Advances in Bioresearch
Adv. Biores., Vol 8 (4) July 2017: 232-239

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.8.4.232239

Advances in Bioresearch

REVIEW ARTICLE

Glutathione-S-Transferase M1 and T1: Inconsistency in Association with Severe Diseases

Prem Chandra Suthar*
Anthropological Survey of India, Western Regional Centre,
Udaipur, India-313001
Faculty of Science, Pacific Academy of Higher Education and Research University,
Udaipur, India-313003
Email: - premsuthar_1@yahoo.co.in

ABSTRACT
Development of cancer involves both genetic and environmental factors. Drug or xenobiotic compound metabolizing enzymes (XMEs) like Glutathione-S-Transferase enzyme are capable of converting the active carcinogens or toxic compounds to inactive or non toxic compounds and are crucial for healthy life of an individual. The Glutathione-S-Transferase enzyme family has their role in protection against toxic chemicals including anticancer agents and is involved in the adaptive responses to electrophiles and to oxidative stress. A large number of studies about Glutathione-S-Transferase enzyme have appeared advocating the role of null genotype of Glutathione-S-Transferase M1-T1 resulting in loss of activity of the enzyme and consequently a disease phenotype. Knowledge of the distributions of these genotypes in different populations is important for the investigation of polymorphisms as risk factors in epidemiological studies, related to their geographic and inter-ethnic variation frequency. In this article we discover that the studies on Glutathione-S-Transferase enzyme M1 and T1 are necessary to have a clear picture of the disease association and inconsistency. To find out their genetic variation among populations more studies and data are required to show variable responses to different populations located in same area as well as geographically distinct zones.
Key Words: *Cancer, XMEs, Glutathione-S-Transferase, Null Genotype, Inconsistency.*

Received 03/02/2017 Revised 10/03/2017 Accepted 07/06/2017

How to cite this article:
Prem Chandra Suthar. Glutathione-S-Transferase M1 and T1: Inconsistency in Association with Severe Diseases. Adv. Biores., Vol 8 [4] July 2017: 232-239.

INTRODUCTION

Various defense mechanisms have evolved to protect cells against toxic compounds. Such protective mechanisms include drug efflux pumps, drug sequestration, drug metabolism and repair of drug-target sites. Cellular detoxification mechanisms provide protection against diverse and dangerous agents in the environment and thus maintain the health [1]. Alternated activity of proteins or enzymes is involved in drug metabolism and drug transport to resist cytotoxic drugs in the cells [2]. Drug metabolizing enzymes involved in phases I of activation and II of detoxification are the most studied biotransforming enzymes. Xenobiotic compound metabolizing enzymes (XMEs) are essential for a range of disease-free state of an individual. They are capable of converting the active carcinogens or toxic compounds to inactive or non toxic compounds [3]. These compounds include catechol estrogen metabolites [4], activated metabolites of carcinogens, PAHs, Long-term ethanol exposure, diol epoxides [5]. Polycyclic aromatic hydrocarbons (PAHs) are present in incomplete combustion process including vehicles exhaust, chimney emissions, smoked foods, cigarette smoke, and indoor heating and cooking systems [6-8]. Certain natural toxins, including mold aflatoxins, phorbol esters, and pyrrolizidine toxins, are among the most potent carcinogenic and clastogenic compounds known.

PHASE I AND II METABOLISM

Phase I involves an initial oxidation or metabolic activation of the xenobiotics by cytochrome P450 (CYP) [9-10] supergene family monooxygenases enzymes to their ultimate forms and then bind to DNA, forming

aromatic-DNA adducts that are thought to be an early step in tumorigenesis [11-12]. They activate many environmental procarcinogens by adding or exposing their functional groups [13] followed by phase II metabolism, involving conjugation reactions catalyzed by glutathione-S-transferases [14], N-acetyl transferase, epoxide hydrolase and other xenobiotics metabolizing enzymes (XMEs) [15-17] are involved in the detoxification of all of these products.

Glutathione-S-Transferase (GSTs)

The glutathione S-transferases (GSTs) characterize a key group of isoenzymes which detoxify both endogenous compounds and extraneous chemicals such as environmental contaminants, pharmaceuticals and providing protection against electrophiles and of oxidative stress products. GSTs exhibit remarkably wide substrate specificity as well as possess the ability to sequester nonsubstrate drugs and hormones. These multifunctional dimeric proteins catalyse many reactions between glutathione (GSH) and lipophilic compounds with electrophilic centers [15]. These enzymes are involved in the antioxidant systems and conjugation reactions in phase II metabolism of wide range of xenobiotics including environmental carcinogens, chemotherapeutic agents, and reactive oxygen species [18], catalyzing conjugation of reduced glutathione (GSH) with products of oxidative stress, DNA-reactive intermediates and a variety of electrophilic compounds including Polycyclic Aromatic Hydrocarbon (PAHs) [19-21]. Due to the detoxifying action, it has been suggested that these enzymes play an important role in cancer susceptibility [22-24]. Variation in drug metabolism capacity may be attributable to genetic variation in the population, or they may be due to other factors, such as enzyme induction, affected by diet or drugs, environment-gene interaction. Genetically determined susceptibility to cancer and other detoxification pathway related defects may depend on the metabolic balance between phase I and phase II enzymes which are either polymorphic within the population or inducible, or both. [1, 25-30].

