RESEARCH ARTICLE

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Association Analysis of GSTP1-rs1695 Polymorphism with the Risk of Oral Cancer: A Literature Review, an Updated Meta-Analysis, and a Structural Assessment

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Abstract

Background: This study aimed to investigate the association of rs1695 polymorphism in glutathione S-transferase P1 (GSTP1) with risk of oral cancer in a meta-analysis which was followed by a bioinformatics approach. **Materials and methods:** Related articles were collected through a systematic search in PubMed, Google Scholar, and EMBASE databases up to June 2022 and then screened. Finally, seven studies, including 1249 cases of oral cancer and 1861 healthy individuals, were included in our meta-analysis. Seven different genetic models including G vs. A, GG+GA vs. AA, GG vs. GA+AA, GA vs. GG+AA, GG vs. GA, GG vs. AA, and GA vs. AA were used for the calculation of odds ratio and 95% confidence interval in order to assess the association between GSTP1-rs1695 polymorphism and oral cancer risk. Also, the ethnicity-based stratified analyses were performed using the seven mentioned models. Some bioinformatics software was used to investigate the effect of rs1695 polymorphism on the primary, secondary, and three-dimensional structure of GSTP1. **Results:** Our results showed that rs1695 polymorphism was not associated with the risk of oral cancer in any seven genetic models (G vs. A: OR= 0.9331, 95%CI= 0.6339-1.3737, P= 0.726; GG vs. GA+AA: OR= 0.9112 , 95%CI= 0.6865-1.2093, P= 0.520; GG+GA vs. AA: OR= 0.9006, 95%CI= 0.5522-1.4690, P= 0.675; GA vs. GG+AA: OR= 0.8732, 95%CI= 0.5763-1.3230, P= 0.522; GG vs. AA: OR= 0.9516, 95%CI= 0.5503-1.6456, P= 0.859; GG vs. GA: OR= 1.0645, 95%CI= 0.7891-1.4359, P= 0.683; GA vs. AA: OR= 0.8825, 95%CI= 0.5499-1.4162, P= 0.604). Also, we did not observe any significant associations in ethnicity-based stratified analyses. But bioinformatics studies have shown that this polymorphism can alter the physicochemical properties and secondary structure of the protein. **Conclusions:** Based on results, the rs1695 polymorphism could not be considered a risk factor for oral cancer.

Keywords: Oral cancer- GSTP1- rs1695 polymorphism- meta-analysis

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Introduction

Oral cancer is considered an important public health issue, especially in developing countries containing two-thirds of world cases attributed to the high occurrence of alcohol use, smoking, and tobacco chewing (Pelucchi et al., 2006). Oral cancer which is most often a squamous cell carcinoma inflicts the cavity of oral and oropharyngeal tissues with a poor prognosis and significant cosmetic and functional defects (Scully and Porter, 2001). Environmental and genetic factors can change the risk of oral cancer. Tobacco and alcohol consumption are among the most important environmental causes (Worakhajit et al., 2021). Tobacco carcinogens are mostly metabolized through mechanisms of an enzymatic complex involved in both phase I (activation) and phase II (detoxification) reactions (Lazarus and Park, 2000). Glutathione S-transferases (GSTs) in human encompasses the phase II enzymes gene family with an important role in the detoxification of several possible oncogenic substances in tobacco (Hayes and Pulford, 1995). GSTs are dimer peptides catalyzing the conjugation of tobacco substances including benzo[a]pyrene and other substrates with the glutathione to facilitate their elimination (Hayes and Pulford, 1995; Wongpratate et al., 2020). Diverse patterns of expression and functional GSTs activity as a result of genetic variations are able to modulate cancer risk through alteration of personal capacity to encounter biological damages induced by carcinogen exposure. Thus, GSTs are essential for the maintenance of the integrity of the cellular genome that might play an astonishing role in cancer predisposition. Amongst GST members, gene deletions in GSTT1 and GSTM1 genes, result in genotypes null which are associated with deficient expression of functional proteins (Seidegård et al., 1990; Pemble et al., 1994; Babekir et al., 2019). Being negative or positive for

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possessing the GSTT1 gene was observed to be associated with having non-conjugator (GSTT1) or conjugator (GSTT1+) phenotypes, respectively (Pemble et al., 1994; Kagita et al., 2021). Additional to the null allele of GSTM1 (GSTM1*0), GSTM1*A and GSTM1*B are two other GSTM1 alleles in which their products combine together to create a heterodimer or homodimer functional enzyme. The absence of the mentioned enzymes has been proposed to possibly enhance cancer predisposition because of the reduced capacity to detoxify carcinogens. Null genotypes of GSTT1 and/or GSTM1may be associated with the risk of some cancers such as colorectal, laryngeal, and oral cancers (Hatagima et al., 2008b). Indeed, persons with two functional alleles of the GSTM1 A/B genotype have been suggested to be at lower cancer risk because of higher enzymatic activity and efficacy of detoxification (Brockmöller et al., 1994; Heagerty et al., 1994). Another member of the GST gene family, glutathione S-transferase pi (GSTP1), functionally codifies various GSTP1 variant proteins. GSTP1 gene contains a common variation including rs1695 (c.313A > G), a single nucleotide polymorphism (SNP) in the coding sequences at codon 105 (Ile105Val). This alteration is located in the active site of the GSTP1 enzyme (Ali-Osman et al., 1997; Barati et al., 2020; Karimian et al., 2020a). This polymorphism is associated with substantial deviation in H-site leading to the development of an altered catalytic activity that could be associated with increased amounts of adducts of DNA and subsequently enhanced cancer risk (Hatagima et al., 2008b).

