Catecho1-O-Methyltransferase Gene Val158Met Polymorphism and Prostate Cancer Susceptibility

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Abstract

Prostate cancer is one of the most common and a serious malignancy of males and it is well reported that estrogen plays a pivotal role in prostate carcinogenesis. Catecho1-O-Methyltransferase (COMT) catalyzes the inactivation of estrogens. Several studies have investigated the association of COMT gene Val158Met polymorphism with prostate cancer, but results were inconsistent and inconclusive. Hence, to assess this association, we performed a meta-analysis of all published case-control studies. PubMed, Springer link, Google Scholar, Elsevier and Springer link databases were searched for case-control studies. Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were used as association measure. Statistical analysis was performed with the software program MIX and Meta Analyst. In the current meta-analysis, 11 case-control studies with 3,381 prostate cancer cases and 3,276 healthy controls were considered. The results indicated no significant association between COMT Val158Met polymorphism and prostate cancer risk using allele contrast, co-dominant and homozygote models (allele contrast: OR \(_{AG \rightarrow GG} = 0.92; 95\% \text{ CI } 0.85-0.98; p=0.02;\) co-dominant: OR \(_{AG \rightarrow GG} = 0.81; 95\% \text{ CI } 0.85-1.07; p=0.04;\) homozygote: OR \(_{AA \rightarrow GG} = 0.81; 95\% \text{ CI } 0.70-0.95, p=0.008), but showed significant association with dominant and recessive models (dominant: OR \(_{AG+GG \rightarrow GG} = 1.54; 95\% \text{ CI } 1.15-2.07; p=0.003).\) In subgroup analysis meta-analysis using recessive genetic model showed significant association between COMT Val158Met polymorphism and prostate cancer risk in both Asian and Caucasian populations. In conclusion, results of present meta-analysis support that the COMT Val158Met polymorphism is risk factor for prostate cancer.

Keywords: Prostate cancer; Catecho1-O-Methyltransferase; COMT; Val158Met; Polymorphism; Meta-analysis

Abbreviations

COMT: Catecho1-O-Methyltransferase; Val158Met: Valine158Methionine; OR: Odd Ratio; CI: Confidence Interval

Introduction

Prostate cancer is the second most common cancer in men worldwide [1]. Intrepidthelialneoplasia, adenocarcinoma androgen-dependent and adenocarcinoma androgen-independent or castration-resistant are three developmental stages of prostate cancer. Although the etiology of prostate cancer remains unknown, but age, ethnicity, family history and steroid hormones appear to play a role [2,3]. Its prevalence is disproportionately high in African population, and is less common in Caucasian and Asian populations [4]. There is ample evidence supporting the notion that genetics plays a key role [5-7]. Estrogens, and/or catechol metabolites, have been identified as potential carcinogens for prostate cancer [8]. Various studies have investigated the associations between polymorphisms of genes encoding enzymes involved in estrogen metabolism and the risk of prostate cancer [9,10].

Three major estrogens exist in vivo: estrone (E1), estradiol (E2), and estriol (E3) and these estrogens are metabolized by phase I metabolizing enzymes like cytochrome 450. These enzymes metabolically activate procarcinogens to reactive electrophilic forms, reactive oxygen species (ROS), which can damage DNA if they are not detoxified by phase II enzymes. Catechol-O-Methyltransferase (COMT) is a critical phase II enzyme, which methylate catechol estrogens. If the methylation reaction is incomplete, these catechol estrogens will be oxidized to semiquinones and quinones, produce reactive oxygen species, which causes DNA damage and tumor initiation [11].

COMT gene is present on chromosome 22q11.2, contains six exons, and expresses at high levels in many tissues including the liver, kidney, breast and endometrium. The COMT Val158Met (rs4680, G-->A) polymorphism has been identified in coding region of protein [12] leads to the substitution of Valine (Val) with Methionine (Met) at codon 158. This substitution reduced the enzyme activity; individuals with the Met/Met genotype have a 3 to 4 folds lower enzyme activity than those with wild-type Val/Val genotype [13]. The frequency of the mutant Met (A) allele vary greatly among the different populations studied, frequency of Met allele is reported as 0.56 in American, 0.5 in European, and 0.27 in Asian populations [14]. Since COMT Val158Met polymorphism can reduce the enzymatic activity and may consequently increase the concentration of circulating carcinogenic catechol estrogens, COMT Val158Met polymorphism is reported a risk factor for prostate cancer initiation which is estrogen dependent. Val158Met has long been the focus of hormone-related cancers such as breast [15] endometrial [16] and ovary [17] cancer etc.

