RESEARCH ARTICLE

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 the 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 sub group 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=0.42) and Africans (P= 0.40). As a whole GSTT1 null deletion (OR 0.85; CI 0.28-2.58; P= 0.77) did not show anyt 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

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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

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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 include small sample size and low statistical power. Therefore, we are aimed to estimate the accurate strength of association between GSTM1, GSTT1 and prostate cancer by conducting a meta- analysis of recent studies.

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.

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

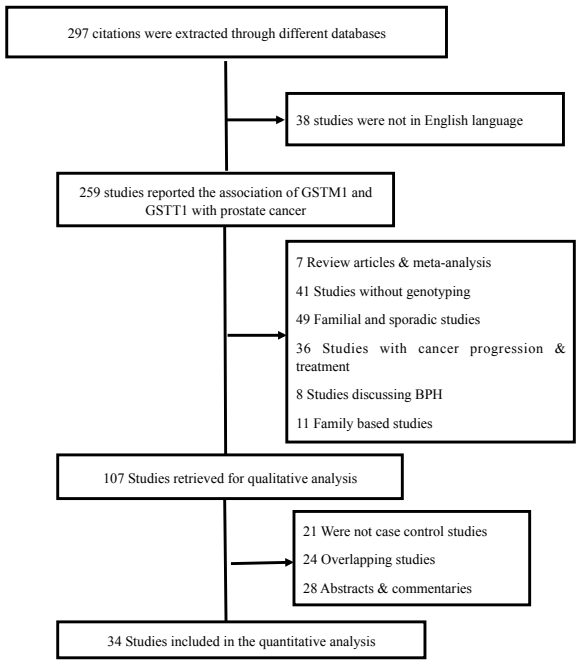

Figure 1. Flow Chart of Literature Search

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

Table 1. Study Characteristics Included in the Meta-Analysis

Country	Cases	Controls	GSTM1= OR (CI) P value	GSTT1 = OR (CI) P value	Reference
India	103	117	(1.54- 4.67) p=0.001	(2.03 – 8.34) p=0	Mittal et al., 2004
USA (New York)	428	537	1.04 (0.71- 1.52)	1.51 (0.98- 2.31)	Joseph et al., 2004
Southern Europe	150	185	1.20 (0.75-1.90) p= 0.42	p= 0.038	Medeiros et al., 2004
Turkey	100	107	1.55 (0.73–3.30)		Aktas et al., 2004
South India	75	100	1.79 (0.78-4.11) p=0.18		Vijayalakshmi et al., 2005
Japan	190	294	0.76 (0.52–1.12)	1.39 (0.95–2.03)	Komiya et al., 2005
China	81	90	1.48 (0.81-2.71) p=0.19	0.99 (0.54-1.80) p=0.97	Ya-lin et al., 2005
China	83	115	1.9 (1.10-1.34) p=0.025		Guan et al., 2005
China	96	121	p=0.04		Lai et al., 2005
Chile	103	132	1.1 (0.12–10.02) p=0.02	6.2 (0.51–75.89) p=0.19	Caceres et al., 2005
China	163	202	-	2.23 (1.09- 4.57)	Yang et al., 2006
India	54	105	2.34 (1.22-4.69) p=0.01	2.37 (1.19-4.72) 0.014	Mittal et al., 2006
USA (San Francisco)	439	479	1.0 (0.7-1.3)	0.9 (0.6-1.3)	Nock et al., 2006
Turkey	152	169	4.08 (2.50-6.69) p=0.00001	1.23 (0.69–2.20) p=0.46	Silig et al., 2006
Washington	590	538	1.54 (1.19-2.01)		Agalliu et al., 2006
New York	395	244	p=0.31		Nock et al., 2007
Africa	134	134	1.4 (0.7 - 2.5)	2.6 (1.4 - 4.9)	Mallick et al., 2007
Brazil	125	100	p=0.7883	p= 0.073	Lima et al., 2008
China	208	230	1.0 (1.1–3.4) p=0.033		Li et al., 2008
Africa	208	665	1.08 (0.65-1.82) p=0.718	1.15 (0.66-2.02) p=0.62	Lavender et al., 2009
Slovakia	129	228	0.87 (0.55-1.37) p=0.52	0.93 (0.51-1.66) p=0.8	Sivonova et al., 2009
Tunisia	110	122	0.89 (0.66–1.88)	2.17 (1–3.79)	Souiden et al., 2010
Germany	428	492	0.74 (0.55-0.99) p=0.38	0.75 (0.42-1.36) p= 0.53	Steinbrecher et al., 2010
Iran	65	65	0.54 (0.27-1.08) p= 0.08	0.66 (0.27-1.62) p=0.36	Ansari et al., 2010
India	150	172	2.45 (1.56-3.82) p=0.00008	2.39 (1.36-4.20) p=0.001	Thakur et al., 2011
India	57	46	p= 0.01		Kumar et al., 2011
Iran	110	100	0.88 (0.48–1.64) p=0.70	0.87 (0.45–1.64) p=0.66	Ashtiani et al., 2011
Iran	168	336	3.28 (2.47-5.64) p=0.005	3.21 (2.52-5.64) p=0.005	Safarinejad et al., 2011
Korea	166	327	1.53 (1.20- 1.96)p=0.001	1.04 (0.81-1.33) p=0.849	Kwon et al., 2011
USA	204	360	p= 0.03	p= 0.01	Hemelrijck et al., 2012
USA	497	760	0.94 (0.74–1.16) p=0.19	1.68 (1.19–2.38) p=0.06	Catsburg et al., 2012
USA	936	760	1.15 (0.95–1.45) p=0.19	1.18 (0.92–1.52) p=0.06	Catsburg et al., 2012
Pakistan	84	300	0.78 (0.4-1.29) P>0.05	0.87 (0.4-1.56) P>0.05	Masood et al., 2014
Pakistan	300	350	0.78 (0.3-1.5) p=0.14	0.89 (0.6-1.2) p=0.54	Malik et al., 2015