Some investigations have evaluated the association between Ile105Val SNP in the GSTP1 gene and the risk of oral cancer, although results are inconclusive yet. This study aimed to evaluate the association between this polymorphism and the risk of oral cancer through a meta-analysis approach accompanied by bioinformatics analysis.

Materials and Methods

Search Strategy

We have searched PubMed, Google Scholar, and EMBASE databases for all the relevant genetic association studies performed on the GSTP1-rs1695 variant and the related risk of oral cancer. The search was performed up to June 2022. Diverse combinations of all the following keywords were applied for search including “GSTP1”, “Oral cancer”, “glutathione S transferase”, “rs1695”, “Ile105Val”, “polymorphism”, “single nucleotide polymorphism”, “SNP”, and “variant”. We have included merely English language articles in the search bar. The cited references in the review articles or original studies related to the subject were assessed to widen the search for further relevant papers.

Inclusion and exclusion criteria

The following inclusion criteria were used for the paper selection: (a) explored the association between GSTP1-rs1695 polymorphism and oral cancer; (b) performed case-control or cohort design in human subjects; (c) adequate accessible genotype frequencies to estimate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The exclusion criteria were as follows: (a) insufficient available data on the frequency of genotypes; (b) duplicate publications or published literature with overlapping data; (c) investigations on the non-human origin; (d) meta-analyses, review articles, case reports and so on.

Data Extraction

Data was carefully extracted from all eligible included studies in the meta-analysis by two independent researchers via a usual protocol and data-gathering form according to the above-mentioned criteria. Another investigator checked out the original extracted data, and all inconsistencies were cleared through discussion between the three mentioned investigators. The extracted data were as follows: first author name, publication year, population ethnicity, sample size, Hardy-Weinberg equilibrium (HWE) in the control group, genotyping method, and frequencies of the different genotypes in cases and controls.

Statistical analysis

The HWE test was performed on the control groups for the evaluation of the genetic equilibrium of each study. A P value less than 0.05 implicates a non-significant disequilibrium. The strength of the correlation between the risk of rs1695 polymorphism and oral cancer was evaluated by pooled ORs and 95%CIs. The significance of the pooled ORs was evaluated using the Z test and a two-sided P-value less than 0.05 was considered statistically significant. The chi-square-based Q statistical test was applied for the analysis of heterogeneity. In this study, P values<0.1 was considered as statistically significant heterogeneity among included studies in the meta-analysis. When there was significant heterogeneity, the random-effects model was used, and otherwise, the fixed-effects model was used. Seven different genetic models including G vs. A (allele contrast), GG+GA vs. AA (dominant model), GG vs. GA+AA (recessive model), GA vs. GG+AA (over-dominant model), GG vs. GA, GG vs. AA, and GA vs. AA were used for the calculation of OR, while A and G represent the major and minor alleles, respectively. Ethnicity-based stratified analyses were performed using seven models in order to assess the association between GSTP1-rs1695 polymorphism and oral cancer risk. Besides, sensitivity analyses were used to confirm the reliability and stability of our outcomes. Egger’s test and visual inspection of Begg’s funnel plot were used to evaluate the publication bias in the meta-analyses while P values less than 0.05 was considered statistically significant. All statistical analyses were performed using the online Metagenyo software (https://metagenyo.genyo.es/).

Analysis of DNA and amino acid sequences

DNA and coding sequence of the GSTP1 gene were obtained from National Center for Biotechnology Information database (NCBI, http://www.ncbi.nlm.nih.gov/nucleotide; Accession NO. NM_000852). The coding DNA sequence was translated to amino acid

sequences of GSTP1 by Expasy software (https://www.expasy.org/). These sequences were analyzed via the following bioinformatics tools: the primary structure and physicochemical features of the protein were analyzed by ProtParam software (https://web.expasy.org/protparam/); while Bioinf software was used for the prediction of the secondary structure of the protein (http://bioinf.cs.ucl.ac.uk/psipred/). The proteins' three-dimensional structure was taken from RCSB (https://www.rcsb.org/) and analyzed using Discovery Studio Visualiser.

Results

Characteristics of included studies in the meta-analysis

The flowchart of the search strategy procedure is depicted in Figure 1. After the initial search, 255 articles were found, and after the final screening, 7 qualified articles, containing 1249 cases of oral cancer and 1861 healthy individuals, were included in our meta-analysis (Jourenkova-Mironova et al., 1999; Leichsenring et al., 2006; Hatagima et al., 2008a; Chen et al., 2010b; Ruwali et al., 2011; Rajesh et al., 2019; Yadav et al., 2020). Of these, four were related to the Asian population, two to the Brazilian population, and one to the Caucasian population (Table 1). All studies used the PCR-RFLP method to determine the genotype of the samples. The frequency of genotypes in all control groups was in Hardy-Weinberg equilibrium. All the details extracted from the articles are summarized in Table 1.