Diseases under GSTs association studies

Although the etiologies of most commonly occurring cancers, recurrent miscarriages (RM) and infertility, liver defects, heart diseases, diabetes, kidney diseases cannot be explained by allelic variability at a single locus, the major burden of these body defects in the general population probably results from the complex interactions of multiple genetic and environmental factors over time. An understanding of the interplay of xenobiotic exposures, endogenous physiology, and genetic variability of GSTs will facilitate our knowledge about these etiologies and the identification of individuals who are at increased risk for developing such abnormalities.

Cancer

Most cancers are caused by exposure to environmental carcinogens and not by the inheritance of specific susceptibility genes. Studies have shown that both GSTT1 and GSTM1 enzymes protect cells from the toxic products of phase I detoxification reactions [31-32]. Individuals having the null genotype of GSTM1 and GSTT1 has a decreased capability in detoxifying some carcinogens are at increased risk of major types of cancers, including Lung cancer [33-47] Colorectal cancer [48-57], Urinary bladder cancer [58-65], Breast Cancer [66-70], Oral cancer [72-74], Multiple skin cancer [75-76], Bronchogenic carcinoma [34, 39,77], Head and neck cancer [78-80], Adenocarcinoma [77, 81], Gastric cancer [42,48,82], Acute myeloid leukemia [83], Laryngeal cancer [61], Colon cancer [52], Esophageal cancer [84], Cervical cancer [85], Chronic Myeloid leukemia [86], Prostate cancer [87], Thyroid cancer [88].

Liver cirrhosis

It has been reported that genetic polymorphism of the GSTT1 locus may be important in the inherited susceptibility to liver cirrhosis [89] because of its patho-biological association with alcohol-induced liver damage.

Endometriosis and Recurrent Miscarriages (RM)

Association between the GSTM1 null mutation and endometriosis has been reported in one study [90]. In another study twenty six (26.8%) women with endometriosis and 15 (14.7%) of the controls had the GSTM1 null genotype, which showed significant association (P=0.03) with endometriosis indicating that GSTM1 null polymorphism might have an increased susceptibility of endometriosis [91]. Allelic variants of the detoxification genes that have impaired biotransformation functions may increase susceptibility to reproductive toxicity leading to endometriosis, recurrent miscarriage (RM) or poor pregnancy outcome. Significant protective effects of phase I wild-type genotypes and association of the GSTT1 null genotype with RM has been reported and through combined analyses the importance of the balance of phase I/phase II detoxification systems has been highlighted in the etiology of RM [92].

Infertility

The possible role of GSTM1 and GSTT1 gene variants in male infertility has been already suggested with inconsistent data [93-94]. One study investigated the association between the GSTM1 and GSTT1 gene

deletion and MTHFR C677T mutation and male infertility encompassing 52 infertile and 56 fertile males they found that the carriers of double GSTM1/GSTT1 deletion and the MTHFR 677CC genotype are at higher risk of infertility [95]. Sperms are susceptible to oxidative damage and excessive reactive oxygen species (ROS) generation may lead to subfertility or infertility. A literature-based meta-analysis of 6934 individuals case-control study showed the GSTM1 null genotype was significantly associated with idiopathic oligozoospermia, while the null genotype of GSTT1 was significantly associated with normozoospermia and azoospermia [96].

Chronic kidney disease (CKD)

It has been found that the patients with GSTM1 or GSTT1 null genotypes are more vulnerable to oxidative stress compared with those who possess normal gene expression in chronic kidney disease [97]. There is significant association between the genetic risk factors of GSTT1 and GSTM1 genes in the end stage renal disease (ESRD), and low level of GST enzyme in the ESRD patients so the GSTM1 and GSTT1 (null) genotypes were suggested independent risk factors for ESRD [98].

Coronary artery disease (CAD)

A Meta analysis to assess the association between polymorphism of GSTM1 null genotype and coronary artery disease risk found a significantly increased myocardial infarction risk [99].

Type2 diabetes

Significant association was seen in GSTM1 null and GSTP1 (I/V) and multiple association in GSTM1 null, T1 present and P1 (I/I), in a representative cohort of Indian patients with T2DM. The research revealed that these polymorphisms can be screened in the population to determine the diabetic risk [100].

Inconsistency about the association

Several polymorphic genes encoding the XMEs involved are currently being investigated as a possible basis for inter-individual variability in disease susceptibility. But studies provide inconsistent associations among ethnically/regionally different populations [43,101-103]. Both positive and negative results have been reported for associations between GSTM1 and GSTT1 null genotype and disease risk. The effect of the GSTM1 deletion and lung cancer among Caucasians and African Americans in Southern California suggests that, in these populations the association of the GSTM1-null deletion and breast cancer is not strong and yielded inconsistent results [51, 104-106]. Another study found that there was no increased risk associated with the GSTM1 null allele in postmenopausal breast cancer risk study in either smokers or nonsmokers [107]. No consistent associations between GSTM1 or GSTT1 genotype and colorectal cancer have been observed by other studies [42, 50, 52, 54]. In Japanese population, there is no association of endometriosis with the GSTM1 and GSTT1 null mutations [108] which is consistent with the previous reports the OXEGENE collaborative group [109]. There was also no significant relation in GSTT1 genotypes among histopathology types of lung cancers in Turkish population [46]. No association for GSTM1 null genotype in pre or postmenopausal women has been reported [110]. In Korean population also association of endometriosis with the GSTM1 mutations was not found significant [111-113]. Results suggest that the four genetic polymorphisms studied in the CYP1A1, GSTM1, GSTT1 and GSTP1 metabolic genes are not associated with lung cancer risk in total population of Caucasians from Northern Spain [114]. A Meta-analysis aimed to examine the associations GSTM1, GSTT1, and GSTP1 genetic polymorphisms with thyroid cancer risk found no significant associations for subgroup analyses performed by ethnicity and histological type concluded that these three polymorphisms are unlikely to be major determinants of susceptibility to thyroid cancer [115]. No significant association was found between lung cancer and GSTT1 deletion either overall or in Caucasians but among Asians, a positive association was found in the meta-analysis, whereas the association was not confirmed in the pooled analysis. GSTM1, GSTT1, and GSTP1 gene polymorphisms are not associated with susceptibility of developing diabetic neuropathy in T2DM Romanian patient [116]. The research on GSTs polymorphism has become challenging to draw any inference about disease risk. Thus additional research in a directed way is required.

