RESEARCH ARTICLE

Impact of Catechol-O-Methyltransferase Val 158Met (rs4680) Polymorphism on Breast Cancer Susceptibility in Asian Population

Vandana Rai*, Upendra Yadav, Pradeep Kumar

Abstract

Background: Catechol-O-methyltransferase (COMT) is an important estrogen-metabolizing enzyme. Numerous case-control studies have evaluated the role COMT Val 158Met (rs4680;472G->A) polymorphism in the risk of breast cancer and provided inconclusive results, hence present meta-analysis was designed to get a more reliable assessment in Asian population. **Methods:** A total of 26 articles were identified through a search of four electronic databases- PubMed, Google Scholar, Science Direct and Springer link, up to March, 2016. Pooled odds ratios (ORs) with 95% con¬fidence intervals (CIs) were used as association measure to find out relationship between COMT Val158Metpolymorphism and the risk of breast cancer. We also assessed between study heterogeneity and publication bias. All statistical analyses were done by Open Meta-Analyst. **Results:** Twenty six case-control studies involving 5,971 breast cancer patients and 7,253 controls were included in the present meta-analysis. The results showed that the COMT Val158Met polymorphism was significantly associated with breast cancer risk except heterozygote model(allele contrast odds ratio (ORAvsG)= 1.13, 95%CI=1.02-1.24,p=0.01; heterozygote/co-dominant ORGAvsGG= 1.03, 95%CI=0.96-1.11,p=0.34; homozygote ORAAvsGG= 1.38, 95%CI= 1.08-1.76,p=0.009; dominant model ORAA+GAvsGG= 1.08, 95%CI=1.01-1.16,p=0.02; and recessive model ORAAvsGA+GG= 1.35, 95%CI=1.07-1.71,p=0.01). In addition, we also performed subgroup analysis based on source of controls and menopausal state of patients. **Conclusions:** In conclusion, the COMT Val158Met polymorphism was related to increased breast cancer susceptibility in the Asian population.

Keywords: Catechol-O-methyltransferase- COMT- Val158Met- 472G->A- breast cancer-Asian population

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Introduction

Breast cancer (BC)is the leading cause of cancer death among females (Jemal et al., 2011; Guo et al., 2012) and its development is a multifactorial complex process influenced by multiple genetic variants and environmental factors (Nathanson et al.,2001; Guo et al., 2012). Estrogen hormones affect the cell growth and proliferation during breast carcinogenesis and metabolized by several enzyme including COMT, which metabolized itinto biologically non-hazardous methoxyestrogens(Onay et al., 2008). COMT enzyme are found in two isoforms in the cells: a cytoplasmic smaller protein (S-COMT; 221 aa) and a membrane-bound longer protein (MB-COMT 271 aa) (Tenhunen et al. 1994).

COMT gene is present at chromosome 22q11.1 and a single base pair G-->A substitution at position 472(G472A/Val158Met)in exon 4, results in substitution of valine by methionine in COMT enzyme (Lotta et al., 1995; Lachman et al., 1996). The two alleles are referred to as Val(G) and Met(A). Val allele encodes the thermostable high activity COMT enzyme and Met allele encodes the thermolabile low activity COMT enzyme (Spielman and Weinshilboum, 1981; Lotta et al., 1995; Nobile et al., 2010). Both the alleles are co-dominant, i.e. heterozygous individuals (Val/Met) have an intermediate level of COMT activity (Lotta et al., 1995).The frequency of the mutant Met allele vary greatly among the populations studied, frequency of Met allele is reported as 0.56 in American (Vandenbergh et al., 1997), 0.5 in European (Kunugi et al., 1997), and 0.27 in Asian (Chen et al., 1997)populations. COMT gene Val158Met is a clinically functional polymorphism, and reported as risk factor for several disorders/diseases- schizophrenia (Kayahan et al., 2013), attention-deficit hyperactivity disorder (Retz et al., 2008), autism (Gadow et al., 2009),drug abuse (Vinkers et al., 2013), posttraumatic stress disorder (Valente et al., 2011), and cancer (Omrani et al., 2009) etc.