Table 2. Summary of Odds Ratios (ORs) and Confidence Intervals (CIs)

Polymorphism	Cases/ Controls	Heterogeneity Test	Cochran's Q	Summary OR (95% CI)	Hypothesis Test Z	P
Total studies for GSTM1	7118/8880	P= 0.29	1.125	3.67 (1.39-9.85)	14.84	P=0.001
Total studies for GSTT1	5677/7379	P= 0.84	0.04	0.85 (0.28-2.58)	0.28	P=0.77
Subgroup analysis by ethnicity	for GSTM1					
Asians	2093/3002	-	-	4.84 (1.08-21.5)	2.06	P=0.03
Americans	3614/3778	-	-	0.11 (0.01-1.06)	1.9	P=0.05
Europeans	707/905	-	-	4.00 (0.13-119)	0.80	P=0.42
Africans	452/921	-	-	0.25 (0.008-7.4)	0.76	P=0.40
Eurasians	252/276	-	-	17.6 (9.87-31.7)	9.66	P<0.001
Subgroup analysis by ethnicity	for GSTT1					
Asians	1737/2590	-	-	0.99 (0.89-1.10)	0.12	P=0.90
Americans	2629/2996	-	-	0.5 (0.06-3.84)	0.66	P=0.50
Europeans	707/905	-	-	0.99 (0.85-1.14)	0.13	P=0.89
Africans	452/921	-	-	1.95 (1.57-2.39)	6.24	P<0.001
Eurasians	152/169	-	-	1.00 (0.73-1.36)	0.00	P=1.00

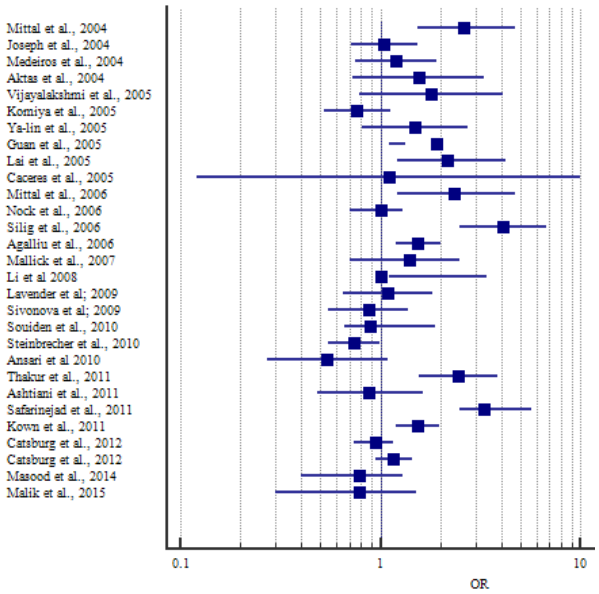

Figure 2. Forest Plot Analysis Showing an Association between GSTM1 Deletion and Risk of Prostatic Carcinoma

