Genetic Polymorphism of GSTM1 and GSTT1 and Risk of Prostatic Carcinoma - a Meta-analysis of 7,281 Prostate Cancer Cases and 9,082 Healthy Controls

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Abstract

Genetic polymorphisms constitute one of the reasons behind the racial variation in prostate cancer occurrence. Published studies regarding genetic associations of glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1) null deletion polymorphisms with prostatic carcinoma have generated inconsistent results among different populations. To date, even a single meta-analysis is not available representing the association of these genes with prostate cancer in different ethnic groups. Therefore, the aim of the current study was to provide a clear picture of GSTM1 and GSTT1 null deletion and risk of prostate cancer among different ethnic groups (i.e. Asians, Europeans, Americans, Africans and Eurasians). A systematic search was performed with the help of various search engines to find out all the recent studies (2004 to 2015) evaluating the role of GSTM1 and GSTT1 deletion in prostate cancer development. Odds ratios (ORs) with 95% confidence interval (CI) of a total of 34 studies with 7,281 cases and 9,082 controls was analyzed using STATA and MedCalc software. Overall, GSTM1 deletion (OR 3.67; CI 1.39-9.85; P= 0.001) was strongly associated with prostatic cancer. In the subgroup analysis GSTM1 null deletion was also significantly associated with prostate cancer among Asians (OR 4.84; CI 1.08-21.5; P= 0.03), Eurasians (OR 17.69; CI 9.87-31.70; P< 0.001) and Americans (OR 0.11; CI 0.01-1.06; P= 0.05). No association was observed among Europeans (P= 0.90), Africans (P= 0.40). As a whole GSTT1 null deletion (OR 0.85; CI 0.28-2.58; P= 0.77) did not show any significant association with prostate cancer risk among different populations. When the data were stratified into different groups, however, Africans demonstrated a significant association of GSTT1 null deletion (OR 1.95; CI 1.57-2.39; P<0.001) with prostate cancer, whereas no association was found among Asians (P= 0.90), Americans (P= 0.50), Europeans (P= 0.89) and Eurasians (P= 1.0). In conclusion, both GSTM1 and GSTT1 may contribute to prostate cancer development but GSTM1 may prove to be a stronger candidate risk factor.

Keywords: Prostate cancer - risk factors - GSTM1 - GSTT1 - polymorphism - genetic variation

Introduction

Prostate cancer is the major public health issue worldwide because of its increased mortality and morbidity rates. It is evaluated as a most frequently observed solid neoplasm. It is the second leading cause of cancer related deaths among Europeans, Americans and to some extent in Africans as well (Foley et al., 2004; Crawford et al., 2015). Environmental factors together with the genetic predisposition plays vital role in prostate cancer development however, its etiology remains unclear.

Incident rates of prostate cancer vary remarkably among different geographic regions and ethnic groups. Highest incidence rate was investigated among Americans, intermediate among Africans and Caucasians while lowest among Asians (Pan et al., 2012; Rebecca et al., 2013). Different ethnic variations suggests that genetic and environmental factors may be involved in the development of prostate cancer. Epidemiological and clinical data suggests that prostate cancer development is a multiphase process (Detchokul and Frauman, 2011). Various lifestyle and environmental factors, including smoking, pollutant exposure, diet, and increased age as well as racial and geographical factors have been evaluated as possible contributors to prostate cancer risk.

Family history together with the individual’s susceptibility to the development of prostate cancer plays an important role in cancer initiation and progression (Cao et al., 2011). Genetic variations can modify environmental exposures effect and explains the cause...
behind the difference among the incidence rate of prostate cancer throughout the world (Amankwah et al., 2012). Prostate cancer susceptibility can possibly be evaluated by polymorphisms in various metabolic genes specifically by the inter-individual differences of procarcinogens bio-activation and carcinogens detoxification (Pan et al., 2012).

Glutathione S-transferases (GSTs) comprises a superfamily of multifunctional and ubiquitous phase II metabolic enzymes (Ali et al., 2015). They are involved in the detoxification of various exogenous and endogenous carcinogens but also plays an important role in the activation and inactivation (oxidative metabolites) of carcinogenic compounds to protect the DNA from any type of oxidative damage. It has been observed through a huge number of publications among different populations that GSTs were involved in cancers development. Enzymes are extensively distributed in nature and present in all the eukaryotic species so, genetic differences may affect the GSTs activity level and cancer susceptibility at individual’s level (Zhang et al., 2014). There are eight different classes of GSTs discovered so far including alpha, kappa, mu, omega, pi, sigma, theta, and zeta. Genetic polymorphism of these genes may affect carcinogen activation, detoxification and DNA repair. GSTM1 and GSTT1 genes are located on chromosome 1p13.3 and 22q11.23 respectively (Oakley, 2011). Both of the two genes exhibit inherited homozygous deletion polymorphism which has been associated with complete loss of enzymatic activity. Hence individuals are at greater risk towards the development of malignancies (Economopoulos et al., 2010; Huang et al., 2015).

