Effects of Glutathione S-Transferases (GSTM1, GSTT1 and GSTP1) gene variants, alone and in combination with smoking or drinking, on cancers: a meta-analysis

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Abstract

This meta-analysis aimed to systematically describe the association between cancer risks and Glutathione S-Transferases (GSTs) among smokers and drinkers. Literatures were searched through PubMed, Web of science, CNKI and WANFANG published from 2001 to 2022. Stata was used with fixed-effect model or random-effect model to calculate pooled odds ratios (ORs) and the 95% confidence interval (95% CI). Sensitivity and heterogeneity calculations were performed, and Begg and Egger's test was used to look for publication bias. Regression analysis was performed on the correlated variables about heterogeneity, and the false-positive report probabilities (FPRP) and the Bayesian False Discovery Probability (BFDP) were calculated to measure the confidence of a statistically significant association. A total of 83 studies were eligible for GSTs and cancer with smoking status (19311 cases and 23194 controls), including 13 articles referred to drinking status (4308 cases and 5476 controls). *GSTM1*-null had significant associations with cancer risks, alone (OR = 1.362, 95%CI=(1.204–1.540) and in combination with smoking (OR = 1.305, 95%CI=(1.149–1.482); *GSTT1*-null had significant associations with cancer risks in combination with smoking (OR = 1.265, 95%CI = 1.032–1.552) or drinking (OR = 1.423, 95%CI = 1.042–1.942); and negative associations were found between *GSTP1rs1695*(AG + GG/AA) and cancer risks among Caucasians in combination with smoking (OR = 0.788, 95%CI = 0.653–0.950) or drinking (OR = 0.724, 95%CI = 0.571–0.919). Thus, the effect of *GSTM1*-null on cancer risks might not be augmented in combination with smoking; *GSTT1*-null might increase cancer susceptibility among smokers and drinkers; while a negative association between *GSTP1rs1695* genetic variants and cancer risks could be seen in Caucasians.

Introduction

Cancer is one of the main reasons for the decline of life quality of people all over the world for its high mortality rate, and it brings great challenges to clinical therapy. A former study demonstrated that the number of patients diagnosed as cancer increased by 19.3 million and cases dying from cancer were up to 10 million worldwide in 2020[1]. Moreover, some lifestyle factors were considered as extremely influential stimulus of the occurrence of cancer. Polycyclic aromatic hydrocarbon (PAH) is an emission of tobacco, which has been regarded as the major organic pollutants affecting human health. Long-term and heavy smokers had a much higher cancer risk than the general population, according to former studies[2–4]. A prospective study in 2018 suggested that smokers diagnosed with cancer might associated with lower survival rate[5]. In the process of alcohol metabolism, acetaldehyde is the main toxic and harmful substance which is classified as the group 1 of human carcinogens in the report of International Agency for Research on Cancer (IARC). In the study of Im, P. K. et al in 2022, combined effects of genes and alcohol consumption increased susceptibility to certain cancers, and this effect was more obvious in Asian populations[6]. Another report showed that alcohol consumption increased cancer susceptibility via compromising human immune system and destroying immune mechanism[7].

Glutathione S-transferases (GSTs) supergene family which was mainly produced by liver, is one of the most significant phase II enzymes in biotransformation in vivo. Each member of GSTs, with different