COMT enzyme metabolized estrogen and its carcinogenic derivatives, hence study of COMT gene polymorphisms as risk for cancer is of particular interest. In the past years, several case-control studies have been investigated the association between COMT Val158Met polymorphisms and breast cancer susceptibility (Kocabas

*Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur-222 003, UP, India. *For Correspondence: raivandana@rediffmail.com*

et al.,2002; Wen et al., 2005;Chang et al.,2006; Wang et al., 2010; Naushad et al., 2011;Lajin et al.,2013). However, individual study limitations contributed to divergent conclusions among them. Aim of the present meta-analysis was to find out the relationship between COMT Val158Met polymorphism and breast cancer risk in Asian population.

Materials and Methods

Data Sources, Search Strategy, and Selection Criteria

The articles for the present meta-analysis were retrieved by searching the PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://scholar.google.com), Science Direct (http://www.sciencedirect.com), and Springer Link (http://link.springer.com) databases up to March, 2016, using the keywords "breast cancer", "Val158Met", "Catechol-O-methyltransferase" and "COMT".

Article selection for the present meta-analysis used the following inclusion criteria:(i) study should be case-control; (ii) sufficient genotype/allele data to calculate the odds ratios (ORs) with 95% confidence intervals should be reported (CIs).Exclusion criteria were the following: (i) only cases were analyzed; (ii) editorial, review articles etc.;(iii)not sufficient data/information to calculate odds ratio with 95%CI were reported; (v) other cancer type were investigated in the study and (vi) non-Asian breast cancer cases were investigated.

Data Extraction and Quality Assessment

Data extraction and quality assessment were performed by two investigators (PK and UY). From each included relevant article, the following data were extracted: the family name of first author, the publication year, journal name, country name, the study design i.e. source of controls, the sample size, and the genotype distribution for the participants. Method of Guo et al., (2012) was adopted for study quality assessment. The quality scores ranged from 0 to 10 and studies with score <5 was defined as low quality, and studies with score ≥7 was defined as high quality.

Statistical Analysis

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used as the measure of association between the COMT Val158Met polymorphism and breast cancer susceptibility. Data were pooled using the fixed effect (Mantel and Haenszel,1959) and random effect (DerSimonian and Laird, 1987) methods. $p<0.05$ was considered as statistically significant. Heterogeneity between conducted by X2-based Q-test and quantified by I2 (Cochran,1954; Higgins and Thompson, 2002; Whitehead, 2002). For this polymorphism all five genetic models, the additive model (Met vs. Val; A v.s G), homozygote model (Met/Met vs .Val/Val; AA vs. GG), heterozygote model (Val/Met vs Val/Val; GA vs GG), dominant model (Met/Met+Val/Met vs Val/Val; AA+GA vs GG) and recessive model (Met/Met vs Val/Met + Val/Val; AAvs GA+GG) were chosen to calculate the pooled ORs. x^2 test was done to evaluate Hardy-Weinberg Equilibrium (HWE) for control subjects in each study. Publication bias was assessed by Begg's funnel plot and Egger's linear regression test (Egger et al., 1997). All statistical analyses were performed by Open Meta-Analyst (Wallace et al., 2013).

Results

Literature Search

Initial search of four databases, 203 articles were retrieved, but 141 articles did not meet the inclusion criteria after reviewing abstract. The excluded articles include results of drug treatments of breast cancer, book chapter, comments, editorials, reviews, meta-analysis and articles investigated other genes. Out of remaining sixty two articles, we also excluded thirty nine articles, in which investigated subjects were not from Asian population. After applying inclusion/exclusion criteria, total 23articles (Figure 1) were suitable for the present meta-analysis (Huang et al., 1999; Hamajima et al., 2001; Yim et al., 2001; Kocabas et al., 2002; Tan et al., 2003; Wu et al., 2003; Sazci et al., 2004; Cheng et al., 2005; Lin SC et al., 2005; Lin WY et al., 2005; Wen et al., 2005; Chang et al., 2006; Akisik and Dalay, 2007; Fan et al., 2007; Hu et al., 2007; Sangrajrang et al., 2009; Yadav et al., 2009; Syamala et al., 2010; Xu et al., 2010; Naushad et al., 2011; Wang et al., 2011; Lajin et al., 2013; Li et al., 2013).These studies were published between 1999 to 2013. One author (Syamala et al.,2010) studied sporadic and familial cases both and reported separately in their article, so we also included both groups of data as separate studies. Wu et al., 2003 reported three individual populations (Chinese,

