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ORIGINAL RESEARCH ARTICLE

Glutathione S-Transferase P1 313 (A > G) Ile105Val Polymorphism Contributes to Cancer Susceptibility in Indian Population: A Meta-analysis of 39 Case–Control Studies

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Abstract *GSTP1* involved in the metabolism of carcinogens and toxins, reduces damage of DNA and act as a suppressor of carcinogenesis. Many studies have reported that 313 A > G polymorphism is associated with different cancer in Indian population, but the results remain conflicting rather than conclusive. Therefore, we have performed meta-analysis to clarify the more precise association of *GSPT1* 313 A > G polymorphism with cancer risk in Indian population. We retrieved all relevant published literature from PubMed (Medline) and Google scholar web database and included those study only based on the established inclusion criteria. Pooled ORs and 95% CIs were used to appraise the strength of association. Publication bias and sensitivity analysis was also evaluated. A total of 6581 confirmed cancer cases and 8218 controls were included from eligible thirty nine case–controls studies. Pooled analysis suggested that the variant genotypes significantly increased the risk of cancer in allele (G vs. A: OR 1.266, 95% CI 1.129–1.418, $p = 0.001$), heterozygous (AG vs. AA: OR 1.191, 95% CI 1.047–1.355, $p = 0.008$), homozygous (GG vs. AA: OR 1.811, 95% CI 1.428–2.297, $p = 0.001$), dominant (GG + AG vs. AA: OR 1.276, 95% CI 1.110–1.466, $p = 0.001$) and recessive (GG vs. AG + AA: OR 1.638, 95% CI 1.340–2.002, $p = 0.001$) genetic models. The stability of these observations was confirmed by a sensitivity analysis. Begger's funnel plot and Egger's test did not reveal any publication bias. This meta-analysis suggests that the *GSTP1* 313 A > G polymorphism may contribute to genetic susceptibility to cancer in Indian population. However, larger studies and randomized clinical trial will be required to elucidate the biological and molecular mechanism of *GSTP1* gene in cancer.

Keywords Cancer · Meta-analysis · Metabolic gene · Polymorphism · Indian population

Introduction

Cancer is the most dreadful disease and is the leading cause of high morbidity and mortality in worldwide [1]. Approximately 70% of deaths from cancer occur in developing countries. In India, cancer incidence is predicted to reach 1,148,757 cases in the year 2020 that may lead to a huge socio-economic burden [2]. Cancer is considered as a polygenic disease, whose pathogenesis and molecular mechanism are still intricated and difficult to resolve [3]. Epidemiological studies indicate that interaction between genetic susceptibility genes with an environmental factors and metabolism dysfunction play a key role in development of cancer [4]. Host genetic factors make it even more complex as all individuals who are exposed to these risk factors will not develop the disease since inter-individual differences in genetic susceptibility exist. Identification of host genes and genetic variation in an individual patient may contribute to new approaches to treatment and prevent cancer adeptly [5].

The genes responsible for metabolizing the tobacco carcinogens appear to be prime candidates for the

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investigative search of cancer susceptibility genes. Glutathione S-Transferases (GSTs) superfamily consists of the broadly expressed phase II xenobiotic metabolizing enzymes located in cytosol. GSTs mediate the conjugation of reduced glutathione with a variety of endogenous and exogenous electrophilic compounds, including several potentially toxic carcinogens and chemotherapeutic drugs, thereby reducing the reactivity of the compounds by making them water soluble and facilitating their elimination from the body for critical defense against carcinogens [6].

Pi-class glutathione-S-transferase (*GSTP1*) gene spanning approximately 2.84 kb is located on chromosome 11q13 encodes a phase II metabolic enzyme [7], play a key role in the inactivation of toxic and carcinogenic electrophiles [8]. Several single nucleotide polymorphisms (SNPs) has been reported in *GSTP1* that lead to changes in amino acids. Among them one is characterized by an A → G transition at nucleotide 313, which replaces ATC (isoleucine) at codon 105 with GTC (valine) (I105V) within the active site of the enzyme [9]. This substitution results in a lower enzymatic activity and is associated with higher hydrophobic adduct levels and higher levels of polycyclic aromatic hydrocarbon-DNA adducts in human lymphocytes [10]. Recent genome-wide association studies (GWAS) have clearly unveiled that SNPs is the most common forms of human genetic variation have an important role in defining individual susceptibility to cancer [11].

Considering the importance of *GSTP1* in the detoxification process and protect cell from various carcinogens, the possible influence of 313 (A > G) (rs1695) polymorphism in *GSTP1* gene on different cancer risk in Indian population has been investigated extensively [12–50]. However, the results from these studies are inconsistent. Individual published studies contained small number of subjects and may have been underpowered to detect the modest effects of the *GSTP1* 313 (A > G) polymorphism on cancer susceptibility. To overcome this situation, nowadays meta-analysis statistical tool is used to explore the host risk factors associated with the complex diseases, because it employs a quantitative method to combine the data drawn from individual studies where sample sizes are small to provide reliable conclusions [51]. Given these inconclusive results and the limits of a single study with a small sample size, we performed the present meta-analysis on all eligible published studies in Indian populations to estimate the cumulative association of *GSTP1* 313 (A > G) gene polymorphism and overall cancer susceptibility.

Materials and Methods

Identification and Eligibility of Studies

The relevant research studies were searched in PubMed, Medline and Google Scholar electronic databases updated in February 2018. The search key words were ""cancer", "carcinoma," "malignancy", and "tumor", "Glutathione-S-transferase", "*GSTP1*", "Glutathione-S-transferase P1", and "genetic polymorphism", "single nucleotide polymorphism", "genetic variants", and ''Indian", "India''. Furthermore, manual retrieval was undertaken additionally by browsing the references from retrieved articles for other eligible studies. If the same study was researched by more than one study, only the one with the largest sample size was included in our study. If one study investigated multiple cancers, each cancer type was counted as a separate comparison in the group stratified by cancer type. All retrieved articles were downloaded and further screened to identify potentially eligible studies.

