Evaluation of COMT Gene rs4680 Polymorphism as a Risk Factor for Endometrial Cancer

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Abstract Catechol-O-methyltransferase (COMT) enzyme is involved in the inactivation of catecholamine and catechol estrogens. Catechol estrogens have carcinogenic potential and DNA damaging ability. Several studies investigated COMT Val158Met polymorphism as risk factor for endometrial cancer but the results were inconclusive. Hence the objective of present study was to find out exact association between COMT gene Val158Met polymorphism and endometrial cancer by a meta-analysis. Pubmed, Google Scholar, Springer Link and Science Direct databases were searched for case–control articles which investigated COMT Val158Met polymorphism in endometrial cancer cases. All statistical analysis was performed using MetaAnalyst and Mix programs. The results of meta-analysis suggested that there were no association between COMT Val158Met polymorphism and endometrial cancer risk (allele contrast model— $OR_{A \text{ vs. } G} = 0.97$, 95% CI = 0.86–1.10, $p = 0.67$; co-dominant model— $OR_{AG \text{ vs. } GG} = 0.91$, 95% CI = 0.77–1.06, $p = 0.23$; homozygote model— $OR_{AA \text{ vs. } GG} = 1.01$, 95% CI = 0.84–1.19, $p = 0.29$; dominant model— $OR_{AA+AG \text{ vs. } GG} = 0.93$, 95% CI = 0.77–1.11, $p = 0.43$; recessive model— $OR_{AA \text{ vs. } AG+GG} = 1.02$, 95% CI = 0.89–1.20, $p = 0.62$). Publication bias was absent. Subgroup analysis based on source of controls was also performed. In conclusion, results of present meta-analysis showed no association between COMT Val158Met polymorphism and susceptibility to endometrial cancer.

Keywords Endometrial cancer · COMT · Val158Met · Meta-analysis · Polymorphism

Introduction

Endometrial cancer is the fourth common cancer among women [1, 2]. Several environmental and genetic factors are reported risk factor for endometrial cancer such as hormone therapy, obesity, metabolic disorder and allelic variants/genetic polymorphisms of small effect genes etc. Estrogen biosynthesis and metabolism are closely associated with endometrial carcinogenesis. The functional gene polymorphisms regulating estrogen metabolism can influence the levels of estrogen and intermediate products, which may potentially contribute to the susceptibility to endometrial cancer [3]. 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 [4].

COMT gene is present on chromosome 22q11.2 and is expressed in various mammalian tissues including liver, kidney, and breast [5, 6]. Several polymorphisms are reported in COMT gene, but the most widely studied and clinically important polymorphism is Val158Met polymorphism [7]. Val158Met polymorphism (rs4680) is a substitution of guanine to adenine nucleotide (G472A) in exon 4 of COMT gene, leading to substitution of valine to methionine amino acid at 158th position in protein. The homo-zygous mutant Met/Met (AA) genotype has been reported to decrease the COMT enzyme activity by 3–4 folds compared with wild-type Val/Val (GG) genotype; whereas the heterozygous Val/Met (AG) genotype has intermediate activity [8]. In the past decade, many studies have investigated the relationship between COMT

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158Met allele with different types of cancer in different ethnic populations and reported 158Met allele as a risk factor for—esophageal cancer [9], colorectal cancer [10], hepatocellular carcinoma [11], lung cancer [12, 13], breast cancer [14, 15], ovary cancer [16], bladder cancer [17, 18], renal cell cancer [19], prostate cancer [20], testicular germ cell tumor [21] etc. The frequency of the mutant Met (A) allele vary greatly among the different populations, and is reported as 0.56 in American [22], 0.5 in European [23], and 0.27 in Asian [24, 25] populations.

Several studies have investigated the relationship between COMT Val158Met polymorphism and endometrial cancer susceptibility [26–28] however, the results are inconclusive. To update the results of previously published case control studies, authors performed a meta-analysis by including the most recent articles.

