Review paper

Evaluation of the association between glutathione S-transferase polymorphisms and susceptibility to cutaneous melanoma: a systematic review and meta-analysis

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Abstract

Introduction: Glutathione S-transferase (GST) enzymes play a crucial role in detoxification by catalysing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione. Polymorphisms in *GST* genes may influence the susceptibility to various cancers, including melanoma.

Aim: We reported a systematic review and meta-analysis to evaluate the association between *GST* polymorphisms and susceptibility to cutaneous melanoma.

Material and methods: A comprehensive search of four databases, namely PubMed, Scopus, Cochrane Library, and Web of Science, was conducted to gather pertinent studies up until 24 August 2023. No restrictions were imposed during the search. The analysis included 32 studies and was broken down into subgroups based on ethnicity, control source, control matching, quality score, and sample size.

Results: The forest plot analyses on *GSTM1, GSTT1*, combined *GSTM1/GSTT1*, and *GSTP1* polymorphisms in relation to melanoma risk showed no statistically significant differences between the case and control groups, except for the recessive model of *GSTP1* polymorphism. The analysis revealed significant associations between *GSTM1* polymorphisms and melanoma risk in Asians and in studies with a sample size of less than 200. For the combined *GSTM1/GSTT1* polymorphisms, a significant association was found in hospital-based controls.

Conclusions: While this study enhances our understanding of the genetic factors influencing melanoma risk, it also highlights the need for further research. The current evidence is not sufficient to confirm or reject the intervention effect. Future research should consider gene-gene and gene-environment interactions, which could offer a more comprehensive understanding of the complex biology of melanoma.

Key words: glutathione S-transferases, polymorphism, melanoma, cancer risk, meta-analysis.

Introduction

Melanoma, a form of skin cancer, originates from melanocytes, the cells responsible for producing melanin, the pigment that colours our skin [1]. It is estimated that in 2023, around 97,610 new cases of melanoma will be diagnosed in the United States, with approximately 58,120 in men and 39,490 in women. Sadly, about 7,990 individuals are projected to succumb to this disease, including roughly 5,420 men and 2,570 women [2]. On a global scale, over 150,000 new cases of skin melanoma were reported in 2020 [3]. The development of melanoma is largely attributed to lifestyle and genetic risk factors [4].

In human beings, there are three unique gene families that produce soluble glutathione S-transferase (GST); these include mu (*GSTM1*) located on chromosome 1, theta (*GSTT1*) on chromosome 22, and pi (*GSTP1*) on chromosome 11 [5]. The GSTs are enzymes that facilitate the conjugation of glutathione (GSH) to a wide range of electrophiles, such as organic halides, unsaturated carbonyls, arene oxides, and other substrates [6]. There is a growing recognition of the polymorphic nature of an increasing number of *GST* genes [7]. The dynamic roles of GST and their varying expression patterns in individuals position them as a promising target for the development

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of new drugs [8]. The most prevalent polymorphisms at the *GSTM1* and *GSTT1* gene loci involve the total removal of the genes. Regarding the pi class, point mutations in exon 5 (codon 105) of *GSTP1* (*Ile105Val*) have been detected and found to influence the enzyme's activity [9].

GSTs can regulate several signalling pathways that play a role in melanoma, including c-Jun N-terminal kinase (JNK), nuclear factor-κB (NF-kB), and p53 [10]. Furthermore, GSTs can alter the metabolism and pH levels of melanosomes, which are the organelles responsible for the production and storage of the pigment melanin. While melanin can shield melanocytes from damage caused by UV rays, it can also impact the progression of melanoma and the response to drugs [11]. It has been observed that polymorphisms in the *GST* family can impact the risk of various types of cancers, including non-melanoma skin cancers [12, 13] and multiple cutaneous skin cancers [14, 15]. Moreover, two meta-analyses [12, 16] have highlighted the correlation between *GST* polymorphisms and the risk of melanoma. One of these analyses [12], conducted in 2015, and focused on the *GSTP1 Ile105Val* polymorphism across four studies. Another analysis [16] in 2011 examined *GSTM1* and *GSTT1* polymorphisms across eight and five studies, respectively.

Aim

In our research, we assessed three *GST* polymorphisms (*GSTM1*, *GSTT1*, and *GSTP1 Ile105Val*) through a meta-analysis that included a larger number of studies and incorporated trial sequential analysis (TSA).

Material and methods

The study followed the guidelines for PRISMA protocol [17]. The PECO framework (Population, Exposure, Comparison, and Outcome) was used to formulate research questions. Population (P): Individuals with GST polymorphisms. Exposure (E): Prevalence of GST polymorphisms. Comparison: Individuals with cutaneous melanoma compared with healthy or free-cancer controls. Outcome (O): Risk of cutaneous melanoma.

Study selection

We conducted a comprehensive search of four databases, namely PubMed, Scopus, Cochrane Library, and Web of Science, to gather pertinent studies up until 24 August 2023. We did not impose any restrictions during our search. The keywords or terms we used included: ("GSTM1" OR "GSTT1" OR "GST*" OR "GSTP1" OR "Glutathione S-transferase*") AND ("melanoma" OR "skin cancer" OR "skin carcinoma" OR "Skin neoplasms") AND ("polymorphism*" OR "variant*" OR "gene*" OR "genotype*" OR "allele*"). To ensure we did not overlook any study, we also searched "Google Scholar" and citations related to articles, reviews, and meta-analyses on the topic. This entire process was carried out by a single author.

Eligibility criteria

Criteria for including studies:

1. Studies of any type that report on melanoma cases and controls.
2. Studies in any language.
3. Cases where melanoma has been diagnosed either clinically or pathologically.
4. Studies that report on the prevalence of *GST* polymorphisms (*GSTM1*, *GSTT1*, and/or *GSTP1*).

