Association of \textit{GSTM1} and \textit{GSTT1} Null Deletions and \textit{GSTP1} rs1695 Polymorphism with the Risk of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

Mohammad Hossein Khosravi\textsuperscript{1,2,3}, Heidar Sharafi \textsuperscript{1} and Seyed Moayed Alavian \textsuperscript{1, *}

\textsuperscript{1}Middle East Liver Diseases (MELD) Center, Tehran, Iran
\textsuperscript{2}Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Baqiyatallah University of Medical Sciences, Tehran, Iran
\textsuperscript{3}Department of Research, Arka Education and Clinical Research Consultants, Tehran, Iran

*Corresponding author: Middle East Liver Diseases (MELD) Center, Tehran, Iran. Email: alavian@thc.ir

Received 2020 May 23; Revised 2020 November 15; Accepted 2020 December 12.

Abstract

\textbf{Context:} Hepatocellular carcinoma (HCC), as the most common type of primary liver cancer (accounting for 70\%-90\% of all liver cancers), is the seventh most common malignancy worldwide. Glutathione S-transferases (GSTs) are a specific group of enzymes that are responsible for the detoxification of carcinogens. According to the available literature, genetic variations in this group of enzymes may be associated with the risk of HCC. In this study, we aimed to assess the association of \textit{GSTM1} and \textit{GSTT1} null deletions and \textit{GSTP1} rs1695 polymorphism with the risk of HCC.

\textbf{Methods:} We systematically searched electronic databases, including PubMed, Scopus, and Web of Science, using appropriate keywords to gather relevant data until March 2019. Studies that met the inclusion criteria were included in the meta-analysis, using either fixed- or random-effects models based on the presence of heterogeneity.

\textbf{Results:} This meta-analysis pooled 19 studies for \textit{GSTM1} null deletions, 14 studies for \textit{GSTT1} null deletions, and five studies for \textit{GSTP1} rs1695 polymorphism. In terms of heterogeneity, the pooled odds ratio (OR) was calculated in a random-effects model for both Asian and non-Asian populations. HCC was found to be associated with \textit{GSTM1} null deletions (OR = 1.26, 95\% CI: 1.00 - 1.58, \(P = 0.05\)) and \textit{GSTT1} null deletions (OR = 1.39, 95\% CI: 1.10 - 1.74, \(P = 0.005\)); however, no significant association was found between HCC and \textit{GSTP1} rs1695 polymorphism (OR = 1.14, 95\% CI: 0.86 - 1.50, \(P = 0.36\)).

\textbf{Conclusions:} We found that \textit{GSTM1} and \textit{GSTT1} null deletions increased the risk of HCC; however, the \textit{GSTP1} rs1695 polymorphism did not have a similar effect.

\textbf{Keywords:} Liver Cancer, Meta-analysis, GSTP1, GSTT1, GSTM1, Hepatocellular Carcinoma

1. Context

Hepatocellular carcinoma (HCC), as the most common type of primary liver cancer, accounting for 70\%-90\% of all liver cancers, is recognized as the seventh most common malignancy and the fourth cause of cancer-related death worldwide (1-4). Both environmental and individual genetic factors play important roles in the pathogenesis of HCC (5, 6). So far, several risk factors have been introduced for HCC, including chronic viral hepatitis (hepatitis B or C), non-alcoholic steatohepatitis (NASH), genetic predisposition with a history of HCC, and heavy alcohol or tobacco consumption (7, 8).

Previous research has confirmed the role of genes and metabolism-associated pathways in the development of HCC. Many upregulated and downregulated metabolic genes, such as those involved in the metabolism of carbohydrates and amino acids, are considered as key parameters in hepatocarcinogenesis (9). Glutathione S-transferases (GSTs), including glutathione S-transferase Pi (GSTP1), glutathione S-transferase T1 (GSTT1), and glutathione S-transferase M1 (GSTM1), are a specific group of enzymes, responsible for the detoxification of carcinogens (10).

Previous studies have shown that null deletions of \textit{GSTM1} gene may be a predisposing factor for lung, blood, and colorectal cancers (11, 12). Moreover, there is some evidence regarding the effects of \textit{GSTT1} null deletions and \textit{GSTP1} rs1695 polymorphism on the risk and prognosis of head and neck squamous cell carcinomas and lung can-
Identification of the role of GST family in the hepatocarcinogenesis can improve risk and prognosis prediction in patients with HCC. Besides, the development of novel gene therapies, including clustered regularly interspaced short palindromic repeats (CRISPR), highlights the importance of identifying the underlying genetic disorders.