An association between the functional Val158/108Met polymorphism of the COMT gene and prostate cancer has been investigated in a number of studies, but with contradictory results due to small sample size and different background of included subjects. The aim of the present study was to find out association between COMT Val158Met polymorphism and prostate cancer risk by meta-analysis.
Methods

Meta-analysis was carried out according to meto-met-analysis of observational studies in epidemiology (MOOSE) guidelines [18].

Retrieval strategy and selection criteria

Published studies were retrieved through PubMed, Science Direct, Springer Link and Google Scholar databases up to December 31, 2019, using following key words: ‘Catecho-O-Methyltransferase’ or ‘COMT’ or ‘Val158Met’ and ‘Prostate Cancer’ or ‘Cancer. References of retrieved articles were searched for other eligible articles.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) investigate the association between COMT Val158Met polymorphism and prostate cancer risk, (2) included studies investigated cases of all types of prostate cancers i.e., adenoma, squamous and transitional etc., (3) studies with complete information of COMT Val158Met genotype/ allele numbers in prostate cancer cases and controls and (4) sufficient information for calculating the Odds Ratio (OR) with 95% Confidence Interval (CI). Major reasons for studies exclusion were as follows: (1) no prostate cancer cases analyzed, (2) the Val158Met polymorphism distribution information missing, and (3) duplicate article.

Data extraction

The following information was extracted for each eligible study using standard protocols: (i) first author's family name, (ii) country name, (iii) ethnicity, (iv) year of publication, (v) journal name, (vi) number of cases and controls, (vii) number of genotypes/alleles in cases and controls and (viii) genotyping method etc. Number of alleles or genotypes in both cases and controls were extracted or calculated from published data to recalculate ORs.

Statistical analysis

Pooled ORs with 95% Confidence Intervals (CIs) were calculated using five genetic models: the allele model (A vs. G), the dominant model (AA+AG vs. GG), the homozygote model (AA vs. GG), co-dominant/heterozygote model (AG vs. GG) and the recessive model (AA vs. AG+GG). Heterogeneity was investigated using Q test and quantified by I^2 statistic [19]. Both fixed effect and random effect models were used to calculate ORs with their 95% CIs [20,21], but model adopted on the basis of heterogeneity in this meta-analysis. The distribution of the genotypes in the control groups were examined for Hardy-Weinberg Equilibrium (HWE) using the Chi-square test. Sensitivity analysis was performed by removing studies not in HWE from the meta-analysis. Subgroup analysis was conducted by ethnicity. Funnel plots, Begg's and Egger's test were used to assess possible publication bias [22,23]. All the P values were two sided, and P value <0.05 was considered statistically significant. All statistical analyses were done using MIX [24] and Meta Analyst [25] program.

Results

Fifty-three articles have been extracted from the databases described above. According to inclusion and exclusion criteria, 42 articles were excluded, not suitable for inclusion in present meta-analysis (review, comments, meta-analysis, other disease analysed, unrelated to prostate cancer etc.). Selection of study details is shown in Figure 1. Total 10 individual case-control studies were found suitable for inclusion into meta-analysis [10,26-34]. One author [33] investigated prostate cancer patients from two populations (African and Caucasian), we considered both the samples as separate study. Hence total eleven studies were included in the present meta-analysis.

Table 1: Details of eleven studies included in meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Case No.</th>
<th>Control No.</th>
<th>Case Genotype</th>
<th>Control Genotype</th>
<th>P value of HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki et al. [23]</td>
<td>Japan</td>
<td>Asian</td>
<td>101</td>
<td>114</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.76</td>
</tr>
<tr>
<td>Nock et al. [27]</td>
<td>USA</td>
<td>Caucasian</td>
<td>439</td>
<td>479</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.89</td>
</tr>
<tr>
<td>Low et al. [28]</td>
<td>UK</td>
<td>Caucasian</td>
<td>75</td>
<td>157</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.09</td>
</tr>
<tr>
<td>Tanaka et al. [29]</td>
<td>Japan</td>
<td>Asian</td>
<td>178</td>
<td>131</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.4</td>
</tr>
<tr>
<td>Suzuki et al. [30]</td>
<td>Japan</td>
<td>Asian</td>
<td>419</td>
<td>342</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.46</td>
</tr>
<tr>
<td>Cassen et al. [10]</td>
<td>France</td>
<td>Caucasian</td>
<td>1039</td>
<td>828</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.94</td>
</tr>
<tr>
<td>Omrani et al. [31]</td>
<td>Iran</td>
<td>Asian</td>
<td>41</td>
<td>107</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.0</td>
</tr>
<tr>
<td>Pazarbasi et al. [32]</td>
<td>Turkey</td>
<td>Caucasian</td>
<td>34</td>
<td>14</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.81</td>
</tr>
<tr>
<td>Brueaul et al. [33]</td>
<td>USA</td>
<td>Caucasian</td>
<td>150</td>
<td>139</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.96</td>
</tr>
<tr>
<td>Brueaul et al. [33]</td>
<td>USA</td>
<td>African</td>
<td>456</td>
<td>548</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.67</td>
</tr>
<tr>
<td>Tang et al. [34]</td>
<td>USA</td>
<td>Caucasian</td>
<td>449</td>
<td>417</td>
<td>Val/Val</td>
<td>Val/Met</td>
<td>0.15</td>
</tr>
</tbody>
</table>

