Association of CYP1A1, GSTM1 and GSTT1 gene polymorphisms with risk of prostate cancer in Algerian population

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Abstract
Background: Prostate cancer is the most common cancer in the world, and its etiology involves the interaction of genetic and environmental factors. Interindividual differences observed in the metabolism of xenobiotics may be due to polymorphisms of genes encoding the detoxification enzymes. This genetic variability seems to be associated with differences in susceptibility to certain types of cancers, including prostate cancer. Our study has been made in order to investigate a possible genetic predisposition to prostate cancer in an Algerian population, through the analysis of genetic polymorphisms of three enzymes metabolizing xenobiotics namely cytochrome P450 (CYP) 1A1, glutathione S-transferase mu 1 (GSTM1) and GST theta 1 (GSTT1).

Methods: The current case–control study included 101 prostate cancer patients and 101 healthy controls. Genotyping of CYP1A1 T3801C polymorphisms and GSTM1/GSTT-Null was made, respectively, by PCR-RFLP and multiplex PCR.

Results: No significantly positive associations were found for the CYP1A1 T3801C [p = 0.71, OR = 1.23 (0.56–2.72)] and GSTM1-Null [p = 0.26, OR = 1.37 (0.76–2.4)] polymorphisms and prostate cancer susceptibility. However, we detect a highly significant association between GSTT1-Null genotype [p = 0.03, OR = 2.03 (1.06–3.99)], GSTM1/GSTT1-double null genotype [p = 0.027, OR = 2.6; CI (1.07–6.5)] and prostate cancer risk. Furthermore, no statistically significant differences between the studied polymorphisms and tumor parameters (the Gleason score and clinical stages of aggressiveness) at diagnosis of PCa.

Conclusions: The risk of developing prostate cancer in Algeria does not appear to be associated with CYP1A1 T3801C genotypes and GSTM1-Null, but GSTT1-Null and GSTM1/GSTT1-double null genotypes increased the risk of prostate cancer.

Keywords: Prostate cancer, Genetic polymorphism, Cytochrome P450 1A1, Glutathione S-transferase (GST), GSTM1, GSTT, PCR-RFLP, multiplex PCR

1 Introduction
Prostate cancer (PCA) is considered as a major public health problem in the world because of its increased mortality and morbidity rates. It is evaluated as a most frequently diagnosed solid neoplasm. Overall, PCA is the second major cause of cancer-related death among men (Europeans, Americans and to some extent in Africans as well) [1, 2]. In Algeria, it is the most common male cancer (10% of cancers in men) with 1645 new cases with an average incidence of 10.8/100,000 [3]. According to Globocan 2018, PCA is the third most common cancer in men with 2578 new cases.

In order to understand the biology, etiology and to develop new interventions of PCA, complete analysis of...
different risk factors along with their comparison with genetics is essential [4].

Clinical and epidemiological data suggest that the development of PCa is a multiphase process. [5]. Smoking, dietary habits, lifestyle factors, environmental factors, as well as geographical/racial factors and genetics factors may be involved in PCa development. Also, modification in carcinogen metabolism genes may play a critical role in PCa development due to their activation or detoxification functions [6].

Xenobiotic-metabolizing enzymes (XME), coded by a family of xenobiotic-metabolizing genes (XMG), have a major role in elimination of many xenobiotics or environmental chemical compounds from the body. This mechanism of detoxification occurs in two phases [7]. In phase I, cytochrome P450 enzymes play an important role in the metabolism of estrogen and polycyclic aromatic hydrocarbons (PAHs). They catalyze the activation of procarcinogenic PAHs and their dysfunctions can cause damage to DNA, leading to carcinogenesis.

The CYP1A1 gene is located on 15q22-q24 [8], contains 7 exons and 6 introns and spans 5810 base pairs. Eleven polymorphisms of CYP1A1 have been described, four of which have been the most studied for their involvement in modifying the risk of carcinogenesis: m1 (T3801C), m2 (A2455G), m3 (T3205C) and m4 (C2453A) [9]. The CYP1A1 3801T/C (also named MspI polymorphism, *2A or m1), results from a replacement of thymine by a cytosine at the 3801st base pair in the 3′ flanking region of the gene [9, 10].