Inclusion and Exclusion Criteria

Studies included in the meta-analysis had to meet the following inclusion criteria: (1) original case–control or cohort studies; (2) Cancers cases should have been confirmed by histology or pathology; (3) must have investigated the association between *GSTP1* 313 A > G polymorphism and cancer susceptibility in Indian population; (4) provided detailed frequency of genotype distribution in the cases and controls. The criteria for exclusion were (1) case reports, editorial, reviews, overlapped data, animal or mechanism studies; (2) no genotype frequency or genotype information provided; (3) no usable data reported.

Data Extraction and Quality Assessment

To minimize the bias and improve the reliability, the methodological quality assessment and data extraction were independently extracted from all eligible studies by two researchers according to the inclusion–exclusion criteria mentioned above. The data collected from each study were as follows: first author's name, publication year, cancer type, genotyping method, and genotype distribution in cases and controls. Based on the main cancer type of the included studies, cancer types were classified. Disagreement was solved by full discussion until a consensus was reached.

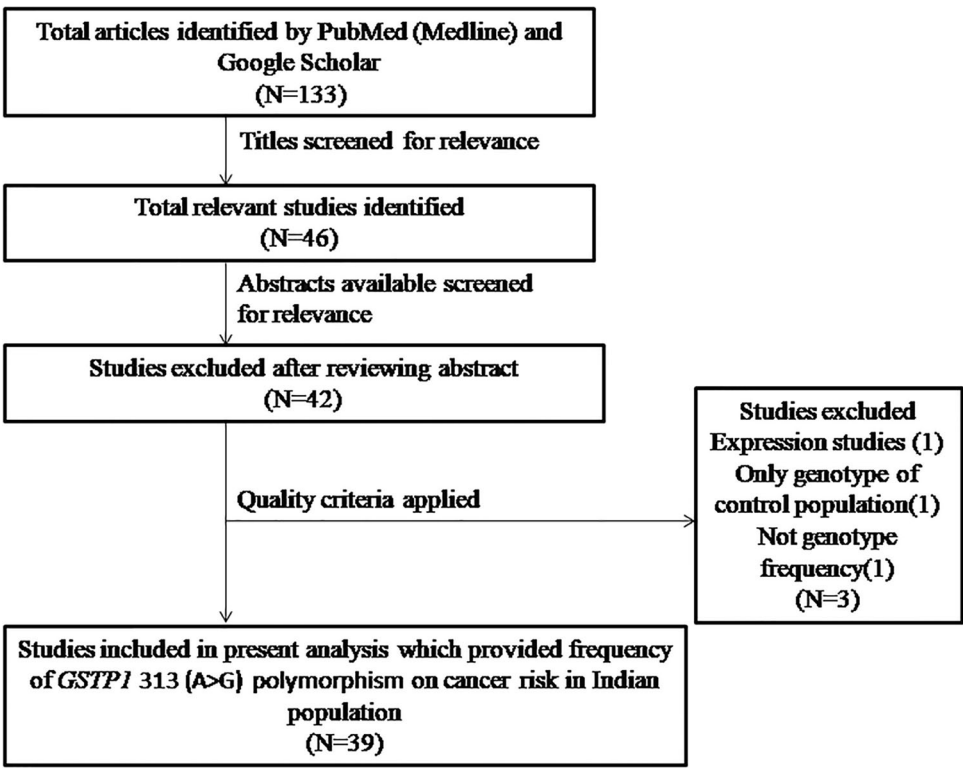

Fig. 1 Prisma flow diagram for inclusion and exclusion of studies in the meta-analysis on *GSTP1* 313 A > G polymorphism

Statistical Analysis

The strength of relationships between *GSTP1* 313 (A > G) polymorphism and cancer risk was estimated by calculating pooled ORs and their corresponding 95% CIs. Heterogeneity assumption between studies was evaluated by the Chi square-based Q-statistic and I^2 statistic [52]. The random effects model (DerSimonia and Laird method) was used to assess pooled OR when there was a significant difference in terms of heterogeneity (if $p < 0.05$) [53]. Otherwise fixed effects model (the Mantel–Haenszel method) was used [54]. Potential publication bias was estimated by funnel plots and Egger's test [55]. Moreover, the stability of the results was assessed using sensitivity analysis by deleting each single study involved in the meta-analysis one at a time to reflect the influence of the individual study to the pooled ORs. All p values were two sided and statistical significance level was considered for any test was p value < 0.05.The statistical analysis involved in this meta-analysis was performed by Comprehensive meta-analysis (CMA) version 2 software program (Biostat Inc., USA). To ensure the reliability and accuracy of the statistical analysis, two researchers entered the data into the software program independently and reached a consensus.

Results

Literature Search and Meta-analysis Databases

We have identified one hundred thirty three studies through literature search from the PubMed (Medline) and Google scholar for detailed evaluation. As per the pre-set selection (inclusion–exclusion) criteria, a total thirty nine published studies on association with the *GSTP1* 313 A > G gene polymorphism and susceptibility to multiple cancers were included in the meta-analysis (Fig. 1). Studies either showing *GSTP1* polymorphism to predict survival OR as an indicator for response to therapy of patients were excluded straightaway. Similarly, research articles investigating the levels of *GSTP1* mRNA or protein expression and relevant review articles were also excluded. We included only case–control or cohort design studies having frequency of all three genotypes. Eligible studies, publication year, cancer types, total numbers of controls and cases, genotyping methods, distribution of genotypes and minor allele frequency (MAF) in the controls have been shown in Tables 1 and 2.