Overall outcomes of the meta-analysis

The overall results of the meta-analysis are detailed in Table 2. Our data showed that the frequency of the mutant allele in the control group is lower in cases than in controls, but this difference is not statistically significant. Association analysis showed that there are no significant associations between GSTP1-rs1695 polymorphism and risk of oral cancer in any seven genetic models (G vs. A: OR= 0.9331, 95%CI= 0.6339-1.3737, P= 0.726; GG vs. GA+AA: OR= 0.9112 , 95%CI= 0.6865-1.2093, P= 0.520; GG+GA vs. AA: OR= 0.9006, 95%CI= 0.5522-1.4690, P= 0.675; GA vs. GG+AA: OR= 0.8732, 95%CI= 0.5763-1.3230, P= 0.522; GG vs. AA: OR= 0.9516, 95%CI= 0.5503-1.6456, P= 0.859; GG vs. GA: OR= 1.0645, 95%CI= 0.7891-1.4359, P= 0.683; GA vs. AA: OR= 0.8825, 95%CI= 0.5499-1.4162, P= 0.604) (Figure 2 and 3). Heterogeneity analysis showed there are significant heterogeneities among studies in 5 genetic models (G vs. A: P= 0, I2= 0.895; GG+GA vs. AA: P= 0, I2= 0.8944; GA vs. GG+AA: P= 0, I2= 0.848; GG vs. AA: P= 0.004, I2= 0.6828; GA vs. AA: P= 0, I2= 0.8743). Publication bias analysis showed that there is significant publication bias in four genetic models (G vs. A: P= 0.040; GG+GA vs. AA: P= 0.031; GA vs. GG+AA: P= 0.036; GA vs. AA: P= 0.033). Sensitivity analysis showed that removing a study in each analysis could not affect overall results (data not shown). Funnel plots for overall analyses are demonstrated in Figure 4.

Stratified analysis

Stratified analysis based on ethnicity was performed and the results are summarized in Tables 3-5. Meta-analysis results in the Asian population revealed there are no significant associations between the studied SNP and oral cancer risk in seven G vs. A, GG vs. GA+AA, GG+GA vs. AA, GA vs. GG+AA, GG vs. AA, GG vs. GA, and GA vs. AA genetic models. Also, heterogeneity analysis showed true heterogeneities among included studies in six G vs. A, GG vs. GA+AA, GG+GA vs. AA, GA vs. GG+AA, GG vs. AA, and GA vs. AA models. Publication bias analysis showed significant publication bias in two G vs. A and GG vs. GA genetic models.

Also, we performed a stratified analysis for the Indian and Brazilian populations. Our data for Indian population showed that there is no significant association between rs1695 polymorphism and risk of oral cancer in any

Table 1. Characteristics of Included Studies in Meta-Analysis for GSTP1-rs1695

Author, Year (Reference)	Country (Ethnicity)	Sample size (Case/ Control)	Genotyping method	Genotype frequencies						P HWE[a]
				Case			Control			
				AA	AG	GG	AA	AG	GG	
(Jourenkova-Mironova et al., 1999)	France (Caucasian)	238 (67/171)	PCR-RFLP	28	29	10	85	64	22	0.08
(Leichsenring et al., 2006)	Brazil (Mixed)	132 (72/60)	PCR-RFLP	30	34	8	30	25	5	0.948
(Ana Hatagima et al., 2008)	Brazil (Mixed)	443 (231/212)	PCR-RFLP	97	102	32	80	102	30	0.783
(M. K. Chen et al., 2010)	Taiwan (Asian)	438 (164/274)	PCR-RFLP	101	56	7	192	76	6	0.633
(Ruwali et al., 2011)	India (Asian)	670 (170/500)	PCR-RFLP	111	52	7	285	195	20	0.058
(Rajesh et al., 2019)	India (Asian)	300 (100/200)	PCR-RFLP	46	40	14	97	78	25	0.142
(Yadav et al., 2020)	India (Asian)	889 (445/444)	PCR-RFLP	332	98	15	213	195	36	0.35