In eleven included studies, the smallest case sample size was 34 [32] and largest sample size was 1034 [10]. Total cases and controls were 3,381 and 3,276 respectively. In controls genotypes, percentage of GG, AG and AA were 31.75%, 49.60% and 18.65% respectively. In total cases, genotype percentage of GG, AG and AA was 34.13%, 49.01% and 16.86% respectively (Table 1). These studies were performed in different countries-France [10], Iran [31], Japan [26,29,30], Turkey [32], UK [28], USA [27,33,34].

Meta-analysis

Table 2 summarizes the odds ratio with corresponding 95% Confidence intervals for association between COMT Val158Met polymorphism and risk of prostate cancer in allele contrast, dominant, recessive, homozygote and co-dominant models. Meta-

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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 I² metric: overall analysis.

<table>
<thead>
<tr>
<th>Genetic Models</th>
<th>Fixed effect (OR (95% CI), p</th>
<th>Random effect (OR (95% CI), p)</th>
<th>Heterogeneity p-value (Q test)</th>
<th>I² (%)</th>
<th>Publication Bias (p of Egger's test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele Contrast (A vs. G)</td>
<td>0.92(0.85-0.98), 0.02</td>
<td>0.93(0.84-1.02), 0.13</td>
<td>0.13</td>
<td>32.96</td>
<td>0.38</td>
</tr>
<tr>
<td>Co-dominant (AG vs. GG)</td>
<td>0.96(0.85-1.07), 0.46</td>
<td>0.96(0.85-1.07), 0.74</td>
<td>0.86</td>
<td>0</td>
<td>0.98</td>
</tr>
<tr>
<td>Homozygote (AA vs. GG)</td>
<td>0.81(0.70-0.95), 0.008</td>
<td>0.83(0.66-1.03), 0.10</td>
<td>0.1</td>
<td>36.69</td>
<td>0.55</td>
</tr>
<tr>
<td>Dominant (AA+AG vs. GG)</td>
<td>1.18(1.03-1.34), 0.01</td>
<td>1.17(0.96-1.41), 0.11</td>
<td>0.12</td>
<td>34.65</td>
<td>0.59</td>
</tr>
<tr>
<td>Recessive (AA vs. GG+AG)</td>
<td>1.5(1.13-1.68), &lt;0.0001</td>
<td>1.54(1.15-2.07), 0.003</td>
<td>&lt;0.0001</td>
<td>72.02</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Asian studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele Contrast (A vs. G)</td>
<td>1.1(0.93-1.28), 0.26</td>
<td>1.12(0.91-1.36), 0.27</td>
<td>0.24</td>
<td>28.21</td>
<td>0.54</td>
</tr>
<tr>
<td>Co-dominant (AG vs. GG)</td>
<td>1.11(0.88-1.39), 0.38</td>
<td>1.16(0.87-1.39), 0.38</td>
<td>0.65</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>Homozygote (AA vs. GG)</td>
<td>1.22(0.82-1.81), 0.22</td>
<td>1.31(0.70-2.45), 0.39</td>
<td>0.16</td>
<td>41.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Dominant (AA+AG vs. GG)</td>
<td>0.86(0.69-1.24), 0.42</td>
<td>0.81(0.43-1.48), 0.50</td>
<td>0.16</td>
<td>41.82</td>
<td>0.68</td>
</tr>
<tr>
<td>Recessive (AA vs. GG+AG)</td>
<td>2.58(1.79-3.71), &lt;0.0001</td>
<td>2.4(1.04-5.52), 0.03</td>
<td>0.02</td>
<td>68.6</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Caucasian studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allele Contrast (A vs. G)</td>
<td>0.88(0.81-0.96), 0.007</td>
<td>0.88(0.81-0.96), 0.007</td>
<td>0.44</td>
<td>0</td>
<td>0.72</td>
</tr>
<tr>
<td>Co-dominant (AG vs. GG)</td>
<td>0.89(0.77-1.04), 0.15</td>
<td>0.90(0.77-1.04), 0.15</td>
<td>0.91</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Homozygote (AA vs. GG)</td>
<td>0.79(0.66-0.94), 0.01</td>
<td>0.79(0.66-0.94), 0.01</td>
<td>0.42</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>Dominant (AA+AG vs. GG)</td>
<td>1.18(1.02-1.37), 0.02</td>
<td>1.18(1.01-1.37), 0.02</td>
<td>0.39</td>
<td>2.76</td>
<td>0.84</td>
</tr>
<tr>
<td>Recessive (AA vs. GG+AG)</td>
<td>1.44(1.25-1.65), &lt;0.0001</td>
<td>1.37(1.01-1.85), 0.04</td>
<td>0.01</td>
<td>66.46</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Analysis with allele contrast did not show significant association between 158Met allele and prostate cancer with both fixed effect (OR_A vs. G = 0.92; 95% CI=0.85-0.98; p=0.02) and random effect model (OR_A vs. G = 0.93; 95% CI=0.84-1.02) (Table 1). Co-dominant (OR_AG vs. GG = 0.81; 95% CI=0.85-1.07; p=0.46) and homozygote (OR_AA vs. GG = 0.81; 95% CI=0.70-0.95; p=0.008) genetic models also did not show any association between COMT Val158Met polymorphism and prostate cancer (Table 2). An increased significant association was found between prostate cancer and dominant model (AA+AG vs. GG) with fixed effect model (OR_AA+AG vs. GG = 1.18; 95% CI=1.03-1.34; p=0.01) (Table 2, Figure 2). Association of COMT Val158Met recessive genotype (AA vs. AG+GG) was observed significant with prostate cancer using fixed (OR_AA vs. AG+GG = 1.5; 95% CI=1.31-1.68; p<0.0001) and random (OR_AA vs. AG+GG = 1.54; 95% CI=1.15-2.07; p=0.003) effect models (Table 2, Figure 3).