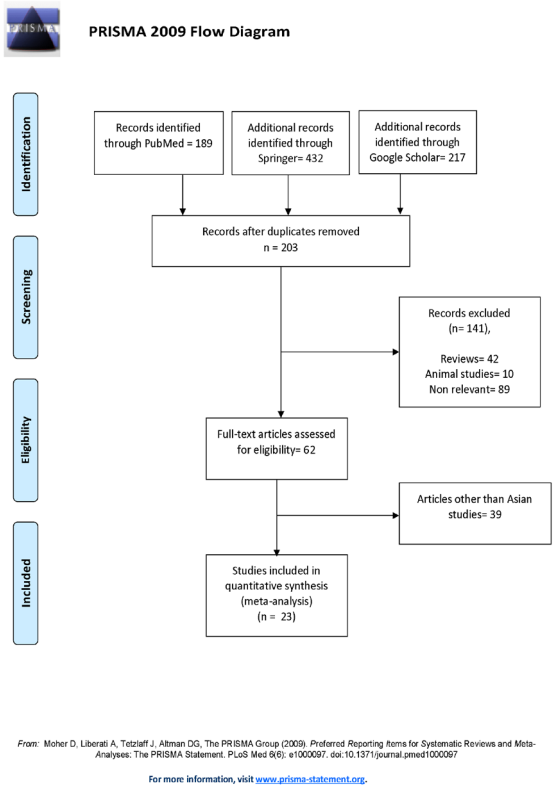

Figure 1. Flow Diagram of Study Search and Selection Process

Table 1. Characteristics of Twenty Four Studies Included in the Present Meta-Analysis

Study	Country	Source of Control	Menopausal Status	Case/Control	Case Genotypes			Control Genotypes			HWE	Quality Score
					Val/Val (GG)	Val/Met (AG)	Met/Met (AA)	Val/Val (GG)	Val/Met (AG)	Met/Met (AA)		
Huang et al., 1999	China	HB	Pre-,Post-	113/124	66	35	12	65	55	4	0.06	8.5
Hamajima et al., 2001	Japan	HB	Pre-,Post-	150/165	60	72	18	79	63	23	0.08	8.5
Yim et al., 2001	Japan	HB	Pre-,Post-	163/163	81	79	3	101	46	16	0.004*	5.5
Kocabas et al., 2002	Turkey	HB	Pre-,Post-	84/103	28	42	14	35	55	13	0.23	5.5
Tan et al., 2003	China	HB	Pre-,Post-	250/250	121	103	26	132	105	13	0.17	
Wu et al., 2003	China	PB	Mixed	178/199	97	67	14	106	78	15	0.9	8.0
	Japan	PB	Mixed	193/197	88	89	16	86	87	24	0.78	
	Philippines	PB	Mixed	218/166	143	57	18	90	64	12	0.89	
Sazci et al., 2004	Turkey	PB	Pre-	130/224	33	69	28	62	146	16	0.00*	6.0
Cheng et al., 2005	China	HB	Mixed	469/740	237	197	35	420	262	58	0.06	7.5
Lin WY et al., 2005	China	PB	Mixed	87/341	51	31	5	190	133	18	0.39	7.5
Lin SC et al., 2005	Taiwan	PB	Mixed	99/366	58	35	6	205	138	23	0.97	6.5
Wen et al., 2005	China	PB	Pre-,Post-	1120/1191	612	425	83	628	470	93	0.69	9.5
Chang et al., 2006	China	HB	Mixed	189/320	103	77	9	131	159	30	0.06	6.5
Akisik et al., 2007	Turkey	NR	Mixed	114/108	29	59	26	34	53	21	0.96	3.0
Fan et al., 2007	China	NR	Mixed	200/100	96	75	29	51	44	5	0.24	7.5
Hu et al., 2007	China	HB	Pre-,Post-	112/110	65	36	11	66	41	3	0.25	6.5
Sangrajrang et al., 2009	Thailand	HB	Mixed	565/486	290	233	42	266	190	30	0.6	9.0
Yadav et al., 2009	India	HB	Pre-,Post-	59/99	23	30	6	32	53	14	0.28	7.0
Syamala et al., 2010a	India	PB	Mixed	140 /367	48	64	28	138	164	65	0.18	7.0
Syamala et al., 2010b	India	PB	Mixed	219/ 367	74	104	41	138	164	65	0.18	7.0
Xu et al., 2010	China	NR	Mixed	140/122	60	42	38	68	44	10	0.45	6.5
Naushad et al., 2011	India	HB	Mixed	212/233	71	94	47	115	103	15	0.2	6.0
Wang et al., 2011	China	PB	Pre-,Post-	400/400	187	145	68	208	156	36	0.39	7.0
Lajin et al., 2013	Syria	PB	Pre-,Post-	135/107	34	70	31	23	54	30	0.88	6.5
Li et al., 2013	China	HB	Mixed	120/120	58	45	17	73	42	5	0.73	7.0

