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HEAD AND NECK

Association between XRCC3 Thr241Met polymorphism and laryngeal cancer susceptibility in Turkish population

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Abstract DNA repair systems are essential for normal cell function. Genetic alterations in the DNA repair genes such as X-ray repair cross-complementing group 3 (XRCC3), can cause a change in protein activity which results in cancer susceptibility. The aim of this study was to investigate the association of XRCC3 Thr241Met single nucleotide polymorphism (SNP), smoking and alcohol consumption with the risk of laryngeal cancer in Turkish population. The frequencies of Thr241Met SNP were studied in 58 laryngeal cancer cases (SSC) and 67 healthy individuals. Genomic DNA was isolated from peripheral blood samples of both controls and laryngeal cancer cases. Thr241Met SNP was genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) method. The genotype and allele frequencies of Thr241Met polymorphism were not statistically significant between the laryngeal cancer and control groups. Carrying mutant allele was not associated with the risk of laryngeal cancer. On the other hand, smoking and chronic alcohol consumption were associated with the risk of laryngeal cancer but there is no association between Thr241Met, smoking and alcohol consumption in laryngeal cancer cases. These results indicate that Thr241Met polymorphism was not associated with the development of laryngeal cancer in Turkish population. However, it should be kept in mind that the association of a polymorphism with cancer susceptibility can differ due to several factors such as cancer type, selection criteria, ethnic differences and size of the studied population.

Keywords Laryngeal cancer · SNP · XRCC3 · DNA repair

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Introduction

Laryngeal cancer is one of the largest subgroup of head and neck cancers [1]. According to the American Cancer Society, the incidence is 5 in 100,000 in the USA, being listed as a "rare disease" by the office of Rare Diseases of the National Institutes of Health [2]. The majority of the laryngeal cancer cases are males [3]. Most common histopathological type of the laryngeal cancer is squamous cell carcinoma (85–90 %) reflecting their origin from the squamous cells of the laryngeal epithelium [4, 5]. It can be develop in any part of the larynx [4]. Treatment strategy depends on the location, type and stage of the tumor which involves surgery, radiotherapy and/or chemotherapy [6].

However, the mortality rate of the disease remains high, with a 5-year survival rate of approximately 65 % [7].

Smoking is one of the most important risk factor for laryngeal cancer while heavy chronic consumption of alcohol is another important factor for the development of the disease. When combined, these two factors appear to have synergistic effect [8, 9]. Although smoking and consumption of alcohol account for laryngeal cancer, specific carcinogenic mechanisms are unclear [8–10].

There is growing evidence that cancer can be initiated by DNA damage caused by radiation and environmental chemical agents [11]. Due to the metabolites of tobacco and alcohol, DNA damage can occur as a result of oxidative stress, alkylation, bulky adducts and strand breaks. Moreover, altered DNA repair mechanisms can increase the development risk of laryngeal cancer [12, 13].

To maintain proper functioning of the genome, there are several response mechanisms which ensure repair of DNA lesions. The homologous recombination (HR) pathway which repairs double-strand DNA breaks in the S-G_2 phases of the cell cycle is one of them [14]. The HR is a multistage process and requires the involvement of various proteins, such as RAD51 family. The X-ray repair cross-complementing group 3 (XRCC3), a member of the RAD51 family of proteins that participate in HR, is a highly suspected candidate gene for cancer susceptibility [15–17]. Genetic alterations in the XRCC3 gene can cause a change in protein activity or interaction with the other target proteins [18]. The Thr241Met polymorphism due to (C > T) transition at exon 7 (rs861539) is most throughly investigated polymorphism in XRCC3 gene. Carriers of the variant allele of Thr241Met had relatively high DNA adduct levels in lymphocyte DNA, indicating low DNA repair capacity [19, 20]. In terms of cancer risk, Thr241Met polymorphism has been studied in several cancer types, including bladder, colorectal, breast, lung, head and neck and also in hematological malignancies. However, the findings of the studies in the literature are inconsistent, indicating both negative and positive association of Thr241Met polymorphism and cancer susceptibility. As a result, the association is still unclear [21–23].

In this study, we aimed to assess the association of XRCC3 polymorphism, smoking and alcohol consumption with the risk of laryngeal cancer in Turkish population.