substrate affinities, is located on different chromosomes and encoded by one or several highly polymorphic genes[8]. Researches have reported that GSTs might played an essential role in the defense mechanism that protects against cytotoxic electrophilic substances, and indirectly modulates some other metabolizing enzymes' activity[2, 9, 10]. The main function of GSTs is to catalyze toxic electrophilic substances and to increase hydrophobicity of them, make it easy for them to pass through the cell membrane, so that they can be easily excreted from the body. Former studies have found that GSTs could reduce the cytotoxic effect by regulating chaperone proteins, ubiquitin-proteasome components, inflammation-related proteins, and apoptosis-related proteins [11, 12]. In recent years, many studies have reported that lifestyle factors such as smoking and drinking might lead to changes in enzyme activity levels due to mutations of associated genes. Therefore, it is imperative to explore the mutual regulation and interaction between GSTs polymorphisms and cancers among smoking and drinking population. Among the members of GSTs, *GSTM1*, *GSTT1* and *GSTP1* are the mainstream of research at present. *GSTM1* is located on chromosome 1p13.3, encoding the u class of enzymes. *GSTM1* can detoxifies cellular electrophilic substances by hormonally controlling under induction by phenobarbital and propylthiouracil[13]. *GSTT1* is located on chromosome 22q11.2, encoding for θ class of enzymes. Similar to *GSTM1*, *GSTT1* can be found in almost all eukaryotes and prokaryotes. As former studies showed, *GSTM1* and *GSTT1* owned three polymorphisms, including one deletion gene named 'null', and two variant genes named 'presence'. The homozygous deletion mutations of *GSTM1* and *GSTT1* might lead to enzyme inactivation and alter the growth activity of certain tumor factors. Due to different coding sites of amino acids, *GSTM1*-null (*GSTM1* -/-) and *GSTT1*-null (*GSTT1* -/-) present the detoxification functional gene deficiency[14], thus altering susceptibility to some cancers aroused by environmental and lifestyle factors. A large number of valuable evidence suggested that mutations of *GSTM1* and *GSTT1* might result in the increasing cancer risks[15–17]. *GSTP1rs1695*(AA, AG, GG), located on chromosome 11q13, is the most studied gene encoding the π class of enzymes. *GSTP1* polymorphisms were highly associated with alcohol consumption, drug-resistance and the development of cancer[18]. Some studies suggested that cancer risk differs significantly in patients with mutations of GSTs when smoking, drinking, ethnicity and source of controls were taken into account. For example, Katiyar et al, in 2020' study demonstrated *GSTM1* mutations have been linked to an increased risk of cancer among smokers [19]; however, ThekkePurakkal et al., in 2019, explained that there was no statistically significant difference in the effect of *GSTM1* gene polymorphisms on cancer among smokers[20]. Because of the bias of language expression, regions, source and number of cases, many research results could be inconsistent.

Meta-analysis is a robust and scientific statistical analysis method based on huge data, which has incomparable advantages over other research methods, usually having a high credibility. In recent years, the relationship between various cancers and GSTs gene has been studied by scholars worldwide. Xavier et al, in 2017, found that Asian country people with *GSTM1–n*ull gene were more easily to develop gastric cancer than European and American[21]. Hernández et al, in 2017, demonstrated that *GSTM1* and *GSTT1* deletion could not be regarded as a separate factor influencing the survival of lung cancer[22]. According to Lee et al in 2020, *GSTP1rs1695* polymorphism was useful for the treatment of chronic myeloid leukemia patients[23]. Hoxhaj et al in 2020, found that *GSTM1*, *GSTT1* and *GSTP1* polymorphisms might

increase the risk of developing a second primary cancer among head and neck cancer survivors in different degrees[24]. However, there is still lack of a consistent conclusion. Therefore, a large scale of samples and suitable model designs are needed to further evaluation of the relationship between GSTs gene and cancer development among smokers and drinkers. Based on previous studies, we collected case-control studies on cancer and GSTs gene polymorphism in smoking and drinking population; and subgroup analyses were conducted to explore the differences between various types of cancers as well as ethnicities. The purpose of this study was to reach the most recent conclusions on the relationship between *GSTM1*, *GSTT1* and *GSTP1* gene polymorphism and cancer occurrence among smokers and drinkers. Before us, no similar article has been found to systematically analyze the association between GSTs alone or in combination with smoking or drinking and all kinds of cancers, and we hope that these results will provide some insights into cancer prevention.

Methods

Literature search and selection criteria

Electronic literatures were searched by using the following databases: Web of Science, PubMed, WANFANG and CNKI. The keywords included (*GSTM1* or *GSTT1* or *GSTP1* polymorphisms) and (smoking or cigarettes or tobacco) or (drinking or alcohol) and cancer by different combinations. The databases were searched in chronological order, from January, 2001 to the latest publication due date March, 2022. Only the case-controls about the association between cancers related to *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms among smokers or drinkers that had been published in English or Chinese journals were kept. To reduce omissions as possible, we also searched and consulted references of relevant review articles and meta-analyses. Smokers diagnosed with cancers were classified as light smokers (<20 pack-year) and heavy smokers (>20 pack-year)to further study the relationship between the degree of smoking and cancer risks.