Criteria for excluding studies: Studies will be excluded if they are animal studies, lack a control group, are reviews or meta-analyses, are book chapters or conference papers, or do not provide the necessary data for calculating odds ratios (OR) and 95% confidence interval (CI).

Data extraction

One author retrieved any data related to each study entered into the analysis including publication year, country, ethnicity, number of cases and controls, control source, control matching, quality score, and the prevalence of genotypes and alleles of *GST* polymorphisms.

Quality evaluation

The quality scoring of the study was conducted by one author using the Newcastle-Ottawa Scale (NOS) tool [18]. This tool assessed a study from three main aspects: the selection process of the study groups (4 points), the comparability of the groups (2 points), and the determination of the exposure of interest for case-control studies (3 points). The highest score achievable was nine, with a score of seven or more indicating high quality. The scores were then reviewed by another author. Any disagreements between the authors were settled through a brief discussion.

Statistical analysis

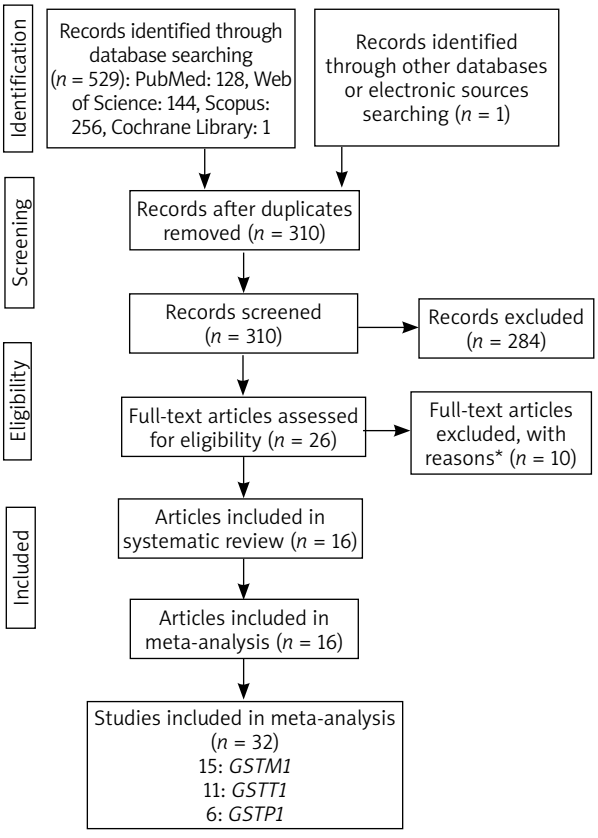
The Review Manager 5.3 software (RevMan 5.3; the Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark) was utilized to calculate the effect sizes, displaying the OR along with a 95% CI of the prevalence of genotypes of *GST* polymorphisms in melanoma patients and controls. The significance of the pooled OR was determined using the *Z*-test, with a two-sided *p*-value less than 0.05 deemed significant. In cases where $P_{heterogeneity}$ was less than 0.1 (I^2 greater than 50%), indicating significant heterogeneity, a random-effects model [19] was employed. If heterogeneity was not significant, a fixed-effect model [20] was used.

A subgroup analysis was conducted to ascertain if the combined effect sizes in these subgroups significantly differed from each other. A fixed-effects meta-regression analysis was also performed to establish a linear correla-

tion between auxiliary variables in the study and effect size.

The potential for publication bias was assessed using a Begg's funnel plot and Begg's test, with the degree of asymmetry tested using Egger's test. The *p*-values of Egger's and Begg's tests were extracted, with a 2-sided *p*-value less than 0.10 indicating potential publication bias. Sensitivity analysis was conducted using both "one-study-removed" and "cumulative" analyses to evaluate the stability/consistency of pooled ORs. Both publication bias and sensitivity analyses were performed using Comprehensive Meta-Analysis version 3.0 software (CMA 3.0; Biostat Inc., Englewood, NJ, USA).

To mitigate the risk of false-positive or negative conclusions from meta-analyses [21], TSA was carried out using TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) [22]. TSA allowed for testing of a futility threshold to determine a result of no effect before reaching the required information size. The required information size (RIS) was calculated with an α risk of 5%, a β risk of 20%, and a two-sided boundary type. Heterogeneity was assessed for the prevalence of the genotypes of *GST* polymorphisms in melanoma patients and controls. If the *Z*-curve reached the RIS line or followed the boundary line or futility area, it indicated that sufficient cases were included in the studies and the conclusions were reliable. If not, more data would be needed as the information available was not sufficient.



*1 review, 2 meta-analyses, 1 animal study, 4 studies had no control group, 1 duplicate study, 1 study had no full text.

Figure 1. Flowchart of the study selection

Results

Study selection

In the databases, we initially identified 530 records (Figure 1). After the removal of duplicates and irrelevant records, we were left with 26 full-text articles. Upon further review, 10 of these articles were excluded for various reasons. Consequently, we included 16 articles [23–38] in our analysis, which collectively encompassed 32 studies.

Characteristics of studies

Table 1 shows the characteristics of studies conducted in different countries, primarily focusing on Caucasian, Asian, and mixed ethnicities. The studies, which ranged from population-based to hospital-based, investigated the outcomes of *GSTM1*, *GSTT1*, and *GSTP1 Ile105Val* polymorphisms. The number of cases and controls varied across studies, as did the control matching for age and sex. Each study was assigned a quality score reflecting its credibility.

Figure 2 shows a forest plot analysis of 15 studies reporting the association of *GSTM1* polymorphism with the risk of melanoma based on 2650 cases versus 2779 controls. The total number of events across all studies was 411 and 504 for the two groups, respectively. The overall effect size, represented as an OR, was 1.10 with a 95% CI of 0.90 to 1.35. This result was not statistically significant ($p = 0.33$), indicating no substantial difference between the two groups across all studies. The heterogeneity of the studies, which measures the variability among the studies' results, was relatively low ($I^2 = 0\%$), suggesting that the studies were fairly consistent in their findings.

