cancer	PCR-RFLP	371 (50-69 years)	420 (age-matched)	PB
TA.Sellers	2005	Ovarian cancer	NanoChip	489 (>20 years)	596 (age-matched)	HB
MH.Tao	2006	Endometrial cancer	Taqman Assay	1,031 (30-69 years)	1,026 (age-matched)	PB
SK.Holt	2007	Ovarian cancer	Taqman assay	310 (35-54 years)	576 (35-54 years)	PB
K.Szyllo	2007	Endometrial cancer	PCR-RFLP	151 (68.8±6.7)	197 (age-matched)	HB
XM.Zhao	2007	Endometrial cancer	PCR-RFLP	132 (46-55 years)	110 (40-45 years)	HB
L.Delort	2008	Ovarian cancer	Taqman assay	51 (NA)	1000 (NA)	PB
H.Hirata	2008	Endometrial cancer	PCR-RFLP	150 (60.0±9.8)	165 (60.0±9.6)	HB

2007; Szyllo et al., 2007; Zhao et al., 2007; Delort et al., 2008; Hirata et al., 2008). As summarized in (Table 1), the eligible studies were selected for this meta-analysis, including 1, 293 cases and 2, 647 controls for ovarian cancer (from eight studies) and 2, 174 cases and 2, 699 controls for endometrial cancer (from seven studies). All these studies indicated that the distribution of genotypes in controls was consistent with Hardy-Weinberg equilibrium (Tables 2). And the subjects of controls were matched for age. Among these studies, seven were population-based, and six were hospital-based. All of the cases were pathologically confirmed.

Quantitative Synthesis

(Table 3) lists the main results of the meta-analysis for ovarian cancer: overall, no significant associations were found between COMT Val158Met polymorphism and ovarian cancer risk when all studies pooled into the meta-analysis (Val/Met versus Val/Val: OR=0.91, 95% CI=0.76-1.08, p=0.613 for heterogeneity; Met/Met versus Val/Val: OR=0.90, 95% CI=0.73-1.10, p=0.897 for heterogeneity; dominant model: OR=0.90, 95% CI=0.77-1.06, p=0.620 for heterogeneity; recessive model: OR=0.95, 95% CI=0.80-1.13, p=0.927 for heterogeneity). There was no evidence for the association between COMT Val158Met polymorphism and ovarian cancer risk in subgroup analyses based on ethnicity and source of control.

(Table 3) also lists the main results of the meta-analysis for endometrial cancer: overall, no significant associations were found between COMT Val158Met polymorphism and endometrial cancer risk when all studies pooled into the meta-analysis (Val/Met versus Val/Val: OR=0.97, 95% CI=0.77-1.21, p=0.042 for heterogeneity; Met/Met versus Val/Val: OR=1.02, 95% CI=0.73-1.42, p=0.012 for heterogeneity; dominant model: OR=0.98, 95% CI=0.77-1.25, p=0.010 for heterogeneity; recessive model: OR=1.02, 95% CI=0.87-1.20, p=0.116 for heterogeneity). There was substantial heterogeneity among these studies in overall comparisons. Therefore, we assessed the source of heterogeneity by source of controls and ethnicity. It was detected that the systemic results were not affected by these characteristics (p>0.270 for ethnicity and p>0.248 for source of control). There was no evidence for the association between COMT Val158Met polymorphism and endometrial cancer risk in subgroup analyses based on ethnicity and source of control. And the homozygote genotype Met/Met did not show a significant increased risk of endometrial and ovarian cancer (Figure 1).

Publication Bias Test

We performed Begg's funnel plot and Egger's test to assess the publication bias of literatures. The shape of

Table 2. Distribution of COMT Val158Met Polymorphism of Ovarian and Endometrial Cancer and Hardy-Weinberg Equilibrium Results

First author	Ethnicity	Case (genotype No.)			Control (genotype No.)			HWE
		Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met	
ovarian cancer								
JE.Goodman [2000]	Caucasian	27	54	27	25	52	29	0.905
MT.Goodman [2001]	Mixed	52	57	16	68	57	19	0.827
EI.Garner [2002]	Caucasian	59	103	48	52	119	54	0.861
TA.Sellers [2005]	Caucasian	110	224	119	127	269	147	0.903
TA.Sellers [2005]	African	19	17	0	23	30	0	0.059
SK.Holt [2007]	Caucasian	72	129	76	104	209	137	0.948
SK.Holt [2007]	African	19	10	4	52	58	16	0.200
L.Delort [2008]	Caucasian	11	22	18	237	480	283	0.916
endometrial cancer								
M.McGrath [2004]	Caucasian	55	105	55	161	308	172	0.874
TS.Zimarina [2004]	Caucasian	29	65	30	23	73	44	0.996
JA.Doherty [2005]	Caucasian	97	174	100	90	207	123	0.953
MH.Tao [2006]	Asian	563	383	85	534	425	67	0.683
K.Szyllo [2007]	Caucasian	46	81	24	48	110	39	0.253
XM.Zhao [2007]	Asian	39	77	16	52	50	8	0.779
H.Hirata [2008]	Caucasian	32	81	37	48	90	27	0.277