Articles that conformed with the following criteria would be included: (a) Case-control study; (b) Detailed data on the association of *GSTM1*, *GSTT1* or *GSTP1* polymorphisms with smoking and alcohol consumption were available for calculating the odds ratios (ORs) and estimating the 95% confidence intervals (95% CI); (c) The disease studied was clinically diagnosed cancer; (d) Full text available.

The reasons for exclusion were as follows: (a) Review articles and meta-analyses as well as repeated articles in different databases; (b) Minutes of meeting and clinical trials; (c) No detailed data of case group and control group; (d) No original data linking *GSTM1*, *GSTT1* or *GSTP1* gene polymorphisms to smoking and drinking.

Data extraction

After screening all articles according to the exclusion and inclusion criteria, we performed detailed data extraction for the articles including first author's last name, year of publication, ethnicity, country, source of control, cancer type, smoking or drinking status and genotype. For case-control studies on the same

cancer published by the same author in different years, we kept the latest articles or the maximum sample size in principle. Two researchers used the same keywords to search articles independently. When an article contained unextractable data or some doubts, the two researchers would discuss together whether to keep this article. Subgroup analyses were conducted on the ethnicity (Caucasian, Asian, and mixed groups), the source of control group (hospital-based group and population-based group), and the types of cancer (lung cancer, liver cancer, bladder cancer, and so on) to calculate the differences in the prevalence of cancers, respectively.

Moreover, in the final step of analysis of this research, articles including head and neck cancer, nasopharyngeal cancer, laryngeal cancer, esophageal cancer and thyroid cancer were defined as head and neck neoplasm, and analysis was conducted to research the relationship between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and head and neck neoplasm among smokers.

Statistical analysis

The Stata software was applied to calculate the *GSTM1*-null/presence, *GSTT1*-null/presence, and *GSTP1*rs1695 GG+AG/AA of the case group and control group among different smoking and drinking status. The OR value and 95% CI were calculated to assess the relationship between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and cancer risks among smokers and drinkers. Heterogeneity was measured by using the I-square and P values. If the I-square in heterogeneity test was less than 50% (P>0.05), it demonstrated that the heterogeneity between researches was not statistically significant, and therefore the fixed model should be utilized to calculate the results; otherwise, the random model would be applied.

In this study, year, ethnicity, and population origin were considered to be the sources that could influence heterogeneity, and the meta-regression analysis were used to find these variables. At the same time, combined with the use of sensitivity analysis, any study that had an impact on the overall results of the study could be identified. We also used the Begg and Egger's test to calculate possible bias between studies. All P values calculations were two-sided, and when P value < 0.05, it was considered to be statistically significant.

In order to improve the accuracy and credibility of this experiment's findings, we calculated the false positive reporting probability (FPRP)and the Bayesian false discovery probability (BFDP). As in previous studies, the threshold of FPRP was set to 0.2, and the prior probability was set to 0.25, 0.1, 0.01, 0.001 and 0.0001, to detect an OR of 1.5 associated with cancer risk in the study; and results with FPRP values less than 0.2 should be of concern[25]. Likewise, the BFDP results should be noted when the P value was less than 0.8[26].

Results

Study characteristics

By using keywords, a total of 2422 related reports were found in digital databases. After scanning the titles and abstracts firstly, 2078 articles were excluded, including reviews, meta-analyses, clinical trials, irrelevant reports and duplicate reports. By carefully reading the whole text of remaining studies, we further removed 261 articles for the following reasons: (a) lack of the information for number of samples; (b) lack of research content on the association between genetic polymorphisms and cancers among smoking or drinking population. Finally, 83 articles (19311 cases and 23194 controls) were kept (Fig 1 Table 1, 2), of which 69 articles (15,897 cases and 19,249 controls) were about the relationship between *GSTM1* and cancers[27–31, 19, 32–36, 20, 37–81, 3, 82–84, 4, 85–91]; 50 articles (11,800 cases and 14,857 controls) were about the relationship between *GSTT1* and cancers[3, 4, 19, 27, 28, 30–34, 36, 37, 39–42, 44, 45, 47–52, 54, 55, 59, 61, 63, 64, 66, 68–71, 73, 77–79, 82, 83, 85–88, 90–95]; and 30 articles (8,417 cases and 9,715 controls) were about *GSTP1* and cancers[4, 19, 20, 28, 33, 34, 37, 39, 45, 47, 48, 50, 52, 55, 62, 69, 70, 73, 82, 91, 96–105] among smokers. Among these researches, 8 articles mentioned the classification of smoking levels (20 pack-year) [31, 32, 50, 56, 85, 88, 90, 95]. For alcohol consumption, there were 13 articles (4,308 cases and 5,476 controls) were about the association between *GSTM1* and cancers[19, 31, 36, 38, 39, 43, 68, 69, 72, 75, 77, 78, 100], 8 articles (2,949 cases and 4,025controls) were about *GSTT1* and cancers[19, 31, 36, 39, 68, 69, 77, 78] and 4 articles (1,797 cases and 2,358 controls) were about *GSTP1* and cancers[19, 39, 69, 100] among drinkers.