Publication Bias

Begg's funnel plot and Egger's linear regression test were conducted to estimate the possible publication bias among the included studies for this meta-analysis. In the funnel

Table 1 Main characteristics of all studies included in the meta-analysis

First authors and year	Population	Type of cancer	Control	Cases	Genotyping method	Association
Satinder et al. [12]	North India	Cervical	150	150	PCR–RFLP	No
Ghatak et al. [13]	North East	Gastric	80	80	PCR–RFLP	Yes
Ghosh et al. [14]	West bengal	Gastric	82	70	PCR–RFLP	Yes
Sharma et al. [15]	North India	Lung	270	270	PCR–RFLP	No
Kimi et al. [16]	North East	Breast	10	22	PCR–RFLP	Yes
Moulik et al. [17]	North India	Leukemia	300	100	PCR–RFLP	Yes
Pandith et al. [18]	Kashmir	Bladder	210	180	PCR–RFLP	No
Abbas et al. [19]	North India	Cervical	165	150	PCR–RFLP	No
Sameer et al. [20]	Kashmir	Colorectal	160	86	PCR–RFLP	No
Dunna et al. [21]	South India	Leukemia	248	290	PCR–RFLP	Yes
Ahmad et al. [22]	North India	Renal cell	250	196	PCR–RFLP	Yes
Saxena et al. [23]	North India	Breast	215	215	PCR–RFLP	No
Chauhan et al. [24]	North India	Leukemia	199	230	PCR–RFLP	No
Qadri et al. [25]	Kashmir	Prostate	80	50	PCR–RFLP	Yes
Wang et al. [26]	South India	Colorectal	291	302	PCR–RFLP	No
Ihsan et al. [27]	North East	Lung	290	188	PCR–RFLP	No
Sailaja et al. [28]	South India	Leukemia	248	260	PCR–RFLP	Yes
Kaushal et al. [29]	North East	Breast	174	117	PCR–RFLP	Reduced
Malik et al. [30]	Kashmir	Esophageal	195	135	PCR–RFLP	No
Ruwali et al. [31]	North India	Head and neck	350	350	PCR–RFLP	Reduced
Malik et al. [32]	North India	Gastric	195	108	PCR–RFLP	No
Saxena et al. [33]	North India	Breast	410	413	PCR–RFLP	Yes
Kumar et al. [34]	North India	Lung	253	93	Sequencing	No
Suneetha et al. [35]	South India	Leukemia	150	92	PCR–RFLP	No
Syamala et al. [36]	South India	Breast	250	347	PCR–RFLP	No
Rajkumar et al. [37]	South India	Breast	500	250	PCR–RFLP	No
Singh et al. [38]	North India	Head and neck	200	175	PCR–RFLP	Reduced
Sobti et al. [39]	North India	Lung	151	151	PCR–RFLP	No
Tripathi et al. [40]	North India	Gastric	100	76	PCR–RFLP	No
Soya et al. [41]	South India	Upper aerodigestive	220	408	PCR–RFLP	No
Samson et al. [42]	South India	Breast	500	250	PCR–RFLP	Yes
Pandey et al. [43]	North India	Gallbladder	201	106	PCR–RFLP	Yes
Jain et al. [44]	North India	Esophageal	137	100	PCR–RFLP	No
Sobti et al. [45]	North India	Cervical	103	103	PCR–RFLP	Yes
Mittal et al. [46]	North India	Prostate	105	54	PCR–RFLP	Yes
Mittal et al. [47]	North India	Bladder	162	106	PCR–RFLP	Yes
Srivastava et al. [48]	North India	Bladder	370	106	PCR–RFLP	Yes
Vijayalakshmi et al. [49]	South India	Prostate	100	75	PCR–RFLP	Reduced
Srivastava et al. [50]	North India	Prostate	144	127	PCR–RFLP	Yes

plots, standard error of the log (OR) of each study was plotted against it log (OR). The appearances of funnel plot were symmetrical in all of the comparison models. Furthermore, Egger's regression test, a linear regression approach for measuring funnel plot on the natural logarithm scale of the OR was used to provide statistical evidence to the funnel plot symmetry and showed no publication bias for all the genetic models (Table 3).

Evaluation of Heterogeneity

In order to test heterogeneity among the selected studies, Q-test and I^2 statistics were employed. Heterogeneity was

Table 2 Genotypic distribution of *GSTP1* gene polymorphism included in meta-analysis