CONCLUSIONS

Cancer has been the main target for research studies involving the Glutathione-S-Transferase polymorphism all over the world. Pregnancy loss is another problem major among Indian women and it has also been given weightage for research along with other diseases. While investigating such diseases interrelated to detoxification pathways significant results for disease association are expected because detoxification mechanism is the basic which keeps an individual healthy by means of eliminating the toxicity of the body and failing of which they can't even survive. Positive as well as negative finding have been reported in preceding years but the explanation to the inconsistency in the association with diseases

is still awaited. The main reasons for the inconsistent findings seem to be derived from the gene environment interactions and/or gene-gene interactions as hypothesized by Hamajima et al. [117]. The discrepancies can be partially explained as the result of interpopulational differences in genetic backgrounds of susceptibility and/or of geographical differences in environmental exposure to carcinogens. Though huge reviews and research articles are available on worldwide research a handful of information is available on Indian populations with reference to GSTM1 and T1 null genotype as very few studies have been conducted in this context. Therefore, extensive population-specific studies on GSTs including other polymorphic loci are needed to have an explored view of such polymorphism and their significance for particular diseases.

REFERENCES

1. Klaassen, C.D. (1996).Casarett and Doull's Toxicology. The Basic Science of Poisons. New York, McGraw-Hill, 5th edition.
2. Hayes, J.D., Wolf C.R. (1990). Molecular mechanisms of drug resistance. Biochem. J., 272, 281–295.
3. Lacko, M., Ophuis, M.B., Peters, H.M., Manni, J.J. (2009). Genetic polymorphisms of smoking-related carcinogen detoxifying enzymes and head and neck cancer susceptibility. Anticancer Res, 29, 753-761.
4. Yager, J. D. and Liehr, J. G. (1996). Molecular mechanisms of estrogen carcinogenesis. Annu. Rev. Pharmacol. Toxicol. 36, 203–232.
5. Coles, B. and Ketterer, B. (1990). The role of glutathione and glutathione transferases in chemical carcinogenesis. Crit. Rev. Biochem. Mol. Biol. 25, 47–70.
6. Monn, C., Fuchs, A., Hogger, D., Junker, M., Kogelschatz, D., Roth, N., Wanner, H.U. (1997). Particulate matter less than 10 microns (PM10) and fine panicles less than 2.5 microns (PM2.5): relationships between indoor, outdoor and personal concentrations. Sci. Total Environ. 3, 15-21.
7. Adonis, M., Riquelme, R., Rios, C., Rodriguez, L., Rodriguez, E., Martinez, V., Gil, L. (2003). PAHs and mutagenicity of inhalablc and respirable particulate matter from diesel exhaust in Santiago, Chile. Polycycl. Aromat. Comp. 23,495-514.
8. Gil, I., Martinez, V., Riquelme, R., Ancic, P., Gonzalez, G., Rodriguez, L., Adonis, M. 2003. Occupational and environmental levels of mutagenic PAHs and respirable particulate matter associated with diesel exhaust in Santiago, Chile. J. Occup. Env. Med. 45, 984-992.
9. Buhler, R., Lindros, K., von Bouslawsky, K., Karkktlinen, P., Makinen, J. and Ingelman-Sundberg, M. (1991) Perivenous expression of ethanol-inducible cytochrome P450 IIE1 in livers from alcoholics and chronically ethanol-fed rats. Alcohol Alcohol Suppl., 1, 311-315.
10. Takahashi, T., Lasker, J.M., Rosman, A.S. and Lieber, C.S. (1993) Induction of cytochrome P-4502E1 in the human liver by ethanol is caused by a corresponding increase in encoding messenger RNA. Hepatology, 17, 236-245.
11. Miller, E.C. (1978). Some current perspectives on chemical carcinogenesis in humans and experimental animals: presidential address. Cancer Res., 38, 1479 –96.
12. Lewis, D.F., Ioannides, C. and Parke, D.V. (1998) Cytochromes P450 and species differences in xenobiotic metabolism and activation of carcinogen. Environ. Health Perspect., 106, 633-641.
13. Kawajiri, K., and Fujii-Kuriyama. Y. (1991). P450 and human cancer. Jpn. J. Cancer Res.,82, 1325-1335.
14. Vanhaecke,T., Lindros,K.O., Oinonen,T., Coecke,S., Debast,G., Phillips,I.R., Shephard,E.A., Vercrayne,A. and Rogiers,V. (2000) Effect of ethanol on the expression of hepatic glutathione S-transferase: an in vivo/in vitro study. Biochem. Pharmacol., 60, 1491-1496.
15. Hayes, J.D., Pulford, D.J., (1995). The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit. Rev. Biochem. Mol. Biol. 30, 445–600.
16. Guengerich, F.P., (2000). Metabolism of chemical carcinogens. Carcinogenesis 21 (3), 345–351.
17. Boyer, T.D. (1989) The glutathione S-transferases: Na update. Hepatology, 9, 486-496.
18. Wang, G., Zhang, L. and Li, Q. (2006). Genetic polymorphisms of GSTT1, GSTM1, and NQO1 genes and diabetes mellitus risk in Chinese population. Biochem. Biophys. Res. Commun. 341, 310-313.
19. Rushmore, T. H., and Pickett, C. B. (1993) J. Biol. Chem. 268, 11475–11478
20. Smith, G., Stanley, L.A., Sim, E., Strange, R.C., Wolf, C.R. (1995). Metabolic polymorphisms and cancer susceptibility. Cancer Surv., 25, 27–65.
21. Strange, R.C. and Fryer, A.A. (1999). The glutathione S-transferases: Influence of polymorphism on cancer susceptibility. IARC Sci. Pub., 148, 231– 249.
22. Taningher, M., Malacarne, D., Izzotti, A., Ugolini, D. and Parodi, S. (1999). Drug metabolism polymorphisms as modulators of cancer susceptibility. Mutat. Res. 436, 227-261.
23. Landi, S. (2000). Mammalian class theta GST and differential susceptibility to carcinogens: a review. Mutation Research, 463, 247-283.
24. Wunsch Filho, V. and Gattas, G.J.F. (2001). Molecular biomarkers in cancer: implications for epidemiological research and public health. Cad. Saude Publica., 17: 467-480.
25. Seidegard, J. and Ekstrom, G. (1997). The role of human glutathione transferases and epoxide hydrolases in the metabolism of xenobiotics. Envir. Health Perspect,105 (suppl 4), 791–799.