GSTM1 gene polymorphism studies among smokers and drinkers

Based on the 69 reports on smoking, there were 24 articles for lung cancer, 8 articles for bladder cancer, 6 articles for liver cancer, 5 articles for gastric cancer, 5 articles for cervical cancer, 4 articles for head and neck cancer, 3 articles for esophageal cancer, 2 articles for nasopharyngeal cancer, 2 articles for breast cancer, and 2 articles for prostate cancer; the other types of cancer were not conducted subgroup analysis due to no more than one articles involved. Among subgroup of ethnicities, 34 studies were from Caucasian, 30 studies were from Asian, and 5 studies were mixed.

Of the 13 reports on drinking, 3 articles were for gastric cancer, 2 articles were for head and neck cancer, 2 articles were for liver cancer, and 5 other cancers (breast cancer, thyroid cancer, esophageal cancer, colorectal cancer, and lung cancer). Among subgroup of ethnicities, 6 studies were from Caucasian, 5 studies were from Asian, and 2 studies were mixed (Table 3).

GSTT1 gene polymorphism studies among smokers and drinkers

Of the 50 articles on smoking, 13 articles were for lung cancer, 6 articles were for bladder cancer, 5 articles were for gastric cancer, 5 articles were for cervical cancer, 4 articles were for liver cancer, 2 articles were for head and neck cancer, 2 articles were for breast cancer, 2 articles were for pancreatic cancer, 2 articles were for prostate cancer, as well as other 9 articles that were not performed subgroup analysis for the same reasons as above. Among subgroup of ethnicities, 31 studies were from Caucasian, 14 studies were from Asian, and 5 studies were mixed.

Of the 8 studies on drinking, 2 articles were for gastric cancer and 6 articles were for other cancers (breast cancer, thyroid cancer, esophageal cancer, colorectal cancer, lung cancer, and liver cancer). Among subgroup of ethnicities, 4 studies were from Caucasian, 2 studies were from Asian, and 2 studies were mixed (Table 4).

GSTP1 gene polymorphism studies among smokers and drinkers

Of the 30 reports on smoking, 9 articles were for lung cancer, 4 articles were for bladder cancer, 3 articles were for head and neck cancer, 3 articles were for gastric cancer, 2 articles were for pancreatic cancer, and 2 articles for esophageal cancer as well as other 7 articles without subgroup analysis for the same reasons as above. Among subgroup of ethnicities, 21 studies were from Caucasian, 6 studies were from Asian, and 3 studies were mixed.

Of the 4 studies on drinking, articles were for gastric cancer, head and neck cancer, esophageal cancer, and colorectal cancer; 3 studies were from Caucasian and 1 study was from Asian (Table 5).

GSTM1, *GSTT1* and *GSTP1* polymorphisms studies in head and neck neoplasm among smokers

For *GSTM1*, a total of 12 studies were classified as head and neck neoplasm, 6 studies for Caucasian, 4 articles for Asian and 2 articles for mixed. For *GSTT1*, a total of 7 studies were classified as head and neck neoplasm, 4 studies for Caucasian, 1 article for Asian and 2 articles for mixed. For *GSTP1*, A total of 6 studies were classified as head and neck neoplasm, 4 studies for Caucasian, 1 article for Asian and 1 article for mixed ethnicities (Table 6).

