**RESEARCH ARTICLE**

**GSTM1 and GSTT1 Polymorphisms and Susceptibility to Prostate Cancer: A Case-Control Study of the Algerian Population**

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Abstract

**Objective:** Prostate cancer (PCa) is a major public health problem worldwide, with high morbidity and mortality levels. Advanced age, androgen stimulation, and ethnicity have been reported to be possible risk factors. It has been suggested that particular genetic polymorphisms in glutathione S-transferases (GST), xenobiotic-metabolising enzymes, could predispose to prostate cancer through heritable deficiency in detoxification of environmental carcinogens. Conflicts in the published results and the absence of similar in depth studies in Algeria prompted us to perform the present case-control study of GSTM1 and GSTT1 polymorphisms and their possible association with PCa in an Algerian population.  

**Methods:** We determined GSTM1 and GSTT1 genotypes for 49 histologically verified prostate cancer patients and in 41 age-matched healthy controls by multiplex polymerase chain reaction (PCR) using peripheral blood DNA samples.  

**Result:** While an association between the GSTM1 null genotype and PCa risk (OR= 3.69, 95% CI= 1.30-10.44; P = 0.01) was evident, the GSTT1 null genotype (OR= 0.92, 95% IC= 0.32-2.62; P = 0.49) appeared without influence. Furthermore, no statistically significant differences between the double null genotype and PCa is detected, also no statistically significant differences between smoking status and PCa is detected.  

**Conclusion:** The GSTM1 null genotype may increase individual susceptibility to prostate cancer. On the other hand, the null-activity genotype of GSTT1 did not appear to contribute to the risk of prostate cancer in our population.  

**Keywords:** Prostate cancer- GSTM1- GSTT1- genetic polymorphism

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**Introduction**

Prostate cancer (PCa) is the most commonly occurring malignancy among elderly men and is ranked as the fifth leading cause of cancer death worldwide (Roussel et al., 2015). According to the WHO (World Health Organization), the burden from this disease is anticipated to increase to 1.7 million new cases and 499,000 deaths by 2030. In 2012, 1.1 million men were diagnosed with PCa and 307,000 were died from it (Globocon, 2012; Center et al., 2012).

In Algeria, the PCa presents an incidence of 10 and rank fourth in terms of male cancers (Abid, 2009).

Current diagnosis and treatment decisions for PCa involve digital rectal examination, serum Prostate Specific Antigen (PSA) measurements and biopsies for histopathological grading (Velonas et al., 2013). The etiology of this disease remains unknown; however, clinical and epidemiological data suggested that the development of prostate cancer is a multiphase process (Rodrigues et al., 2011).

Genetic polymorphisms are natural genetic variations in the gene sequence that could increase the risk of cancer. Inherited differences in the activity of xenobiotic metabolizing enzymes have been described to be one of the prime factors in genetic susceptibility to cancer is through inherited deficiency in detoxification pathways for environmental carcinogens (Hsing et al., 2000; Reska et al., 2006).

Glutathione S-transferases (GSTs) are a supergene family of detoxifying enzymes which are found in virtually all life forms (Hayes et al., 2005). GSTs are considered to be phase II detoxifying enzymes that catalyze the conjugation of reduced glutathione with a wide variety of electrophilic substrates (Hayes et al., 1995). In addition to their function in xenobiotic detoxification, GSTs have peroxidase and isomerase activities that can inhibit the c-Jun N-terminal kinase (JNK) (Awasthi, 2007). GSTs can also bind non catalytically with a wide range of endogenous and exogenous ligands (Awasthi, 2007).

In humans, GST enzymes consist of many cytosolic, mitochondrial, and microsomal proteins, and the cytosolic...
family has eight distinct classes: alpha (A), kappa (K), mu (M), omega (O), pi (P), sigma (S), theta (T), and zeta (Z) (Strange et al., 2001; Hayes et al., 2005).

Particular genetic polymorphisms of these enzymes have been shown to be associated with increased susceptibility to various pathologies as well as cancer, cardiovascular and respiratory diseases. Several allelic variations within GST classes, including GSTM1 (MIM: 138,350), GSTT1 (MIM: 600,436) and GSTP1 (MIM: 134,660) have been described in genetic epidemiological studies (Matic et al., 2014). For both GSTM1 (chromosome 1p13.3) and GSTT1 (chromosome 22q11.23), the variant allele is a deletion of the gene (Rebeck, 1997; Eaton and Bammler, 1999). The homozygous deletion frequently referred to as GSTM1-null and GSTT1-null genotypes (i.e., GST *0/*0 null genotype), may have an impaired ability to metabolically eliminate carcinogenic compounds and may therefore be at increased risk of bladder, lung, colorectal, head and neck, breast, renal and prostate cancers (Awasthi et al., 2007; Grando et al., 2009; Ayshah et al., 2016). Moreover, a varied distribution of GSTM1 and GSTT1 null genotypes was reported in different populations (Ginsberg et al., 2009). By combining various unfavorable deletion genotypes theoretically, a higher risk to patients with prostate cancer might be conferred (Nakazato et al., 2003).