Authors and year	Controls				Cases				
	Genotype			Minor allele	Genotype			Minor allele	HWE
	AA	AG	GG	MAF	AA	AG	GG	MAF	*p* value
Satinder et al. [12]	46	96	8	0.37	44	97	9	0.38	0.00
Ghatak et al. [13]	60	16	4	0.15	28	32	20	0.45	0.053
Ghosh et al. [14]	61	18	3	0.14	41	19	10	0.27	0.27
Sharma et al. [15]	233	32	5	0.07	225	40	5	0.09	0.04
Kimi et al. [16]	10	0	0	0.00	15	5	2	0.20	–
Moulik et al. [17]	195	89	16	0.20	57	28	15	0.29	0.17
Pandith et al. [18]	159	48	3	0.12	129	45	6	0.15	0.77
Abbas et al. [19]	108	48	9	0.20	93	50	7	0.21	0.24
Sameer et al. [20]	118	34	8	0.15	65	14	7	0.16	0.01
Dunna et al. [21]	140	105	3	0.22	108	139	43	0.38	0.01
Ahmad et al. [22]	126	103	21	0.29	71	99	26	0.38	0.99
Saxena et al. [23]	101	75	39	0.35	81	89	45	0.41	0.01
Chauhan et al. [24]	103	79	17	0.28	111	100	19	0.30	0.73
Qadri et al. [25]	59	17	4	0.15	26	17	7	0.31	0.08
Wang et al. [26]	160	107	24	0.26	141	132	29	0.31	0.31
Ihsan et al. [27]	179	96	15	0.21	102	77	9	0.25	0.65
Sailaja et al. [28]	140	105	3	0.22	141	102	17	0.26	0.01
Kaushal et al. [29]	108	62	4	0.20	62	48	7	0.26	0.15
Malik et al. [30]	111	75	9	0.23	72	48	15	0.28	0.41
Ruwali et al. [31]	199	138	13	0.23	224	112	14	0.20	0.06
Malik et al. [32]	111	75	9	0.23	62	36	10	0.25	0.01
Saxena et al. [33]	200	171	32	0.29	147	193	66	0.40	0.58
Kumar et al. [34]	132	106	15	0.26	55	35	3	0.22	0.29
Suneetha et al. [35]	81	57	12	0.27	43	40	9	0.31	0.65
Syamala et al. [36]	125	109	16	0.28	186	140	21	0.26	0.22
Rajkumar et al. [37]	230	219	51	0.32	118	103	29	0.32	0.91
Singh et al. [38]	104	92	4	0.25	106	64	5	0.21	0.01
Sobti et al. [39]	62	83	6	0.31	78	68	5	0.25	0.01
Tripathi et al. [40]	52	36	12	0.30	46	26	4	0.22	0.15
Soya et al. [41]	120	88	12	0.25	219	162	27	0.26	0.42
Samson et al. [42]	230	219	51	0.32	118	106	29	0.32	0.91
Pandey et al. [43]	112	76	13	0.25	42	54	10	0.34	0.98
Jain et al. [44]	72	56	9	0.27	56	35	9	0.26	0.66
Sobti et al. [45]	32	68	3	0.35	31	68	4	0.36	0.01
Mittal et al. [46]	58	42	5	0.24	17	28	9	0.42	0.45
Mittal et al. [47]	95	61	6	0.22	33	57	16	0.41	0.31
Srivastava et al. [48]	191	166	13	0.25	33	58	15	0.41	0.01
Vijayalakshmi et al. [49	42	52	6	0.32	49	22	4	0.20	0.05
Srivastava et al. [50]	83	56	5	0.22	46	77	4	0.33	0.22

MAF, Minor allele frequency, *HWE*, Hardy–Weinberg equilibrium

observed in all genetic models, i.e., allele (G vs. A), homozygous (GG vs. AA), heterozygous (AG vs. AA), recessive (GG vs. AG + AA) and dominant (GG + AG vs. AA). Thus, random effects model was applied to synthesize the data for above models (Table 3).

Association of GSTP1 313 A > G Polymorphism and Overall Cancer Susceptibility

We pooled all thirty nine studies together and it resulted into 6581 confirmed cancer cases and 8218 healthy

Table 3 Statistics to test publication bias and heterogeneity in meta-analysis

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for meta-analysis
	Intercept	95% Confidence Interval	*p* value	Q value	$P_{heterogeneity}$	I^2 (%)	
G versus A	1.25	− 1.03 to 3.54	0.27	160.44	0.001	76.32	Random
GG versus AA	0.79	− 0.68 to 2.27	0.28	99.40	0.001	61.77	Random
AG versus AA	1.30	− 0.64 to 3.25	0.18	113.44	0.001	66.50	Random
GG + AG versus AA	1.59	− 0.64 to 3.83	0.15	146.23	0.001	74.01	Random
GG versus AG + AA	0.78	− 0.45 to 2.02	0.20	75.44	0.001	49.63	Random