Methods

Identification and Eligibility of Relevant Studies

Pubmed, Google Scholar, Science Direct and Springer Link databases were searched to retrieve relevant articles published before March 31, 2018. Following key words “COMT”, “Val158Met”, and “endometrial cancer” were used for search. The criteria for study selection were: (a) studies should be case–control association studies evaluated the COMT polymorphism as risk factor in endometrial cancer patients, (b) study should reported genotype distributions in both cancer cases and controls, (c) study should be published. The studies were excluded if (a) studies were without details of genotype or allele data of cases/controls; (b) studies were on benign endometrial disease and (c) only cancer cases were studied, (d) studies were case reports, editorials, review articles, or meta-analysis.

Data Extraction

Following information were extracted from each included articles—first author’s family name, country name, ethnicity, journal name, year of publication, number of cases and controls and number of different COMT genotypes in cases and controls.

Statistical Methods

Authors performed a meta-analysis to estimate the risk of endometrial cancer associated with COMT Val158Met polymorphism. Odd ratio (OR) with the corresponding 95% Confidence Interval (CI) was used as association measure and calculated in each included study. A pooled

OR was then estimated on the basis of the individual ORs. The OR was estimated either by using fixed effect [29] or random effects [30] model depending upon heterogeneity. The heterogeneity between studies was tested using the Q-statistics and quantified by I^2 statistic [31]. If $I^2 > 50\%$ then random effect model was used [32]. Genetic models were chosen according to the method of Thakkestian et al. [33], briefly calculating and comparing the ORs of A(Met) vs. G (Val) (allele contrast), AA(Met/Met) vs. GG(Val/Val) (homozygote), AG(Met/Val) vs. GG(Val/Val) (co-dominant), AA(Met/Met) + AG(Met/Val) vs. GG (Val/Val) (dominant) and AA(Met/Met) vs. AG(Met/Val) + GG(Val/Val) (recessive) models. Subgroup analysis based on source of control samples was also performed. To test for the selection bias of control population, the distribution of genotypes in control subjects of each study was tested for departure from Hardy–Weinberg equilibrium (HWE) by means of Chi square goodness-of-fit test, and a p value of < 0.05 was considered significant.

Quality Score Assessment

The quality of included studies was also evaluated according to the predefined quality assessment method described by Jiang et al. [34]. Papers scoring < 10 were classified as “low quality” and those scoring ≥ 10 as “high quality.”

Publication Bias Assessment

Publication bias was investigated by visual inspection funnel plots; viz. funnel plot of standard error by log odds ratio and funnel plot of precision (1/standard error) by log odds ratio and formally evaluated with Begg’s adjusted rank correlation test [35] and Egger’s regression asymmetry test [36]. All statistical analyses were undertaken using the program MetaAnalyst [37] and MIX [38].

Results

Meta-analysis is done according to MOOSE [39] guidelines.

Eligible Studies

A flow diagram schematizing the study selection process is presented in Fig. 1. The article search of four databases concerning the association of COMT Val158Met polymorphism with endometrial cancer resulted in 215 studies in total. After examination of abstracts, 151 studies were excluded, which were reviews, editorials and comments etc. Full text of remaining 64 articles was examined and

Fig. 1 Flow diagram of study search and selection process

again 48 articles were excluded. Out of 16 remaining articles, six articles were not relevant for present meta-analysis. Total ten articles that investigated the association between COMT Val158Met polymorphism and endometrial cancer were found suitable for the inclusion in the present meta-analysis [26–28, 40–46]. In two articles, case

samples were categorized into two groups i.e. premenopausal and post menopausal, so we included these samples as separate studies in the meta-analysis. Hence total twelve studies were included in the present meta-analysis.

Characteristics of Included Studies

Details of included twelve articles were summarized in Table 1. All these studies were performed in different countries—America [40, 42, 43, 45], Australia [46], China [27, 28, 44], Poland [26], Russia [41]. The studies were published between 2004 and 2010. In all twelve studies, total numbers of endometrial cancer cases were 2536 with GG (1,030), AG (1,120) and AA (413) genotypes and number of controls were 3173 with GG (1,122), AG (1,486), and AA (565) genotypes (Table 1). In case genotypes percentage of GG, AG and AA were 40.19%, 43.70% and 16.11% respectively. In controls genotype percentages of GG, AG and AA were 35.36%, 46.83% and 17.81% respectively. Except Liu et al. [44], distribution of the Val158Met genotype in the control group of all 11 studies was in Hardy–Weinberg equilibrium ($p < 0.05$), indicating no sampling errors in eleven studies [47] (Table 1).