Quantitative synthesis

The relationship between *GSTM1* polymorphism and cancer risks alone and in combination with smoking or drinking

GSTM1 (null/present) might rise the overall cancer risk in both smokers (I^2=72.20%, OR (95%CI) =1.305(1.149-1.482), *P*<0.001) and non-smokers (I^2=61.90%, OR (95%CI) =1.362(1.204-1.540), *P*<0.001) with a similar increase. The subgroup results demonstrated that *GSTM1*-null might increase the risks of lung and nasopharyngeal cancer in both smokers and non-smokers, but high cancer risks were found in stomach, cervix uteri and prostate among non-smokers, instead of smokers. Moreover, *GSTM1*-null could increase the ORs in Caucasians, Asians and hospital-based group, regardless of smoking status. (Table 3).

The overall finding showed no statistical association was found between cancer risks and *GSTM1*-null in either drinkers or non-drinkers. Subgroup results demonstrated that drinking increased the risks of head and neck cancer with a 3.747-fold and liver cancer with a 4.244-fold among *GSTM1*-null carriers. Moreover, alcohol consumption increased the cancer risk of *GSTM1*-null carriers by 2.132 times among Caucasians, but no association was found among Asians (Table 3).

The relationship between *GSTT1* polymorphism and cancer risks alone and in combination with smoking or drinking

GSTT1 (null/present) and the overall cancer risk were found to have a significant positive correlation (I^2=81.00%, OR (95%CI) =1.265(1.032-1.552), *P*=0.024) among smokers, but no statistical association was found between *GSTT1* (null/present) and cancer risks among non-smokers. Subgroup analysis found that smoking might raise the risks of lung and prostate cancer by 1.6-fold and 2.8-fold in *GSTT1*-null carriers, respectively, whereas this risk was not observed in non-smokers. Moreover, the increased cancer risks in combination with smokingdid not differ by ethnicities among *GSTT1*-null carriers (Table 4).

GSTT1-null significantly increased the overall cancer risk (I^2=61.30%, OR (95%CI) =1.423(1.042-1.942), *P*=0.026) among drinkers, while no statistical association between *GSTT1*-null and cancer risk exited among non-drinkers. Subgroup analysis found that *GSTT1*-null in combination with alcohol consumption might increase the risk of gastric cancer to 1.877 times, but no statistical significance was found among non-drinkers. Moreover, drinking might be more likely to increase the cancer susceptibility of Asian *GSTT1*-null carriers by 2.246 times compared with 1.543 times in Caucasians (Table 4).

The relationship between *GSTP1* polymorphism and cancer risks alone and in combination with smoking or drinking

GSTP1 polymorphism (AG+GG/AA) was not statistically related to the overall cancer risk in either smokers or non-smokers. However, subgroup analysis indicated a negative correlation might exit between the risk of head and neck cancer and *GSTP1* polymorphism in combination with smoking (OR (95%CI) = 0.833(0.715-0.970), *P*=0.019), whereas no statistical correlation was found among non-smokers. Moreover, *GSTP1* polymorphism might reduce the risk of cancers to 0.788-fold among Caucasian smokers.

GSTP1 polymorphism might not statistically affect the overall cancer risk in either drinkers or non-drinkers. However, *GSTP1* (AG+GG) carriers might have a reduced risk of cancer with 0.724-fold among Caucasian drinkers, whereas such change was not found among non-drinkers (Table 5).

GSTM1, *GSTT1* polymorphisms and the risk of head and neck neoplasm alone and in combination with smoking

For *GSTM1*,no statistical difference was found between the risk of head and neck neoplasm and *GSTM1*-null, either alone or in combination with smoking. But subgroup results showed that the risk of head and neck neoplasm in *GSTM1*-null increased to 1.620 (95%CI=1.072-2.449, *P*=0.022) among Caucasian smokers. For *GSTT1*, no statistical association exited between the risk of head and neck neoplasmand *GSTT1*-null, either alone or in combination with tobacco consumption (Table 6).

Publication bias

The results of publication bias for *GSTM1*, *GSTT1*, and *GSTP1* gene polymorphisms with cancer risks were illustrated in Table 3, 4 and 5, respectively. Some results showed publication bias: Egger testfor *GSTM1*: 0.007(non-smoking); for *GSTT1:* 0.016/0.025(smoking/non-smoking) (Table 3).