**Heterogeneity and sensitivity analysis**

A true heterogeneity existed between studies for allele contrast (P_heterogeneity=0.13, Q=14.91, I²=32.96%, t²=0.007), homozygote(P_heterogeneity=0.10, Q=15.79, I²=36.69%, t²=0.044), co-dominant (P_heterogeneity=0.86, Q=5.34, I²=0%, t²=0), dominant (P_heterogeneity=0.12, Q=15.30, I²=34.65%, t²=0.03) and recessive (P_heterogeneity=0.0001, Q=35.73, I²=72.02%, t²=0.13) models. Heterogeneity was observed higher only in recessive model.

Sensitivity analysis was performed by eliminating studies with control population deviating from HWE. Control population of one study was not in HWE [31], hence meta-analysis using recessive genetic model was performed after eliminating this study, but heterogeneity did not decrease after exclusion of this study.

**Subgroup analysis**

Sub-group analysis based on ethnicity was performed. Out of 11 included studies, 4 studies were from Asian population, 6 studies were from Caucasian population and 1 study was from African population. In Asian population (number of studies=4; 739 cases/694 controls), allele contrast (OR_AA vs. GG =1.1; 95% CI =0.93-1.28; p=0.26), co-dominant (OR_AG vs. GG =1.11; 95% CI =0.88-1.39; p=0.38), homozygote (OR_AA vs. GG =1.22; 95% CI =0.82-1.81; p=0.22) and dominant models (OR_AA+AG vs. GG =0.86; 95% CI =0.69-1.24; p=0.42) did not show any association between COMT Val158Met polymorphism and prostate cancer using both fixed and random effect models (Table 2). Recessive model
meta-analysis showed strong statistical association between COMT Val158Met polymorphism and prostate cancer risk using both fixed effect (OR = 2.58; 95% CI = 1.79-3.71; P<0.0001) and random effect (OR = 2.4; 95% CI = 1.04-5.52; P=0.03) models (Table 2, Figure 4). In Caucasian population (number of studies=6; 2,186 cases/2,034 controls), allele contrast, homozygote and co-dominant meta-analysis did not show association between COMT Val158Met polymorphism and prostate cancer risk (Table 2). Meta-analysis using dominant model showed significant association with both the fixed effect (OR = 2.4; 95% CI = 1.02-1.37; P=0.02) and random effect (OR = 2.1; 95% CI = 1.01-1.37; P=0.02) models. The recessive model meta-analysis also showed statistically significant association with fixed effect (OR = 1.4; 95% CI = 1.25-1.65; P<0.0001) and random effect (OR = 1.37; 95% CI = 1.01-1.85; P=0.04) models (Table 2, Figure 5).