Meta-Analysis

Table 2 summarizes the pooled ORs with corresponding 95% CIs for association between COMT Val158Met polymorphism and risk of endometrial cancer in allele

Table 1 Details of included twelve studies

Study	Country	Ethnicity	Control Source	Pre or post-menopausal cases	Case no.	Control no.	Case Genotypes			Control Genotypes			P value of HWE	Quality score
							Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met		
McGrath [40]	America	Caucasian	Hospital	Pre	54	94	11	29	14	23	48	23	0.83	> 10
McGrath [40]	America	Caucasian	Hospital	Post	157	533	43	73	41	134	253	146	0.24	> 10
Zimarina [41]	Russia	Caucasian	Hospital	NR	124	140	29	65	30	23	73	44	0.42	< 10
Doherty [42]	America	Caucasian	Population	NR	371	420	97	174	100	90	207	123	0.86	> 10
Tao [43]	America	Caucasian	Population	Pre	447	394	229	176	42	204	160	30	0.85	> 10
Tao [43]	America	Caucasian	population	Post	584	632	334	207	43	330	265	37	0.086	> 10
Liu [44]	China	Asian	Hospital	NR	80	84	42	33	5	35	46	3	0.009	< 10
Szylo [26]	Poland	Caucasian	Hospital	Post	151	197	46	81	24	48	110	39	0.09	< 10
Zhao [27]	China	Asian	Hospital	NR	132	110	39	77	16	52	50	8	0.38	< 10
Hirata [45]	America	Caucasian	Population	NR	150	165	32	81	37	48	90	27	0.16	< 10
Ashton [46]	Australia	Caucasian	Population	NR	191	290	38	98	55	64	149	77	0.61	> 10
Li [28]	China	Asian	Hospital	NR	122	114	90	26	6	71	35	8	0.21	> 10

Table 2 Summary estimates for the odds ratio (OR) in various allele/genotype contrasts, the significance level (*p* value) of heterogeneity test (*Q* test), and the *I*² metric: overall analysis

Genetic models	Fixed effect OR (95% CI), <i>p</i>	Random effect OR (95% CI), <i>p</i>	Heterogeneity <i>p</i> value (<i>Q</i> test)	<i>I</i> ² (%)	Publication Bias (<i>p</i> of Egger's test)
Allele contrast (A vs. G)	0.97 (0.89–1.04), 0.42	0.97 (0.86–1.1), 0.67	0.02	51.55	0.83
Co-dominant (AG vs. GG)	0.91 (0.77–1.06), 0.23	0.91 (0.76–1.08), 0.24	0.06	43.0	0.36
Homozygote (AA vs. GG)	1.01 (0.84–1.19), 0.92	1.02 (0.81–1.30), 0.81	0.07	40.01	0.49
Dominant (AA + AG vs. GG)	0.91 (0.81–1.02), 0.12	0.93 (0.77–1.11), 0.43	0.01	53.2	0.63
Recessive (AA vs. GG + AG)	1.04 (0.89–1.20), 0.62	1.04 (0.89–1.20), 0.63	0.42	1.87	0.42

contrast, dominant, recessive, homozygote and co-dominant models. Allele contrast meta-analysis did not show any association between Val158Met polymorphism with endometrial cancer using fixed effect model ($OR_{A \text{ vs. } G} = 0.97$; 95% CI: 0.89–1.04; $p = 0.42$; $I^2 = 51.55\%$; $P_{\text{heterogeneity}} = 0.02$) and random effect model ($OR_{A \text{ vs. } G} = 0.97$; 95% CI = 0.86–1.10; $p = 0.67$) (Table 2). High significant heterogeneity ($I^2 = 51.55\%$; $P_{\text{heterogeneity}} = 0.02$) was found, so random effect model was adopted.