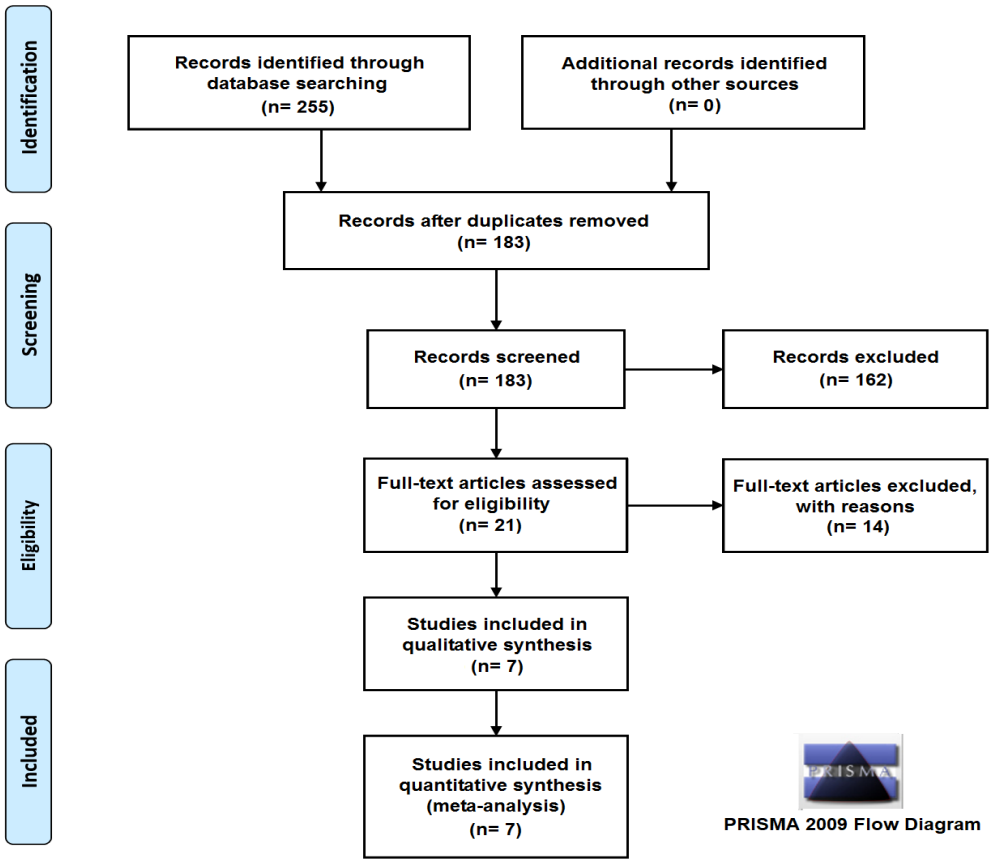

Figure 1. Flow Diagram for the Procedure of Study Selection

seven genetic models. Same as the Asian population there are true heterogeneities among studies in all genetic models except GG vs. GA genetic model. But there was no significant publication bias in any genetic models. In addition, the analysis for the Brazil population showed that there is no significant association between GSTP1-rs1695 genetic variation and oral cancer in any seven G vs. A, GG vs. GA+AA, GG+GA vs. AA, GA vs. GG+AA, GG vs. AA, GG vs. GA, and GA vs. AA genetic models. Heterogeneity analysis showed that there are no true heterogeneities between included studies in Brazil's population.

Bioinformatics outcomes

The data from the Protparam server revealed that the rs1695 polymorphism could affect some features of GSTP1 protein such as molecular weight, aliphatic index, and grand average of hydropathicity (GRAVY). However, some features including theoretical pI, estimated half-life, and instability index do not change after amino acid substitution. Analysis of the secondary structure of the protein by the Bioinf online server revealed that the rs1695 polymorphism may affect the secondary structure of GSTP1 in some regions including around the rs1695 variation (Figure 5). In addition, the three-dimensional structure of GSTP1 was deduced from the RCSB protein databank. The 3D structure of this protein initially was obtained as a dimer structure and it was analyzed by Studio Discovery software. The location of rs1695 SNP was detected near the ligand binding site of the protein (Figure 6).

Discussion

Table 2. Meta-Analysis Outcomes for Overall Assessment

Model	Association test			Heterogeneity		
	OR	95% CI	P-value	Model	P-value	I^2
G vs. A	0.9331	[0.6339; 1.3737]	0.726	Random	0	0.895
GG vs. GA+AA	0.9112	[0.6865; 1.2093]	0.520	Fixed	0.111	0.4204
GG+GA vs. AA	0.9006	[0.5522; 1.4690]	0.675	Random	0	0.8944
GA vs. GG+AA	0.8732	[0.5763; 1.3230]	0.522	Random	0	0.848
GG vs. AA	0.9516	[0.5503; 1.6456]	0.859	Random	0.004	0.6828
GG vs. GA	1.0645	[0.7891; 1.4359]	0.683	Fixed	0.973	0
GA vs. AA	0.8825	[0.5499; 1.4162]	0.604	Random	0	0.8743