Methods

Study subjects

Fifty-eight unrelated laryngeal (squamous cell carcinoma) cancer patients diagnosed clinically at Dışkapı Yıldırım Beyazıt Training and Research Hospital; Department of Otorhinolaryngology and 67 unrelated healthy volunteers were randomly selected from different geographic regions of Turkey. Control group was matched to the patient group by age and sex. Peripheral blood samples and the consent of local ethical committee were obtained from Dışkapı Yıldırım Beyazıt Traning and Research Hospital (# 13/30). The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

DNA isolation and polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP)

Genomic DNA was isolated from peripheral blood samples of both controls and laryngeal cancer cases using NucleoSpin® DNA isolation kit (Macherey-Nagel, Germany) according to manufacturer's instructions. DNA amplification was carried out on a Techne TC-512 PCR system in a 50-µl reaction mixture containing 10× PCR buffer (BioLabs Inc. New England, Hertfordshire, UK), 25 mM magnesium chloride (BioLabs Inc. New England, Hertfordshire, UK), 200 µM dNTP (BioLabs Inc. New England, Hertfordshire, UK), 10 pmol of forward (F: 5′-GGTCGAGTGACAGTCCAAAC-3′) and reverse (R: 5′-TGCAACGGCTGAGGGTCTT-3′) primers (Iontek, İstanbul, Turkey), 0.5 µU Taq DNA polymerase (BioLabs Inc. New England, Hertfordshire, UK) and 50 ng genomic DNA. The PCR cycling conditions consisted of an initial denaturation step at 95 °C for 5 min followed by 40 cycles of 94 °C for 1 min, 56 °C for 1 min, 72 °C for 1 min and final extension step at 72 °C for 5 min. The 456 bp PCR products were digested at 37 °C for 15 min with 10U CutSmart, NlaIII restriction endonuclease enzyme (BioLabs Inc. New England, Hertfordshire, UK). The products with the 241Thr genotype result in 315 and 141 bp products, while 241Met genotype gives 210, 141 and 105 bp products. The XRCC3 variants were separated on a 2.5 % agarose gel electrophoresis at 120 V, stained with ethidium bromide (0.5 µg/ml) and visualized under a UV transilluminator (Vilber Lourmat, Marne-la-Vallée, France).

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 16.0 software was used for statistical analysis. The frequencies of XRCC3 alleles and genotypes were obtained by direct count and departure from the Hardy–Weinberg equilibrium was evaluated by Chi square analysis. A p value <0.05 was considered as statistically significant. Odd ratios (OR) and 95 % confidence intervals (CI) were also calculated.

Results

Genotype distribution for Thr241Met polymorphism of laryngeal cancer cases and controls was determined using PCR–RFLP method. DNA fragments representing homozygote wild type (C/C), heterozygote (C/T) and homozygote mutant (T/T) type are shown in Fig. 1.

Distribution of Thr241Met polymorphism genotype in cases ($\chi^2 = 0.388$; $p = 0.752$) and controls ($\chi^2 = 0.448$; $p = 0.603$) corresponds to Hardy–Weinberg expectation. Genotype and allele frequencies of XRCC3 gene polymorphism are given in Table 1. Among 58 laryngeal cancer cases, 48 % were found to be homozygote for wild type (C/C), 45 % were heterozygote (C/T) and 7 % were homozygote mutant type (T/T). The C allele frequency was 61 % and T allele was 25 %. On the other hand, in the control group, 40 % were found to be homozygote for wild type, 43 % were heterozygote and 17 % were homozygote mutant type. The C allele frequency was found as 62 % while T allele frequency was 38 %. The results indicate that the genotype and allele frequencies of Thr241Met polymorphism were not statistically significant between the laryngeal cancer cases and control group ($p > 0.05$). Moreover, carrying mutant allele 241Met was not associated with the risk of laryngeal cancer (OR 1.4819; 95 % CI 0.8717–2.5190).

Subsequently, we performed an analysis of the influence of smoking and chronic alcohol consumption with the risk of laryngeal cancer and also association with Thr241Met polymorphism. Among 58 laryngeal cancer cases, 93 % were smoking and 39 % were using alcohol, while for the control group these ratios were only 23 and 3 %, respectively ($p < 0.05$). These results indicate that people who are smoking and having chronic alcohol consumption have more risk in developing laryngeal cancer with respect to non-smokers and no alcohol users. However, there is no association between Thr241Met polymorphism, smoking ($p = 0.083$) and alcohol consumption ($p = 0.213$) among laryngeal cancer cases (Table 2).

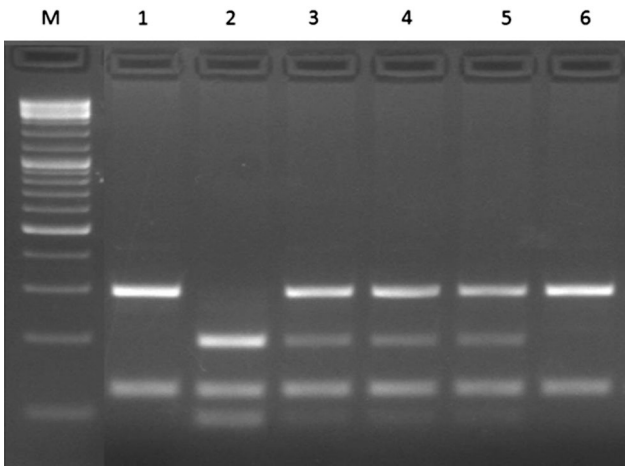

Fig. 1 A representative agarose gel image of digested PCR products with NlaIII restriction endonuclease enzyme. *M* 100 bp marker, *lanes 1* and *6* homozygote wild type (C/C), *lane 2* homozygote mutant type (T/T), *lanes 3*,*4* and *5* heterozygote (C/T)