26. Autrup, H. (2000). Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. Mutation Res., 464, 65–76.
27. Albert, A. (1985). Selective Toxicity. The PhysicoChemical Basis of Therapy, ed 7. London, Chapman & Hall.
28. Law, M.R.(1990). Genetic predisposition to lung cancer. Br. J. Cancer, 61,195–206.
29. Nakachi, K., Imai, K., Hayashi, S., Kawajiri, K. (1993). Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res.,53, 2994–2999.
30. Kiyohara, C., Wakai, K., Mikami, H., Sido, K., Ando, M., Ohno, Y. (2003) Risk Modification by CYP1A1 and GSTM1 Polymorphisms in the Association of Environmental Tobacco Smoke and Lung Cancer: A Case-Control Study in Japanese Nonsmoking Women. Int. J. Cancer: 107, 139–144.
31. Wiencke, J.K., Kelsey, K.T., Lamela, R.A., et al. (1990). Human glutathione S-transferase deficiency as a marker of susceptibility to epoxide-induced cytogenetic damage. Cancer Res 1990; 50:1585–90.
32. Norppa, H., Hirvonen, A., Jarventaus, H., et al. (1995). Role of GSTT1 and GSTM1 genotypes in determining individual sensitivity to sister chromatid exchange induction by diepoxybutane in cultured human lymphocytes. Carcinogenesis, 16, 1261–4.
33. Seidegard, J., Pero, R. W., Miller, D. G., Beattie, E. J. (1986). A glutathione transferase in human leukocytes as a marker for the susceptibility to lung cancer. Carcinogenesis, 7, 751-753.
34. Hayashi, S., Watanabe, J., and Kawajiri, K. (1992). High susceptibility to lung cancer analysed in terms of combined genotypes of P4501A1 and μ class glutathione-S-transfcrase genes. Jpn. J. Cancer Res., 83, 886-870.
35. Nakachi, K., Imai, K., Hayashi, S., Kawajiri, K. (1993) Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res. 53, 2994–2999.
36. Narzar-Stewart, V., Motulsky, A. G., Eaton, D. L., White, E., Homung, S. K.,Leng, Z. T., Stapleton, P., and Weiss, N. S. The glutathione S-transferase polymorphism as a marker for susceptibility to lung carcinoma. Cancer Res., 53:2313-2318, 1993.
37. Kihara, M., Kihara, M., Noda, K. (1994). Lung cancer risk of GSTM1 null genotype is dependent on the extent of tobacco smoke exposure. Carcinogenesis, 15, 415-8.
38. Zhong, S., Howie, A. F., Ketterer. B. Taylor, J., Hayes, J. D., Beckett, G. J., Wathen. C. G., Wolf, C. R., and Spurr, N. K. (1991). Glutathione-S-transferase μ locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility. Carcinogenesis,12, 1533-1537.
39. Hirvonen, A., Husgafvel-Pursiainen, K., Anttila, S., and Vainio, H. (1993). The GSTM1-null genotype as a potential risk modifier for squamous cell carcinoma of the lung. Carcinogenesis, 14, 1479-1481.
40. Anttila, S., Hirvonen, A., Husgafvel-Pursiainen, K., Karjalainen, A., Nurminen, T.,and Vainio, H. (1994). Combined effect of CYP1A1 inducibility and GSTMI polymorphism on histological type of lung cancer. Carcinogenesis, 15, 1133-1135.
41. McWilliams, J. E., Sanderson, B. J. S., Harris, E. L., Richert-Boe, K. E.. and Henner, W. D. (1995). Glutathione S-transferase M 1 (GSTM1) deficiency and lung cancer risk. Cancer Epidemiol. Biomark. Prev., 4, 589-594.
42. Deakin, M., Elder, J., Hendrickse, C., Peckham, D., Baldwin, D., Pantin, C.,Wild, N., Leopard. P., Bell, D. A., Jones, P., Duncan, H., Brannigan, K., Alldersea, J., Fryer, A. A., and Strange, R. C. (1996).Glutathione S-transferase GSTT1 genotypes and susceptibility to cancer: studies of interactions with GSTM I in lung, oral, gastric and colorectal cancers. Carcinogenesis, 17, 881-884.
43. Kiyohara, C., Yamamura, K., Nakanishi, Y., et al. (2000). Polymorphism in GSTM1, GSTT1 and GSTP1 and susceptibility to lung cancer in a Japanese population. Asian Pac. J. Cancer Prev., 1, 293-298.
44. Hung, R.J., Boffetta,P., Brockmoller,J. et al. (2003) CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis. Carcinogenesis, 24, 875-882.
45. Adonis, M., Martinez,V., Marin, P. and Gil, L.(2005). CYP1A1 and GSTM1 genetic polymorphisms in lung cancer populations exposed to arsenic in drinking water. Xenobiotica, 35(5), 519-530.
46. Demir, S. Altin, I. Demir, V. Koksal, U. Cetincelik, S. I. Dincer. (2005). The frequency of GSTT1 null genotype in Turkish population and lung cancer risk. Indian J. Hum. Genet. 11(2), 89-93.
47. Shukla, R.K., Tilak, A.R., Kumar, C., Kant, S., Kumar, A., Mittal, B., Bhattacharya, S. (2013). Associations of CYP1A1, GSTM1 and GSTT1 Polymorphisms with Lung Cancer Susceptibility in a Northern Indian Population. Asian Pac. J. Cancer Prev., 14 (5), 3345-3349.
48. Katoh, T., Nagata, N., Kuroda, Y., et al. (1996). Glutathione 5-transferase M1 (GSTM1) and T1 (GSTT1) genetic polymorphism and susceptibility to gastric and colorectal adenocarcinoma. Carcinogenesis, 17, 1855-1859.
49. Lee, E., Huang, Y., Zhao, B., et al. (1998). Genetic polymorphism of conjugating enzymes and cancer risk: GSTM1, GSTT1, NAT1 and NAT2. J. Toxicol. Sci., 23, 140-142.
50. Cotton, S. C., Sharp, L., Little, J., and Brockton, N. (2000).Glutathione S-Transferase Polymorphisms and Colorectal Cancer: A HuGE Review. Am. J. Epidemiol., 151, 7-32.
51. Zhong, S., Wyllie, A. H., Barnes, D., Wolf, C. R., Spurr, N. K. (1993). Relationship between the GSTM1 genetic polymorphism and susceptibility to bladder, breast and colon cancer. Carcinogenesis, 14, 1821-1824.
52. Gertig, D.M., Stampfer, M., Haiman, C.H., et al. (1998). Glutathione-S-transferase GSTM1 and GSTT1 polymorphisms and colorectal cancer risk: a prospective study. Cancer Epidemiol. Biomarkers Prev., 7, 1001-1005.