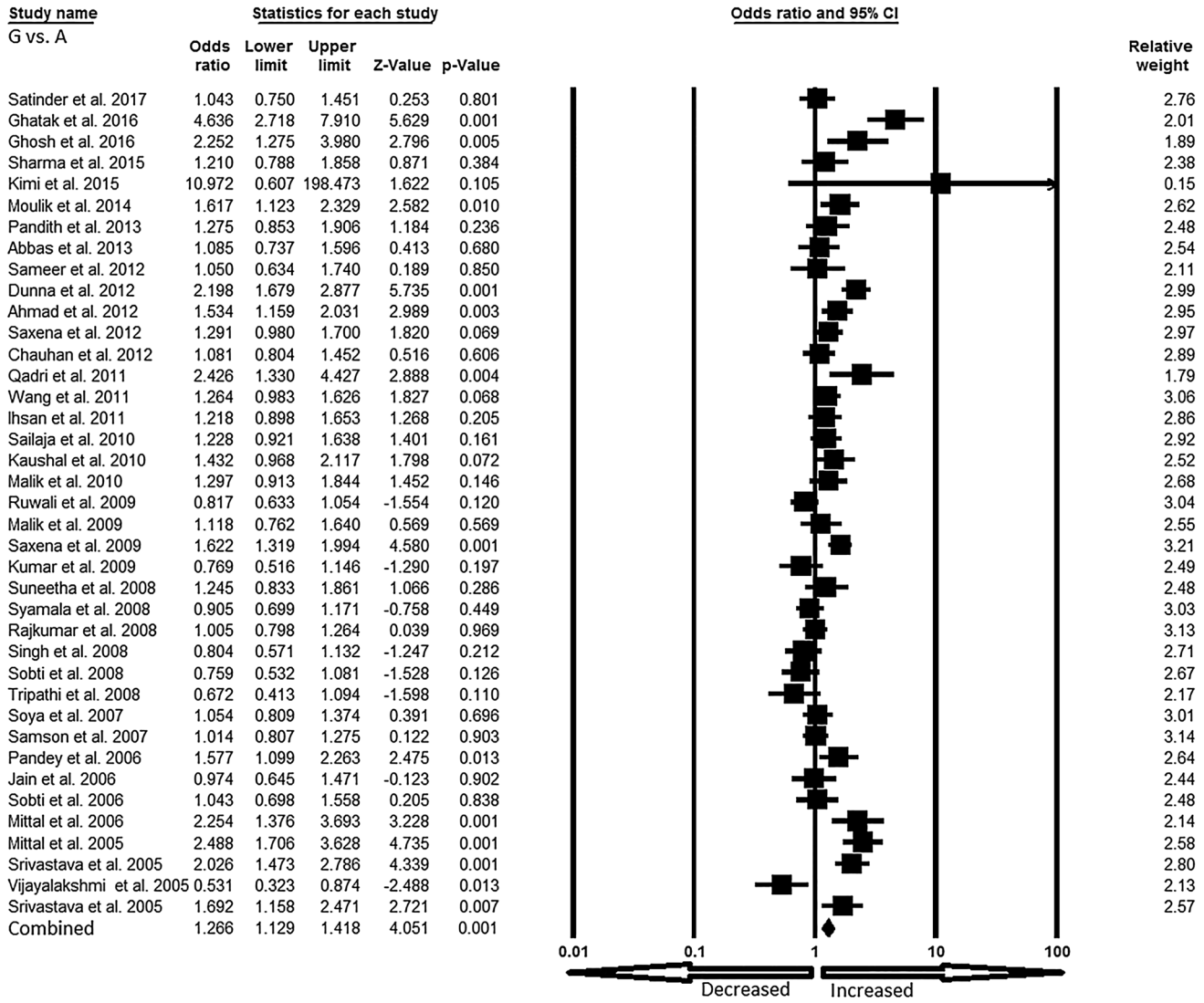

Fig. 2 Forest plot of allele (G vs. A) model for overall cancer risk. The squares and horizontal lines correspond to the study specific OR and 95% CI

controls to examining the overall association between *GSTP1* 313 A > G gene polymorphism and cancer risk. The pooled OR from overall analysis indicated that it was significantly associated with increased risk of cancer in allele (G vs. A: OR 1.266, 95% CI 1.129–1.418, p = 0.001), heterozygous (AG vs. AA: OR 1.191, 95% CI 1.047–1.355, $p = 0.008$), homozygous (GG vs. AA: OR 1.811, 95% CI 1.428–2.297, $p = 0.001$), dominant (GG +

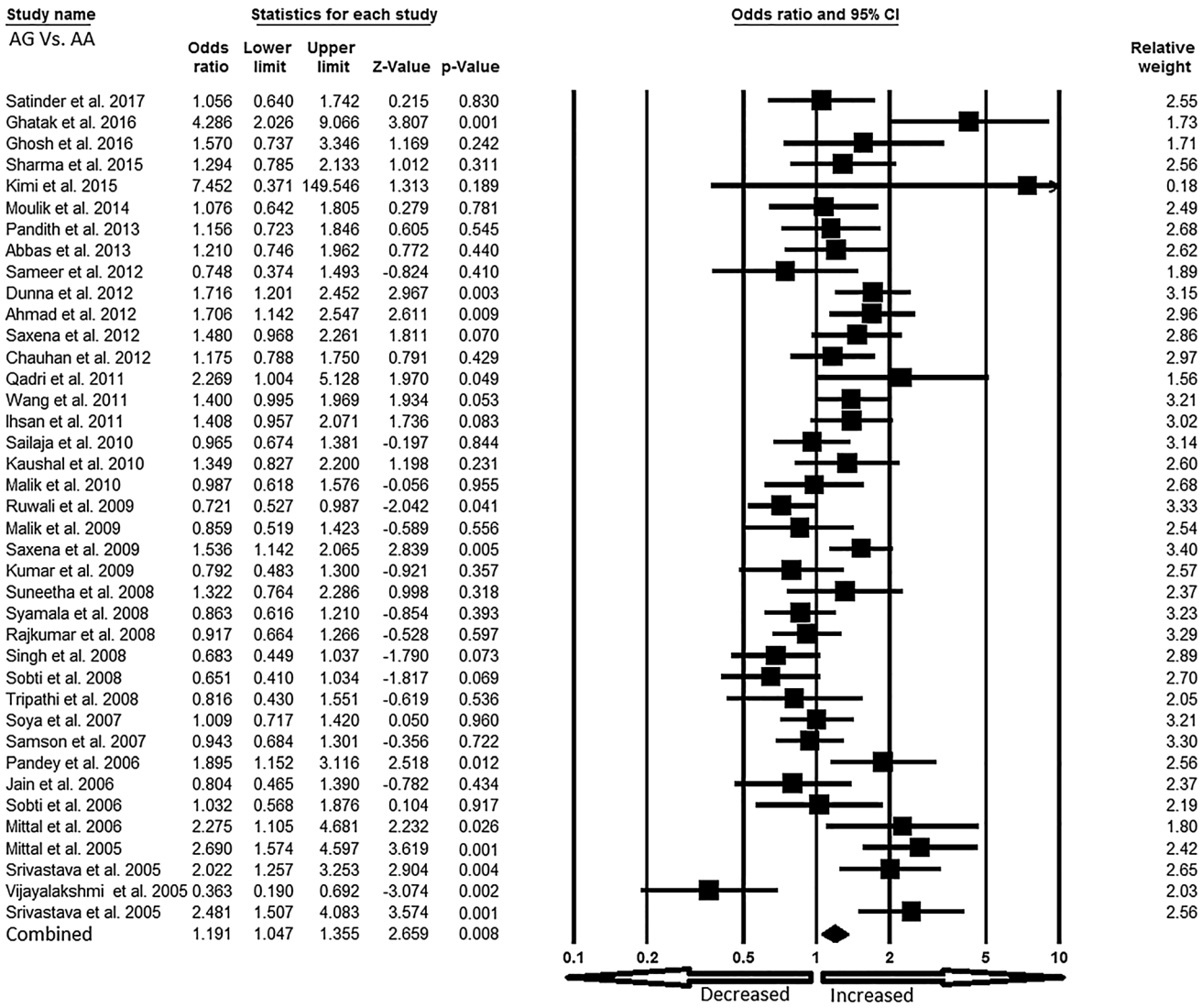

Fig. 3 Forest plot of heterozygous (AG vs. AA) model for overall cancer risk. The squares and horizontal lines correspond to the study specific OR and 95% CI

AG vs. AA: OR 1.276, 95% CI 1.110–1.466, $p = 0.001$) and recessive (GG vs. AG + AA: OR 1.638, 95% CI 1.340–2.002, $p = 0.001$) comparison models (Figs. 2, 3, 4, 5, 6).