Many studies investigated the association between GSTM1 and/or GSTT1 polymorphisms and PCA risk but inconsistent and conflicting results have been reported (Gong et al., 2012). The objective of the current study is to establish whether GSTM1 and GSTT1 polymorphisms are associated with PCA risk in the Algerian population. A case-control study was conducted including newly diagnosed prostate-cancer cases and age-matched men with non-tumoral diseases as control.

Materials and Methods

Study population
A total of 90 unrelated Algerian men consisting of 49 PCA patients and 41 men age-matched as controls were recruited between September 2015 and January 2016 from the same population, ethnically similar, living in North-East Algeria. The mean age of patients is ranging from 49 to 89 years. The diagnosis of PCA was confirmed histologically for all the patients. The PSA values were measured in all cases before treatment with enzyme-linked fluorescent assay (ELFA) through mini-VIDAS TPSA kit (BioMérieux, France). We prospectively collected information’s from all participants for clinical characteristics including age at diagnosis, residence, smoking, Gleason pathological grade, and family history. The PSA levels of control group were within the normal limit (<4 ng/ml) and showed no signs of prostate hyperplasia, PCA or other malignancies.

This study was approved by the Hospital Ethical Committee (HD06.016) with the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all participants.

DNA isolation and genotyping
Peripheral blood (5ml) was collected from each subject into a sterile EDTA tube. Genomic DNA was extracted from blood leukocytes with FlexiGene®DNA kit (Qiagen, Hilden, Germany) in accordance with the manufacturer’s instructions. DNA was quantified by the NanoPhotometerTM (Implen, Germany) then stored at 4°C until use.

The genetic polymorphism of GSTM1 and GSTT1 was determined in a single assay using a multiplex PCR modified from Abdel-Rahman (1996). This procedure detects the presence (at least one allele present, homozygote or heterozygote) or absence (complete deletion of both alleles, homozygote) of genotype.

The primer sequences were as follows: GSTM1 forward: 5’-GTGGGGCTCAATATACGGTGG-3’ and reverse: 5’-GAGACTTCCCT -GAAAAGCTAAAAGC-3’; GSTT1 forward: 5’-TCACCGGATCATGAGGCCAGCA-3’ and reverse: 5’-TTCCTTACTGTCCACTACATCTC-3’. Exon 7 of the CYP1A1 was used as an internal control using the following primers: CYP1A1 forward: 5’-GAACTGCACA- CTTGAGGCTCT-3’ and reverse: 5’-CGGCTGATTTGGAAGTCTC-3’. All primers used in this study were purchased from Sigma-Aldrich, Germany. Genomic DNA was amplified in a total of 25 μl reaction volume containing: 2.5 μl 10X PCR buffer, 200 μM dNTPs, 2 μl of 25 mM MgCl2, 1 μl of each of primer and 0.3 μl of Taq polymerase (AmpliTaq Gold® DNA polymerase, applied biosystems, Germany).

PCR was performed in an Applied Biosystems Veriti Thermal Cycler (ThermoFisher Scientific, Germany) and the PCR conditions consisted of an initial melting temperature of 95°C (10 min) followed by 40 cycles of denaturing (95°C, 1 min), annealing (68°C, 2 min) and extension (72°C, 1.5 min). A final extension step (72°C) of 7 min was used. Amplified products (GSTM1: 215 pb, GSTT1: 480 pb and CYP1A1: 312 pb) were resolved electrophoretically on 5% polyacrylamide gel stained with EuroSafe Nucleic Acid Staining Solution (EuroClone, Italy).

Statistical analysis
Data of continuous variables were expressed as mean ± standard deviation (SD) and data of non continuous variables as frequency (N, %). The experiments were repeated three times. Statistical analysis was carried out using Statistical Package for the Social Sciences version 20.0 software (SPSS) (Chicago, IL, USA). The odds ratio (OR) and its 95% confidence interval (CI) were used to illustrate the association between genetic variants and their risk for disease. A P-value <0.05 was considered statistically significant.

Results
The clinical and pathological characteristics of the patients investigated in this study were listed in Table 1. The mean (± SEM) age of cases and controls was 73.26 (± 1.10) and 70.53 (± 3.83), respectively. As observed, controls were on average three years younger than cases. In relation to Gleason score, 40.81% of the cases were diagnosed with a low Gleason score (<7), and 59.18 % with a high Gleason score (≥7). The number of smokers
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The frequencies of GSTM1 null genotype (GSTM1 0/0) were 38.77% in patients and 14.63% in controls. However, for the GSTM1 active genotype frequencies (GSTM1 +/+ ) were 61.22% in patients' group and 85.36% in controls' group. Statistically, significant differences were observed (OR= 3.69, 95% CI= 1.30-10.44; P = 0.01) (Table 2).