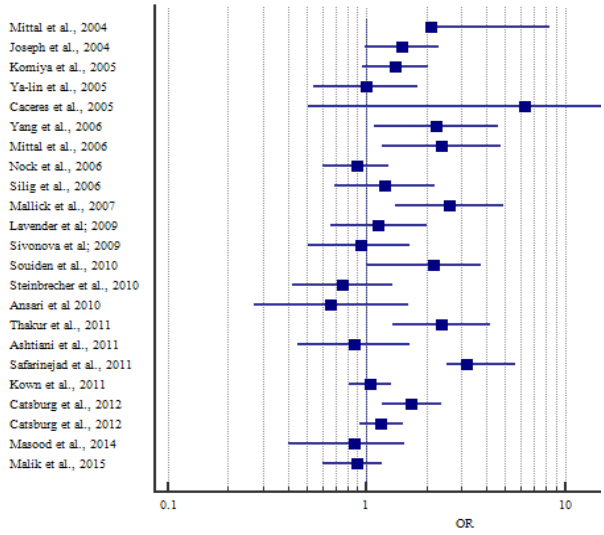

Figure 3. Forest Plot Analysis Showing No Association between GSTT1 Deletion and Risk of Prostatic Carcinoma

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=

0.03) and Eurasians (OR 17.69; CI 9.87-31.70; P< 0.001) 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 (0R 0.25; CI 0.008-7.4; P= 0.40). All the results were explained statistically in table 2.

GSTT1 deletion and prostate cancer

Total 25 studies with 5677 cases and 7379 controls were obtained to analyze the association of GSTT1 null genotype with prostatic carcinoma. Overall, statistically non-significant results were obtained for GSTT1 deletion polymorphism (OR 0.85; CI 0.28-2.58; P= 0.77) and risk of prostate cancer in the total population. When subgroup analysis was conducted GSTT1 null deletion polymorphism and prostate cancer risk was also found not to be statistically associated with Asians (OR 0.99; CI 0.89-1.10; P= 0.90), Americans (OR 0.5; CI 0.06-3.84; P=0.50), Europeans (OR 0.99; CI 0.85-1.14; P= 0.89) and Eurasians (OR 1.0; CI 0.73-1.36; P=1.0). While, the results showed significant association of GSTT1 null deletion polymorphism with the risk of prostatic carcinoma in (OR 1.95; CI 1.57-2.39; P<0.001) among Africans.

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 at greater risk towards the cancer development (Malik et al., 2015). In the light of evidences, it was necessary to explore the clear picture of GSTM1 and GSTT1 null deletion relationship with prostate cancer by performing a detailed review of literature. Some of the meta-analysis investigated the association of GSTM1 and GSTT1 null deletion polymorphism with Asian and specifically Chinese population (Hu et al., 2013; Liu et al., 2013; Cao et al., 2015). But in this meta-analysis detailed literature review of different populations (Americans, Asians, Europeans, Africans and Eurasians) regarding GSTM1 and GSTT1 deletion polymorphism in the prostatic carcinoma was conducted to get the results on a broad category. This meta-analysis focused on the recent studies (2004 - 2015) for the analysis to represent the exact situation in the present time. There were 33 studies with 7118 cases and 8880 controls to explore association of GSTM1 deletion 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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References