Sensitivity Analysis

To evaluate the stability of the pooled results, sensitivity analysis was conducted. The influence of each study on the pooled OR was checked by repeating the meta-analysis while omitting each study, one at a time. The result of sensitivity analysis showed the corresponding pooled OR value did not significantly change when omitting any single study (figure not shown). This revealed that our results were statistically robust.

Discussion

Diagnosis and prevention of cancer have become one of the most important challenges of this era. Potent markers for screening high-risk populations are urgently needed for early detection and preventive actions. It is therefore, important to identify molecular markers that may help in the diagnosis of this dreadful disease in Indian populations. Several studies have supported an important role for genetics in determining the risk for cancer, and association studies are pertinent for searching susceptibility genes involved in cancer [56].

Metabolism is a cellular process required for the survival and proliferation of all cells, and increased proliferation and sustained survival are hallmarks of cancer [57]. As detoxifying enzyme, GSTs plays an important role in

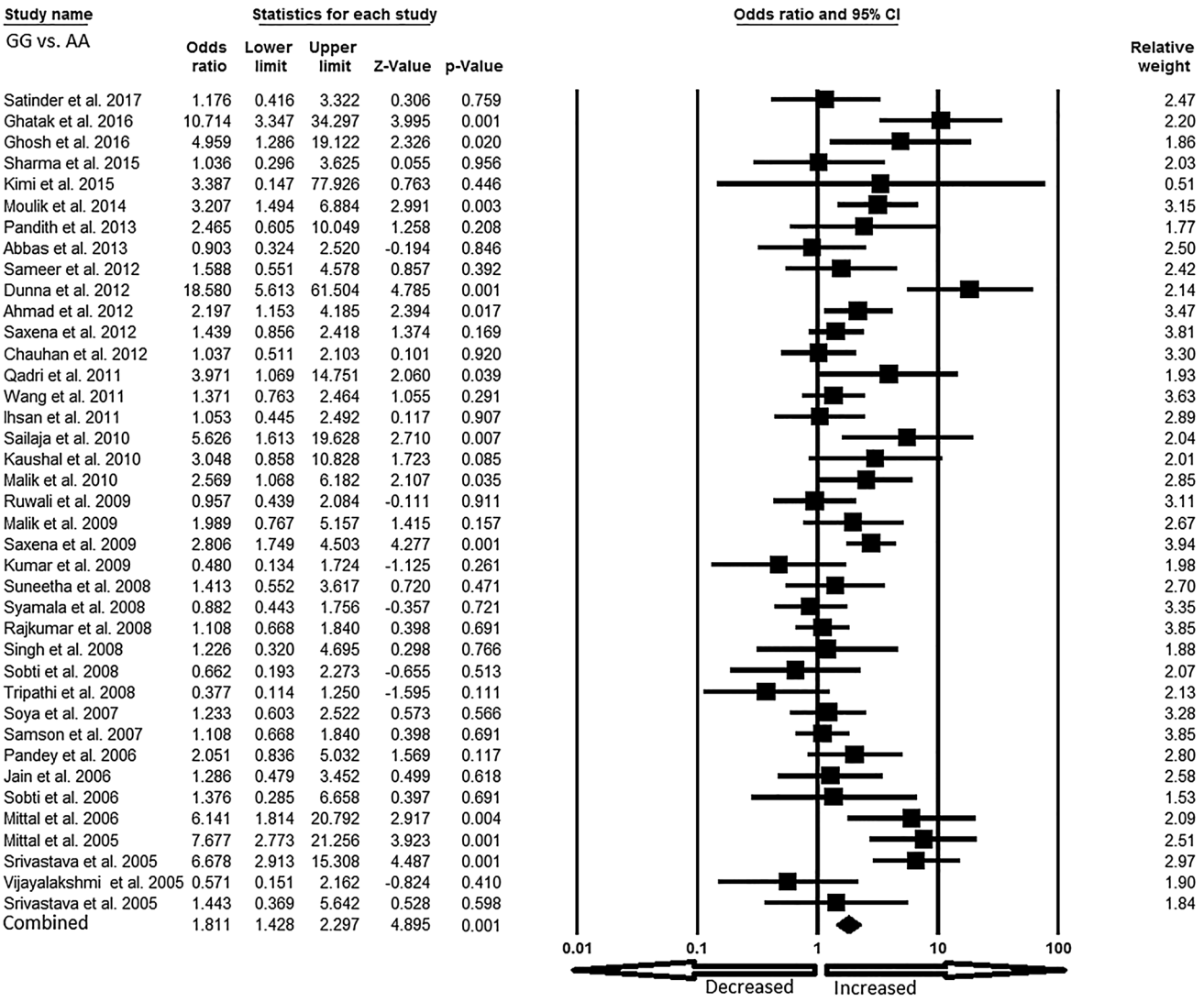

Fig. 4 Forest plot of homozygous (GG vs. AA) model for overall cancer risk. The squares and horizontal lines correspond to the study specific OR and 95% CI

protecting cells from cytotoxic and carcinogenic agents in the defense system. Evidence suggests that the level of expression of GST is a crucial factor in determining the sensitivity of cells to a broad spectrum of toxic chemicals. The altered GST activity associated with the polymorphisms is expected to affect cancer risk through decreased protection against DNA damage from reactive electrophiles.

GSTP1 is widely expressed in normal epithelial cells and metabolize large hydrophobic electrophiles, such as polycyclic aromatic hydrocarbon-derived epoxides [58]. Studies have shown that GSTP1 was present at high levels in many solid tumors and in a wide range of cancer cell lines [59], *GSTP1* null mice disposed with carcinogen polycyclic aromatic hydrocarbons demonstrated highly significantly increased risk of cancer [60]. This signified the role of *GSTP1* as an important determinant in cancer susceptibility.