The distribution of GSTT1 variants in the patient and control groups showed a high similarity. In fact, the frequencies of GSTT1 0/0 and GSTT1 +/+ genotypes were 19.51% and 80.48%, respectively, in the controls’ group and 18.36% and 81.63% respectively in the patients’ group. The statistical analysis showed no association.

Table 1. Clinicopathologic Characteristics of Individuals with and without Prostate Cancer

| Characteristics         | Cases (n=49) | Controls (n=41) | P-value |
|-------------------------|-------------|----------------|---------|
| Age (yr)                |             |                |         |
| mean (±SD)              | 73.26 (±10.13) | 70.53 (±8.38) | 0.18    |
| Residence               |             |                |         |
| Urban                   | 44 (89.79)  | 41 (100)       |         |
| Rural                   | 5 (10.20)   | 0              |         |
| Family history of PCa   |             |                |         |
| Yes                     | 3 (6.12)    |                |         |
| No                      | 46 (93.87)  |                |         |
| Smoking status          |             |                |         |
| Nonsmokers              | 10 (20.40)  | 9 (21.95)      |         |
| Smokers                 | 39 (79.59)  | 32 (78.04)     |         |
| Clinical stage          |             |                |         |
| Localized               | 18 (36.73)  |                |         |
| Advanced                | 31 (63.26)  |                |         |
| Gleason score           |             |                |         |
| <7 (Low)                | 20 (40.81)  |                |         |
| 7-10 (High)             | 29 (59.18)  |                |         |
| PSA at diagnosis (ng/ml)|             |                |         |
| mean (±SD)              | 80.72 (±24.34) | 4.26 (±3.48) | 0       |
| <4                      | 2 (4.08)    | 32 (78.04)     |         |
| 4-10                    | 6 (12.24)   | 7 (17.07)      |         |
| >10                     | 41 (83.67)  | 2 (4.87)       |         |

SD, Standard Deviation

Table 2. GSTM1 and GSTT1 Genotypes Distribution among Individuals with and without Prostate Cancer

| Genotype                | Patients (n = 49) | Controls (n = 41) | OR (95% CI) | P value |
|-------------------------|-------------------|-------------------|-------------|---------|
| Single genotypes        |                   |                   |             |         |
| GSTM1 non-null          | 30 (61.22)        | 35 (85.36)        |             |         |
| GSTM1 null              | 19 (38.77)        | 6 (14.63)         | 3.69 (1.30- 10.44) | 0.01    |
| GSTT1 non-null          | 40 (81.63)        | 33 (80.48)        |             |         |
| GSTT1 null              | 9 (18.36)         | 8 (19.51)         | 0.92 (0.32-2.62) | 0.49    |
| Double genotype         |                   |                   |             |         |
| GSTM1 null/ GSTT1 null  | 4 (8.16)          | 3 (7.31)          | 0.88 (0.18- 4.21) | NS      |

NS, No Significant

Table 3. Distribution of the Genotypic Frequencies According to Gleason Score of Prostate Cancer

| Genotype/variable       | GS <7 (n = 20) | GS ≥7 (n = 29) | OR (95% CI) | P value |
|-------------------------|---------------|---------------|-------------|---------|
| GSTM1 non-null          | 11 (22.45)    | 19 (38.78)    | 0.66 (0.16 – 2.66) | NS      |
| GSTM1 null              | 9 (18.36)     | 10 (20.40)    |             |         |
| GSTT1 non-null          | 17 (34.69)    | 24 (48.97)    | 1.41 (0.22 – 8.98) | NS      |
| GSTT1 null              | 3 (6.12)      | 5 (10.21)     |             |         |

GS, Gleason Score; OD, Odds Ratio; NS, No Significant
between GSTT1 null genotype and the risk of PCa (OR= 0.92, 95% CI= 0.32-2.62; P = 0.49). Individuals with combined genotypes (GSTM1 0/0 and GSTT1 0/0), exhibited no change in the risk for PCa compared to controls (OR= 0.88, 95 % CI= 0.18-4.21) (Table 2).

Table 3 presents the results of association between the studied polymorphisms and the Gleason score at diagnosis of PCa and differences were not significantly important with either the low or high grade cancer.

The smoking status was not associated with GSTM1 and GSTT1 polymorphisms (Table 4).

### Discussion

Prostate Cancer is a multi-factorial disease with a complex etiology to which combined genetic and environmental factors contribute to the pathogenesis of the disease. Among the genetic factors, the role of GSTs has received particular attention as a factor that might contribute to the risk of PCa (Acevedo et al., 2003; Hsing and Chokkalingam, 2006).