Sensitivity analysis

No statistically significant variables were found in the sensitivity analysis of *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms. The meta-regression analysis found that the year, the ethnicity, and the source of control population were not associated with experimental heterogeneity.

FPRP and BFDP test

The FPRP and BFDP analysis values of GSTs gene polymorphisms and smoking or drinking were shown in Tables 3, 4, 5 and 6, respectively. According to the results of the FPRP analysis, a part of the results in GSTs polymorphisms models were noteworthy in the FPRP test at the OR of 1.5 with prior probabilities of 0.25 and 0.1, but very few results were noteworthy in the BFDP test at the OR of 1.5 with prior probabilities of 0.01, 0.001 and 0.000001, which suggested that the results of this study should be interpreted with caution and euphemism.

Discussion

Numerous studies have shown that smoking and drinking contributed to the development of many cancers, but cancers did not occur in all smokers and drinkers. The occurrence of cancers had a certain probability which might closely relate to the genetic metabolism of genes. Smoking and drinking might have a synergistic effect with the biological metabolic enzymes regulated by GSTs genes. The goal of this meta-analysis was to explore and summarize the relationship between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and cancer risks with the influence of smoking or alcohol status in the largest sample size available. And the results of this study revealed that *GSTM1*, *GSTT1* and *GSTP1* polymorphisms, alone or in combination with smoking or drinking, might affect the overall cancer risk differently, and the effects might be related to ethnicities.

For *GSTM1*, plenty of meta-analyses have shown that *GSTM1*-null could increase the risk of various cancers. Among them, some scholars have found that *GSTM1*-null combined with smoking or drinking could promote the risk of cancers in some organs[17, 106–109], while some scholars suggested that *GSTM1*-null promoting cancer risks might not be augmented by the effect of smoking or drinking[110, 111]. The outcome of this meta-analysis indicated that *GSTM1*-null, both alone and in combination with smoking, was linked to the overall increased cancer risk, but the interaction of *GSTM1*-null and alcohol consumption might not associate with cancer risks. Moreover, subgroup analysis showed that the effect of *GSTM1*-null combined with smoking on the prevalence of cancer was organ-specific, especially for head and neck tumors and nasopharyngeal cancer. Likewise, we found that *GSTM1*-null might significantly increase the risk of liver cancer and head and neck cancer among drinkers. However, cumulative data about the role of smoking habits in *GSTM1*-null promoting the risk of lung cancer was

controversial[106, 111]. In addition to smoking, the pathogenesis of lung cancer was affected by various factors such as living habits, environment, genetics, etc. The findings in this study revealed that the risk of lung cancer was higher among non-smokers (OR = 1.362, $P < 0.001$) than that among smokers (OR = 1.305, $P < 0.001$). Consistent with cumulative evidence, we also found that tobacco was not a contributing factor to stomach[55], cervical[49, 112, 113], and bladder[114] cancers. Among studies of ethnic differences in *GSTM1* gene polymorphisms, in 2001, Garte et al discovered that Asians had a greater frequency of *GSTM1*-null than Caucasians[115]. Zhang et al in 2011 discovered that when *GSTM1*-null and smoking were combined, Asians had a higher risk of oral cancer than Caucasians[116]. The overall cancer risks in *GSTM1*-null carriers were 1.434-fold among Asian and 1.263-fold among Caucasian smokers, respectively, suggesting that cancer risks related to *GSTM1*-null might be slightly higher in Asian smokers. But the interaction of *GSTM1*-null and drinking might increase cancer risk in Caucasian drinkers. In conclusion, *GSTM1*-null was associated with the general elevated cancer risk, among smokers and non-smokers alike. High risks of head and neck tumors and nasopharyngeal cancer might be associated with the interaction of *GSTM1*-null and smoking, and high risks of liver cancer and head and neck cancer might be associated with the interaction of *GSTM1*-null and drinking. And *GSTM1*-null and alcohol consumption may be synergistic factors for increased cancer risk in Caucasians.