Some original studies have investigated the association of GSTM1 null deletions, GSTP1 rs1695 polymorphism, and GSTT1 null deletions with HCC; however, they could not reach a definite conclusion, which might be due to the small sample size of these studies or limitations of methods and facilities. Therefore, in the present study, we aimed to assess the association of GSTM1 null deletions, GSTP1 rs1695 polymorphism, and GSTT1 null deletions with the risk of HCC.

2. Methods

2.1. Data Resources and Search Strategy

We systematically searched electronic databases, including PubMed, Scopus, and Web of Science, using combinations of the following keywords: “hepatocellular carcinoma”, “HCC”, “GSTM1”, “GSTT1”, and “GSTP1” (Appendix 1 in Supplementary File). First, a systematic search was conducted in November 2018, which was updated in March 2019. All selected articles were written in English. Besides, we screened the reference lists of all included studies for identifying any additional papers.

2.2. Eligibility Criteria

We included case-control studies that assessed the relationship between HCC and GSTM1 null deletions, GSTP1 rs1695 polymorphism, and GSTT1 null deletions. The diagnosis of HCC was mainly confirmed by imaging and measuring the serum alpha-fetoprotein level in all included studies. Studies that had not reported the exact number of patients with polymorphism genotypes in each group were not included. Also, studies without healthy controls were excluded. Healthy controls were defined as hospital- or community-based people with no history of liver diseases.

2.3. Study Selection, Quality Assessment, and Data Extraction

Two authors (M.H.K and H.S.) independently reviewed all identified papers (15). Any disagreements between the authors were resolved by neutral discussion. The Newcastle-Ottawa scale was applied for the evaluation of case-control studies (16). Next, the publication details and data about the patients were extracted from each study. Also, the first author’s name, publication year, sample size, age, gender, and underlying diseases of patients, and frequency of each polymorphism genotype in each group were determined.

2.4. Data Analysis

For determining the heterogeneity of data, chi-square and I-square (I² range: 0% - 100%) tests were performed. P-value less than 0.1 was considered statistically significant for the heterogeneity of data, based on the chi-square test. If I² was less than 50%, there was no significant heterogeneity, and the fixed-effects model was used. On the other hand, if I² was above 50%, the random-effects model was selected to calculate the pooled odds ratio (OR), 95% confidence interval (CI), and P-value. Statistical analysis and generation of forest and funnel plots were performed in Review Manager version 5.3.

3. Results

3.1. Study Screening

After searching the databases, we found 525 records and investigated 190 papers after removing duplicates. We excluded 112 articles by title screening and 34 articles by abstract screening. Also, during title and abstract screening, we excluded 37 articles owing to the study design (not case-control). Finally, after updating our search, 23 studies were included in this review (Figure 1).

3.2. Risk of Bias Assessment

The results of quality assessment for the case-control studies, based on the Newcastle-Ottawa scale, are shown in Table 1. All case-control studies were categorized as low risk. No study was excluded after this assessment.

3.3. Characteristics of the Selected Studies

The included papers were case-control studies published after 1995. These studies assessed the effects of all or at least one GSTM1 null deletion, GSTP1 rs1695 polymorphism, and/or GSTT1 null deletion on the risk of HCC. The characteristics of these studies are presented in Table 2.

3.4. Outcome Evaluation

We evaluated the association of GSTM1 null deletions, GSTP1 rs1695 polymorphism, and GSTT1 null deletions with the risk of HCC. Figures 2-4 present a summary of the results for GSTM1 null deletions, GSTT1 null deletions, and GSTP1 rs1695 polymorphism as forest plots, respectively. Figure 5 shows the funnel plots for all of the assessed polymorphisms.
3.4.1. Association of \textit{GSTM1} Null Deletions with the Risk of HCC

We found the heterogeneity of data regarding the association of \textit{GSTM1} null deletion with the risk of HCC in both Asian ($I^2 = 75\%$, $P < 0.0001$) and non-Asian ($I^2 = 87\%$, $P < 0.00001$) populations. Therefore, the pooled OR for the association of \textit{GSTM1} null deletions and HCC was calculated using the random-effects model (OR = 1.26, 95\% CI: 1.00 - 1.58, $P = 0.05$). In the subgroup analysis regarding ethnicity, the OR was estimated at 1.32 (95\% CI: 1.00 - 1.73, $P = 0.05$) for Asians and 1.18 (95\% CI: 0.78 - 1.78, $P = 0.43$) for non-Asians. Figure 2 shows the forest plot of these pooled analyses.
3.4.2. Association of GSTT1 Null Deletions with the Risk of HCC