Understanding the contribution of GSTs polymorphisms and their interactions with other relevant factors may improve screening diagnostic assays for PCa (Sivonova et al., 2009).

To the best of our knowledge, the present study is the first report on the polymorphic distribution of GSTs in PCa patients and healthy controls from the Algerian population. Several population-based studies have reported prevalence ranging from 47% to 58% for the GSTM1 deletion genotype and from 13% to 25% for the GSTT1-null genotype among white Europeans (Rebbech, 1997). The prevalence rates of GSTM1 and GSTT1 in our study were found to be 38.77 % and 18.36 respectively.

Our results indicate that, while the null genotype of GSTM1 is associated with a higher risk for PCa than in controls, the null GSTT1 and combined GSTM1 and GSTT1 null genotypes are not associated with PCa susceptibility. Interestingly, these findings are consistent with previous reports in a meta-analysis conducted by Cai et al., (2014) which exhibited an increased risk of PCa for the GSTM1 null genotype and no significant association for the GSTT1 null genotype with PCa susceptibility.

Regarding GSTM1, our data was in agreement with previously published findings which revealed a significant association between the GSTM1 null genotype and the risk of PCa (Acevedo et al., 2003; Silig et al., 2006; Kumar et al., 2011). However, our results are in apparent contrast with other studies which reported a lack of significant association of homozygous null GSTM1 with PCa (Komiya et al., 2005; Sivoňová et al., 2009; Catsburg et al., 2012).

Regarding GSTT1, similar to our findings, other studies found no evidence of an association between GSTT1 polymorphism for an increased risk of PCa (Agalli et al., 2006; Silig et al., 2006; Sivoňová et al., 2009; Kumar et al., 2011; Kwon et al., 2011). On the contrary, other studies reported a significant elevation in risk of PCa for the GSTT1 null genotype (Safarinejad et al., 2011; Thakur et al., 2011; Catsburg et al., 2012). Moreover, our results are in disagreement with the study of the Tunisian population which did not find an association of GSTM1 or GSTT1 polymorphisms and PCa risk (Souiden et al., 2010). Although we expected that the combination of GSTT1 and GSTM1 double null type might be strongly linked to PCa, we did not find significant difference between cases and controls. Recent studies have evaluated the combined effect of GSTM1 and GSTT1 genotypes, but most of them failed to show any significant association between the deficiency of these genes and prostate cancer risk (Gsur et al., 2001; Katoh et al., 2008). In addition, individuals with homozygous deletions of GSTM1 or GSTT1 lack glutathione S-transferase and therefore may be unable to eliminate electrophilic carcinogens as efficiently, which may increase the risk of somatic mutations leading to tumor formation (Coughlin and Hall, 2002). Therefore, we conducted a stratified study of the variant GSTs on Gleason scores of the patients that did not reveal any significant association suggesting that the genotypes are not associated with the aggressiveness of PCa.

The genes implicated in the metabolic activation or detoxification of carcinogens do not act isolated, and the evaluation of multiple genes is necessary to fully understand this phenomenon. In the same way as in the analysis of the genotypes separately, when Rodrigues et al., (2011) evaluated the combination between the heterozygous, rare, and prevalent genotypes of phase I enzymes, phase II enzymes and both phases I and II they did not observe any positive or negative associations.

Glutathione S-transferase M1 and T1 have been studied as risk candidates for tobacco-related cancers. Some reports suggest that PCa should be added to the list of tumors for which cigarette smoking is a risk factor (Plaskon et al., 2003). Therefore, we investigated the possible correlation between GSTM1 and GSTT1 null genotypes and PCa susceptibility in smokers’ subgroup and did not find an evidence of statistically significant differences. These findings might be considered with more attention due to the relatively small sample size.

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Finally, the use of molecular biomarkers such as GSTs in the management of patients with PCa may improve their clinical outcomes. Therefore, it is believed that understanding the potential role of GST variant alleles in PCa risk could be a good contribution to this field. Undoubtedly, more research is required in these variant alleles, taking into account that including new biomarkers...
in the clinical practice require several steps and diverse validation analyses, particularly for PCAs, a highly prevalent and heterogeneous illness (Acevedo et al., 2014).

In summary, we observe evidence suggesting an association between the GSTM1 null genotype and PCa risk and no association between GSTTI null genotype and PCa risk. Therefore, the null-genotype of GSTM1 increases individual susceptibility to prostate cancer. Nevertheless GSTTI null genotype does not seem to contribute to the risk of prostate cancer in the studied population.

Unfortunately, the effects of polymorphisms of low-penetrance genes such as GSTs require several hundred patients to identify. Hence, it could be considered as an outset of future studies.

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