Figure 3 shows a forest plot analysis of 11 studies reporting the association of *GSTT1* polymorphism with the risk of melanoma based on 2104 cases versus 2131 controls. Across all studies, there were 443 events in the case group and 453 in the control group. The overall OR was 1.07, falling within a 95% CI of 0.91 to 1.25. This outcome was not statistically significant ($p = 0.41$), suggesting that there was no significant difference between the two groups in all the studies. The studies' heterogeneity was relatively low ($I^2 = 5\%$), indicating that the studies were fairly consistent in their findings.

Figure 4 presents a forest plot analysis of eight studies that examine the relationship between combined *GSTM1/GSTT1* polymorphisms and melanoma risk, based on 1176 cases and 1355 controls. The studies collectively reported 151 events in the case group and 143 in the control group. The overall OR was 1.25, with a 95% CI ranging from 0.97

Table 1. Characteristics of studies

First author, publication year	Country	Ethnicity	Control source	Number of cases/ controls	Control matching (age and sex)	Outcome	Quality score
Dolzan, 2006 [23]	Slovenia	Caucasian	PB	137/116	None	GSTM1, GSTT1, and GSTP1	7
Shanley, 1995 [27]	Australia	Caucasian	PB	124/200	None	GSTM1	7
Heagerty, 1994 [25]	UK	Caucasian	PB	64/153	Both	GSTM1	9
Fortes, 2016 [24]	USA	Caucasian	HB	177/148	Both	GSTM1	8
Rinck-Junior, 2019 [26]	Brazil	Mixed	HB	229/258	None	GSTM1, GSTT1	6
Leite, 2007 [28]	Brazil	Mixed	PB	5/124	None	GSTM1, GSTT1, and GSTP1	7
Kanetsky, 2001 [29]	USA	Caucasian	HB	362/271	None	GSTM1, GSTT1	6
Lafuente, 1995 [30]	Spain	Caucasian	HB	183/147	None	GSTM1	6
Fortes, 2011 [31]	Italy	Caucasian	HB	188/152	Both	GSTM1, GSTT1	8
Ibarrola-Villava, 2012 [32]	Spain	Caucasian	HB	560/337	None	GSTM1, GSTT1, and GSTP1	5
Bu, 2007 [33]	Sweden	Caucasian	HB	154/203	None	GSTM1, GSTT1, and GSTP1	6
Mössner, 2007 [34]	Germany	Caucasian	HB	322/347	None	GSTM1, GSTT1	6
Xie, 2011 [35]	China	Asian	HB	77/107	None	GSTM1, GSTT1	5
Vlaykova, 2012 [36]	Turkey	Caucasian	HB	22/124	None	GSTM1, GSTT1	6
Chiyomaru, 2013 [37]	Japan	Asian	HB	46/92	Both	GSTM1, GSTT1, and GSTP1	8
Oliveira, 2013 [38]	Brazil	Mixed	PB	146/146	Both	GSTP1	9

PB – population-based, HB – hospital-based.

to 1.61. This result was not statistically significant (p = 0.09), indicating no substantial difference between the two groups across all studies. The heterogeneity of the studies was low (I^2 = 15%), suggesting a low degree of discrepancy in the findings across different studies.

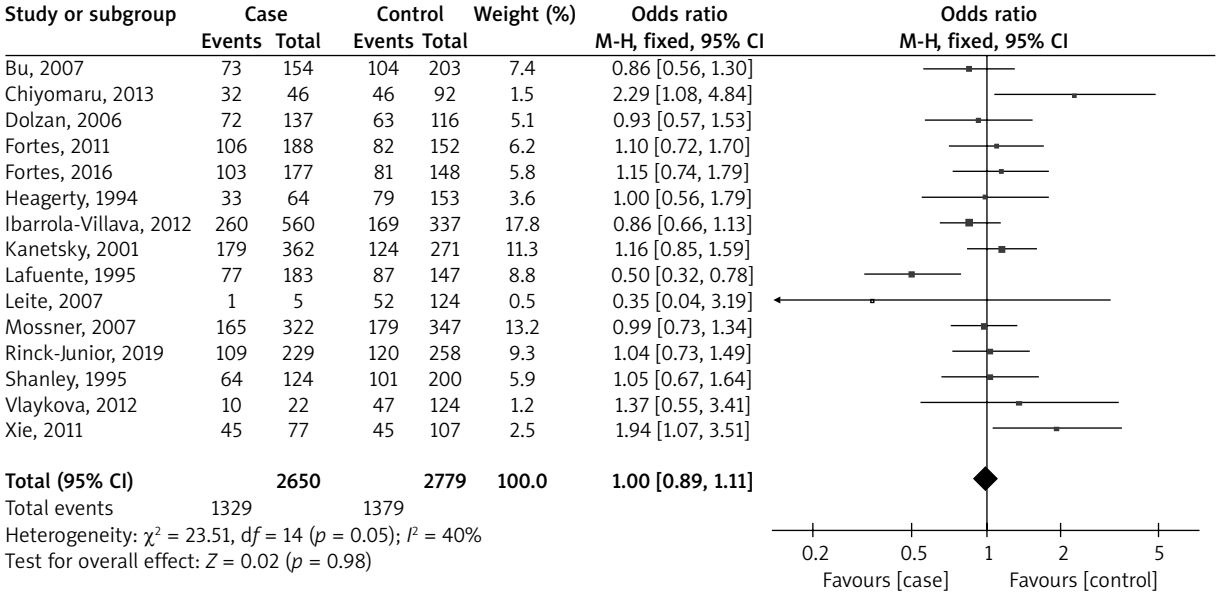


Figure 2. Forest plot analysis of the association between GSTM1 polymorphism and the risk of melanoma