HB, hospital-based; PB, population-based; NR, not reported; Pre, premenopausal; Post, postmenopausal

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, and Subgroup Analyses.

	Genetic Contrast	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)
All	Allele Contrast (A vs. G)	1.10 (1.05-1.17), <0.001	1.13 (1.02-1.24), 0.01	<0.001	63.71	0.36
	Dominant (AA+AG vs. GG)	1.08 (1.01-1.16), 0.02	1.09 (0.99-1.21), 0.07	0.009	43.9	0.61
	Homozygote (AA vs. GG)	1.32 (1.17-1.49), <0.001	1.38 (1.08-1.76), 0.009	<0.001	68.73	0.33
	Co-dominant (GA vs. GG)	1.03 (0.96-1.11), 0.34	1.03 (0.93-1.14), 0.48	0.04	35.21	0.87
	Recessive (GG+GA vs. AA)	1.29 (1.15-1.45), <0.001	1.35 (1.07-1.71), 0.01	<0.001	70.64	0.27
Pre	Allele Contrast (A vs. G)	1.11 (1.00-1.23), 0.03	1.17 (1.01-1.36), 0.03	0.09	38.27	0.05
	Dominant (AA+AG vs. GG)	1.06 (0.93-1.22), 0.36	1.06 (0.92-1.22), 0.36	0.45	0.00	0.02
	Homozygote (AA vs. GG)	1.38 (1.09-1.75), 0.006	1.53 (0.98-2.40), 0.05	0.004	61.58	0.29
	Co-dominant (GA vs. GG)	1.00 (0.86-1.15), 0.96	1.02 (0.86-1.21), 0.77	0.34	10.84	0.13
	Recessive (GG+GA vs. AA)	1.38 (1.11-1.71), 0.003	1.48 (0.95-2.29), 0.07	<0.001	66.84	0.45
Post	Allele Contrast (A vs. G)	1.04 (0.92-1.18), 0.46	1.04 (0.90-1.21), 0.53	0.25	20.18	0.58
	Dominant (AA+AG vs. GG)	1.04 (0.88-1.22), 0.62	1.04 (0.86-1.25), 0.65	0.32	13.04	0.61
	Homozygote (AA vs. GG)	1.11 (0.83-1.47), 0.47	1.05 (0.65-1.70), 0.81	0.03	49.89	0.53
	Co-dominant (GA vs. GG)	1.01 (0.85-1.21), 0.83	1.01 (0.81-1.26), 0.88	0.2	26.09	0.77
	Recessive (GG+GA vs. AA)	1.11 (0.85-1.44), 0.43	1.07 (0.68-1.67), 0.76	0.02	52.54	0.59
Mixed	Allele Contrast (A vs. G)	1.13 (1.05-1.21), <0.001	1.14 (0.98-1.32), 0.08	<0.001	73.06	0.58