Currently, relationship between *GSTP1* polymorphisms and cancer is a major area of research focus. The *GSTP1* 313A > G polymorphism was shown to be a predisposing risk factor for a number of human malignancies, but small size of study is a common limitation of biomarker validation studies. In the present meta-analysis, our main focus was to establish a more conclusive association between the *GSTP1* 313A > G polymorphism and overall cancer susceptibility in Indian population. Meta-analysis increases statistical strength and precision in estimating effects by combining the results of previous studies, thus overcoming the problem of small sample size and the inadequate statistical strength of complex trait genetic studies [61].

To the best of our knowledge, this meta-analysis is the first study to investigate the association between the

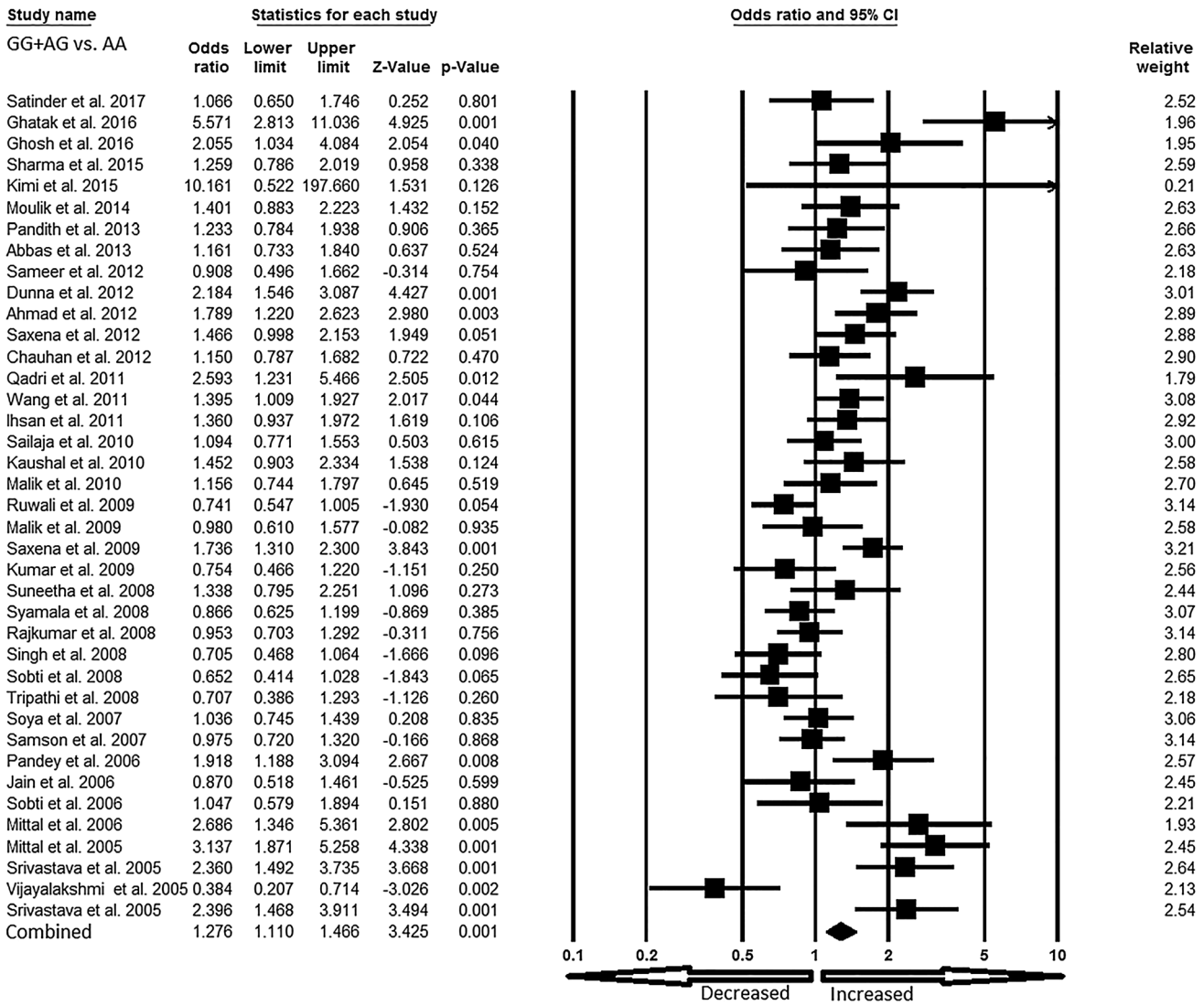

Fig. 5 Forest plot of dominant (GG + AG vs. AA) model for overall cancer risk. The squares and horizontal lines correspond to the study specific OR and 95% CI

GSTP1 313 A > G polymorphism and susceptibility to overall cancer in a large number of Indian populations. After rigorous statistical analysis has been performed for overall comparison of pooled ORs, we found significant increased risk between the *GSTP*1 313 A > G polymorphism and susceptibility to cancer in allele, homozygous, heterozygous, dominant and recessive genetic models. This result suggested that the *GSTP1* 313 A > G polymorphism may be a possible susceptibility factor for cancer in the Indian population, especially in individuals with mutant allele and mutant homozygous genotype. Alteration of *GSTP1* activity due to 313 A > G polymorphism may lead to increased cell vulnerability to oxidative DNA damage and the accumulation of DNA base adducts, which can precede other genetic alterations lead to carcinogenesis. Numerous studies supported that G allele of *GSTP1* 313 A > G polymorphism substantially reduced enzyme activity and increased the risk of DNA mutation, resulting in poor elimination of hydrophilic metabolites and consequently increasing the susceptibility to cancer when individuals are exposed to carcinogens [62].