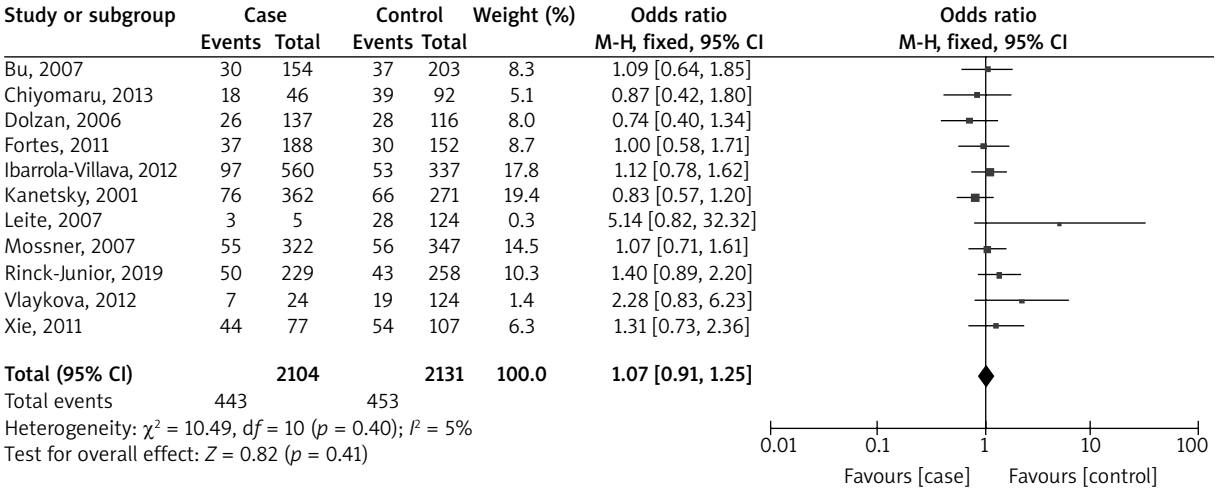


Figure 3. Forest plot analysis of the association between GSTT1 polymorphism and the risk of melanoma

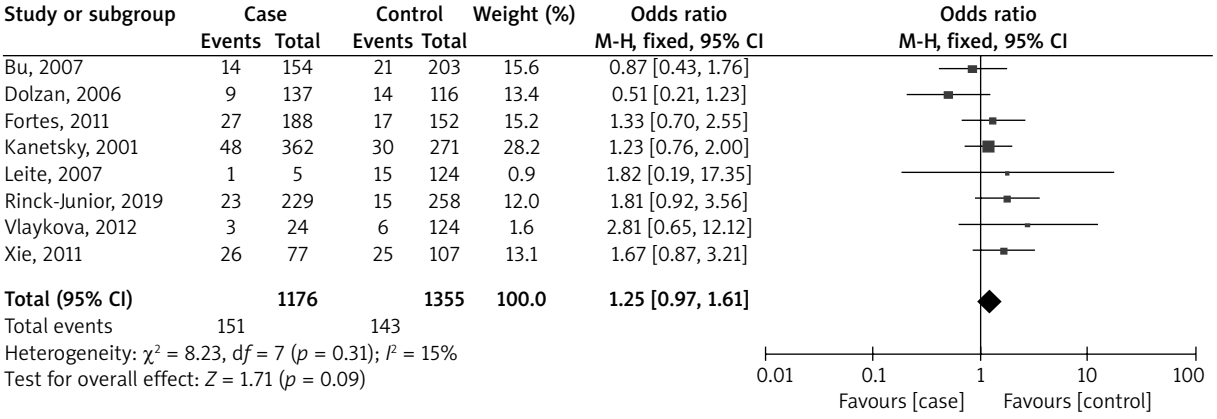


Figure 4. Forest plot analysis of the association between combined GSTM1/GSTT1 polymorphisms and the risk of melanoma

Figure 5 identifies a forest plot analysis of the association between *GSTP1 Ile105Val* polymorphism and the risk of melanoma based on six studies for recessive models and five for other models. The allelic model (V vs. I) and the homozygous model (VV vs. II) were analysed based on different numbers of cases and controls. In both models, the overall odds ratio (OR) and the 95% confidence intervals were calculated, but neither showed a statistically significant result ($p = 0.72$ and $p = 0.29$, respectively), indicating no significant difference between the groups in all studies. However, the level of heterogeneity, which measures the variability in results across studies, was high in the allelic model ($I^2 = 98\%$) and moderate in the homozygous model ($I^2 = 53\%$), suggesting varying degrees of inconsistency in the findings across different studies. In the heterozygous model (IV vs. II), the overall OR was 1.20, indicating no significant difference between the two groups ($p = 0.08$). The recessive model (VV + IV vs. II) showed a statistically significant OR of 1.21 ($p = 0.04$), suggesting a potential association between the *GSTP1* polymorphism and melanoma risk. However, the dominant model (VV vs. II + IV) showed an OR of 1.23, but it was not statistically significant ($p = 0.18$). The heterogeneity of the studies varied from low to moderate across the models.