GSTM1 is involved in the detoxification of different electrophilic substances comprising of carcinogens like ethylene oxide, styrene, polycyclic aromatic hydrocarbons and epoxides. The expression of GSTM1 could be controlled by hormones and induced by propythiouracil or phenobarbital. It is thought that GSTM1 might be associated with detoxification of various xenobiotics, free radical mediated cellular damage and defensive against oxidative stress (Masood et al., 2011; Shukla et al., 2013; Zhang et al., 2014). A huge number of studies have been reported regarding the genetic status of GSTM1 and GSTT1 polymorphism and prostate cancer development. But the impact of polymorphisms of these two genes on prostate cancer is still unclear because of inconsistent results among different populations (Yang et al., 2013).

Other important factors contributes in the low validity of results among different populations (Yang et al., 2013). Various combinations of keywords used were “glutathione S transferase M1” or “GSTM1”, “glutathione S transferase T1” or “GSTT1”, “prostate cancer” or “urothelial cancer”, “prostate carcinoma” or neoplasm”, “genetic polymorphism” or “polymorphisms” or “variations”. The reference list of different review articles and case control studies were also scanned for eligible studies.

**Eligibility of study**

**Eligibility criteria includes:** (i) Only full text available research articles with case-control studies. (ii) English language articles were included in this meta-analysis (iii) Studies focusing specifically on polymorphisms of GSTM1 and GSTT1 with prostate cancer were considered. (iv) Odds ratio (OR) with corresponding confidence interval (95% CI) of the selected studies were used to statistically quantify the associations of GSTM1, GSTT1 and prostatic carcinoma.

**Exclusion criteria comprises of:** (i) editorials, review articles and meta-analysis. (ii) Studies that used GSTM1 and GSTT1 gene polymorphisms to observe severity, survival, progression and response to respective treatment with prostate cancer. (iii) Studies without genotyping (iv) Family based studies were also not included in this meta-analysis. (v) Studies reporting association of GSTs with benign prostate hyperplasia. Study scheme was illustrated in the form of a flow diagram and shown in Figure 1.

**Data Extraction**

Two researchers independently extracted data and resolved the disagreements through consensus. Following information was extracted from the selected studies: Authors, publication year, geographical location (country), design of study, number of controls and cases, GSTM1 and GSTT1 deletion polymorphism. Different ethnic decants like Asians, Europeans, Americans, Africans and Eurasians were categorized into groups. Individual

**Materials and Methods**

**Search strategy**

A comprehensive search of NCBI, PUBMED, EMBASE, Wangfang databases and Web of science databases (2004 to November 2015) was performed to elucidate the association of GSTM1 and GSTT1 gene polymorphisms with the risk of prostate carcinoma.

Various combinations of keywords used were “glutathione S transferase M1” or “GSTM1”, “glutathione S transferase T1” or “GSTT1”, “prostate cancer” or “urothelial cancer”, “prostate carcinoma” or neoplasm”, “genetic polymorphism” or “polymorphisms” or “variations”. The reference list of different review articles and case control studies were also scanned for eligible studies.

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![Figure 1. Flow Chart of Literature Search](image-url)
authors, patients or controls were not contacted for any information extracted from published articles.

**Statistical analysis**

The strength of association among GSTM1 and GSTT1 deletion polymorphism and prostate cancer risk was measured by odds ratio (OR) with 95% confidence interval (CI). Cochrane Q test was used to measure heterogeneity. Both random effects model and fixed effects model were used for the estimation of odds ratio. When no heterogeneity was obtained fixed effects model was a preferred choice (DerSimonian and Laird, 1986). Statistical analysis was done by using STATA13.0 software and MedCalc. Results with a P value of less than 0.05 were taken as statistically significant.

**Results**

A database was constructed from the information extracted by considering the inclusion and exclusion criteria from available articles published in 2004 to November 2015. Necessary data was arranged in Table 1, which includes country, year of publication, number of cases and controls, Odds ratio (OR), confidence interval (CI) and p value of relationship of GSTM1 and GSTT1 deletion with risk of prostatic carcinoma as well.

Excluding overlapping data, total 34 studies with

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7281 cases and 9082 controls regarding the GSTM1 and GSTT1 polymorphism with the risk of prostatic carcinoma were included in this meta-analysis. All research articles selected prostate cancer patients on the bases of histopathology reports or prostatectomy. Overall 33 studies represent the relationship of GSTM1 with prostate cancer while 25 case studies were included to analyze the association of prostate cancer risk and GSTT1 deletion polymorphism (table 1). Among them 18 studies were of Asians, 7 Americans, 3 Europeans, 3 Africans and 2 was of Eurasian origin because of the geographical location of Turkey (a country between Asia and Europe). Uptil now, no such review is available which sheds light on the role of these genes with prostate cancer in different populations separately.