Table 3. Results of Meta-Analysis for COMT Val158Met Polymorphism and Ovarian and Endometrial Cancer Risk

Study group	Val/Met versus Val/Val		Met/Met versus Val/Val		Dominant model		Recessive model	
	OR(95%)	P/P_{het}	OR(95%)	P/P_{het}	OR(95%)	P/P_{het}	OR(95%)	P/P_{het}
Ovarian cancer	0.91(0.76-1.08)	0.269/0.613	0.90(0.73-1.10)	0.308/0.897	0.90(0.77-1.06)	0.217/0.620	0.95(0.80-1.13)	0.566/0.927
Control source								
Population-based	0.89(0.71-1.12)	0.318/0.310	0.88(0.67-1.16)	0.363/0.708	0.89(0.72-1.10)	0.283/0.311	0.96(0.76-1.20)	0.695/0.761
Hospital-based	0.93(0.71-1.21)	0.593/0.761	0.92(0.67-1.27)	0.614/0.849	0.92(0.72-1.19)	0.521/0.775	0.95(0.73-1.22)	0.672/0.813
Ethnicity								
African	0.57(0.31-1.03)	0.064/0.542	0.68(0.20-2.31)	0.540/ -	0.59(0.33-1.04)	0.069/0.632	0.95(0.29-3.05)	0.929/ -
Caucasian	0.91(0.75-1.10)	0.313/0.942	0.89(0.72-1.11)	0.301/0.781	0.90(0.75-1.08)	0.252/0.884	0.95(0.80-1.13)	0.575/0.750
Endometrial cancer	0.97(0.77-1.21)	0.773/0.042	1.02(0.73-1.42)	0.923/0.012	0.98(0.77-1.25)	0.888/0.010	1.02(0.87-1.20)	0.772/0.116
Control source								
Population-based	0.86(0.74-1.00)	0.048/0.638	0.97(0.78-1.21)	0.790/0.206	0.89(0.77-1.02)	0.095/0.600	1.02(0.84-1.24)	0.830/0.245
Hospital-based	1.12(0.68-1.82)	0.662/0.025	1.14(0.53-2.45)	0.740/0.004	1.12(0.64-1.95)	0.692/0.004	1.03(0.77-1.39)	0.840/0.060
Ethnicity	1.27(0.54-3.00)	0.580/0.003	1.32(0.96-1.82)	0.085/0.120	1.34(0.58-3.11)	0.499/0.002	1.34(0.98-1.83)	0.066/0.518
Caucasian	0.89(0.73-1.09)	0.254/0.402	0.86(0.68-1.08)	0.200/0.050	0.88(0.73-1.06)	0.187/0.149	0.93(0.77-1.12)	0.436/0.204

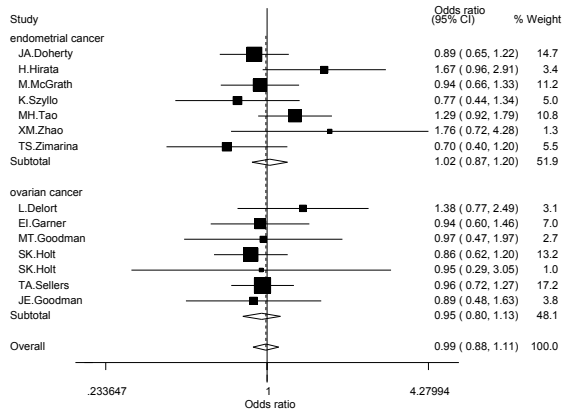

Figure 1. Forest Plot of COMT Val158Met Polymorphism with Endometrial and Ovarian Cancer when Stratified by Cancer Type, Comparing Met/Met genotype to Val/Met+Val/Val Genotype (data for heterogeneity was shown in Table 3)

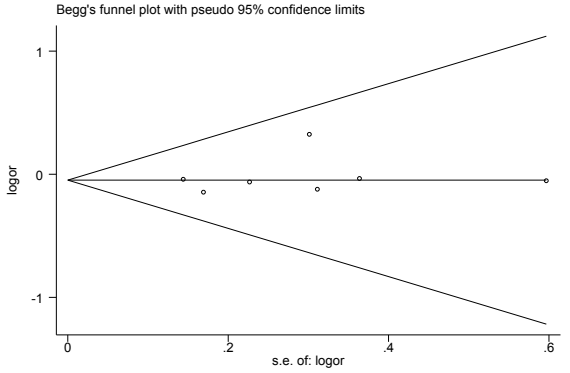

Figure 2-A. Funnel Plot Analysis for Odds Ratios of Recessive Model for of COMT Val158Met in Ovarian Studies