Subgroup analysis

Table 2 presents a detailed analysis of the association between *GSTM1*, *GSTT1*, and combined *GSTM1/GSTT1* polymorphisms and the risk of melanoma. The analysis was broken down into subgroups based on ethnicity, control source, control matching, quality score, and sample size. For the *GSTM1* polymorphism, in terms of ethnicity, the OR was 0.95 for Caucasians, 2.07 for Asians, and 1.01 for mixed ethnicities, with a significant association found in Asians ($p = 0.002$). For control sources, the OR was 0.97 for population-based and 1.04 for hospital-based studies. When considering control matching, the OR was 1.20 for age and sex matching and 0.96 for studies without matching. In terms of qual-

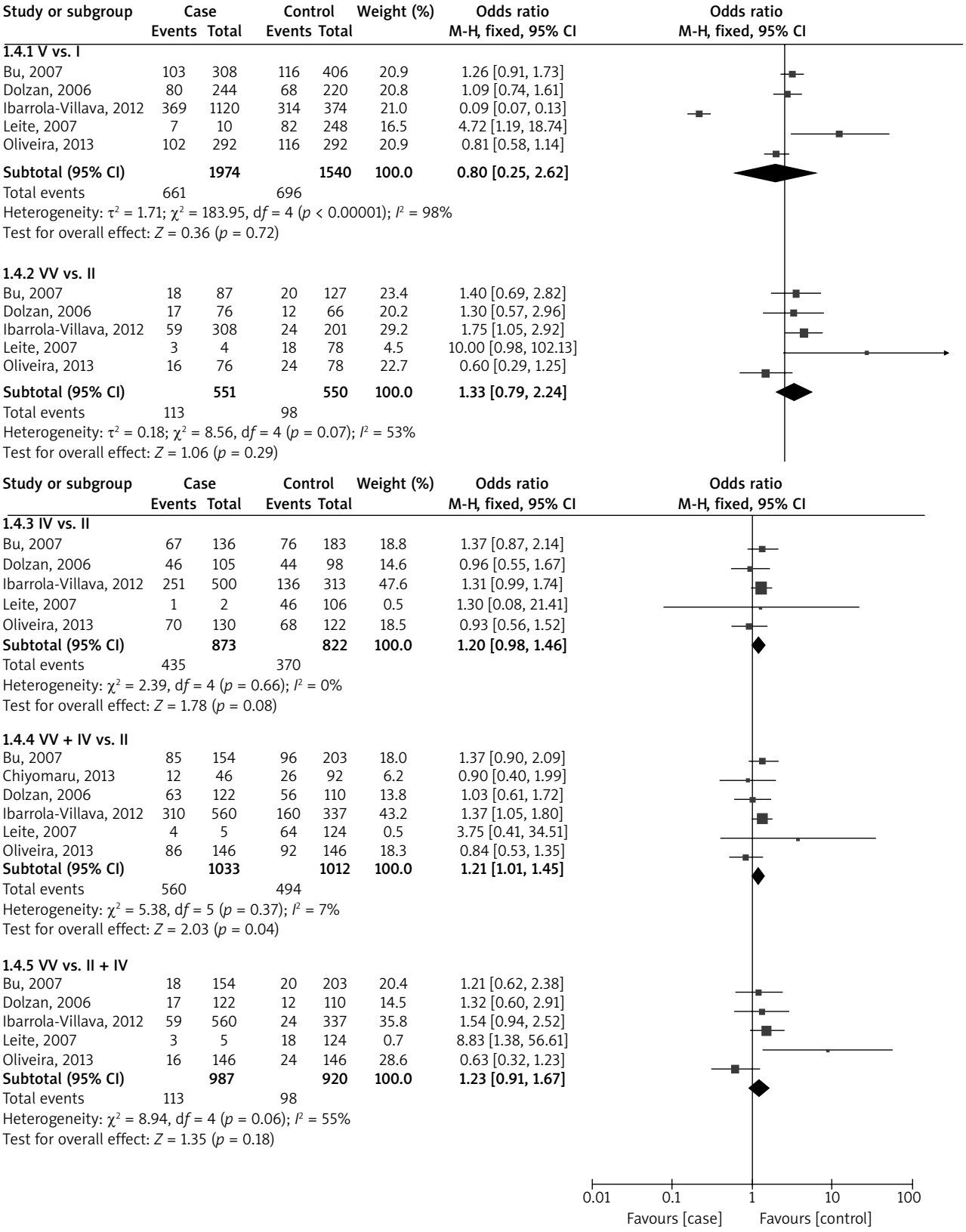


Figure 5. Forest plot analysis of the association between GSTP1 Ile105Val polymorphism and the risk of melanoma

Table 2. Subgroup analysis

Polymorphism	Variable	Subgroup (*N*)	OR	95% CI		*P*-value	I^2
GSTM1	Ethnicity:						
		Caucasian (11)	0.95	0.84	1.07	0.39	20%
		Asian (2)	2.07	1.30	3.29	0.002	0%
		Mixed (2)	1.01	0.71	1.43	0.96	0%
	Control source:						
		Population-based (4)	0.97	0.73	1.29	0.85	0%
		Hospital-based (11)	1.04	0.86	1.26	0.69	56%
	Control matching:						
		Age and sex (4)	1.20	0.93	1.55	0.16	12%
		None (11)	0.96	0.85	1.08	0.49	44%
	Quality score:						
		≥ 7 (7)	1.10	0.90	1.35	0.33	0%
		< 7 (8)	0.97	0.78	1.21	0.79	58%
	Sample size:						
		≥ 200 (11)	0.95	0.85	1.07	0.41	17%
		< 200 (4)	1.76	1.18	2.63	0.006	0%
GSTT1	Ethnicity:						
		Caucasian (7)	1.00	0.84	1.20	0.98	0%
		Asian (2)	1.11	0.71	1.75	0.64	0%
		Mixed (2)	1.50	0.96	2.32	0.07	45%
	Control source:						
		Population-based (2)	1.59	0.25	10.25	0.63	74%
		Hospital-based (9)	1.08	0.92	1.27	0.33	0%
	Control matching:						
		Age and sex (2)	0.95	0.62	1.46	0.82	0%
		None (9)	1.09	0.92	1.28	0.33	21%
	Quality score:						
		≥ 7 (6)	0.94	0.74	1.18	0.58	12%
		< 7 (5)	1.19	0.96	1.46	0.11	0%
	Sample size:						
		≥ 200 (7)	1.03	0.87	1.22	0.74	0%
		< 200 (4)	1.33	0.88	1.99	0.17	33%
GSTM1/GSTT1	Ethnicity:						
		Caucasian (5)	1.08	0.79	1.47	0.63	27%
		Asian (2)	1.81	0.95	3.46	0.07	0%
		Mixed (1)	1.67	0.87	3.21	0.12	-
	Control source:						
		Population-based (2)	0.59	0.26	1.35	0.21	5%
		Hospital-based (6)	1.36	1.04	1.78	0.03	0%
	Control matching:						
		Age and sex (1)	1.33	0.70	2.55	0.39	-
		None (7)	1.24	0.94	1.63	0.14	27%
	Quality score:						
		≥ 7 (5)	1.25	0.85	1.83	0.26	34%
		< 7 (3)	1.25	0.89	1.76	0.20	8%
	Sample size:						
		≥ 200 (5)	1.15	0.86	1.53	0.34	32%
		< 200	1.80	1.01	3.21	0.05	0%