53. Slattery, M.L., Potter, J.D., Samowitz, W., et al. (1998). NAT2, GSTM1, cigarette smoking, and risk of colon cancer. Cancer Epidemiol. Biomarkers Prev., 7, 1079-84.
54. Butler, W.J., Ryan, P., Roberts-Thomson, I.C. (1997). Metabolic genotypes and risk for colorectal cancer increased risk in individuals with glutathione transferase theta1 (GSTT1) gene defect. Gastroenterology, 112, 542.
55. Chenevix-Trench, G., Young, J., Coggan, M., et al. (1995). Glutathione S-transferase M1 and T1 polymorphisms: susceptibility to colon cancer and age of onset Carcinogenesis, 16, 1655-1657.
56. Welfare, M., Adeokun, A.M., Bassendine, M.F., et al (1999). Polymorphisms in GSTP1, GSTM1 and GSTT1 and susceptibility to colorectal cancer. Cancer Epidemiol. Biomarkers Prev., 8, 289-282.
57. Lin, H.J., Probst-Hensch, N.M., Ingles, S.A., et al. (1995). Glutathione transferase (GSTM1) null genotype, smoking and prevalence of colorectal adenomas. Cancer Res, 55, 1224-1226.
58. Brockmoller, J., Kerb, R., Drakoulis, N., Staffeldt, B., and Roots, I. (1994). Glutathione S-transferase M1 and its variants A and B as host factors of bladder cancer susceptibility: a case-control study. Cancer Res., 54, 4103-4111.
59. Bell, D. A., Taylor. J. A., Paulson, D. F., Robertson, C. N., Mohler, J. L., and Lucier, G. W. (1993). Genetic risk and carcinogen exposure: a common inherited defect of the carcinogen metabolism gene glutathione S-transferase M1 (GSTM1) that increases susceptibility to bladder cancer. J. Natl. Cancer Inst., 85, 1159-1164.
60. Lafuente, A., Pujol, F., Carretero, P., Villa, J.P., Cuchi, A. (1993). Human glutathione S-transferase mu (GST mu) deficiency as a marker for the susceptibility to bladder and larynx cancer among smokers. Cancer Lett. 15, 68(1):49-54.
61. Daly, A. K., Thomas, D. J., Cooper, J., Pearson, W. R., Neal, D. E., and Idle, J. R. (1993) Homozygous deletion of gene for glutathione S-transferase M1 in bladder cancer. BMJ. 307, 481–482
62. Kempkes, M., Golka, K., Reich, S. et al. (1996). Glutathione-S-transferase M1 and T1 null genotype as potential risk factor for urothelial cancer of the bladder. Arch. Toxicol., 71, 123-6.
63. Schnakenberg, E., Breuer, R., Werdin, R., Dreikorn, K. and Schloot,W. (2000) Susceptibility genes: GSTM1 and GSTM3 as genetic risk factors in bladder cancer. Cytogenet. Cell Genet., 91, 234-238.
64. Singh, G., Ghosal, U.C., Bid, H.K., Mittal, R.D. (2003). Genetic polymorphism of interleukin–1 receptor antagonist gene in inflammatory bowel disease patient: A study from North India. In: Proceedings of International symposium on molecular toxicology and environmental health. 2003, Lucknow.
65. Srivastava, D.S., Mandhani, A., Mittal, R.D. (2003) Genetic polymorphism of GSTM1, GSTT1 and GSTP1 genes in bladder cancer patients: A study from North India, In: Proceedings of International symposium on molecular toxicology and environmental health.2003, Lucknow.