For *GSTT1*, one meta-analysis in 2013 indicated that *GSTT1* polymorphism might promote cancer development, especially in smokers[17]. But for cancer of different organs, many scholars put forward specific views. Du et al found that smoking could rise the risk of esophageal cancer[107]; Lao et al found that drinking played a critical role in promoting the development of gastric cancer[108]. The outcome in this meta-analysis found that *GSTT1*-null combined with smoking or drinking could significantly increase the overall cancer risks (OR = 1.265 for smoking; OR = 1.423 for drinking). *GSTT1*-null combined with smoking might be obviously related to the pathogenesis of prostate cancer, for the risk being as high as 2.836 times. Moreover, our results implied that *GSTT1*-null might have a greater impact on lung cancer risk than *GSTM1*-null, which was in line with the results of Ritambhara et al[37]. Although Zeng et al in 2016 demonstrated that alcohol consumption was not a co-factor of *GSTT1*-null in the development of gastric cancer[117], our findings suggested that drinking might increase the risk of gastric cancer in *GSTT1* -null carriers (OR = 1.877, $P = 0.021$). In addition, the risk of cancers increased by 1.5-fold among Caucasian and 2.246-fold among Asian for *GSTT1*-null carriers in combination with drinking, respectively. In conclusion, *GSTT1*-null and smoking or drinking were synergistic factors in promoting the overall cancer risk.

For *GSTP1rs1695*, cumulative researches confirmed that no statistical significance was found between *GSTP1* gene polymorphism and cancer risks[118–120]. However, we noticed that Bao et al stated that the interaction of *GSTP1* gene mutation and smoking might lower the risk of developing stomach cancer[121]; and a huge review of Caucasian had estimated that smoking could modify lung cancer risk of *GSTP1* gene mutation in Caucasians[122]. In subgroup analysis, we observed that the *GSTP1rs1695* acted as a protective factor in Caucasian smokers or alcohol drinkers (OR = 0.788 for smoking; OR = 0.724 for drinking). In addition, the risk of head and neck cancer also decreased among smokers. Currently, our findings suggested that *GSTP1rs1695* genetic variants might be negatively associated with

cancer risks in Caucasian smokers or alcohol drinkers. However, due to the relatively small sample data, this conclusion should be treated with caution.

After the above analysis, we further summarized the association between GSTs polymorphisms and head and neck neoplasm (contained with head and neck cancer, nasopharyngeal cancer, laryngeal cancer, esophageal cancer and thyroid cancer in this article) among smokers. The result suggested that smoking was linked to an increased risk of head and neck neoplasm in only Caucasians.

The limitations of this study were: (a) the interactions between GSTs and other possible isozymes on cancer risks were not considered in this analysis. Cancers were caused by multiple factors; therefore, the synergistic or antagonistic effect of other factors should be considered as well as possible. (b) cancer risks might be more pronounced if the effects of genetic polymorphisms ,alcohol and tobacco were combined together[19, 43]. (c) GSTs might have overlapping affinities, and that the combined effects of *GSTM1* and *GSTT1* detoxification functions might have a greater impact on disease than the effect of one independent gene[123]. However, in the process of data extraction, some valuable articles could not be included in the analysis because of a lack of original data provided, resulting in the small sample size of data, particularly for the studies of the association between GSTs and cancers among drinking population. So, the sample data in this study was not available to further investigate the association between the combined effects of gene-gene associations and smoking-drinking associations on cancers. Otherwise, the representativeness might be stronger to further explore the interaction between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and cancers among drinkers.

In conclusion, *GSTM1*deficiency might have an increased risk of cancers, whether alone or in combination with smoking. *GSTT1*-null might not affect cancer risk alone, but it might act as a synergistic factor in promoting cancer risk in combination with tobacco or alcohol. No synergistic effect on the overall cancer risk was found between *GSTP1rs1695* and smoking or drinking. But the role of *GSTM1* or *GSTP1* in combination with smoking or drinking on cancers might be influenced by ethnicities. Broader sample data and appropriate experimental design were needed to further investigate the effects of *GSTM1*, *GSTT1* and *GSTP1* polymorphisms on cancer among smokers or drinkers.

Declarations

Conflict of interest statement:

The authors declare no potential conflicts of interest.

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Author contributions

CPL -Conceptualization; QRH, YHH, ZXW, LC, YL -Methodology and Data collection; QRH, CPL -Calculation and Analyses; QRH -Original manuscript; QRH, CPL, XJL -Manuscript review, polishes and editing.