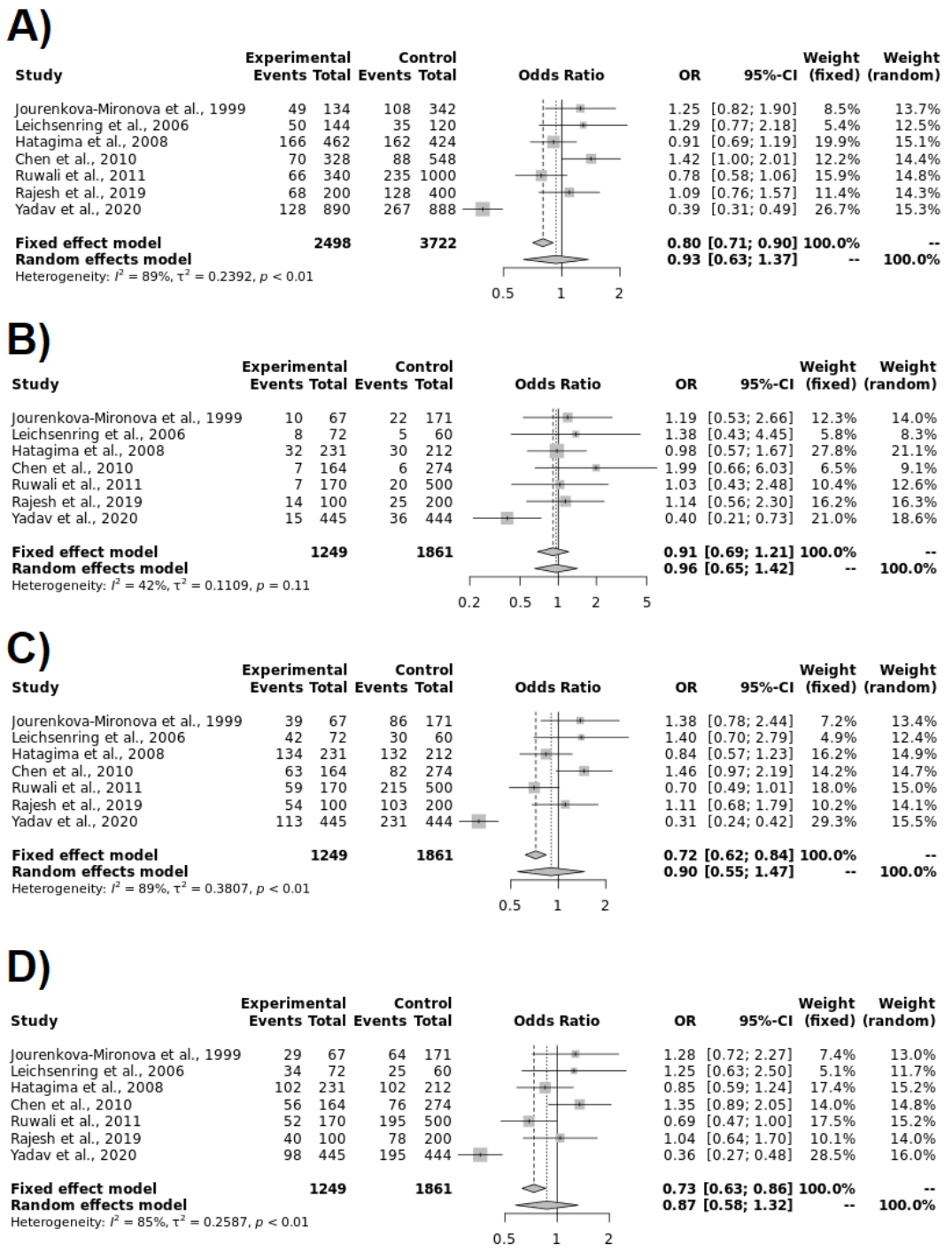

Figure 2. Forest Plot Outcomes in Overall Analysis. The association outcomes for G vs. A (A), GG vs. GA+AA (B), GG+GA vs. AA (C), and GA vs. GG+AA (D) genetic models.

Table 3. Meta-Analysis Outcomes for Asian Population

Model	Association test			Heterogeneity		
	OR	95% CI	P-value	Model	P-value	I^2
G vs. A	0.823	[0.4519; 1.4976]	0.523	Random	0	0.9343
GG vs. GA+AA	0.907	[0.4554; 1.8083]	0.782	Random	0.031	0.6629
GG+GA vs. AA	0.763	[0.3697; 1.5766]	0.466	Random	0	0.9337
GA vs. GG+AA	0.758	[0.4085; 1.4051]	0.378	Random	0	0.9034
GG vs. AA	0.84	[0.3331; 2.1178]	0.712	Random	0.002	0.8044
GG vs. GA	1.066	[0.7103; 1.5986]	0.759	Fixed	0.744	0
GA vs. AA	0.7494	[0.3743; 1.5004]	0.415	Random	0	0.9203

