ABSTRACT

Objective: The single nucleotide polymorphism C677T of the methylenetetrahydrofolate reductase (MTHFR) gene encodes a thermolabile enzyme. This polymorphism was found to be implicated in cancer susceptibility. In this study, we analyzed the distribution of the MTHFR C677T polymorphism in two cohorts; patients and controls native of East of Algeria to explore the possible association between this polymorphism and prostate cancer susceptibility.

Methods: Our examination has been conducted in 98 cases and 98 healthy controls. Genotyping was realized by polymersase chain reaction restriction fragment length polymorphism method.

Results: Compared with CC homozygous, the CT heterozygous was found to have a significantly increased risk of prostate cancer (p=0.04; odds ratio [OR]=2.01, 95% confidence interval [CI]: 1.02–3.95). However, no statistically significant difference was observed concerning the TT homozygous (p=0.74; OR=1.25, 95% CI:0.51–3.04).

Conclusion: Our results indicate that the genotype CT is a risk factor for prostate cancer in East of Algeria.

Keywords: Methylenetetrahydrofolate reductase C677T, Polymorphism, Prostate cancer, East of Algeria.
Statistical analysis
Using Epi Info Version 6, differences in allelic and genotypic frequencies have been tested. *p<0.05 was considered statistically significant.

RESULTS
In our study, patients and controls were aged between 49 and 89 years, with an average age of 70.33±7.65 years. General characteristics of the study population represented by: the age of the two cohorts distributed every 10 years, tumor extension, Prostate Specific Antigen (PSA) levels at the time of diagnosis and the existence of a family history of prostate cancer have been shown in Table 1.

Almost all patients have been diagnosed at age 60 and more. Also, 62.24 % of them at late stage and distant metastasis. Furthermore, 58.16 % of patients with PSA levels above 50 ng/ml, underlining delayed diagnosis.

DNA fragments obtained after digestion by the restriction enzyme HinfI and electrophoresis were TT, mutant homozygote (one band of 175 base pairs [bp]); CT, heterozygote (two bands of 198 bp and 175 bp); and CC, wild-type homozygote (one band of 198 bp).

Distribution of allelic and genotypic frequencies for the polymorphism MTHFR C677T between prostate cancer patients and controls and their relation with risk of prostatic carcinogenesis is presented in Table 2.

Our results showed that the 677 CT genotype was frequent between cases (p=0.04), (odds ratio [OR]: 2.01, confidence interval [CI]: 1.02–3.95), suggesting that they may be a risk factor for prostate cancer. On the other hand, for the 677 TT genotype, any statistically significant difference between cases and controls was observed (p=0.74), (OR: 1.25, CI: 0.51–3.04). Concerning the T allele frequency of the C677T SNP was 0.41 for patients and 0.36 for controls.

DISCUSSION
This paper reports for the first time in Algeria the relation between the MTHFR C677T polymorphism and susceptibility to developing prostatic cancer. Our results showed that there was an association between the MTHFR 677CT heterozygous and prostate cancer: In agreement with our results, Van Guelven et al. [7], Marchal et al. [20], López-Cortés et al. [17] and Abedinzadeh et al. [21] reported a positive association between the polymorphism C677T and risk of prostate cancer in the Swedish population, Spanish population, Ecuadorian, and Asians, respectively.

The significant association between the CT genotype and risk of prostate cancer may be explained by the possibility to keep a sufficient stock of methionine to support neoplastic clone progression compared with the TT homozygous [20].

However, various investigations have not found any relation between this polymorphism and prostate cancer in Caucasians population [4], the Swedish population [6], and Americans [22]. As well, the meta-analysis managed by Collin et al. [23], Zhang et al. [24], and recently, Abedinzadeh et al. [21] has concluded that the C677T polymorphism, in general, has no effect on the occurrence of prostate cancer.

Besides, other authors observed that the T allele exerts a protective impact on prostate cancer risk. Like they indicated Marchal et al. [20], and Guo et al. [25] that the genotype 677 TT is a protective factor in Spanish and Asians, respectively. As well, Cai et al. [26] showed that the TT genotype has been associated with a reduced risk of prostate cancer in the Chinese population, and the T allele exerts probably a protective effect on the risk of this cancer type. Furthermore, Li and Xu [27], who had carried out a meta-analysis, have reported the same result for the T allele. Sahinnejad et al. [28] have studied the association between tumoral aggressiveness and TT, CT, and CC genotypes: The comparison showed that TT homozygous reduced by more than 50 % the risk of high-grade prostate cancer (Gleason score >7).

In addition, Küçükhisyen et al. [29] proposed that the CT genotype and the T allele might be associated with decreased risk of prostate cancer among the Turks. Singal et al. [30] suggested that the CT genotype was associated with a reduced risk of prostate cancer.

To explain the protective effect of the T allele on prostate cancer, it has been proposed that the mutant 677 TT genotype was associated with significantly decreased DNA methylation status. The reduced activity of MTHFR enzyme, coded by the T allele, decreases the SAM synthesis, the headmaster donor of a methyl group for DNA methylation reactions, favor thereby tumor suppressor genes expression [20]. Second, the thermolabile enzyme increases the pool of the 5,10-methylenetetrahydrofolate, requisite for purine and deoxythymidylate triphosphate synthesis, which is the leader nucleotide, required for DNA reparation, consequently, a decrease of uracil incorporation inside DNA, reduce thereby chromosome breaks [20,31]. Furthermore, in vitro experiences approve that inhibition of MTHFR enzyme conduct to decreasing tumor development due to the limited methionine provision, which leads to stop the cell cycle on steps S and G2, damage thus their proliferative potential [20].

The contradictory results from studies of different populations may be explained by the method by which controls have been selected, the ethnic origin of cases and controls, geographical region, lifestyle and exposition to some factors [32-33].

CONCLUSION
The results suggest for the first time, but in a small sample of subjects, that the 677 CT heterozygous is a risk factor for prostatic carcinogenesis. Further researches should be undertaken that includes other possible genes that participate in the homocysteine metabolism, such as MTHFR: Methylenetetrahydrofolate reductase.
methionine synthase. The influence of the environment, the gene-gene as well as gene-environment interactions should also be performed to clarify their possible roles in prostate carcinogenesis.

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AUTHORS CONTRIBUTION

Tellouche-Bouhouhou Samah performed the genotyping, drafted the manuscript, Mrs. Chellat-Rezgoune Djalila “supervisor” and Satta Dallia corrected and revised the manuscript, Abadi Nourreddine director of Biological and Molecular Genetics Laboratory, Dahdouh Abderrezak thesis advisor. The final manuscript has been approved by all authors.

CONFLICT OF INTERESTS

All authors declare that they have any conflict of interest. This article has not been published previously, nor is it under consideration for publication elsewhere.

REFERENCES