ity score, studies with a score of ≥ 7 had an OR of 1.10, while those with a score of < 7 had an OR of 0.97. Lastly, for sample size, studies with ≥ 200 samples had an OR of 0.95, while those with < 200 samples had an OR of 1.76, with a significant association found in the latter group ($p = 0.006$).

For the *GSTT1* polymorphism, in terms of ethnicity, the OR was 1.00 for Caucasians, 1.11 for Asians, and 1.50 for mixed ethnicities, with no significant association found ($p > 0.05$). For control sources, the OR was 1.59 for population-based and 1.08 for hospital-based studies. When considering control matching, the OR was 0.95 for age and sex matching and 1.09 for studies without matching. In terms of quality score, studies with a score of ≥ 7 had an OR of 0.94, while those with a score of < 7 had an OR of 1.19. Lastly, for sample size, studies with ≥ 200 samples had an OR of 1.03, while those with < 200 samples had an OR of 1.33.

Table 3. Fixed meta-regression analysis

Variable	Polymorphism	Coefficient	95% CI Lower	95% CI Upper	*P*-value
Publication year	GSTM1	< –0.0001	– 0.0001	0.0001	0.9882
Sample size		–0.0001	–0.0003	0.0001	0.6086
Quality score		0.0014	–0.0158	0.0187	0.8723
Publication year	GSTT1	< 0.0001	< –0.0001	0.0001	0.3935
Sample size		0.0001	–0.0002	0.0004	0.5442
Quality score		0.0091	–0.0163	0.0344	0.4830
Publication year	GSTM1/GSTT1	0.0001	< –0.0001	0.0002	0.0762
Sample size		0.0005	–0.0001	0.0011	0.1078
Quality score		0.0339	–0.0068	0.0746	0.1030

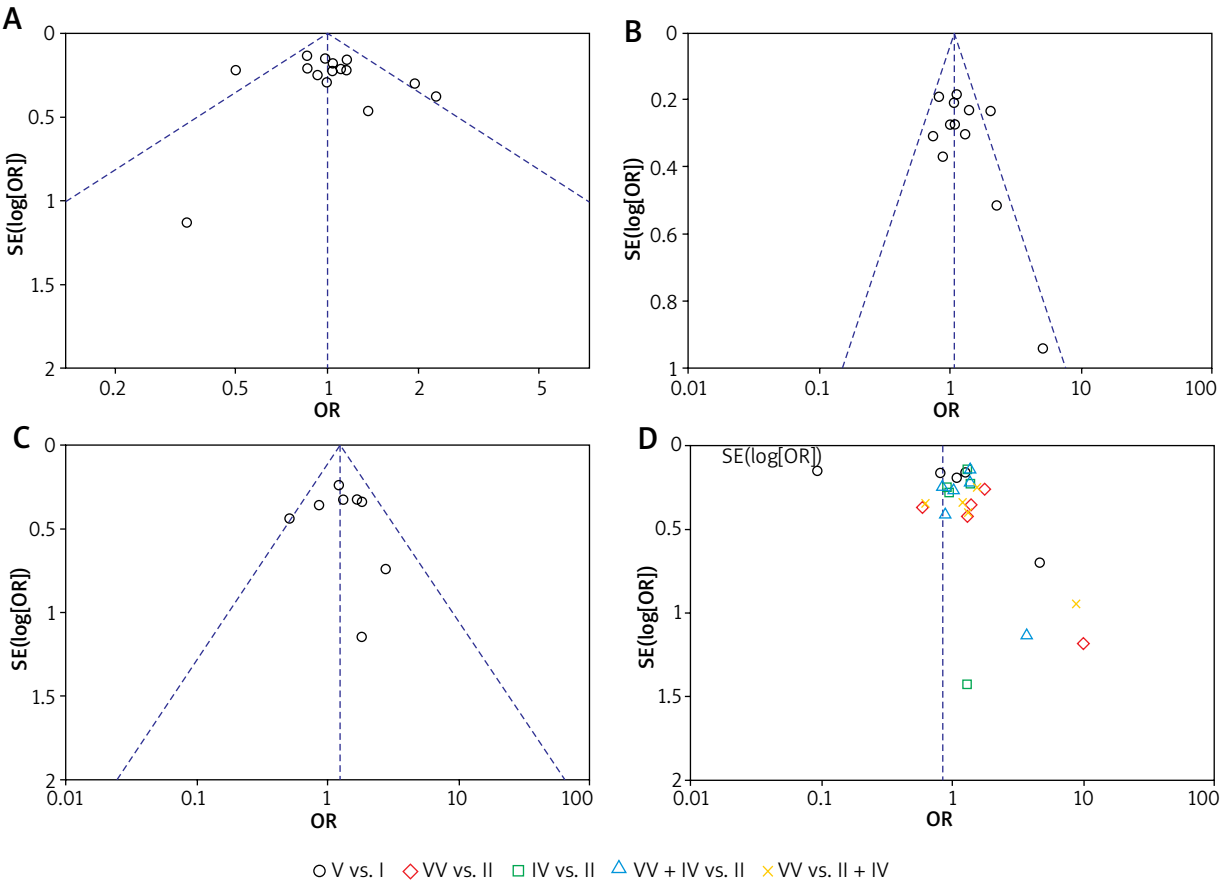


Figure 6. Funnel plot analysis of the association between: **A** – *GSTM1*, **B** – *GSTT1,* **C** – combined *GSTM1/GSTT1*, **D** – *GSTP1 Ile105Val* polymorphisms and the risk of melanoma