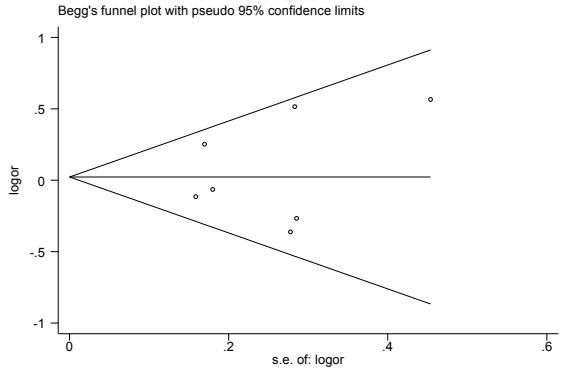

Figure 2-B. Funnel plot Analysis for Odds Ratios of Recessive Model for of COMT Val158Met in Endometrial Studies

the funnel plots did not reveal any evidence of obvious asymmetry. We present funnel plot for ORs in recessive model of COMT Val158Met with ovarian cancer and endometrial cancer in (Figure 2). And the results of Egger's test did not suggest any evidence of publication bias (p=0.525 for ovarian cancer, p=0.666 for endometrial cancer). Although the frequency of demographic variables for cases and controls in one study did not match for age, the corresponding pooled ORs were not qualitatively altered with or without this study.

Discussion

Catechol-O-methyltransferase (COMT) is a phase II enzyme that is involved in the conjugation and inactivation of catechol estrogens (Axelrod et al., 1958). COMT catalyzes the methylation of catechol estrogens to less polar monomethyl ethers. O-Methylation increases the concentrations of 4-methoxyestradiol (4-MeOE2) and 2-methoxyestradiol (2-MeO-E2): 2-MeO-E2 possesses anti-proliferative, cytotoxic and apoptotic activity therefore decreasing the potential for DNA damage (Dawling et al., 2001). Our study sought to examine whether variants in COMT Val158Met are associated with endometrial and ovarian cancer. The present meta-analysis of these fifteen studies, including including 1, 293 cases and 2, 647 controls for ovarian cancer and 2, 174 cases and 2, 699 controls for endometrial cancer, provides most comprehensive analysis on the association of COMT Val158Met polymorphism with endometrial and ovarian cancer risk. We based the interpretation of our results on the magnitude and direction of the ORs, not statistical significance.

Allelic variation in COMT is thought to be directly related to enzymatic activity, including high-activity (Val/Val), intermediate-activity (Val/Met), and low-activity (Met/Met) variants. We observed no evidence for an increased risk of endometrial and ovarian cancer associated with COMT Val158Met polymorphism in the overall studies population. And there was no evidence for the association between COMT Val158Met polymorphism and endometrial and ovarian cancer risk in subgroup analyses based on ethnicity and source of control. Previous studies investigating the relationship of COMT Val158Met polymorphism and hormone-related cancers have had inconsistent results. McGrath et al. did not observe an association between the polymorphism and endometrial cancer (McGrath et al., 2004); whereas Doherty et al. reported that the low-activity allele was associated with a slightly decreased risk of endometrial cancer (Doherty et al., 2005). Results on the COMT Val158Met polymorphism with breast cancer have also been conflicting, with an increased risk for premenopausal breast cancer associated with the low activity variant reported by Thompson et al., 1998, and a null association reported by Millikan et al., 1998. The inconsistency in study findings may result from the ethnic differences of the study populations and the limitations of the study designs.

There were studies also suggested of an interaction between the COMT and CYP1B1 polymorphism and other functional variations might exist. Goodman et al. found that the risk of ovarian cancer associated with the CYP1B1 Val allele was stronger among women with the COMT Met variant than among women with the homozygous COMT Val/Val genotype (Goodman et al., 2001). It is possible that these women had reduced ability to prevent the cytotoxic and genotoxic damage caused by products of 4-hydroxylated catechol estrogen. However, we did not observe a relationship between the COMT Val158Met polymorphism and endometrial and ovarian cancer, and our findings were consistent with most of the related studies as summarized in this meta-analysis. It has

been suggested that the variation at COMT Val158Met polymorphism may not be sufficient to identify all genetic variation in COMT, and COMT haplotypes should be used in association studies to ascertain the contribution of COMT in disease etiology (DeMille et al., 2001).

Strengths of our meta-analysis include the large sample size and increasing the statistical power of the analysis based on substantial number of cases and controls from differential studies, which minimized selection bias and led to relatively stable risk estimation. The limitations of this meta-analysis should be also acknowledged. First, our results were based on single-factor estimates without adjustment for other risk factors including age at diagnosis, lifestyle, and other factors. The results from Yuzhalin et al. suggested that carriage of non-O blood types increased the risk of ovarian cancer by 40-60%, and the magnitude of this relationship was strongest in women with the AB (IV) blood group (Yuzhalin et al., 2012). And by tackling of obesity epidemic in Arab countries, Ortashi et al. indicated that obesity is an important risk factor for endometrial cancer (Ortashi et al., 2013). Second, the controls were not uniformly defined. Some studies used a healthy population as the reference group, whereas others selected hospital patients without organic endometrial and ovarian cancer as the reference group. Therefore, non-differential misclassification bias is possible because these studies may have included the control groups who have different risks of developing endometrial and ovarian cancer.

In conclusion, this meta-analysis did not find any evidence for the association between COMT Val158Met polymorphism and endometrial and ovarian cancer. However, it is necessary to conduct large sample studies using homogeneous patients, and well-matched controls. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between Val158Met polymorphism and endometrial and ovarian cancer.

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