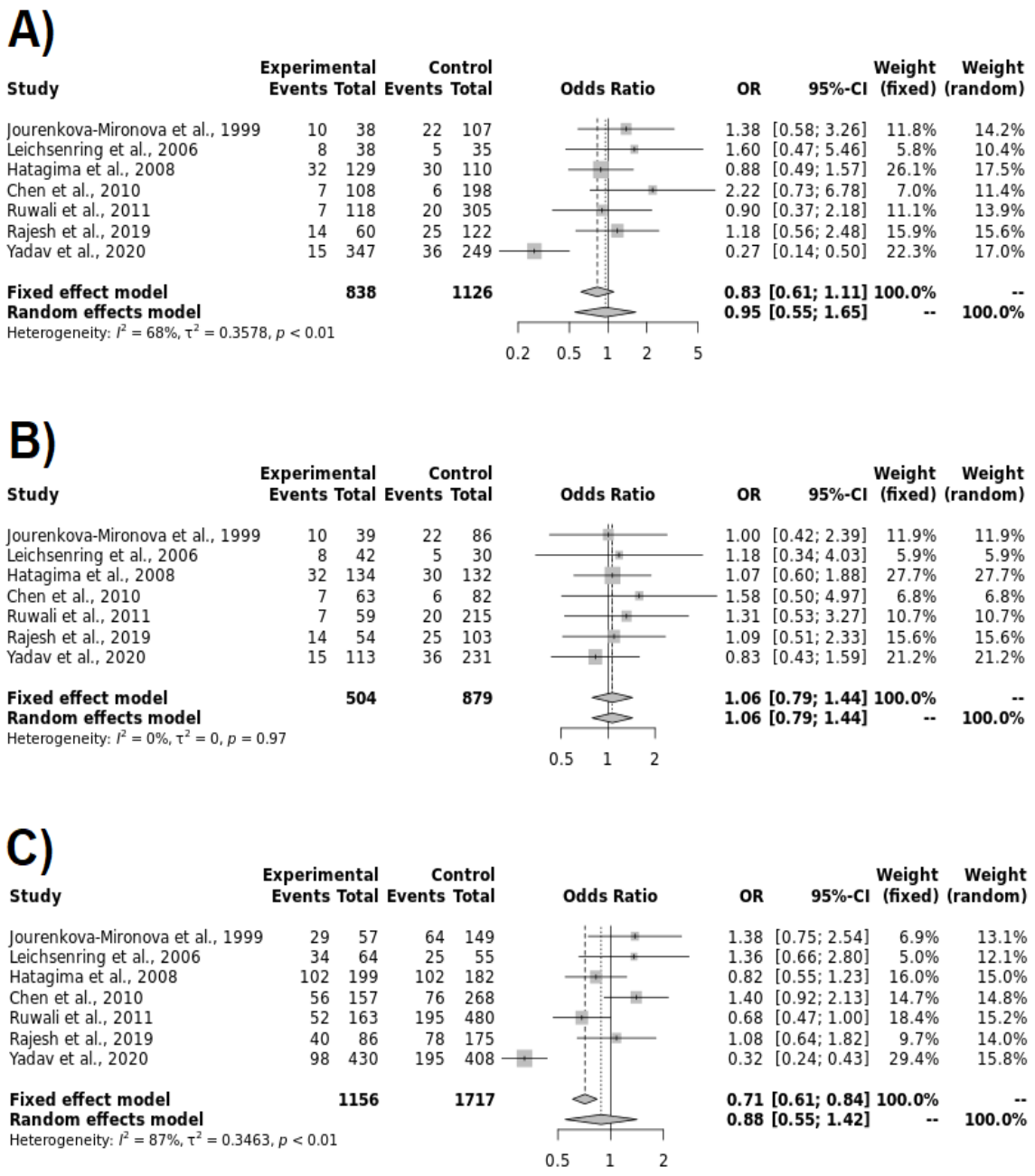

Figure 3. Forest Plot Outcomes in Overall Analysis. The association outcomes for GG vs. AA (A), GG vs. GA (B), and GA vs. AA (C) genetic models.

In this study, we investigated the association of rs1695 polymorphism in the GSTP1 gene with the risk of oral cancer in a meta-analysis approach. Our study showed that this polymorphism is not significantly associated with oral cancer. In the stratified analysis based on ethnicity, it was found that the mentioned polymorphism is not associated

Table 4. Meta-Analysis Outcomes for Indian Population

Model	Association test			Heterogeneity		
	OR	95% CI	P-value	Model	P-value	I^2
G vs. A	0.6872	[0.3685; 1.2812]	0.238	Random	0	0.9241
GG vs. GA+AA	0.7486	[0.3648; 1.5363]	0.43	Random	0.053	0.6597
GG+GA vs. AA	0.6137	[0.2930; 1.2855]	0.196	Random	0	0.9176
GA vs. GG+AA	0.6228	[0.3368; 1.1517]	0.131	Random	4.00E-04	0.8741
GG vs. AA	0.6403	[0.2406; 1.7043]	0.372	Random	0.006	0.8062
GG vs. GA	1.0066	[0.6523; 1.5533]	0.976	Fixed	0.701	0
GA vs. AA	0.6059	[0.3009; 1.2202]	0.161	Random	1.00E-04	0.8977