There were no evidence of association of the COMT AA genotype with endometrial cancer risk in homozygote meta-analysis (random effect- $OR_{AA \text{ vs. } GG} = 1.02$; 95% CI = 0.81–1.30; $p = 0.81$). Since there was no significant heterogeneity ($p = 0.06$, $I^2 = 43\%$) between the studies, the fixed effects pooled OR was considered ($OR_{AA \text{ vs. } GG} = 1.01$; 95% CI = 0.84–1.19; $p = 0.29$) (Table 2). No significant association was observed between COMT Val158Met polymorphism and endometrial cancer using co-

dominant model ($OR_{AG \text{ vs. } GG} = 0.91$; 95% CI = 0.77–1.06; $p = 0.23$), dominant model ($OR_{AA+AG \text{ vs. } GG} = 0.93$; 95% CI = 0.77–1.11; $p = 0.43$) and recessive models ($OR_{AA \text{ vs. } AG+GG} = 1.02$; 95% CI = 0.89–1.20; $p = 0.62$) (Fig. 2; Table 2).

Subgroup Analysis

Subgroup analysis based on control source i.e. controls selected from hospital or population was performed. In 7 studies controls were selected from hospital and in 5 studies control samples were collected from the population. In hospital based control studies (number of studies = 7; 820 cases/1272 controls), homozygote meta-analysis showed no association between endometrial cancer and COMT Val158Met polymorphism adopting both fixed ($OR_{AA \text{ vs. } GG} = 0.87$; 95% CI = 0.65–1.15; $p = 0.34$; $I^2 = 35.83\%$; $P_{\text{heterogeneity}} = 0.15$) and random ($OR_{AA \text{ vs. } GG} = 0.89$;

Fig. 2 Random effect forest plot of dominant model (AA + AG vs. GG) of total 12 studies of COMT Val158Met (G472A) polymorphism

Fig. 3 Random effect forest plot of dominant model (AA + AG vs. GG) of 7 studies with Hospital based control 0fCOMT Val158Met (G472A) polymorphism

Table 3 Summary estimates for the odds ratio (OR) in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric: subgroup analysis based on control source

Genetic models	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p value (Q test)	I^2 (%)	Publication Bias (p of Egger's test)
Hospital based studies (7 studies)					
Allele contrast (A vs. G)	0.92 (0.76–1.13), 0.39	0.91 (0.74–1.11), 0.40	0.06	54.5	0.71
Co-dominant (AG vs. GG)	0.89 (0.72–1.10), 0.29	0.88 (0.63–1.23), 0.47	0.03	56.73	0.95
Homozygote (AA vs. GG)	0.87 (0.65–1.15), 0.34	0.89 (0.62–1.24), 0.57	0.15	35.83	0.44
Dominant (AA + AG vs. GG)	0.88 (0.72–1.08), 0.22	0.88 (0.62–1.24), 0.46	0.01	62.87	0.97
Recessive (AA vs. GG + AG)	0.91 (0.71–1.15), 0.43	0.91 (0.71–1.15), 0.42	0.580.31	0	0.31
Population based studies (5 studies)					
Allele contrast (A vs. G)	0.93 (0.76–1.02), 0.07	0.91 (0.79–1.12), 0.11	0.23	49.2	0.84
Co-dominant (AG vs. GG)	0.85 (0.73–0.99), 0.03	0.86 (0.70–1.04), 0.12	0.21	31.53	0.81
Homozygote (AA vs. GG)	1.08 (0.85–1.37), 0.5	1.15 (0.81–1.62), 0.41	0.12	45.27	0.31
Dominant (AA + AG vs. GG)	0.89 (0.77–1.02), 0.11	0.90 (0.73–1.11), 0.34	0.11	45.83	0.76
Recessive (AA vs. GG + AG)	1.13 (0.92–1.39), 0.23	1.17 (0.91–1.49), 0.20	0.28	20.32	0.15