66. Forrester, L. M., Hayes, J. D., Millis, R., Barnes, D., Harris, A. L., Schlager, J. J., Powis, G. & Wolf, C. R. (1990). Expression of glutathione S-transferases and cytochrome P450 in normal and tumor breast tissue. Carcinogenesis, 11, 2163–2170.
67. Dunning, A., Healey, C., Pharoah, P., Teare, M., Ponder, B. and Easton, D. (1999). A systematic review of genetic polymorphisms and breast cancer risk. Cancer Epidemiol. Biomarkers Prev. 8,843–854.
68. Mitrunen, K., Jourenkova, N., Kataja, V., Eskelinen, M., Kosma, V.M., Benhamou, S., Vainio, H., Uusitupa, M. and Hirvonen, A. (2001) Glutathione-S-transferase M1, M3, P1 and T1 genetic polymorphisms and susceptibility to breast cancer. Cancer Epidemiol. Biomarkers Prev., 10, 229-236.
69. Samson, M., Swaminathan, R., Rama, R., Sridevi,V., Nancy, KN., Rajkumar, T. (2007). Role of GSTM1 (Null/Present), GSTP1 (Ile105Val) and P53 (Arg72Pro) Genetic Polymorphisms and the Risk of Breast Cancer - A Case Control Study from South India. Asian Pac. J. Cancer Prev., 8, 253-257.
70. Yu, K.D., Di, G.H., Fan, L., Wu, J., Hu, Z., Shen, Z.Z., Huang, W., Shao, Z.M. (2009). A functional polymorphism in the promoter region of GSTM1 implies a complex role for GSTM1 in breast cancer. FASEB J. 23, 2274–2287.
71. Trizna, Z., Clayman. G. L., Spitz. M. R., Briggs. K. L., and Goepfert. H. (1995). Glutathione S-transferase genotype as risk factors for head and neck cancer. Am. J. Surg., 170, 499-501.
72. Buch, S.C., Notani, P.N. and Bhisey, R.A. (2002). Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population. Carcinogenesis, 23, 803-807.
73. Nair, U.J., Nair, J., Mathew, B., Bartsch, H. (1999). Glutathione-S-transferase M1 and T1 null genotypes as risk factors for oral leukoplakia in ethnic Indian betel quid/tobacco chewers. Carcinogenesis, 20, 743-748.
74. Chatterjee, S., Rudra, T., Poddar, S., Chakrabarti, S., Sengupta, B., Biswas, D.,and Sengupta, S. (2008). GST & CYP Polymorphism Related to Tea Drinking and Oral Pathology. Int. J. Hum. Genet., 8(3), 295-299.
75. Heagerty, A., Smith, A., English, J., Lear, J., Perkins, W., Bowers, B., Jones, P., Gilford, J., Alldersea, J., Fryer, A., and Strange, R. C. (1996). Susceptibility to multiple cutaneous basal cell carcinomas: significant interactions between glutathione S-transferase GSTM1 genotypes, skin type and male gender. Br. J. Cancer 73(1), 44–48.
76. Lafuente, A., Molina, R., Palou, J., Castel, T., Moral, A., Trias, M., and The Multidisciplinary Malignant Melanoma Group (1995). Phenotype of glutathione-S-transferases (GSTM1) and susceptibility to malignant melanoma. Br. J. Cancer, 72, 324-326.
77. Seidegard, J., Pero, R. W., Markowitz, M. M., Roush, G., Miller, D. G., and Beattie, E.J. (1990). Isoenzyme(s) of glutathione transferase (class mu) as a marker for the susceptibility to lung cancer: a follow up study. Carcinogenesis, 11, 33-36.
78. Mulder, T. P. J., Manni, J. J., Roelofs, H. M. J., Peters, H. M., and Wiersma, A. (1995). Glutathione S-transferases and glutathione in human head and neck cancer. Carcinogenesis (Land.), 16, 619-624.