Test of heterogeneity

The heterogeneity of GSTM1 and GSTT1 polymorphism with prostatic carcinoma was analyzed for 33 and 25 selected case control studies respectively. The results showed no heterogeneity of GSTM1 and GSTT1 polymorphisms and prostatic carcinoma. Therefore, fixed-effects model was used to calculate the summary odds ratios for both of the genes deletion polymorphism.

Quantitative data analysis

The quantitative analysis was summarized in Table 2 representing the summary odds ratio of GSTM1 and GSTT1 deletion polymorphism related to prostatic carcinoma with different ethnic groups. The data was not only analyzed by combining all the studies on the bases of 7281 cases and 9082 controls but also by organizing into different ethnic groups like Asians, Americans, Europeans, Africans and Eurasians as well.

GSTM1 deletion and prostate cancer

The results illustrated an increased association of GSTM1 deletion polymorphism (OR 3.67; CI 1.39-9.85; P= 0.001) and prostatic carcinoma with a total of 33 studies including 7118 cases and 8880 controls. In subgroup analysis for Asians (OR 4.84; CI 1.08-21.5; P=
an increased risk of prostate cancer with the deletion polymorphism of GSTM1 was observed. The results also depicted an increased risk of GSTM1 deletion (OR 0.11; CI 0.01-1.06; P= 0.05) with prostate cancer among Americans. In this meta-analysis no association have been reported, when the data was stratified for GSTM1 deletion and risk of prostate cancer among Europeans (OR 4.0; CI 0.13-119; P=0.42) and Africans (OR 0.25; CI 0.008-7.4; P= 0.40). All the results were explained statistically in table 2.

**Discussion**

Prostate cancer incidence varies racially and geographically (Siegel et al., 2015) and to find out its etiology both environmental and genetic factors were considered (Latil et al., 2001). It is well reported that individual susceptibility to cancer varies even with the same cancer and environmental conditions. Therefore, it is necessary to study the causative agents (genetic factors) at-least in different populations to explore the exact mechanism of carcinogenesis involved in prostate cancer development (Yang et al., 2013). GSTM1 and GSTT1 have diverse substrate specifications and are considered as active candidates for carcinogenesis. Because their null deletion polymorphism results in the loss of enzymatic activity and therefore, individuals are considered as active candidates for carcinogenesis. In conclusion, GSTM1 deletion polymorphism is strongly associated with prostate cancer development whereas GSTT1 null genotype was a low penetrant risk factor. GSTT1 deletion polymorphism may be a strong candidate for prostatic carcinoma among Africans.

**Acknowledgements**

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**References**

Agalliu I, Lin DW, Salinas CA, et al (2006). Polymorphisms in the glutathione S-transferase M1, T1, and P1 genes and polymorphism and prostatic carcinoma. In sub-group analysis, there were 18 studies of Asians (2093 cases and 3002 controls), 7 of Americans (cases 3614 and controls 3778), 3 of Europeans (707 cases and 905 control) and Africans (452 cases and 921 controls) each and 2 was of Eurasians with 252 cases and 276 controls. It was observed that on the whole GSTM1 deletion polymorphism is strongly associated with the development of prostate cancer (Figure 2) in mixed population. GSTM1 null deletion was also significantly associated with Eurasians, Americans and Asians as represented in table 2. No association of GSTM1 deletion and risk of prostatic carcinoma was observed among Europeans and Africans. However, the results showed statistically non-significant association of GSTM1 deletion polymorphism with the risk of prostate cancer in mixed population (Figure 3). But when sub-group analysis was performed GSTT1 deletion genotype revealed significant association with prostate cancer development among Africans. Whereas in other populations like Americans, Europeans, Asians and Eurasians GSTT1 null genotype was not statistically associated with prostatic carcinoma.

This is the first meta-analysis illustrating the role of GSTM1 and GSTT1 deletion polymorphism with prostate cancer in such a diverse populations collectively as well as separately. The findings provide evidence for the importance of GSTs in the development of carcinogenesis. In addition, GSTs have been proved as strong candidates for cancer development in colon, kidney and lungs (Liu et al., 2012; Wang et al., 2012; Masood et al., 2013; Huang et al., 2015). Whereas some of the cancers like oral are not associated with the deletion of GSTM1 and GSTT1 (Zhang et al., 2011). Our results that GSTM1 null deletion was associated with cancer development was also supported by another meta-analysis conducted only on Asian population (Cao et al., 2015).

Some of the possible limitations in this meta-analysis includes small sample size of selected studies. This meta-analysis includes only open access studies which are in English language. So, many studies available in Chinese and other language and those whose full length articles were not available does not included. So, there might be some publication bias exists. Gene and its relationship with the environmental factors was not explored due to lack of data.

In conclusion, GSTM1 deletion polymorphism is strongly associated with prostate cancer development whereas GSTT1 null genotype was a low penetrant risk factor. GSTT1 deletion polymorphism may be a strong candidate for prostatic carcinoma among Africans.


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