Glutathione S-transferases (GSTs) involve a superfamily of multifunctional and ubiquitous phase II metabolic enzymes. It catalyzes the conjugation of electrophilic substrates to soluble glutathione to facilitate their cellular excretion. Additionally, GSTs are able to detoxify noxious products of the cellular metabolism, such as reactive oxygen and nitrogen species through their glutathione peroxidase activity [11, 12]. GSTs constitute the major antioxidant defensive system against oxidative stress by reducing reactive oxygen species, which are generated by many toxic xenobiotics [13].

In human, these enzymes are found in cytosol, microsome and mitochondria. The superfamily of genes encoding cytosolic glutathione S-transferases consists of eight classes: α (GSTA), κ (GSTK), μ (GSTM), ω (GSTO), π (GSTP), ε (GSTS), θ (GSTT) and ζ (GSTZ) [14]. GSTM1 and GSTT1 genes are situated on chromosome 1p13.3 and 22q11.23, respectively [15]. GSTM1 preferentially detoxifies carcinogens which are found in tobacco (epoxides and hydroxylated derivatives), whereas GSTT1 is specific for the biotransformation of many smaller toxins derived from tobacco smoke such as butadiene and ethylene oxides [16].

Homozygous deletions of the GSTM1 and GSTT1 genes are common and result in a complete loss of enzymatic activity. Hence, individuals are at greater risk toward the development of malignancies [17, 18].

Previous studies have been reported regarding the genetic status of GSTM1 and GSTT1 polymorphism and prostate cancer development. But the effect of polymorphisms of these two genes on PCa is still unclear because of inconsistent results among different populations [19].

The aim of the present study was to assess the influence of CYP1A1 and glutathione S-transferases (GSTM1, GSTT1) on the risk of PCa.

2 Methods
2.1 Subjects
The study population consisted of 101 patients with prostate cancer and 101 healthy controls.

All patients were histologically diagnosed with prostate cancer; thus, all stages of this tumor development have been included. Cases were recruited from the Uro-Nephrology Hospital “the Department of Urology and Renal Transplantation,” Constantine, Algeria. The criteria for patient inclusion was a suspicious finding upon digital rectal examination (DRE) and/or elevated serum levels of PSA (>4 ng/ml) followed by a histopathologic confirmation of prostate cancer.

Control subjects were volunteers, healthy men, without a family history of malignant disease. Their PSA levels were within the normal limit (<4 ng/ml) and showed no signs of prostate hyperplasia or prostate carcinoma by DRE.

A detailed questionnaire was elaborated and used to obtain study information.

2.2 Ethics statement
Our research has been approved by the local Ethics Committee. The use of human blood sample and the protocol in this study strictly conformed to the principles expressed in the Declaration of Helsinki, and informed (written) consent was obtained from all participants.

3 Molecular analysis of CYP1A1, GSTM1 and GSTT1 gene polymorphisms
3.1 Blood collection and DNA isolation
Blood samples (10 ml) were obtained from peripheral veins of patients and controls in vacutainer K3EDTA tubes. Genomic DNA isolation followed a standard procedure for NaCl extraction and ethanol precipitation. Genomic DNA samples were stored at −20 °C until use.
3.2 CYP1A1 T3801C genotyping
Detection of CYP1A1 T3801C polymorphism was performed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP).

One set of forward 5'-GGCTGAGCAATCTGACCC TA-3 and reverse: 5'-TGGAGTCTTGTCTCATGCTT-3' primers were used for the amplification of a fragment of 340 pb.

DNA was amplified in a total volume of 20 μl, containing H2O, MgCl2 (50 mM), primers (100 ng/μl), dNTP (0.2 mM), PCR buffer 10X and Taq polymerase (Taq DNA 5U/μl). For each individual, 2 μl of DNA (20 to 50 ng/μl) is mixed with 18 μl of the mixture in a PCR tube.