We found the heterogeneity of data regarding the association of GSTT1 null deletions with the risk of HCC in both Asian ($I^2 = 67\%, P = 0.006$) and non-Asian ($I^2 = 81\%, P < 0.0001$) populations. Therefore, the pooled OR for the association of GSTT1 null deletions with HCC was calculated in a random-effects model (OR = 1.39, 95% CI: 1.10 - 1.74, $P = 0.005$). In the subgroup analysis by ethnicity, OR was 1.37 (95% CI: 1.02 - 1.83, $P = 0.03$) for Asians and 1.40 (95% CI: 0.96 - 2.05, $P = 0.08$) for non-Asians. Figure 3 demonstrates the forest plot of these pooled analyses.

3.4.3. Association of GSTP1 rs1695 Polymorphism with the Risk of HCC

We found heterogeneity of data regarding the association of GSTP1 rs1695 polymorphism with the risk of HCC in both Asian ($I^2 = 60\%, P = 0.08$) and non-Asian ($I^2 = 65\%, P = 0.09$) populations. Accordingly, the pooled OR for the association of GSTP1 rs1695 polymorphism with HCC was calculated in a random-effects model (OR = 1.14, 95% CI: 0.86 - 1.50, $P = 0.36$). In the subgroup analysis by ethnicity, the OR was 1.07 (95% CI: 0.75 - 1.54, $P = 0.69$) for Asians and 1.45 (95% CI: 0.62 - 3.40, $P = 0.40$) for non-Asians. Figure 4 shows the forest plot of these pooled analyses.

3.5. Publication Bias

According to Figure 5, we found significant publication bias in the evaluated studies.

4. Discussion

Chronic viral hepatitis and exposure to aflatoxins are two main risk factors for HCC in developing countries, making it a major cancer type in these regions (40). The metabolism of aflatoxins varies genetically among different populations, which justifies differences in the prevalence of HCC, despite the similarity of viral hepatitis infection and aflatoxin exposure (41). Therefore, GSTM1 and GSTT1...
GSTT1 null deletions and GSTP1 rs1695 polymorphism can predispose people in contact with environmental factors to HCC.

The hemostasis of amino acids (including leucine, isoleucine, and valine) and carbohydrate metabolism are necessary for liver function. All metabolism pathways are controlled by enzymes that are produced by specific genes. Some abnormalities in metabolic pathways, such as redox metabolism, fatty acid metabolism, amino acid metabolism, and drug/hormone metabolism, besides genes involved in these pathways, have been shown to affect the risk and prognosis of HCC (42). By identifying the relationship between the expression level of these genes and the risk of HCC, researchers and physicians can find new methods of treatment and prevention for HCC, according to the individual’s underlying genetic profile.

Phase II enzymes, including those encoded by GSTM1, GSTT1, and GSTP1 genes, play an important role in the detoxification of aflatoxins, as well as other carcinogens (43, 44). Previous research has shown that null genotypes may lead to enzyme deficiency and act as a predisposing factor for HCC (37). However, there are some discrepancies be-
between the results of these studies, and none of them have reached a definitive conclusion about the association of GST null genotypes with the risk of HCC; this may be related to the low sample size of these studies or differences in the studied populations and study designs. Accordingly, the present meta-analysis aimed to reach a relatively definite conclusion about the association of \textit{GSTM1} and \textit{GSTT1} null deletions and \textit{GSTP1} rs1695 polymorphism with the risk of HCC.

In the present meta-analysis, 23 studies were included, based on the inclusion criteria. All articles were case-control studies, and most of them were conducted among Chinese and Taiwanese populations. The pooled OR in our meta-analysis showed that \textit{GSTM1} and \textit{GSTT1} null deletions had significant relationships with the risk of HCC. However, we did not find any significant relationship between \textit{GSTP1} rs1695 polymorphism and the risk of HCC. In this regard, Wang et al. (45) conducted a similar study to evaluate the association of \textit{GSTT1} and \textit{GSTM1} null deletions with the risk of HCC. After assessing 123 studies, 23 papers were included in their meta-analysis; they included studies written in English and Chinese languages. Statistical analysis revealed that independent or concurrent presence of \textit{GSTM1} and \textit{GSTT1} null deletions significantly increased the risk of HCC in the Asian population, which is consistent with the results of the present study.