Genetically complex diseases differ from simple Mendelian diseases and cancer etiology is polygenic, a single genetic variant is usually inadequate to predict the risk of this deadly disease. Though, we interpreted our findings with full caution, but, some limitation of our meta-analysis should be addressed. Heterogeneity is an important issue while interpreting the results of meta-analysis, although that can be minimized by applying random-effects model. In the present study we detected heterogeneity in the entire genetic model, which might be due to the control sources and mix of cancers. Most of the studies used hospital-based

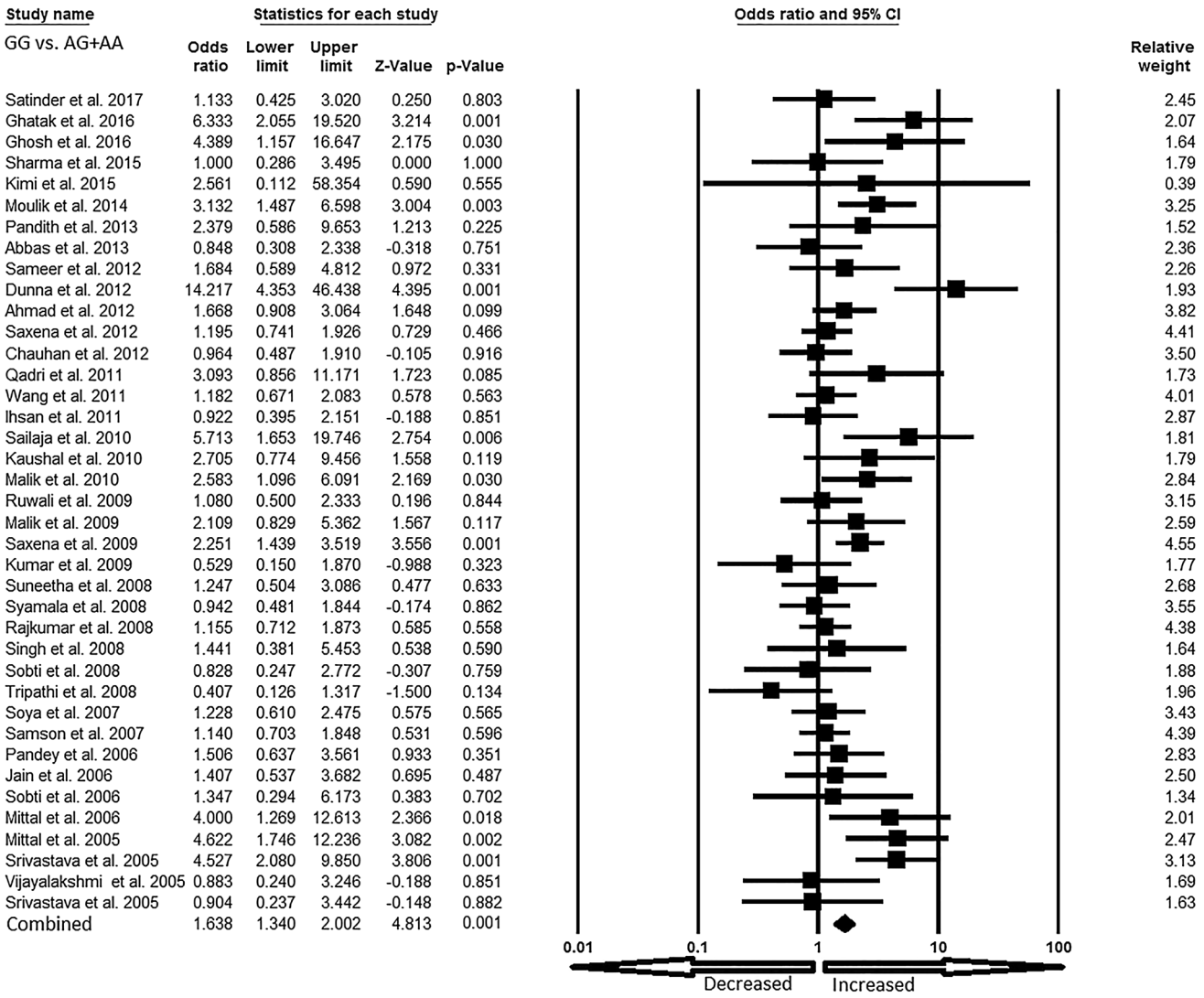

Fig. 6 Forest plot of recessive (GG vs. AG + AA) model for overall cancer risk. The squares and horizontal lines correspond to the study specific OR and 95% CI

patients as controls, who were not strictly healthy individuals and could not represent the general population. Gene environment interaction and adjusted OR have not been performed due to the limited number of data.

In spite of these, our meta-analysis still has some advantages. First, this is the first large association study between *GSTP1* 313 A > G polymorphism demonstrating susceptibility to cancer, which dramatically increase the statistical power of the present analysis than single study. Second, all the eligible studies included in the current meta-analysis researched in Indian population. The participants have the same genetic background, which can reduce the effects of ethnicity on pooled ORs. Third, there was not any publication bias detected, which indicated that the entire pooled result is robust and authentic. Fourth, sensitivity analysis was carried out by deleting each single study involved in the meta-analysis each time and the results did not alter, suggesting that our meta-analysis results were robust and reliable. Moreover, we used strict data extraction criteria and statistical analysis to make satisfactory and consistent conclusion.

Conclusion

Our meta-analysis indicated that the *GSTP1* 313 A > G gene polymorphism is a strong contender as a genetic susceptibility to cancer in Indian population. This could be used as a biomarker for clinical application and early identification and prevention of cancer. Furthermore, larger scale studies and impact of gene–gene and gene-environment interactions on the *GSTP1* 313 A > G polymorphism

and cancer risk is necessary for providing a better comprehensive understanding of the association.

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