	Dominant (AA+AG vs. GG)	1.11 (1.01-1.22), 0.02	1.10 (0.95-1.29), 0.19	0.004	56.41	0.61
	Homozygote (AA vs. GG)	1.37 (1.16-1.62), <0.001	1.40 (1.01-1.95), 0.04	<0.001	69.87	0.53
	Co-dominant (GA vs. GG)	1.06 (0.96-1.17), 0.23	1.04 (0.91-1.18), 0.52	0.1	32.85	0.77
	Recessive (GG+GA vs. AA)	1.31 (1.12-1.54), <0.001	1.35 (1.00-1.83), 0.04	<0.001	67.98	0.59
Hospital based	Allele Contrast (A vs. G)	1.17 (1.07-1.27), <0.001	1.18 (1.01-1.36), 0.02	<0.001	65.22	0.77
	Dominant (AA+AG vs. GG)	1.19 (1.07-1.32), 0.001	1.18 (1.00-1.40), 0.04	0.01	52.18	0.86
	Homozygote (AA vs. GG)	1.38 (1.14-1.68), 0.001	1.44 (0.93-2.24), 0.09	<0.001	75.07	0.68
	Co-dominant (GA vs. GG)	1.15 (1.03-1.29), 0.01	1.13 (0.95-1.35), 0.15	0.01	52.21	0.58
	Recessive (GG+GA vs. AA)	1.30 (1.08-1.57), 0.005	1.37 (0.89-2.11), 0.14	<0.001	75.94	0.59
Population based	Allele Contrast (A vs. G)	1.02 (0.94-1.10), 0.59	1.02 (0.91-1.14), 0.71	0.03	48.22	0.87
	Dominant (AA+AG vs. GG)	0.97 (0.88-1.07), 0.60	0.97 (0.87-1.08), 0.64	0.39	5.11	0.85
	Homozygote (AA vs. GG)	1.15 (0.97-1.36), 0.09	1.15 (0.87-1.51), 0.30	0.01	53.52	0.99
	Co-dominant (GA vs. GG)	0.94 (0.84-1.04), 0.25	0.94 (0.84-1.04), 0.25	0.62	0.00	0.71
	Recessive (GG+GA vs. AA)	1.17 (0.99-1.37), 0.05	1.18 (0.89-1.55), 0.23	0.005	60.11	0.87
Not reported	Allele Contrast (A vs. G)	1.49 (1.20-1.85), <0.001	1.49 (1.08-2.05), 0.13	0.11	53.64	NA
	Dominant (AA+AG vs. GG)	1.36 (1.01-1.83), 0.03	1.36 (1.01-1.83), 0.03	0.52	0.00	NA
	Homozygote (AA vs. GG)	2.66 (1.66-4.25), <0.001	2.63 (1.32-5.22), 0.006	0.13	49.87	NA
	Co-dominant (GA vs. GG)	1.05 (0.77-1.45), 0.72	1.05 (0.77-1.45), 0.72	0.66	0.00	NA
	Recessive (GG+GA vs. AA)	2.36 (1.54-3.61), <0.001	2.45 (1.08-5.56), 0.03	0.03	69.44	NA