79. Janot, F., Massaad, L., Ribrag, V., de Waziers, I.. Beaune. P. H., Luboinski, B., Parise, O.Jr., Gouyette. A. and Chabot. G. G. (1993). Principal xenobiotic-metabolizing enzyme systems in human head and neck squamous cell carcinoma. Carcinogenesis, 14, 1279-1283.
80. Matthias, C., Jahnke, V., Fryer, A.A. and Strange, R.C. (2002). First results on the influence of polymorphisms at glutathione-S-transferase, cytochrome P450 and tumor necrosis factor gene loci on the development of multiple head and neck cancer. Laryngo-rhino-otologie, 82, 25-30.
81. Alexandrie, A-K., Ingelman Sundberg, M., Seidegard,J., Tornling, G., and Rannug, A. (1994). Genetic susceptibility to lung cancer with special emphasis on CYP1A1 and GSTM1: a study on host factors in relation to age at onset, gender and histological cancer types. Carcinogenesis, 15, 1785-1790.
82. Sctiawan, V.W., Zhang, Z.F., Yu, G.P., et al. (2000). GSTT1 and GSTM1 null genotypes and risk of gastric cancer: A case control study in a Chinese population. Cancer Epidemiol. Biomarkers Prev., 9, 73 -80.
83. Mossallam G.I., Abdel Hamid T. M., and Samra, M. (2006). Glutathione S-Transferase GSTM1 and GSTT1 Polymorphisms in Adult Acute Myeloid Leukemia; Its Impact on Toxicity and Response to Chemotherapy. J. Egypt Natl. Canc. Inst., 18(3), 264-273.
84. Wang, L.D., Zhou, Q., Feng, C.W., Liu, B., Qi, Y.J., Zhang, Y.R., Gao, S.S., Fan, Z.M., Zhou, Y., Yang, C.S., Wei, J.P., Zheng, S. (2002). Intervention and follow-up on human esophageal precancerous lesions in Henan, northern China, a high-incidence area for esophageal cancer. Gan To Kagaku Ryoho. 29 (1), 159-172.
85. Sharma, J.K., Sharma, A., Murthy, N.S., Mitra, A.B. (2003). Polymorphisms at GSTM1 and GSTT1 gene loci and susceptibility to cervical cancer in Indian population, In: Proceedings of International symposium on molecular toxicology and environmental health. 2003, Lucknow.
86. Mahmoud, S., Labib, D.A., Khalifa, R.H., Khalil, R.E.A., and Marie, M. A. (2010). CYP1A1, GSTM1 and GSTT1 genetic Polymorphism in Egyptian chronic myeloid leukemia patients. Res. J.Immunol., 3(1), 12-21.
87. Quinones, L.A., Irarrazabal, C.E., Rojas, C.R., Orellana, C.E., Acevedo, C., Huidobro, C., Varela, N.E., Caceres. D.D. (2006). Joint effect among p53, CYP1A1, GSTM1 polymorphism combinations and smoking on prostate cancer risk: an exploratory genotype-environment interaction study. Asian J. Androl., 8 (3): 349–355.
88. Morari, E.C., Leite, J.L., Granja, F., da Assumpcao, L.V., Ward, L.S. (2002). The null genotype of glutathione-S-transferase M1 and T1 locus increases the risk for thyroid cancer. Cancer Epidemiol. Biomarkers Prev., 11, 1485–1488.
89. Savolainen, V.T., Pjarinen, J., Perola, M., Penttila, A. and Karhunen, P.J. (1996) Glutathione-S-transferase GST M1 "null" genotype and the risk of alcoholic liver disease. Alcohol Clin. Exp. Res., 20, 1340-1345.
90. Baranova, H., Bothorishvilli, R., Canis, M., Albuisson, E., Perriot, S., Glowaczowr, E., Bruhat, M.A., Baranov, V. and Malet, P. (1997). Glutathione S-transferase M1 gene polymorphism and susceptibility to endometriosis in a French population. Mol. Hum. Reprod., 3,775–780.
91. Roya, R., Baludu, G. S., Reddy, B. S. (2009). Possible aggravating impact of gene polymorphism in women with endometriosis. Indian J. Med. Res, 129, 395-400.
92. Parveen, F., Faridi, R.M., Das, V., Tripathi, G., and Agrawal. S. (2010). Genetic association of phase I and phase II detoxification genes with recurrent miscarriages among North Indian women. Mol. Hum. Reprod., 16(3) , 207–214.
93. Aydemir, B., Onaran, I., Kiziler, A.R., Alici, B., and Akyolcu, M.C. (2007). Increased oxidative damage of sperm and seminal plasma in men with idiopathic infertility is higher in patients with glutathione S-transferase Mu-1 null genotype. Asian. J. Androl. 9, 108-115.
94. Aydos, S.E., Taspinar, M., Sunguroglu, A., and K. Aydos (2009). Association of CYP1A1 and glutathione S-transferase polymorphisms with male factor infertility. Fertil. Steril. 92, 541-547.
95. Dordevic, V, A. Nikolic, M. Ljujic, A. Nestorovic, M. Ristanovic, C. Tulic And D. Radojkovic. (2010). Combined Effect of GSTM1 Gene Deletion, GSTT1 Gene Deletion and MTHFR C677T Mutation in Male Infertility. Arch. Biol. Sci., Belgrade, 62 (3), 531-530,
96. Tremellen, K. (2008). Oxidative stress and male infertility--a clinical perspective. Hum. Reprod. Update. 14(3):243-58.
97. Farouk, H., Kandil, D., Kamel, S., Elghoroury, E.A., Elshamaa, M.F., Sabry, S., Galal, A. (2013). Effect of GSTM1 and GSTT1 Deletions in the Development of Oxidative Stress in Children with Chronic Kidney Disease. **J.** Clin. **Basic** Cardiol., 16 (1-4), 1-5.
98. Afaf ELS., AbdeL-Aziz, A. F., and Basma AL. (2013). Glutathione S-Transferase Enzyme (GSTT1 and GSTM1) Gene Polymorphisms and Oxidative Stress in Egyptian Patients with End Stage Renal Disease. Int. J. Biochem. Res. Rev. 3(4) 315.
99. Yang, M., Zhao, J., Xing, L., Shi, L. (2014). Association between GSTM1 null genotype and coronary artery disease risk: a meta-analysis. Med. Sci. Monit. 1(20):1550-1555.
100. Bid, H.K., Konwar, R., Saxena, M., Chaudhari, P., Agrawal, C.G., Banerjee, M. (2010) Association of glutathione S-transferase (GSTM1, T1 and P1) gene polymorphisms with type 2 diabetes mellitus in north Indian population. J. Postgrad. Med. , 56(3), 176-81.
101. Gonzalez, F. (1995). Genetic polymorphism and cancer susceptibility: Fourteenth Sapporo Cancer Seminar. Cancer Res., 55, 710–715.
102. Rebbeck, T.R. (1997). Molecular Epidemiology of the Human Glutathione S-Transferase Genotypes GSTM1 and GS7T1 in Cancer. Cancer Epidemiol. Biomarkers Prev., 6, 733-743.