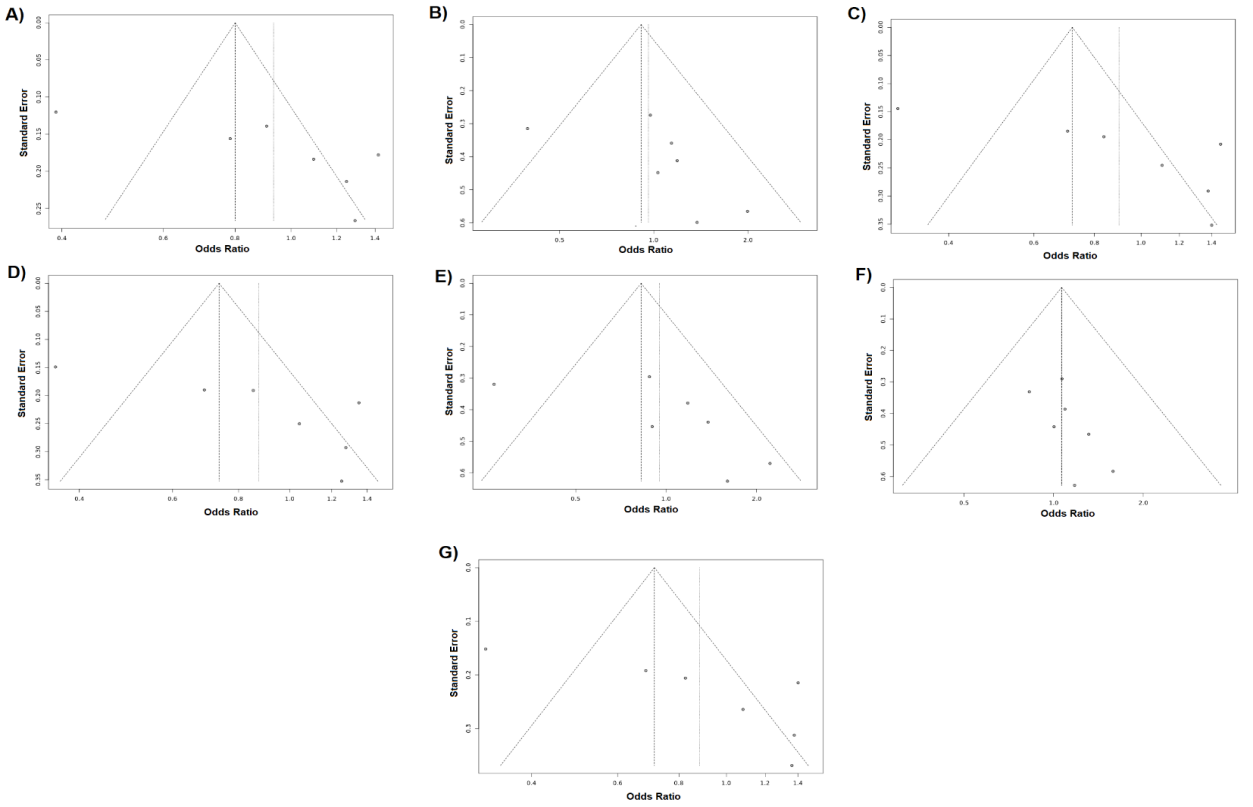

Figure 4. Funnel Plot Outcomes in Overall Analysis. The publication bias outcomes for G vs. A (A), GG vs. GA+AA (B), GG+GA vs. AA (C), GA vs. GG+AA (D), GG vs. AA (E), GG vs. GA (F), and GA vs. AA (G) genetic models.

with the risk of oral cancer in Asian, Brazilian, and Indian populations. However, the number of studies included in this article was limited and more case-control studies in different populations are needed to achieve more accurate results. Some individual case-control studies reported a significant association between the aforementioned polymorphism and the risk of oral cancer, while others did not report a significant association. Perhaps the reasons for these contradictory results are due to geographical differences, race, environmental factors, and so on.

Tobacco and alcohol consumption is observed in 75 percent of all head and neck squamous cell carcinoma (HNSCCs) throughout the United States (Blot et al., 1988; Day et al., 1993). Studies have demonstrated the synergistic, independent role of tobacco and alcohol with a strong dose-response association in the genesis of HNSCC with a multiplicative interaction of both of them in all of the HNSCC data available now (Rothman and Keller, 1972; Blot et al., 1988). Smoking tobacco is known as the main carcinogen, while the underlying

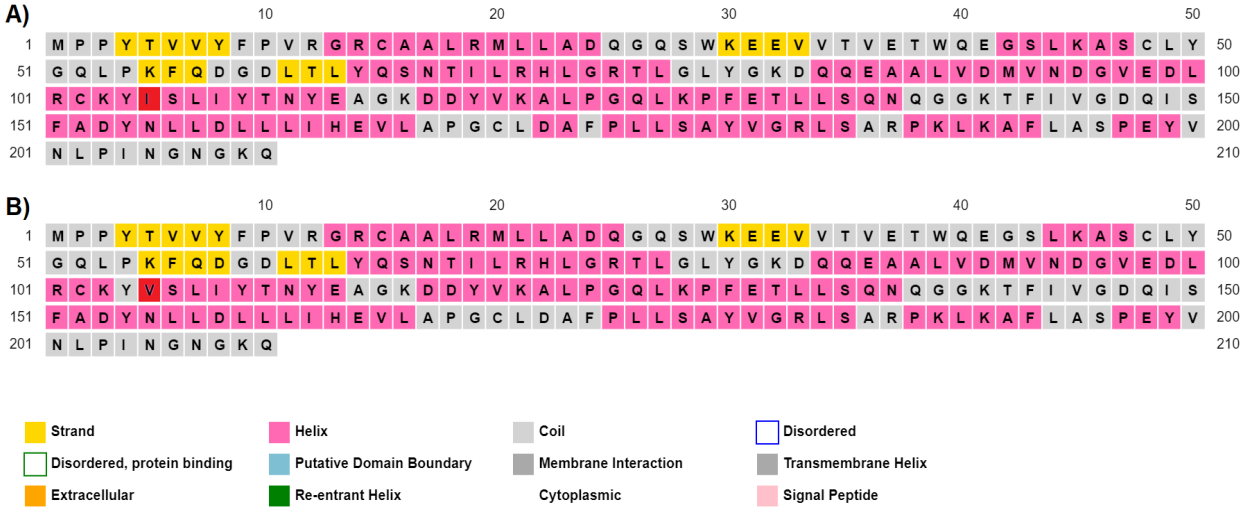

Figure 5. Changes in the Secondary Structure of GSTP1 Protein due to rs1695 Polymorphism. The structure of the protein is altered by the rs1695 polymorphism, and a variety of secondary structures are distinguished by different colors. Secondary structure of protein with leucine allele (A); Secondary structure of protein with valine allele (B). Wild and mutant amino acids are shown in red.