For the combined *GSTM1/GSTT1* polymorphisms, in terms of ethnicity, the OR was 1.08 for Caucasians, 1.81 for Asians, and 1.67 for mixed ethnicities, with no significant association found ($p > 0.05$). For control sources, the OR was 0.59 for population-based and 1.36 for hospital-based studies, with a significant association found in hospital-based controls ($p = 0.03$). When considering control matching, the OR was 1.33 for age and sex matching and 1.24 for studies without matching. In terms of quality score, studies with a score of ≥ 7 had an OR of 1.25, while those with a score of < 7 had an OR of 1.25. Lastly, for sample size, studies with ≥ 200 samples had an OR of 1.15, while those with < 200 samples had an OR of 1.80, without a significant association found in the groups ($p > 0.05$).

Meta-regression analysis

Table 3 presents the results of a meta-regression analysis for the *GSTM1, GSTT1*, and combined *GSTM1/GSTT1* polymorphisms. The analysis examined the relationship between the polymorphisms and various vari-

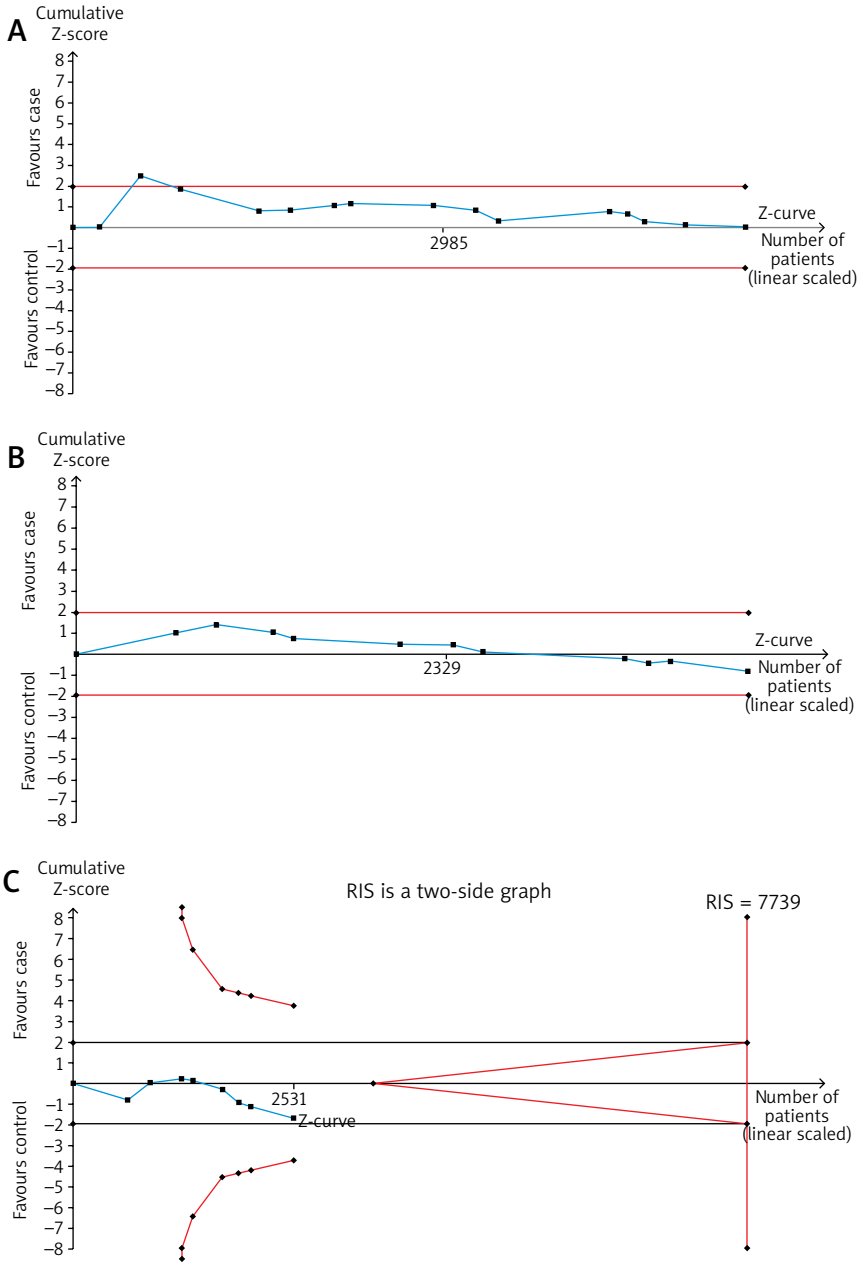


Figure 7. Trial sequential analysis of the association between: **A** – GSTM1, **B** – GSTT1, **C** – combined GSTM1/GSTT1 polymorphisms and the risk of melanoma

ables including publication year, sample size, and quality score. For all three polymorphisms, the coefficients for each variable were very small (less than 0.0001 to 0.0339), and none of them were statistically significant ($p > 0.05$). This suggested that these variables did not significantly influence the association between the polymorphisms and melanoma risk.