Following an initial denaturation step at 94 °C for 4 min. Thirty-seven cycles of amplification were carried out, denaturation (94 °C for 30 s), annealing (60 °C for 30 s) and extension (72 °C for 30 s), with a final extension step at 72 °C for 10 min. The amplified products were electrophoresed on a 2% agarose gel to check PCR product size. The PCR amplicons generated for m1 (340 bp) were subjected to restriction digestion. Msp1 restriction enzyme was used to detect polymorphisms in the CYP1A1 m1. The reaction mixtures were incubated at 37 °C for 12 h, electrophoresed on 3% agarose gel and stained with ethidium bromide for visualization.

3.3 GSTM1 and GSTT1 genotyping
The GSTM1 and GSTT1 gene deletions were analyzed simultaneously by multiplex PCR. β-globulin was used as an internal control, confirming successful PCR amplification to ensure that the GSTM1-null and GSTT1-null were due to deletion of GST alleles and not due to failure of the PCR.

To detect the GSTM1 deletion, the primers used were GSTM1 F (5'-GAACCTCCTGAAAAGCTAAAGC-3') and GSTM1 R (5'-GTTGGGCTCAAATAATACGGTG-3'). For GSTT1, the primers used were GSTT1 F (5'-TTC TTACGTGGTCTCATC-3') and GSTT1R (5'-TCACCGGATCATGGCCACACA-3'); For β-globulin F (5'-ACA CAA CTT GGT TGG TCA GCT-3') and R (5'- CAA CTT CAT CCA CGT TCA CC-3').

The PCR conditions were: 4 min of initial denaturation at 95 °C, followed by 37 cycles of denaturation at 94 °C for 1 min, annealing at 62 °C for 1 min and extension at 72 °C for 1 min with a final extension at 72 °C for 4 min.

The GSTM1 fragment was 230 bp, the GSTT1 fragment was 480 bp, and the β-globulin fragment was 110 bp in size.

3.4 Statistical analysis
Statistical analysis was carried out using R software version 3.2.3. Statistical significance of differences in genotype frequencies between patients and controls was estimated by the Chi-square test. Logistic regression was used to evaluate the effect of genotypes, after adjusting for age and tobacco. We also performed a logistic regression analysis to determine whether the clinical stage and the pathological grade were associated with PCa risk. The odds ratio (OR) and its 95% confidence interval (CI) were used to illustrate the association, with p < 0.05 considered statistically significant in all tests.

4 Results
Relevant characteristics of cases and controls are given in Table 1. In our study, patients and controls were aged between 50 and 89 years, and the average age of prostate cancer patients and controls was 70.66 ± 8.32 and 68 ± 9.19, respectively. No statistically significant difference was observed between cases (63.37%) and controls (55.37%) regarding the smoking status (p = 0.25). Also, the majority of patients population have higher total PSA rate and diagnosed at advanced stage. There was no significant interaction between CYP1A1, GSTM1, GSTT1 genotypes and smoking (data not shown).

Representative CYP1A1 T3801C genotyping results are summarized in Fig. 1. Table 2 shows the distribution of allelic and genotypic frequencies for the polymorphism CYP1A1 T3801C between individuals with and without prostate cancer and their relation with risk of prostatic carcinogenesis.

A total of 101 PCa patients and 101 control subjects were included in this study. Frequencies of CYP1A1 T3801C polymorphism genotypes show that the wild genotype (TT) is the most common in both populations. 82 (81.18%) cases and 85 (84.15%) of controls were (TT). Heterozygote genotype (TC) was found in 19 (18.81%) patients and 16 (15.84%) normal controls. Thus, no mutated genotype (CC) was identified in all genotyped individuals. These results suggest that no statistically significant association of CYP1A1 T3801C gene polymorphism with PCa in the tested population [p = 0.71, OR = 1.23 (0.56–2.72)].

Representative GSTM1 and GSTT1 genotyping results are illustrated in Fig. 2. Table 3 presents genotype frequencies for the GSTM1 and GSTT1.

GSTM1 and GSTT1 genotypes distribution among all population (cases and controls), as well as the estimates of PCa risk, are summarized in Table 3. GSTM1 was deleted in 50.49% of controls and 42.57% of PCa patients. No significant association was found when comparing GSTM1 gene deletions (p = 0.26, OR = 1.37, CI [0.76–2.4]) with risk of PCa.