Publication bias
Funnel plot observation and P value of Egger’s test showed absence of publication bias in meta-analysis using five genetic models (A vs. G, P=0.38; AA+AG vs. GG, P=0.59; AA vs. GG, P=0.55; AG vs. GG, P=0.98; AA vs. AG+GG, P=0.071) (Table 2, Figures 6 and 7).

Discussion
COMT is a phase II enzyme that is involved in the inactivation of catechol estrogens [35]. 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) [36]. Allelic variation in COMT (Val158Met) is likely related to decrease enzymatic activity and consequently increases the risk of carcinogenesis due to accumulation of estrogen metabolites. Hence, COMT Val158Met polymorphism has been extensively investigated for correlation with different cancer risk like - esophageal cancer [37], colorectal cancer [38], hepatocellular carcinoma [39], lung cancer [40], breast cancer [15], ovary cancer [17], endometrial cancer [41], testicular germ cell tumor [42] and bladder cancer [43] etc.

In present meta-analysis, we tried to find out the exact associations between COMT Val158Met polymorphism and prostate cancer susceptibility. Our results indicated that the Val158Met polymorphism is not risk factor for prostate cancer and OR is statistically significant (OR=1.54; 95% CI=1.15-2.07; P=0.003).
Figure 5: Random effect Forest plot of recessive model (AA vs. AG + GG) of 6 Caucasian studies of COMT Val158Met (G472A) polymorphism.

Figure 6: Funnel plot- Precision by log odds ratio for dominant model (AA + AG vs. GG) of total 11 studies of COMT Val158Met (G472A) polymorphism.

Figure 7: Funnel plot- Standard error by log odds ratio allele contrast model (AA + AG vs. GG) of total 11 studies of COMT Val158Met (G472A) polymorphism.

Meta-analysis is an acceptable powerful statistical tool, suitable for the dealing with genetic-association data. Mea-analysis overcome deficiencies of small studies/small sample analysis by combining data from several studies and increasing the statistical power (lower type II error rate) [44]. Several meta-analysis were published which evaluated risk of small effect genes on different disease and disorders- like MTHFR frequency [45], MTRR frequency [46], Down syndrome [47-49], recurrent pregnancy loss [50], cleft lip and palate [51,52], male infertility [53], obsessive compulsive disorder [54], autism [49,50], epilepsy [50], schizophrenia [48,55], depression [51,52], Glucose-6-phosphate dehydrogenase deficiency [56], Alzheimer’s disease [50], hyperuricemia [50], esophageal cancer [57], breast cancer [48,51], digestive tract cancer [58], colorectal cancer [50], prostate cancer [59], endometriol cancer [60] and ovary cancer [50] etc.

Strengths of present meta-analysis include the large sample size and higher statistical power based on large number of cases and controls from differential individual studies. We also performed sensitivity analysis and subgroup analysis. Similar to other meta-analyses, present meta-analysis has also few limitations, which should be acknowledged like- (i) unadjusted OR was used, (ii) control sources were not uniformed, (iii) only four databases were searched for study retrieval, it may be possible that few relevant studies were missed, (iv) single gene polymorphism was considered, (v) other confounding factors such as age, diet, lifestyle, physical activity and environment etc were not considered.

Conclusions
These results indicate that the COMT Val158Met polymorphism is risk factor for prostate cancer (OR=1.54; p= 0.003). Subgroup analysis based on ethnicity also confirmed the results that COMT Val158Met polymorphism is risk factor for prostate cancer using recessive genetic model. In future, studies with larger sample sizes from different ethnic population are required to reach a definitive conclusion regarding this association. Also, it is necessary to take into consideration different inheritance patterns and the interaction of the COMT gene with the environment.

Authors Contributions
VR and PK designed and wrote this manuscript. VR performed the meta-analysis and PK collected data.
References