Agalliu I, Lin DW, Salinas CA, et al (2006). Polymorphisms in the glutathione S-transferase M1, T1, and P1 genes and

prostate cancer prognosis. *Prostate*, **66**, 1535-41.
Aktas D, Hascicek M, Sozen S, et al (2004). CYP1A1 and GSTM1 polymorphic genotypes in patients with prostate cancer in a Turkish population. *Cancer Genet Cytogenet*, **154**, 81-85.
Ali M, Ibrahim AT, Ibrahim MT, et al (2015). Deletion Polymorphism of Glutathione S-transferases M1 and T1 genes in the Sudanese Population. *Am J Med Studies*, **3**, 8-12.
Amankwah EK, Sellers TA, Park JY. (2012). Gene variants in the angiogenesis pathway and prostate cancer. *Carcinogenesis*, **33**, 1259-69.
Ansari SB, Vasudevan R, Bakhshi A, et al (2010). Analysis of glutathione S-transferase (M1, T1 and P1) gene polymorphisms in Iranian prostate cancer subjects. *Afr J Biotechnol*, **9**, 7230-35.
Ashtiani ZO, Hasheminasab SM, Ayati M, Goulian BS, Modarressi MH. (2011). Are GSTM1, GSTT1 and CAG repeat length of androgen receptor gene polymorphisms associated with risk of prostate cancer in Iranian patients? *Pathol Oncol Res*, **17**, 269-5.
Caceres DD, Iturrieta J, Acevedo C, et al (2005). Relationship among metabolizing genes, smoking and alcohol used as modifier factors on prostate cancer risk: Exploring some gene-gene and gene-environment interactions. *Eur J Epidemiol*, **20**, 79-88.
Cao DL, Ye DW, Dai B, et al (2015). Association of glutathione S-transferase T1 and M1 polymorphisms with prostate cancer susceptibility in populations of Asian descent: a meta-analysis. *Oncotarget*, **6**, 35843-50.
Cao DL, Ye DW, Zhang HL, et al (2011). A multiplex model of combining gene-based, proteinbased, and metabolite-based with positive and negative markers in urine for the early diagnosis of prostate cancer. *Prostate*, **71**, 700-10.
Catsburg C, Joshi AD, Corral R, et al (2012). Polymorphisms in carcinogen metabolism enzymes, fish intake, and risk of prostate cancer. *Carcinogenesis*, **33**, 1352-9.
Crawford ED, Higano CS, Shore ND, et al (2015). Treating patients with metastatic castration resistant prostate cancer: *A Comprehensive Rev Available Therapies. J Urol*, **194**, 1537-47.
DerSimonian R, Laird N, (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.
Detchokul S and Frauman AG, (2011). Recent developments in prostate cancer biomarker research: therapeutic implications. *Br J Clin Pharmacol*, **71**, 157-74.
Economopoulos KP, Sergentanis TN, Vlahos NF, (2010). Glutathione Stransferase M1, T1, and P1 polymorphisms and ovarian cancer risk: a meta-analysis. *Int J Gynecol Cancer*, **20**, 732-37.
Foley R, Hollywood D, Lawler M, (2004). Molecular pathology of prostate cancer: the key to identifying new biomarkers of disease. *Endocr Relat Cancer*, **11**, 477-88.
Guan TY, Li M, Na YQ, (2005). Polymorphism of metabolic gene and genetic susceptibility to prostate cancer. *Chin J Surg*, **43**, 1467-70.
Hemelrijck MV, Rohrmann S, Steinbrecher A, et al (2012). Heterocyclic Aromatic Amine [HCA] Intake and Prostate Cancer Risk: Effect Modification by Genetic Variants. *Nutr Cancer*, **645**, 704-43.
Hu ZH, Lin YW, Chen H, et al (2013). Genetic polymorphisms of glutathione S- transferase M1 and prostate cancer risk in Asians: a metaanalysis of 18 studies. *Asian Pac J Cancer Prev*, **14**, 393-98.
Huang W, Shi H, Mo Z, et al (2015). GSTM1 and GSTT1 polymorphisms contribute to renal cell carcinoma risk: evidence from an updated meta-analysis. *Scientific Reports*, **5**.