GSTT1-null genotype was observed in 37.62% of patients with PCa and 22.77% of controls subjects, which
was statistically significant \( p = 0.03, \text{OR} = 2.03, \text{CI} (1.06–3.99) \).

Combined frequencies of \( \text{GSTM1} \) and \( \text{GSTT1} \) polymorphisms \( \text{Wild/Wild} (++) \), \( \text{Wild/Null} (+) \), \( \text{Null/Wild} (\mp) \) and \( \text{Null/Null} (--) \) in healthy control were 40.59, 9.90, 36.63 and 12.87, respectively, whereas in PCa patients, the frequencies were 29.70, 12.87, 32.67 and 24.75, respectively. The significant association was found between \( \text{GSTM1-null/GSTT1-null} \) (double null) \( p = 0.027 \) \( \text{[OR} = 2.6; \text{CI} (1.07–6.5)] \).
Tables 4 and 5 present the relation between the studied polymorphisms and the Gleason score and clinical stages at diagnosis of PCa.

The logistic regression analyses presented in Tables 4 and 5 showed no statistically significant correlations between the **GSTM1**, **GSTT1**, and **CYP1A1** genotypes and different Gleason scores and clinical stages at diagnosis of PCa.

### 5 Discussion

This paper reports for the first time in Algeria the relation between the genetic polymorphism of three enzymes metabolizing xenobiotics (**CYP1A1**, **GSTM1**, **GSTT1**) and susceptibility to developing prostatic cancer. The choice of these allelic variants is justified for each variant's potential as a marker of susceptibility for different types of cancer.

A total of 202 Algerian men were recruited and the association was analyzed between the case and control subjects. This present article shows the effect of the **GSTM1**, **GSTT1**, and **CYP1A1** polymorphism on PCa risk in an Algerian population.

Prostate cancer is a multifactorial disease resulting from the combined effects of multiple environmental and genetic factors. Individual differences in the susceptibility to carcinogens play an essential role in the development of sporadic cancer. Several polymorphic genes encoding enzymes involved in the biotransformation of carcinogens have been studied as possible prostate cancer risk modifiers, including the **cytochrome P450 (CYP)** genes and **GST** system.

Numerous studies have been conducted to determine the association between the **CYP1A1,GSTM1, GSTT1** polymorphisms and PCa. However, the results are conflicting due to differences in the studied populations, various genetic backgrounds, ethnic and geographical variation and different exposures to diverse environmental risk factors. These variations have been linked to increased incidence or aggressiveness of prostate cancer.

In the present study, no links were detected between PCa and **T3801C** polymorphism. Our results are consistent with previous reports: Souden et al. [20], Mandić et al. [21] found that there is no significant

### Table 3

| Polymorphism | Distribution | OR/CI | P value |
|--------------|--------------|------|--------|
| **GSTM1**    | Patients %   | Controls % |      |
| M+           | 43 (42.57)   | 51 (50.49) | /     |
| M−           | 58 (57.42)   | 50 (49.50) | 1.37 [0.76–2.4] | 0.26 |
| T+           | 63 (62.37)   | 78 (77.22) | /     |
| T−           | 38 (37.62)   | 23 (22.77) | 2.03 [1.06–3.99] | 0.03 |
| M+/T+        | 30 (29.70)   | 41 (40.59) | /     |
| M−/T+        | 13 (12.87)   | 10 (9.90) | 1.76 [0.62–5.2] | 0.33 |
| M−/T−        | 33 (32.67)   | 37 (36.63) | 1.21 [0.60–2.5] | 0.61 |
| M+/T−        | 25 (24.75)   | 13 (12.87) | 2.6 [1.07–6.5] | 0.027 |