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Tables

Table 1-6 is available in the Supplementary Files section.

Figures

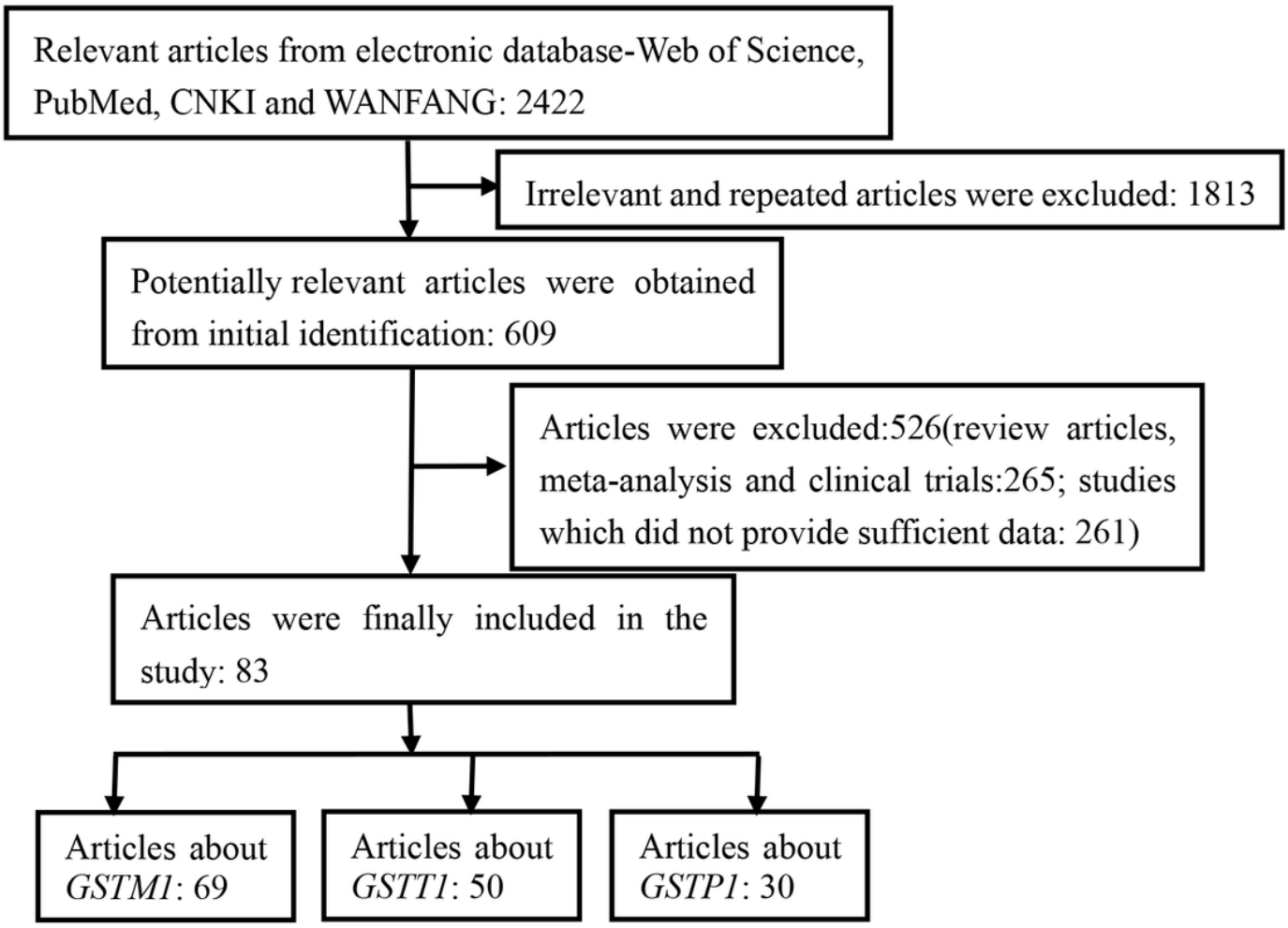

Figure 1

The Whole Flow Diagram of Filtering the Available Articles in this Study

Supplementary Files

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- Table1.xlsx
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- Table4.xlsx
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