In another study, Song et al. (46) evaluated the effects of \textit{GSTT1} and \textit{GSTM1} null deletions on the risk of HCC. After assessing 287 studies, they finally included 34 articles in their meta-analysis. It should be noted that they included both case-control and cohort studies, which might explain the difference in the number of included studies with the present meta-analysis. The authors concluded that these polymorphisms slightly increased the risk of HCC in the Asian and Indian populations. Additionally, Sui et al. (47), by evaluating the effect of the concurrent presence of \textit{GSTM1} and \textit{GSTT1} null deletions, reported no direct interaction between these polymorphisms and the risk of HCC.
Figure 3. The forest plot for GSTT1 null deletions and the risk of HCC.

Figure 4. The forest plot for GSTP1 rs1695 polymorphism and the risk of HCC.
Figure 5. The funnel plots for the assessment of publication bias: A, GSTM1 null deletions; B, GSTT1 null deletions; and C, GSTP1 rs1695 polymorphism

HCC; however, each GSTM1 and GSTT1 deletion had its independent impact on the development of HCC. They also concluded that the concurrent presence of these genetic variations had a more significant effect on the risk of HCC in the Chinese population as compared to other populations.

Moreover, a recently published study evaluated the effects of GSTM1 and GSTT1 null deletions on the risk of HCC. Li et al. (5) evaluated 41 articles, including studies written in English and Chinese languages. They reported that these genetic variations increased the risk of HCC in Asians, but not African or Caucasian populations. Nevertheless, this study did not have any precise or united inclusion criteria, which might account for the differences in the number of included studies.

The present study had some limitations. Since we were required to use the data reported in the selected articles, we were unable to perform a meta-analysis in subgroups in terms of gender or age.

In conclusion, the results of the present study suggest significant associations between GSTM1 and GSTT1 null deletions and HCC. However, no significant relationship was found between GSTP1 rs1695 polymorphism and the risk of HCC.

Supplementary Material

Supplementary material(s) is available [here](#). To read supplementary materials, please refer to the journal website and open PDF/HTML.

Footnotes

Authors’ Contribution: MHK searched the databases, extracted the data, drafted the manuscript, and contributed to data analysis. HS analyzed the data and contributed to drafting the manuscript. SMA designed the study, contributed to drafting the manuscript, and critically revised the final version. All authors approved the final version of the manuscript.

Conflict of Interests: We have no conflict of interest to declare.
Funding/Support: The authors did not receive any support from any organization for this study.

References

1. Wei K, Peng X, Liang Z, Cen H. Liver cancer epidemiology world. China Cancer. 2015;24(8):621-30.

2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. doi: 10.1002/ijc.29281. [PubMed: 25220442].

3. Sengupta B, Siddiqi SA. Hepatocellular carcinoma: important biomarkers and their significance in molecular diagnostics and therapy. Curr Med Chem. 2012;19(22):3722-9. doi: 10.2174/092986712808601059. [PubMed: 22680921].

4. Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. The glutathione S-transferases: an update. Hepat Mon. 2020;20(11):e105632. [PubMed: 33016171].

5. Li S, Xue F, Zheng Y, Yang P, Lin S, Deng Y, et al. GSTM1 and GSTT1 null genotype increase the risk of hepatocellular carcinoma: evidence based on 46 studies. Cancer Cell Int. 2019;19:74. doi: 10.1186/s12935-019-0797-3. [PubMed: 30976201]. [PubMed Central: PMC6441207].

6. Habibi N, Nassiri-Toosi M, Sharafi H, Alavian SM, Shams-Ghasharhoki M, Razzaghi-Abyaneh M. Aflatoxin B1 exposure and the risk of hepatocellular cancer in Iranian carriers of viral hepatitis B and C. Cancer Cell Int. 2018;18(1):41. doi: 10.1007/s12032-018-4466-0.

7. Abdel-Rahman O, Helbling D, Schob O, Eltobgy M, Mohamed H, et al. Interaction between cytochrome P450 1A2 genetic polymorphism, cigarette smoking and hepatocellular carcinoma: a case-control study. Int J Cancer. 2005;115(4):301–7. doi: 10.1002/jso.21643. [PubMed: 15906928]. [PubMed Central: PMC4310264].

8. Chen YL, Tseng HS, Kuo WH, Yang SF, Chen DR, Tsai HT. Glutathione S-transferase P1 (GSTP1) and Risk of Hepatocellular Carcinoma Among Chronic Hepatitis C Patients in Egypt. Biochem Genet. 2016;54(5):696-713. doi: 10.1007/s10528-016-9749-6. [PubMed: 27272622].