Joseph MA, Moysich KB, Freudenheim JL, et al (2004). Cruciferous vegetables, genetic polymorphisms in glutathione Stransferases M1 and T1, and prostate cancer risk. *Nutr Cancer*, **50**, 206-13.
Komiya Y, Tsukino H, Nakao H, et al (2005). Human glutathione S-transferase A1, T1, M1, and P1 polymorphisms and susceptibility to prostate cancer in the Japanese population. *J Cancer Res Clin Oncol*, **131**, 238-42.
Kumar V, Yadav CS, Datta SK, et al (2011). Association of GSTM1 and GSTT1 polymorphism with lipid peroxidation in benign prostate hyperplasia and prostate cancer: a pilot study. *Dis Markers*, **30**, 163-69.
Kwon DD, Lee JW, Han DY, et al (2011). Relationship between the glutathione-S-transferase P1, M1, and T1 genotypes and prostate cancer risk in Korean subjects. *Korean J Urol*, **52**, 247-52.
Lai MT, Chen RH, Tsai FJ, et al (2005). Glutathione S-transferase M1 gene but not insulin-like growth factor-2 gene or epidermal growth factor gene is associated with prostate cancer. *Urol Oncol*, **23**, 225-29.
Latil AG, Azzouzi R, Cancel GS, et al (2011). Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. *Cancer-Am Cancer Soc*, **92**, 1130-37.
Lavender NA, Benford ML, VanCleave TT, et al (2009). Examination of polymorphic glutathione S-transferase (GST) genes, tobacco smoking and prostate cancer risk among men of African descent: a case-control study. *BMC Cancer*, **9**, 397-7.
Li M, Guan T, Li Y, et al (2008). Polymorphisms of GSTM1 and CYP1A1 genes and their genetic susceptibility to prostate cancer in Chinese men. *Chin Med J*, **121**, 305-8.
Lima MMJ, Oliveira MN, Granja F, et al (2008). Lack of association of GSTT1, GSTM1, GSTO1, GSTP1 and CYP1A1 polymorphisms for susceptibility and outcome in Brazilian prostate cancer patients. *Folia Biol (Praha)*, **54**, 102-8.
Liu D, Liu Y, Ran L, et al (2013). GSTT1 and GSTM1 polymorphisms and prostate cancer risk in Asians: a systematic review and meta-analysis. *Tumor Biol*, **34**, 2539-44.
Liu D, Wang F, Wang Q, et al (2012). Association of glutathione S-transferase M1 polymorphisms and lung cancer risk in a Chinese population. *Clin Chim Acta*, **414**, 188-90.
Malik SS, Masood N, Yasmin A. (2015). Prostate cancer and glutathione s-transferase deletions. *EXCLI J*, **14**, 1049-54.
Mallick S, Romana M, Blanchet P, et al (2007). GSTM1 and GSTT1 polymorphisms and the risk of prostate cancer in a Caribbean population of African descent. *Urol*, **69**, 1165-69.
Masood N, Malik FA, Kayani MA, (2011). Expression of xenobiotic metabolizing genes in head and neck cancer tissues. *Asian Pac J Cancer Prev*, **12**, 377-82.
Masood N, Malik SS, (2014). Association of prostate and bladder cancers with genetic deletions of GSTs. *J Rashid Latif Medical College*, **2**, 1-7.
Masood N, Yasmin A, Kayani MA, (2013). Genetic deletions of GSTM1 and GSTT1 in head and neck cancer: review of the literature from 2000 to 2012. *Asian Pac J Cancer Prev*, **14**, 3535-39.
Medeiros R, Vasconcelos A, Costa S, et al (2004). Metabolic susceptibility genes and prostate cancer risk in a southern European population: the role of glutathione S-transferases GSTM1, GSTM3, and GSTT1 genetic polymorphisms. *Prostate*, **58**, 414-20.
Mittal RD, Mishra DK, Mandhani A, (2006). Evaluating polymorphic status of glutathione-S-transferase genes in blood and tissue samples of prostate cancer patients. *Asian*