Japanese and Filipino) so we included them as three separate studies. Hence total twenty six studies were included in the present meta-analysis. Characteristics of all the included studies were given in Table 1. These studies were carried out in different countries- China (Huang et al., 1999; Tan et al.,2003; Wu et al., 2003; Cheng et al., 2005; Lin WY et al.,2005; Wen et al., 2005; Chang et al., 2006; Fan et al., 2007; Hu et al., 2007; Xu et al., 2010; Wang et al., 2011; Li et al., 2013), India (Yadav et al., 2009; Syamala et al., 2010; Naushad et al., 2011), Japan (Hamajima et al., 2001; Yim et al., 2001; Wu et al., 2003), Philippines (Wu et al., 2003), Syria (Lajin et al., 2013), Taiwan (Lin SC et al., 2005),Thailand (Sangrajrang et al., 2009), Turkey (Kocabas et al., 2002; Sazci et al., 2004; Akisik and Dalay, 2007).

Study Characteristics

All twenty six studies were published between 1999 (Huang et al., 1999) to 2013 (Li et al., 2013). Smallest sample size of cases studied was 59 (Yadav et al., 2009) and largest sample size was 1,120 (Wen et al., 2005). In twelve studies, age and sex matched controls are selected from hospital and in eleven studies controls were selected from population. In three studies source of controls were not given. Control population of two studies (Yim et al., 2001; Sazciet al., 2004) were not in HWE. In eleven

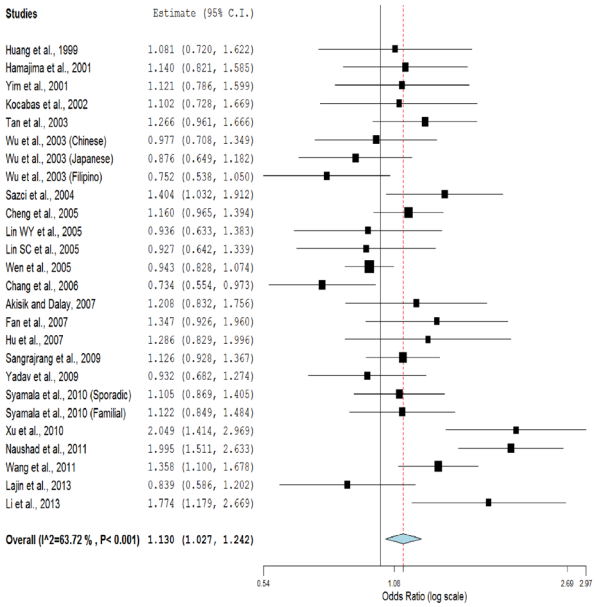

Figure 2. Random Effect Forest Plot of Allele Contrast Model (A vs. G) of *COMT G472A* Polymorphism

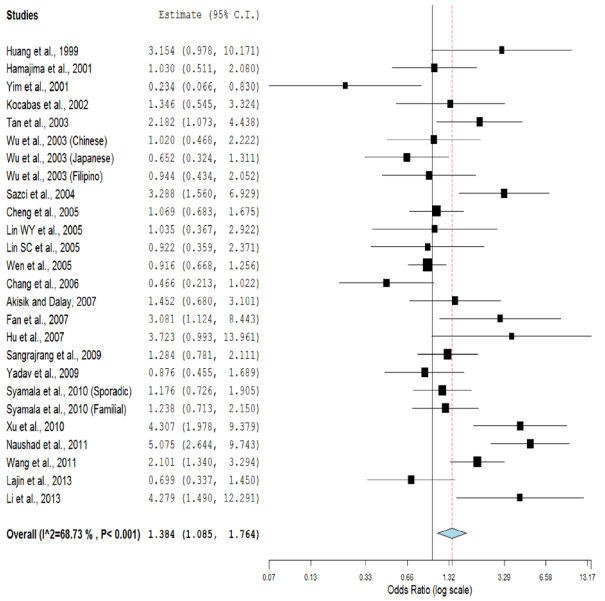

Figure 3. Random Effect Forest Plot of Homozygote Model (AA vs. GG) of *COMT G472A* Polymorphism

studies, selected patients were of premenopausal state and in ten studies cases were at postmenopausal state. In remaining studies menopausal status of patients was not given. Total cases were 5,971 with GG (2,844), GA (2,432) and AA (695) genotypes and controls were 7,253 with GG (3,584), GA (2,998) and AA (671) genotypes. In total cases, genotypes percentage of GG, GA and AA were 47.63%, 40.73% and 11.64% respectively. In controls, genotypes percentage of GG, GA and AA were 49.41, 41.34% and 9.25%respectively.Out of twenty six studies, six studies did not report any association between COMT Val158Met and breast cancer (Lin SC et al., 2005; Lin WY et al., 2005;Wen et al., 2005; Chang et al., 2006; Yadav et al., 2009; Lajin et al., 2013).

Meta-analysis

Meta-analysis with allele contrast (A vs. G) showed significant association with both fixed effect (ORAvsG= 1.10; 95%CI= 1.05-1.17; p= <0.001) and random effect model (ORAvsG= 1.13; 95% CI= 1.02-1.24; p= 0.01) (Table 2, Figure 2). There was observed an increased risk of breast cancer using homozygote model (AA vs GG; homozygote model), with both fixed (ORAAvsGG= 1.32; 95%CI= 1.17-1.49; p= <0.001) and random (ORAAvsGG= 1.38; 95%CI= 1.08-1.76; p=0.009) effect models with high statistical heterogeneity between studies (Table 2, Figure 3). Association of