9. Asim M, Khan LA, Hussain SA, Hussain S, Sarma MP, Ahmad I, et al. Genetic polymorphism of glutathione S-transferase M1 and T1 in Indian patients with hepatocellular carcinoma. Dis Markers. 2010;28(6):369-76. doi: 10.3233/DMA-2010-0771. [PubMed: 20683152]. [PubMed Central: PMC313701].

10. Boccia S, Miele L, Panic N, Turati F, Arzani D, Cefalo C, et al. The effect of CYP, GST, and SULT polymorphisms and their interaction with smoking on the risk of hepatocellular carcinoma. Biomed Res Int. 2015;2015:759867. doi: 10.1155/2015/759867. [PubMed: 26564087]. [PubMed Central: PMC4724340].

11. Borentain P, Gerolami V, Loria A, Martinek E, Schwerin S, et al. The relation between Polymorphisms in GSTT1 and the Risk of Hepatocellular Cancer. Hepat Mon. 2013;9(1):9312. doi: 10.34895/2013012. [PubMed: 23937506]. [PubMed Central: PMC3833703].

12. Hofman MA, Grobbee DE, van der Heijden JP, Kostense PJ, et al. DNA-repair and carcinogen-metabolising enzymes genetic polymorphisms as an independent risk factor for hepatocellular carcinoma in Caucasian liver transplant patients. Br J Cancer. 2005;93(7):1053–60. doi: 10.1038/sj.bjc.6602721. [PubMed: 16084952].

13. Ludwig B, Schütte D, Hahn SA. Glutathione-S-transferase and microsomal epoxide hydrolase polymorphism and viral-related hepatocellular carcinoma risk in India. DNA Cell Biol. 2008;27(12):687-94. doi: 10.1089/dna.2008.0405. [PubMed: 18816717].
27. Kirk GD, Turner PC, Gong Y, Lesi OA, Mendy M, Goedert J, et al. Hepatocellular carcinoma and polymorphisms in carcinogen-metabolizing and DNA repair enzymes in a population with aflatoxin exposure and hepatitis B virus endemicity. Cancer Epidemiol Biomarkers Prev. 2005;14(2):373-9. doi: 10.1158/1055-9965.EPI-04-0161. [PubMed: 15734960].

28. Ladero JM, Martinez C, Fernandez JM, Martin F, Garcia-Martín E, Ropero P, et al. Glutathione S-transferases pi 1, alpha 1 and M3 genetic polymorphisms and the risk of hepatocellular carcinoma in humans. Pharmacogenomics. 2007;8(6):895-9. doi: 10.2217/14622446.8.8.895. [PubMed: 17762244].

29. Ladero JM, Martinez C, Garcia-Martín E, Ropero P, Briceno O, Villagrasa A, et al. Glutathione S-transferase M1 and T1 genetic polymorphisms are not related to the risk of hepatocellular carcinoma: a study in the Spanish population. Eur J Cancer. 2006;42(1):73-7. doi: 10.1016/j.ejca.2005.08.033. [PubMed: 16314088].

30. Li CG, Zhao ZM, Hu MG, Liu R. Predictive role of glutathione-S-transferase gene polymorphisms in risk and prognosis of hepatocellular carcinoma. Asian Pac J Cancer Prev. 2012;13(7):3247-52. doi: 10.7314/apjcp.2012.13.7.3247. [PubMed: 22994742].

31. Long XD, Ma Y, Wei YP, Deng ZL. The polymorphisms of GSTM1, GSTT1, HYL1,2, and XRCC1, and aflatoxin B1-related hepatocellular carcinoma in Guangxi population, China. Hepatol Res. 2006;36(1):48-55. doi: 10.1006/hepr.2006.06.004. [PubMed: 16884947].

32. McGlynn KA, Rosvold EA, Lustbader ED, Hu Y, Clapper ML, Zhou T, et al. Susceptibility to hepatocellular carcinoma is associated with genetic variation in the enzymatic detoxification of aflatoxin B1. Proc Natl Acad Sci U S A. 1995;92(6):2384-7. doi: 10.1073/pnas.92.6.2384. [PubMed: 7892276]. [PubMed Central: PMC42488].

33. Munaka M, Kohshi K, Kawamoto T, Takasawa S, Nagata N, Itoh H, et al. Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and the risk of hepatocellular carcinoma. J Cancer Res Clin Oncol. 2003;129(6):555-60. doi: 10.1007/s00432-003-0439-5. [PubMed: 12759747].