Pac J Cancer Prev, **7**, 444-46.
Mittal RD, Srivastava DS, Mandhani A, et al (2004). Polymorphism of GSTM1 and GSTT1 genes in prostate cancer: a study from North India. *Indian J Cancer*, **41**, 115-19.
Nock NL, Liu X, Cicek MS, et al (2006). Polymorphisms in polycyclic aromatic hydrocarbon metabolism and conjugation genes, interactions with smoking and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, **15**, 756-61.
Nock NL, Tang D, Rundle A, et al (2007). Associations between smoking, polymorphisms in polycyclic aromatic hydrocarbon (pah) metabolism and conjugation genes and PAH-DNA adducts in prostate tumors differ by race cancer. *Epidemiol Biomarkers Prev*, **16**, 1236-45.
Oakley A, (2011). Glutathione transferases: a structural perspective. *Drug Metab Rev*, **43**, 138-51.
Pan DL, Samavedi S, Eldefrawy A, et al (2012). The current status of active surveillance for prostate cancer. *Postgrad Med*, **124**, 50-58.
Pan JZ, Huang JW, Zou HZ, et al (2012). The GSTT1 Null Genotype Contributes to Increased Risk of Prostate Cancer in Asians: a Meta-analysis. *Asian Pac J Cancer Prev*, **13**, 2635-38.
Rebecca S, Naishadham D, Ahmedin Jemal A (2013). Cancer Statistics, 2013. *Ca Cancer J Clin*, **63**, 11-30.
Safarinejad MR, Shafiei N, Safarinejad SH, (2011). Glutathione S-transferase gene polymorphisms (GSTM1, GSTT1, GSTP1) and prostate cancer: a case control study in Tehran, Iran. *Prostate Cancer Prostatic Dis*, **4**, 105-13.
Shukla RK, Tilak AR, Kumar C, et al (2013). Associations of CYP1A1, GSTM1 and GSTT1 polymorphisms with lung cancer susceptibility in a Northern Indian population. *Asian Pac J Cancer Prev*, **14**, 3345-49.
Siegel LR, Miller, DK. Jemal A. (2015). Cancer Statistics, 2015. *Ca Cancer J Clin*, **65**, 5-9.
Silig Y, Pinarbasi H, Gunes S, et al (2006). Polymorphisms of CYP1A1, GSTM1, GSTT1, and prostate cancer risk in Turkish population. *Cancer Invest*, **24**, 41-45.
Sivonova M, Waczulikova I, Dobrota D (2009). Polymorphisms of glutathione-S transferase M1, T1, P1 and the risk of prostate cancer: a case-control study. *J Exp Clin Cancer Res*, **28**, 32-39.
Souiden Y, Mahdouani M, Chaieb K (2010). Polymorphisms of glutathione-S-transferase M1 and T1 and prostate cancer risk in a Tunisian population. *Cancer Epidemiol*, **34**, 598-3.
Steinbrecher A, Rohrmann S, Timofeeva M, et al (2010). Dietary glucosinolate intake, polymorphisms in selected biotransformation enzymes, and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **19**, 135-43.
Thakur H, Gupta L, Sobti RC, et al (2011). Association of GSTM1T1 genes with COPD and prostate cancer in north Indian population. *Mol Biol Rep*, **38**, 1733-39.
Vijayalakshmi K, Vettriselvi V, Krishnan M, et al (2005). Polymorphisms at GSTM1 and GSTP1 gene loci and risk of prostate cancer in a South Indian population. *Asian Pac J Cancer Prev*, **6**, 309-14.
Wang D, Zhang LM, Zhai JX, et al (2012). GSTM1 and GSTT1 polymorphisms and colorectal cancer risk in Chinese population: a meta-analysis. *Int J Colorectal Dis*, **27**, 901-9.
Ya-lin W, Jun J, Luo-fu W, et al (2005). Polymorphisms of glutathione-S-transferase genes GSTM1 and GSTT1 and prostate cancer risk in Chinese population. Journal of Third Military Medical University, **10**.
Yang J, Wu HF, Zhang W, et al (2006). Polymorphisms of metabolic enzyme genes, living habits and prostate cancer susceptibility. *Front Biosci*, **11**, 2052-60.
Yang Q, Du J, Yao X (2013). Significant association of glutathione S-Transferase T1 null genotype with prostate cancer risk: a meta-analysis of 26,393 subjects. *PLOS One*, **8**, 53700.
Zhang J, Grek C, Ye ZW, et al (2014). Pleiotropic functions of glutathione S-transferase P. *Adv Cancer Res*, **122**, 143-75.
Zhang ZJ, Hao K, Shi R, et al (2011). Glutathione S-transferase M1 (GSTM1) and glutathione Stransferase T1 (GSTT1) null polymorphisms, smoking, and their interaction in oral cancer: a huge review and meta-analysis. *Am J Epidemiol*, **173**, 847-57.