103. Houlston, R.S. (2000). CYP1A1 polymorphisms and lung cancer risk: a meta-analysis. Pharmacogenetics, 10, 105-114.
104. Bailey, L.R., Roodi, N., Verrier, C.S., Yee, C.J., Dupont, W.D. and Parl, F.F. (1998). Breast cancer risk and CYP1A1, GSTM1, and GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. Cancer Res. 58, 65-70.
105. Helzlsouer, K. J., Selmin, O., Huang, H., Strickland, P. T., Hoffman, S., Alberg, A. J., Watson, M., Comstock, G. W. & Bell, D. A. (1998). Association between glutathione S-transferase M1, P1, and T1 genetic polymorphisms and development of breast cancer. J. Natl. Cancer Inst. 90, 512–518.
106. Kelsey, K. T., Hankinson, S. E., Colditz, G. A., Springer, K., Garcia-Closas, M., Spiegelman, D., Manson, J. E., Garland, M., Stampfer, M. J., Willett, W. C., Speizer, F. E. & Hunter, E. J. (1997). Glutathione S-transferase deletion polymorphism and breast cancer: results from prevalent versus incident cases. Cancer Epidemiol. Biomark. Prev. 6, 511–515.
107. Ambrosone, C. B., Freudenheim, J. L., Graham, S., Marshall, J. R., Vena, J. E., Brasure, J. R., Laughlin, R., Nemoto, T., Michalek, A. M., Harrington, A., Ford, T. D. & Shields, P. G. (1995a). Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. Cancer Res. 55, 3483–3485.
108. Morizane, M., Yoshida, S., Nakago, S., Hamana, S., Maruo, T. and Kennedy, S. (2004). No association of endometriosis with glutathione S-transferase M1 and T1 null mutations in a japanese population. J. Soc. Gynecol. Investig. 11,118–121.
109. Hadfield, R.M., Manek, S., Weeks, D.E., Mardon, H.J., Barlow, D.H. and Kennedy, S.H. and OXEGENE Collaborative Group (2001). Linkage and association studies of the relationship between endometriosis and genes encoding the detoxification enzymes GSTM1, GSTT1 and CYP1A1. Mol. Hum. Reprod. 7, 1073–1078.
110. Millikan, R., Pittman, G., Tse, C.K., Savitz, D.A., Newman, B., Bell, D. (2000). Glutathione S-transferase M1, T1 and P1 and Breast Cancer. Cancer Epidemiol Biomarkers Prev., 9, 567-573.
111. Hur, S.E., Lee, J.Y., Moon, H.S., Chung, H.W. (2005). Polymorphisms of the genes encoding the GSTM1, GSTT1 and GSTP1 in Korean women: no association with endometriosis. Mol. Hum. Reprod., 11,15-19.
112. Baxter, S.W., Thomas, E.J., Campbell, I.G. (2001). GSTM1 null polymorphism and susceptibility to endometriosis and ovarian cancer. Carcinogenesis, 22, 63-65.
113. Arvanitis, D.A., Koumantakis, G.E., Goumenou, A.G., Matalliotakis, I.M., Koumantakis, E.E. and Spandidos, D.A. (2003). CYP1A1, CYP19, and GSTM1 polymorphisms increase the risk of endometriosis. Fertil. Steril., 79 (1),702-709.
114. Lopez-Cima, M.F., Alvarez-Avellon, S.M., Pascual, T., Fernández-Somoano, A. and Tardon, A. (2012). Genetic polymorphisms in CYP1A1, GSTM1, GSTP1 and GSTT1 metabolic genes and risk of lung cancer in Asturias. BMC Cancer, 12, 433.
115. Li, J., Long, J., Hu, Y., Tan, A., Guo, X., Zhang, S. (2012). Glutathione S-transferase M1, T1, and P1 polymorphisms and thyroid cancer risk: a meta-analysis. Cancer Epidemiol., 36(6), e333-40.
116. Stoian, A., Banescu, C., Balasa, R.I., Motataianu, A., Stoian, M., Moldovan, V.G., Voidazan, S., and Dobreanu, M. (2015). Influence of GSTM1, GSTT1, and GSTP1 Polymorphisms on Type 2 Diabetes Mellitus and Diabetic Sensorimotor Peripheral Neuropathy Risk. Dis. Markers. Volume 2015 , Article ID 638693.
117. Hamajima, N., Yuasa, H., Matsuo, K., Kurobe, Y. (1999). Detection of gene-environment interaction by case-only studies. Jpn. J. Clin. Oncol., 29, 490-93.