**GSTM1** positive (M1 +), **GSTM1** null (M1 −), **GSTT1** positive (T1 +) and **GSTT1** null (T1 −)

**OR** odds ratios, CI confidence intervals. Wild genotypes were used as a reference (**GSTM1** positive, **GSTT1** positive)

| Polymorphism | Clinical stages | OR/CI | P value |
|--------------|----------------|------|--------|
| **GSTM1**    | Localized      | Advanced |
| M+           | 18 (42.85%)    | 25 (42.38%) | 0.99 [0.85–1.16] | 0.98 |
| M−           | 24 (57.15%)    | 34 (57.62%) | /     |
| **GSTT1**    | T+             | T−     |
| T+           | 28 (66.66%)    | 8 (21.63%) | 2.6 [1.07–6.5] | 0.027 |
| T−           | 4 (20.83%)     | 5 (25.42%) | 1.08 [0.6–1.8] | 0.52 |
| **GSTM1/GSTT1** | Both present | Either null |
| M+           | 18 (42.85%)    | 25 (42.38%) | 0.99 [0.85–1.16] | 0.98 |
| M−           | 24 (57.15%)    | 34 (57.62%) | /     |
| **CYP1A1**   | TT             | TC     |
| TT           | 33 (78.57%)    | 9 (21.43%) | 0.84 [0.69–1.03] | 0.10 |
| TC           | 29 (78.37%)    | 8 (21.63%) | 11 (17.19%) | 0.13 |
association between T3801C polymorphism of CYPIA1 and PCAs in the Tunisian and Caucasian populations, respectively. In addition, the results published by Li et al. [22] revealed that no correlation between T3801C polymorphism of CYPIA1 and predisposition to PCAs.

Nevertheless, many studies diverge from our results: Bag et al. [10], Vijayalakshmi et al. [23], Shaik et al. [24] and He et al. [25] postulated a strong involvement of CYPIA1 polymorphism T3801C in PCa development. The results of our study and other reports suggest that the biotransformation enzyme CYPIA1 T3801C is polymorphic in the prostate tissue. Also, CYPIA1 T3801C gene polymorphism is involved with elevated enzymatic activity and/or inducibility which can result in an accumulation of genotoxic compounds and consequently to cancerogenesis.

In the current study, GSTM1 wild and null genotypes were found, respectively, in 42.57 and 57.42% of PCa patients. A similarity was observed in the healthy controls (50.49% wild type and 49.50% null type, respectively). These results indicated no statistically significant association between GSTM1-null genotype and the increased risk of PCa. The lack of significant association of homozygous GSTM1-null gene in our study is consistent with reports from studies in South India, Japanese, American and Africans populations [26]. Also, these results are in agreement with the results of Mallick et al. [27] and Souiden et al. [28] in a Caribbean of African descent and Tunisian populations, respectively.

Conversely, our finding is not consistent with Turkish, [29] Iranian [30], Chilean [31], Japanese [32] and North Indian [33] studies, where significant association was found between the GSTM1-null genotype and risk of sporadic prostate cancer.

A number of studies presented in a meta-analysis of Wei et al. [34] (combined results of 36 studies including 6202 cases and 8209 controls) and Zhong-Yang Wang et al. [35] (contained data from 6741 patients and 9053 controls) were marked an association between the GSTM1-null genotype and PCa risk in the overall population and Asians. These variations may be attributed to the underlying geographical and ethnic factors.

We also investigated the association of GSTT1 and PCa. The frequency of the GSTT1-null genotype was higher among patients (37.62%) than the controls (22.77%); the association was statistically significant (OR = 2.03, CI [1.06–3.99], \( p = 0.03 \)).

In our study, there was an increased risk of PCa with the GSTT1-null genotype, as reported in the Tunisian and Korean populations [28, 36]. Thus, GSTT1-null genotypes were associated with more than threefold increased risk of PCa in Iranian men [30].

Forty-three reports represented in the meta-analysis of Yang et al. [19] were recruited data from 26,393 subjects (9934 cases and 16,459 controls). There was marked an association between the GSTT1-null genotype and prostate cancer risk in the overall population. However, published results of Zhou et al. [37] indicate that GSTT1-null genotype is associated with PCa risk in Caucasians, but not in the overall population. On the contrary, other studies found no evidence of an association between GSTT1 polymorphism for an increased risk of PCa [38, 39].