Publication bias

Figure 6 shows funnel plots of *GSTM1, GSTT1*, and combined *GSTM1/GSTT1* polymorphisms. The *p*-values of Egger's/Begg's tests were 0.476/0.400, 0.094/0.311, and 0.811/0.804 for *GSTM1, GSTT1*, and combined *GSTM1/GSTT1* polymorphisms, respectively. The *p*-values for both Egger's and Begg's tests for *GSTM1* and combined *GSTM1/GSTT1* polymorphisms were greater than 0.10, suggesting no significant publication bias for these polymorphisms according to these tests. However, the *p*-value for Egger's test for *GSTT1* was 0.094, which was less than 0.10, indicating a potential publication bias according to Egger's test. But Begg's test for *GSTT1* gave a *p*-value of 0.311, which was greater than 0.10, suggesting no significant publication bias according to Begg's test.

TSA

For *GSTM1, GSTT1*, combined *GSTM1/GSTT1*, and *GSTP1* (not plotted TSA) polymorphism, the *Z*-curve did not cross the RIS line or boundary lines and did not enter the futility area, it suggested that more evidence was needed (Figure 7). The current evidence was not sufficient to confirm or reject the intervention effect, and more studies should be included in the meta-analysis. This also meant that any conclusions drawn at this point could be misleading.

Discussion

The forest plot analyses on *GSTM1*, *GSTT1*, and combined *GSTM1/GSTT1* polymorphisms in relation to melanoma risk showed no statistically significant differences between the case and control groups. This was also the case for the allelic and homozygous models of *GSTP1 Ile105Val* polymorphism. However, the recessive model of *GSTP1 Ile105Val* polymorphism showed a statistically significant OR, suggesting a potential association with melanoma risk. The analysis of *GSTM1, GSTT1*, and combined *GSTM1/GSTT1* polymorphisms in relation to melanoma risk revealed significant associations in specific subgroups. For *GSTM1*, a significant association was found in Asians and in studies with a sample size of less than 200. For the combined *GSTM1/GSTT1* polymorphisms, a significant association was found in hospital-based controls. A meta-regression analysis showed that variables such as publication year, sample size, and quality score did not significantly influence the association between the polymorphisms and melanoma risk. Publication bias was assessed and found to be insignificant for *GSTM1* and combined *GSTM1/GSTT1* polymorphisms, but potential bias was indicated for *GSTT1* by Egger's test. The evidence was currently insufficient to confirm or reject the intervention effect, indicating a need for more studies.

In the human genome, *GSTs* are denoted by multiple genes. These genes are situated in class-specific clusters on various chromosomes and exhibit unique expression patterns in each organ [39, 40]. The primary *GST* genes identified as polymorphic are the ones that encode for GSTM1, GSTT1, and GSTP1 [9]. Specifically, the null genotypes of *GSTT1* and *GSTM1*, as well as the variants of *GSTP1*, have been studied and found to have a positive correlation with the risk of cancer [9, 41–44]. Several studies reported a positive correlation of *GST* polymorphisms with the risk of melanoma [28, 35, 37] and in contrast, some studies [30, 32] reported a protective role of *GST* polymorphisms in melanoma patients.

The reasons for different results of association between *GST* polymorphisms and the risk of cancer can be due to differences in ethnicity, lifestyle factors such as smoking, study design (control selection and matching criteria), sample size, gene-gene and gene environmental interactions, pathological features of cancer [45–48]. For confirmation of this result, the present meta-analysis showed that sample size and ethnicity could have an effect on the association between *GSTM1* polymorphism and the melanoma risk and control source on combined *GSTM1/GSTT1* polymorphisms.

GST proteins are involved in tumour-related processes such as promoting cell survival, encouraging cell proliferation, and contributing to drug resistance [49]. Elevated levels of GST are linked to a resistance to apoptosis, which can be triggered by various substances, including chemotherapy drugs [50]. This suggests that GST may play a role in preventing MAPK signalling [50]. While GST levels decrease in metastases originating from skin or lymph nodes, they increase with the overall progression of the tumour. GST is directly implicated in the invasion of melanoma and the development of drug resistance, with GSTP1 being the most expressed isoform [51, 52]. The absence of GSTT and GSTM isozymes in a large portion of the population could potentially influence the development of melanoma by reducing oxidative stress [29]. This suggests a complex relationship between GST levels and different stages of cancer development, as well as *GST* polymorphisms. Therefore, more research is needed to fully understand these complex relationships and their implications for cancer treatment and prevention.

The study has several strengths. It was conducted as a comprehensive search of four databases without any restrictions, which increases the likelihood of including all relevant studies. The analysis included 32 studies, enhancing the reliability and generalizability of the findings. The study also performed a subgroup analysis based on

ethnicity, control source, control matching, quality score, and sample size, allowing for a more nuanced understanding of the data. A meta-regression analysis was conducted to examine the influence of various variables on the association between the polymorphisms and melanoma risk.

However, there are also some limitations. Many of the findings were not statistically significant, indicating no substantial difference between the groups across all studies. The study also suggested potential publication bias for some polymorphisms. The evidence is currently insufficient to confirm or reject the intervention effect, indicating a need for more studies. Although the heterogeneity of the studies was relatively low, it varied from low to moderate across the models, suggesting some degree of discrepancy in the findings across different studies.

Conclusions

This comprehensive analysis of *GST* polymorphisms and their association with melanoma risk provides valuable insights but also highlights the need for further research. While significant associations were found in specific subgroups, many of the findings were not statistically significant, indicating no substantial difference between the groups across all studies. These findings have important clinical implications as they enhance our understanding of the genetic factors influencing melanoma risk and could potentially guide the development of personalized treatment strategies. Looking ahead, it would be beneficial to conduct more studies to confirm these findings and explore the potential therapeutic implications of *GST* polymorphisms. Furthermore, future research should also consider gene-gene and gene-environment interactions, which could offer a more comprehensive understanding of the complex biology of melanoma.

Conflict of interest

The authors declare no conflict of interest.

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