Figure 6. Three-Dimensional Structure of GSTP1. The structure of protein is depicted as a dimer that the location of rs1695 polymorphism is depicted in yellow. As shown, this polymorphism is located close to the ligand binding site.

mechanisms explaining alcohol-induced carcinogenicity remained still unknown. Alcohol might function as a solvent for other carcinogens or could possibly create and intensify coincident inflammation which produces abundant reactive oxygen species (Toh et al., 2010; Yalcin and de la Monte, 2016; Zięba et al., 2021). Although combined tobacco and alcohol exposure is accountable for the development of this disorder, the interindividual genetic variations might exert a fundamental role in the modification of their carcinogenetic potency and mediate individual vulnerability to their action or interaction with cancer inducers (Lai and Shields, 1999; Strange and Fryer, 1999; Taioli, 2008). Furthermore, genetic variants with the impact on the expression or function of metabolic enzymes are in charge of tobacco and alcohol detoxification which could influence on person's predisposition to the oral tumor (Peters et al., 2006; Edenberg and Foroud, 2013).

Conjugation of reduced glutathione is catalyzed by phase II GST enzymes which consequently enhance water solubility and subsequently allow renal elimination of different oncogene chemicals produced by the phase I detoxification (Chen et al., 2010b). The total activity of GST was truly increased from typical buccal mucosa to mild, moderate, and severe dysplasia of oral epithelium and squamous cell carcinoma (Chen and Lin, 1997). GSTP1 is identified as the main GST isoenzyme observed in oral tissues, with a significantly enhanced amount in the malignant or premalignant oral damages, submucous fibrosis, laryngeal tumors, and leukoplakias with moderate to severe dysplasia (Zhang et al., 1994; Chen and Lin, 1995; Mulder et al., 1995; Chen and Lin, 1997). Overexpression of GSTP1 in oral cancer is suggested to contribute to the detoxification process. Indeed, decreased enzymatic activity has been observed in carriers of A/G or G/G GSTP1 alleles which impede the excretion of carcinogens leading to the development of carcinogenesis due to defective DNA repair and deficient detoxification with a subsequent predisposition to oral cancer (Jakoby,

Table 5. Meta-Analysis Outcomes for Brazil Population

Model	Association test			Heterogeneity		
	OR	95% CI	P-value	Model	P-value	I2
G vs. A	0.9785	[0.7683; 1.2463]	0.86	Fixed	0.239	0.2775
GG vs. GA+AA	1.0353	[0.6352; 1.6872]	0.889	Fixed	0.602	0
GG+GA vs. AA	0.9443	[0.6764; 1.3184]	0.737	Fixed	0.201	0.3884
GA vs. GG+AA	0.9304	[0.6695; 1.2929]	0.667	Fixed	0.338	0
GG vs. AA	0.9812	[0.5810; 1.6568]	0.943	Fixed	0.388	0
GG vs. GA	1.0852	[0.6476; 1.8185]	0.756	Fixed	0.887	0
GA vs. AA	0.9288	[0.6529; 1.3213]	0.681	Fixed	0.237	0.2865

1978; Chasseaud, 1979; Mulder et al., 1995; Chen et al., 2010a).

The structure of proteins and the expression of genes can be changed due to genetic polymorphisms, which are dependent on the genetic location of the polymorphism. If the polymorphisms are in a non-coding area, they can alter the splicing process. If genetic polymorphisms are upstream of the gene, they can alter gene expression, while coding polymorphisms can alter protein structure and function (Soleimani et al., 2017; Karimian and Hosseinzadeh Colagar, 2018; Bafrani et al., 2019; Zamani-Badi et al., 2019). The polymorphism we studied, rs1695, is a coding variety so it is expected to affect the structure of the enzyme. Investigating the effect of polymorphisms in vivo or in vitro is very difficult and time-consuming. But computational methods can be an effective approach to investigate these effects (Mobasseri et al., 2018; Noureddini et al., 2018; Mobasseri et al., 2019; Karimian et al., 2020b). Our bioinformatics study showed that the rs1695 variety alters some of the physicochemical properties and secondary structure of the protein. This variety is also located near the ligand-binding site of the enzyme and may interfere with the binding of the enzyme to the ligand. Therefore, these effects can justify the pathogenicity of this polymorphism.

In conclusion, in this study, it was found that rs1695 single nucleotide polymorphism of the GSTP1 gene cannot be considered as a molecular risk factor for susceptibility to oral cancer. The limitations of this study are as follows: the number of studies included in the meta-analysis was limited and was obtained by searching English, which can lead to language bias. We did not have access to original data such as BMI, age, sex, smoking, and alcohol usage to adjust our data based on them. There were also no articles from the black population in our meta-analysis. However, in order to obtain more accurate results, it seems necessary to study this polymorphism in larger sample sizes and different ethnicities and regarding environmental and individual factors.

Author Contribution Statement

AK participated in the design of the study. AB and MB participated in searching for content in reputable research databases and categorizing content. AB and MB participated in data analysis and provided an initial draft of the manuscript. AK participated in editing and organizing the manuscript. All authors read and approved the final version of the manuscript.

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Ethical statement

Not applicable.

Availability of data

All data generated or analyzed during this study are included in this paper.

Study registration

This study was not registered in any database.

Conflict of interest

The authors declare no conflict of interests.

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