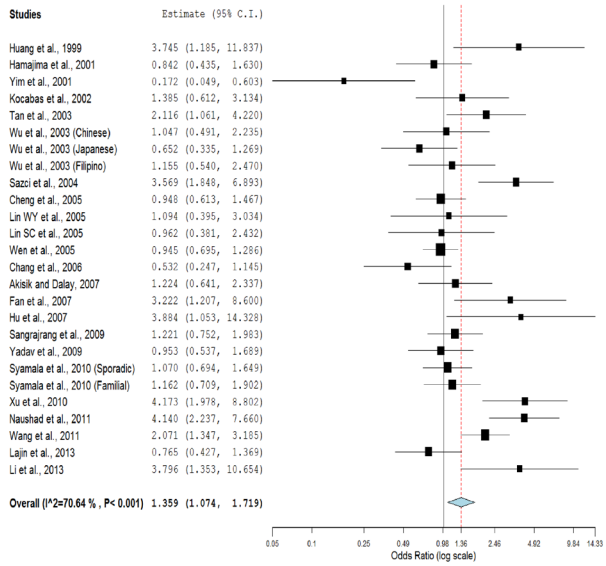

Figure 4. Random Effect Forest Plot of Recessive Model (GG+GA vs. AA) of *COMT G472A* Polymorphism

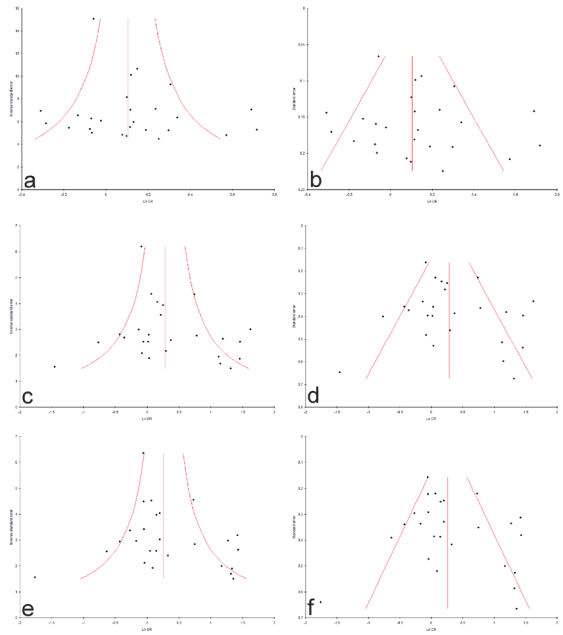

Figure 5. Funnel Plots a-f, a. Precision by log odds ratio for additive model; b, standard error by log odds ratio for additive model; c, precision by log odds ratio for homozygote model; d, standard error by log odds ratio for homozygote model; e, precision by log odds ratio for recessive model; f, standard error by log odds ratio for recessive model.

mutant heterozygous genotype (GAvs.GG; co-dominant model) was not observed significant with both fixed (ORGAvsGG= 1.03; 95%CI= 0.96-1.11; p= 0.34) and random (ORGAvsGG= 1.03; 95%CI= 0.93-1.14; p= 0.48) effect models. Combined mutant genotypes (AA+GA vs GG; dominant model) showed positive association with breast cancer using fixed (ORAA+GAvsGG= 1.08; 95%CI= 1.01-1.16; p= 0.02)effect model (Table 2). Similarly the recessive genotypes model (AA vs. GA+GG) also showed significant strong association with breast cancerusing both fixed (ORAAvsGA+GG= 1.29; 95%CI= 1.15-1.45; p= <0.001) and random (ORAAvsGA+GG= 1.35; 95%CI= 1.07-1.71; p= 0.01) effect models (Table 2, Figure 4).

Subgroup analysis

Subgroup analysis were done on the basis of source of control (i.e. hospital based or population based) and status of menopause (i.e. premenopause and postmenopause).In total 26 studies, in 12 studies controls were selected from hospital and in remaining studies control samples were selected from population. In allele contrast meta-analysis with twelve studied of hospital based, showed significant association between COMT Val158Met polymorphism and breast cancer (ORAvsG = 1.18; 95%CI= 1.01-1.36; p= 0.02; I2=65.2%) and meta-analysis of eleven population based studies did not show any association(ORAvsG = 1.02; 95%CI= 0.94-1.10; p= 0.59; I^2=48.22%).In three studies details of control samples were not given.