In addition, GSTT1 deletion was not correlated with prostate cancer in Asian, Caucasian, Korean, African and American men [40]. Other more meta-analysis have given the same result [41, 42].

When the two genotypes were combined, we observed that the presence of the genotypes GSTM1-null/GSTT1-null (double null) was associated with an increased risk for developing PCa. Similar results have been found in Iran [30].

In this context, we can suggest that the double mutated genotype may play an important role in the susceptibility of PCa. Dual null deletion of GSTM1 and GSTT1 was not associated with prostate cancer in studies of African descent, Brazilian and Caucasians [43]. Another meta-analysis showed no association of these two genes in the development of prostate cancer [44].

The genotypes studied in the present work were also correlated with histopathologic parameters: Gleason scores and clinical stages at diagnosis of prostate cancer. The stratified analysis of studied polymorphisms on grade/stage of the patients did not reveal any significant association suggesting that the genotypes are not associated with the stage or aggressiveness.

Lima et al. [45], Rodrigues et al. [46] did not observe any association with GST and CYPIA1 genotypes and parameters of aggressiveness at diagnosis.

On the other hand, Safarinejad et al. [30] demonstrated that GSTM1-null and GSTT1-null genotype was observed in a higher frequency in patients with a Gleason score > 7.

Since the GSTM1-null genotype is more frequent than GSTT1-null, this indicates that loss of function of GSTT1 has a more deleterious effect than GSTM1. In addition, GSTM1 and GSTT1 polymorphisms could cause disparities in enzyme activities, and GSTM1-null/GSTT1-null individuals have a complete absence of activity of these enzymes. 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 [47].
There was no significant association between the GSTM1, GSTT1, CYPIA1 genotypes and the clinicopathological factors of prostate cancer. To better understand the role of these variants and to study their predictive value, tumor prognostic criteria should be examined, such as cancer-specific survival and overall survival.

The introduction of new molecular biomarkers such as GSTs and CYPs in the management of patients with PCa may improve their clinical results.

Our study has some limitations. First, the sample size for genetic analysis is relatively small. Therefore, further studies should be done on a larger scale for confirmation of our results and functional studies undertaken to explore the effect of GST and CYP variants.

6 Conclusions
This study presents the first data on the frequency of CYPIA1 (T3801C), GSTM1 and GSTT1 polymorphisms in an Algerian population. We did not find significant associations between genetic polymorphisms (CYPIA1 T3801C genotypes and GSTM1-null) and PCa. However, we have indicated that GSTT1-null and GSTM1/GSTT1 double null are associated with increased risk of prostate cancer.

Abbreviations
CYP: cytochrome P450; DRE: digital rectal examination; GSTA: human glutathione S-transferase alpha; GSTB: glutathione S-transferase epsilon; GSTC: glutathione S-transferase kappa; GSTD: glutathione S-transferase mu; GSTG: glutathione S-transferase omega; GSTH: glutathione S-transferase pi; GSTS: glutathione S-transferase sigma; GSTT: glutathione S-transferase theta; GSTT1: glutathione S-transferase zeta; PCR-RFLP: polymerase chain reaction restriction fragment length polymorphism; PSA: prostate-specific antigen; XME: xenobiotic-metabolizing enzymes.

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Authors’ contributions
SM gave idea and contributed to protocol/project development, data collection or management, data analysis and manuscript writing/editing. DR contributed to protocol/project development, manuscript writing/editing and final correction of the manuscript. TK and MC contributed to data analysis. NA contributed to protocol/project development. DS contributed to protocol/project development and final correction of the manuscript. They all approved the final version of the manuscript.

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Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The ethics committee of the Dr. BENBADIS – Constantine University Hospital Centre has approved the study; Ethical approval number 03. The use of human blood sample and the protocol in this study strictly conformed to the principles expressed in the Declaration of Helsinki. We work in accordance with the Declaration of Helsinki (1964): Ethical principles applicable to medical research on human subjects and in accordance with the recommendations of the Algerian national council for ethics in health sciences. Informed consent (written) was obtained from all participants.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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