34. Sophonmiprasert T, Saeloe P, Pongetheerat T. GSTM1 and GSTTI copy number variants and the risk to Thai females of hepatocellular carcinoma. J Gastrointest Oncol. 2019;10(2):324-9. doi: 10.21037/jgo.2018.12.057. [PubMed: 30606699]. [PubMed Central: PMC6412169].

35. Sun CA, Wang LY, Chen CJ, You SL, Wang LW, et al. Genetic polymorphisms of glutathione-S-transferases M1 and T1 associated with susceptibility to aflatoxin-related hepatocarcinogenesis among chronic hepatitis B carriers: a nested case-control study in Taiwan. Carcinogenesis. 2001;22(6):8289-94. doi: 10.1093/carcin/22.8.1289. [PubMed: 11470760].

36. Tiemersma EW, Omer RE, Bunschoten A, van’t Veer P, Kok FJ, Ildiris MO, et al. Role of genetic polymorphism of glutathione-S-transferase T1 and microsomal epoxide hydrolase in aflatoxin-associated hepatocellular carcinoma. Cancer Epidemiol Biomarkers Prev. 2001;10(7):785-91. [PubMed: 11440964].

37. Wei Y, Long X, Liu Z, Ma Y, Deng Z. Genetic polymorphism of glutathione-S-transferase M1 and T1 in associated with carcinogenesis of hepatocellular carcinoma and nasopharyngeal carcinoma. Chin German J Clin Oncol. 2012;11(3):338-41. doi: 10.1007/s10330-011-0945-x. [PubMed: 22259215].

38. Yu MW, Gladek-Yarborough A, Chiamprasett S, Santella RM, Liaw YF, Chen CJ. Cytochrome P450 2E1 and glutathione S-transferase M1 polymorphisms and susceptibility to hepatocellular carcinoma. Gastroenterology. 1995;109(4):1266-73. doi: 10.1016/0041-0045(95)90507-X. [PubMed: 7575094].

39. Ma Y, Deng Z, Wei Y. Study of the deletion mutation of glutathione transferase M1 gene and its role in susceptibility to hepatocellular carcinoma. Chin J Cancer Res. 2001;13(1):176-8. doi: 10.1007/bf02983879. [PubMed: 11440964].

40. London WT, McGlynn KA, Schottenfeld D, Fraumeni JF, editors. Liver cancer. New York: Oxford University Press; 2006. p. 772-93.

41. Parkin DM, Whelan SL, Ferlay J, Young J. Cancer, Incidence in Five Continents VISP. Lyon, France: IARC; 1997.

42. Benfeitas R, Bidhikhi G, Mukhopadhyay B, Klevstig M, Arif M, Zhang C, et al. Characterization of heterogeneous redox responses in hepatocellular carcinoma patients using network analysis. EBioMedicine. 2019;40:471-87. doi: 10.1016/j.ebiom.2018.12.057. [PubMed: 30666699]. [PubMed Central: PMC6412169].

43. Liu YH, Taylor J, Linko P, Lucier GW, Thompson CL. Glutathione S-transferase mu in human lymphocyte and liver: role in modulating formation of carcinogen-derived DNA adducts. Carcinogenesis. 1991;12(12):2269-75. doi: 10.1093/carcin/12.12.2269. [PubMed: 1747926].

44. Chasseaud LF. The role of glutathione and glutathione S-transferases in the metabolism of chemical carcinogens and other electrophilic agents. Adv Cancer Res. 1979;29:175-274. doi: 10.1016/0065-230x(79)80684-9. [PubMed: 474272].

45. Wang B, Huang G, Wang D, Li A, Xu Z, Dong R, et al. Null genotypes of GSTM1 and GSTTI contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. J Hepatol. 2010;53(3):508-18. doi: 10.1016/j.jhep.2010.03.026. [PubMed: 20566999].

46. Song K, Yi J, Shen X, Cai Y. Genetic polymorphisms of glutathione S-transferase genes GSTM1, GSTTI and risk of hepatocellular carcinoma. PloS One. 2012;7(11), e49824. doi: 10.1371/journal.pone.0049824. [PubMed: 23185284]. [PubMed Central: PMC350240].

47. Sui C, Ma J, He X, Wang G, Ai F. Interactive effect of glutathione S-transferase M1 and T1 polymorphisms on hepatocellular carcinoma. Tumour Biol. 2014;35(8):8235-41. doi: 10.1007/s12277-014-2071-4. [PubMed: 24485248].