In eleven studies, subject were of premenopausal state, allele contrast meta-analysis showed meager association between COMT Val158Met polymorphism and breast cancer (ORAvsG= 1.11; 95%CI= 1.00-1.23; p= 0.03; I^2= 38.27%), but meta-analysis of ten studies analysed postmenopausal subject did not show any association (ORAvsG= 1.04; 95%CI= 0.92-1.18; p= 0.46; I^2= 20.18%). In four studies menopausal state of subjects were not mentioned.

Sensitivity analysis

In allele contrast meta-analysis, sensitivity analysis performed by exclusion of studies in which control population was not in HWE. Exclusion of two studies not in HWE (Yim et al., 2001;Sazciet al., 2004) did not affect heterogeneity but increased odds ratio (OR= 1.12; 95%CI= 1.01-1.23; p= 0.02).

Publication bias

Publication bias was absent in all five genetic models and P value of Egger's test was greater than 0.05 (A vs G, p= 0.36; AG vs GG, p= 0.87; AA vs GG, p= 0.33; AA+AG vs GG, p= 0.61; AA vs AG+GG, p= 0.27). Funnel plots using standard error and precision were also symmetrical (Figure 5).

Discussion

Present meta-analysis of the association of the COMT Val158Met polymorphism with BC investigated 5,971 BC patients and 7,253 controls from 26 Asian case–control studies. The overall meta-analysis detected significant genetic association between the COMT Val158Met polymorphism and BC in Asian population. Five meta-analysis studies have been published so far on COMT Val 158Met polymorphism and breast cancer risk (Ding et al.,2010; He et al., 2012; Qin et al., 2012; Li et al., 2014; Wan et al., 2014) and reported no significant association. In all these five meta-analyses, information of Asian population is incomplete, hence present meta-analysis was conducted on case-control reports on Asian population and results suggested that the COMT Val158Met polymorphism is a risk factor for breast cancer development in the Asian population.

The COMT enzyme catalyzes the transfer of a methyl group from the S-adenosyl-L-methionine to the m-hydroxy group of catechol compounds, rendering the catechol estrogens more water soluble and enhancing excretion from the body (Service,1998; Ahsan et al., 2004). Several studies suggested protective role to COMT higher activity isoform, which protect reactive oxygen induced DNA damage, that are produced by estrogen oxidation(Onay et al., 2008). Prolonged exposure to estrogen is a risk factor for breast carcinoma (Hoffman et al., 1979; Amin et al., 1983; Lajin et al., 2013). Catechol estrogen metabolitesare genotoxic andcapable of initiating mammary tumors through their reactive metabolites by formation of depurinatingDNA adducts which are capable of creating de novo oncogenic mutations (Jan et al., 1998; Ahsan et al., 2004; Lajin et al., 2013).

Meta-analysis is a powerful statistical tool for analyzing cumulative data of case-control studies wherein the individual sample sizes are small and potentially investigates a large number of individuals and can estimate the effect of a genetic factor on the risk of the disease (Liwei et al., 2009; Li et al., 2013; Rai et al., 2014; Kumar et al., 2015).Several meta-analyses investigating the association of COMT Val158Met polymorphism with various disease/disorders have been published, like- attention- deficit/hyperactivity disorder (Sun et al., 2014), schizophrenia (Munafo et al., 2005), prostate cancer (Xiao et al., 2013; Zou et al., 2013) etc.

The present meta-analysis has few limitations like-(i) meta-analysis based on unadjusted data, (ii)there is marked heterogeneity among studies, and (iii)owing to the lack of information, gene-gene interactions were not done.

In conclusion, the results of present meta-analysis support significant association between the COMT Val158Met polymorphism and breast cancer risk in Asian population. The results should be interpreted cautiously due to presence of high heterogeneity. In future, case control studies from different ethnic populations with larger sample sizes should be carried out to confirm the association between COMT Val158Met polymorphism and breast cancer. Further, gene-gene and gene-environmental interactions should also be investigated.

Conflict of interest

None.

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