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

RESEARCH ARTICLE

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 date, 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.,...
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 model) 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., 2007). In the meta-analysis all studies should be included, 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).

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 |
|--------------|------|-------------|-------------------|------------|--------------|-------------------|
| J.Goodman    | 2000 | Ovarian cancer | PCR-RFLP           | 108 (58.9±13.1) | 106 (51.0±14.8) | HB                |
| M.Goodman    | 2001 | Ovarian cancer | PCR-RFLP           | 125 (18-84 years) | 144 (age-matched) | PB                |
| E.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                |
| D.Zimarina   | 2004 | Endometrial cancer | PCR-RFLP | 124 (59.0±8.4) | 140 (63.0±5.7) | HB                |
| J.A.Doherty  | 2005 | Endometrial cancer | PCR-RFLP | 371 (50-69 years) | 420 (age-matched) | PB                |
| T.Sellers    | 2005 | Ovarian cancer | NanoChip           | 489 (>20 years) | 596 (age-matched) | HB                |
| M.Tao        | 2006 | Endometrial cancer | Taqman Assay | 0.031 (30-69 years) | 1.026 (age-matched) | PB                |
| S.K.Holt     | 2007 | Ovarian cancer | Taqman assay       | 310 (35-54 years) | 576 (35-54 years) | PB                |
| M.Szylo      | 2007 | Endometrial cancer | PCR-RFLP | 151 (68.8±6.7) | 197 (age-matched) | HB                |
| Y.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                |

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COMT Val158Met Polymorphism is Not Associated with Risk of Endometrial and Ovarian Cancer: a Pooled Analysis

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014  6183

DOI:http://dx.doi.org/10.7314/APJCP.2014.15.15.6181

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      |
| EL.Garner [2002]       | Caucasian | 59      | 103     | 48      | 52      | 119     | 54      | 0.861      |
| TA.Sellers [2005]      | Caucasian | 110     | 224     | 119     | 127     | 269     | 147     | 0.903      |
| SK.Holt [2007]         | African   | 19      | 17      | 4      | 23      | 30      | 0       | 0.059      |
| TA.Sellers [2005]      | African   | 72      | 129     | 76      | 104     | 209     | 137     | 0.948      |
| L.Delori [2008]        | African   | 11      | 22      | 18      | 237     | 480     | 283     | 0.916      |
| endometrial cancer      |           |         |         |         |         |         |         |            |
| MM.McGrath [2004]      | Caucasian | 55      | 105     | 55      | 161     | 308     | 172     | 0.874      |
| SK.Holt [2007]         | Caucasian | 72      | 129     | 76      | 104     | 209     | 137     | 0.948      |
| TA.Sellers [2005]      | African   | 19      | 17      | 4      | 23      | 30      | 0       | 0.059      |
| L.Delori [2008]        | Caucasian | 32      | 81      | 37      | 48      | 52      | 16      | 0.200      |
|                         |           |         |         |         |         |         |         |            |
| (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. And the homozygote genotype Met/Met did not show a significant increased risk of endometrial and ovarian cancer (Figure 1).

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

| Study group             | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val | Val/Met versus Val/Val |
|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
|                        | OR(95%)                | P/P_{het}              | OR(95%)                | P/P_{het}              | OR(95%)                | P/P_{het}              | OR(95%)                | P/P_{het}              |
| Ovarian cancer         |                        |                        |                        |                        |                        |                        |                        |                        |
| Control source         |                        | 0.91(0.76-1.08)         | 0.2690/0.613           | 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            |
| Population-based       | 0.89(0.71-1.12)         | 0.3180/0.510           | 0.88(0.67-1.16)         | 0.363/0.708            | 0.89(0.72-1.10)         | 0.283/0.311            | 0.96(0.74-1.20)         | 0.693/0.761            |
| Hospital-based         | 0.93(0.71-1.21)         | 0.5930/0.761           | 0.92(0.67-1.27)         | 0.614/0.849            | 0.92(0.72-1.19)         | 0.521/0.775            | 0.93(0.73-1.22)         | 0.672/0.813            |
| Ethnicity              |                        |                        |                        |                        |                        |                        |                        |                        |
| African                | 0.57(0.31-1.03)         | 0.0640/0.542           | 0.68(0.20-2.31)         | 0.540/0.90             | 0.59(0.33-1.04)         | 0.069/0.632            | 0.95(0.29-3.05)         | 0.929/0.24             |
| Caucasian              | 0.91(0.75-1.10)         | 0.3130/0.942           | 0.89(0.72-1.11)         | 0.30(0.781)            | 0.90(0.75-1.08)         | 0.252/0.884            | 0.95(0.80-1.13)         | 0.375/0.750            |
| Endometrial cancer     | 0.97(0.77-1.21)         | 0.7730/0.042           | 1.02(0.73-1.42)         | 0.923/0.012            | 0.98(0.77-1.25)         | 0.88/0.010             | 1.02/0.87-1.20         | 0.77/0.161             |
| Control source         |                        |                        |                        |                        |                        |                        |                        |                        |
| Population-based       | 0.86(0.74-1.00)         | 0.0480/0.638           | 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)         | 0.6620/0.025           | 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)         | 0.5800/0.003           | 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)         | 0.2540/0.402           | 0.86(0.68-1.08)         | 0.2000/0.050           | 0.88(0.73-1.06)         | 0.187/0.149            | 0.93(0.77-1.12)         | 0.436/0.204            |
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.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 81302325).

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