95% CI = 0.62–1.24; $p = 0.57$) effect models. Combined mutant genotypes (dominant model) also did not show any association with fixed ($OR_{AA+AG \text{ vs. } GG} = 0.88$; 95% CI = 0.72–1.08; $p = 0.22$) and random ($OR_{AA+AG \text{ vs. } GG} = 0.88$; 95% CI = 0.62–1.24; $p = 0.46$) effect models. In this subgroup heterogeneity between studies ($I^2 = 62.87\%$; $P_{\text{heterogeneity}} = 0.01$) was low and publication bias ($P_{\text{Pb}} = 0.16$) was absent (Fig. 3; Table 3). In population based control studies (number of studies = 5; 1743 cases/1901 controls), homozygote model meta-analysis did not

show association with both fixed ($OR_{AA \text{ vs. } GG} = 1.08$; 95% CI = 0.85–1.37; $p = 0.5$) and random ($OR_{AA \text{ vs. } GG} = 1.15$; 95% CI = 0.81–1.62; $p = 0.41$) (Fig. 4; Table 3) effect models with heterogeneity ($I^2 = 45.27\%$; $P_{\text{heterogeneity}} = 0.12$). The combined mutant genotype (dominant model) also did not show any significant association with fixed effect model ($OR_{AA+AG \text{ vs. } GG} = 0.89$; 95% CI = 0.77–1.02; $p = 0.11$) with no heterogeneity and no publication bias ($P_{\text{Pb}} = 0.76$).

Publication Bias

Both the results of Begg's and Egger's test showed absence of publication bias in all genetic models (Allele contrast model (A vs. G): Begg's test, $p = 0.94$, Egger's test, $p = 0.83$; Co-dominant model (AG vs. GG): Begg's test,

$p = 0.20$, Egger's test, $p = 0.36$; Homozygote model (AA vs. GG): Begg's test, $p = 0.94$, Egger's test, $p = 0.49$; Dominant model (AA + AG vs. GG): Begg's test, $p = 0.53$, Egger's test, $p = 0.63$; Recessive model (AA vs. AG + GG): Begg's test, $p = 0.53$, Egger's test, $p = 0.42$) (Figs. 5, 6).

Fig. 4 Random effect forest plot of dominant model (AA + AG vs. GG) of 5 studies with population based control of COMT Val158Met (G472A) polymorphism

Fig. 5 Funnel plot—precision by log odds ratio for dominant model (AA + AG vs. GG) of 12 studies of COMT Val158Met (G472A) polymorphism

Fig. 6 Funnel plot—standard error by log odds ratio for dominant model (AA + AG vs. GG) of 12 studies of COMT Val158Met (G472A) polymorphism

Discussion

The present meta-analysis included twelve studies with 2563 endometrial cancer cases and 3173 controls and investigated association between COMT Val158Met polymorphism and endometrial cancer risk. Although, results of present analysis reported no significant association between COMT Val158Met polymorphism and endometrial cancer susceptibility, but it is most comprehensive meta-analysis so far. COMT is a phase II enzyme that catalyzes the methylation of catechol estrogens to less polar monomethyl ethers. Methylation process increases the concentrations of 4-methoxyestradiol (4-MeOE2) and 2-methoxyestradiol (2-MeO-E2), out of which 2-MeO-E2 possess anti-proliferative, cytotoxic and apoptotic activity therefore decreasing the potential for DNA damage and tumorigenesis [8, 48].

Meta-analysis is a powerful statistical tool, which overcome deficiencies of small studies and provide more reliable results. Several meta-analysis were published which evaluated risk of small effect genes on different disease and disorders—like Down syndrome [49], recurrent pregnancy loss [50], cleft lip and palate [51, 52], male infertility [53], autism [54], schizophrenia [55], depression [56], breast cancer [57–59], digestive tract cancer [60], colorectal cancer [61], ovary cancer [62, 63] and prostate cancer [64, 65] etc.

Similar to other meta-analyses, present meta-analysis has also few limitations, which should be acknowledged

like—(1) number of included studies was relatively small (ten studies), (2) crude OR was used, (3) the controls were not uniformly defined (some studies included hospital based and some included population based controls) and (4) single gene polymorphism was considered. Along with limitations, our meta-analysis had several strengths also like—higher statistical power and absence of publication biases.

In conclusion, results of present meta-analysis reported that COMT Val158Met polymorphism is not risk factor for endometrial cancer. Future larger studies with higher sample sizes from different ethnic and geographical regions are required to come to a conclusion.

Compliance with Ethical Standards

Conflict of interest None.

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