Table 1 Genotype and allele frequencies of XRCC3 Thr241Met polymorphism in laryngeal cancer cases and controls

	Control ($N = 67$) N (%)	Cases ($N = 58$) N (%)	P value	OR (95 % CI)
Genotype				
C/C	27 (40)	28 (48)	0.245	Ref
C/T	29 (43)	26 (45)		1.0647 (0.5244–2.1613) $P = 0.862$
T/T	11 (17)	4 (7)		0.3771 (0.1131–1.2569) $P = 0.112$
Allele				
C	83 (62)	82 (61)	0.150	Ref
T	51 (38)	34 (25)		1.4819 (0.8718–2.5190) $P = 0.146$

Discussion

Smoking and alcohol consumption are the major risk factors for head and neck cancers including laryngeal cancer, likely due to DNA-damaging processes [8]. Metabolites of tobacco and alcohol cause DNA damage and altered DNA repair capacity may increase the risk of cancer [12, 24, 25]. Functional analysis of the XRCC genes continues to make a contribution of mammalian DNA double-strand break repair processes and mechanisms of genetic instability leading to cancer [26]. XRCC3 is a highly suspected candidate gene for cancer susceptibility and Thr241Met polymorphism in XRCC3 gene has been examined for the association of various cancer types by many research groups [27–31].

In the present study, we investigated the association between Thr241Met polymorphism and laryngeal cancer in Turkish population. In addition, we also searched for the influence of smoking and chronic alcohol consumption with the risk of laryngeal cancer and their association with Thr241Met polymorphism. Our results demonstrate that Thr241Met polymorphism does not correlate with the development of laryngeal cancer and carriers of the polymorphic allele has not an elevated risk in the selected Turkish patient group.

According to the literature, the association between Thr241Met polymorphism and cancer susceptibility

Table 2 Association between Thr241Met polymorphism, smoking and alcohol consumption in laryngeal cancer cases

Cases ($N = 58$)	Smoking ($N = 54$)	Non-smoking ($N = 4$)	P value	Alcohol consumption ($N = 23$)	Not alcohol consumption ($N = 35$)	P value
C/C	28	0	0.083	11	17	0.213
C/T	23	3		12	14	
T/T	3	1		0	4	

remains conflicting. There are studies indicating that T/T genotype for Thr241Met polymorphism is associated with AML in Romanian population [32] where there is a controversial report for AML in Egyptian population [33]. In addition, Thr241Met polymorphism was shown to associate with the risk of glioma in Chinese population [34]. However, some of the studies failed to find a significant association with lung cancer in Caucasians and African Americans [30], colorectal cancer in Polish population [29], and oral cavity cancers in Brazilian patients [35].

Conflicting reports also exist for head and neck cancers. There are various reports which show the association between XRCC3 Thr241Met polymorphism and head and neck cancer susceptibility [10, 28, 36, 37], whereas in one of the study it was shown elevated but not significant risk [27]. On the other hand, in several studies including a meta-analysis [38, 39], it was shown that there is no significant association of Thr241Met polymorphism with laryngeal cancer [38] which support our results. These controversial results can be due to several factors such as cancer type, selection criteria, ethnic differences and size of the studied population.

Smoking and alcohol consumption are the major risk factors for head and neck cancers including laryngeal cancer, due to the generation of reactive oxygen species, which are capable of inducing DSBs in DNA [10, 39]. Polymorphisms in XRCC3 gene, involved in DSBs repair pathways, may alter an individual's susceptibility to smoking-related cancers [39]. In this study, we also investigated the influence of smoking and alcohol consumption with the risk of laryngeal cancer and also association with Thr241Met polymorphism. The results indicated that smoking and chronic alcohol consumption were both significantly associated with the development of laryngeal cancer. However, we did not observe an association between smoking or chronic alcohol consumption and Thr241Met polymorphism in our patient group. Assessment of effect modification may be necessary for the studies of DNA-repair polymorphisms, because a single polymorphism, with weak effects on the individual's phenotype, may not be measurable except in the context of some supporting environmental factors. However, there are very limited studies investigating the interactions between XRCC3 polymorphisms and environmental factors. In a meta-analysis, four studies were combined because of their stratification data on smoking and the effect of smoking on the susceptibility of XRCC3 Thr241Met on different types of cancers [27, 40–43]. There is also a study which shows an association between Thr241Met polymorphism and smoking status as well as alcohol intake in precancerous hyperplastic laryngeal lesions and head and neck squamous cell carcinoma subjects. Our results are not in consistency with these results. The differences can be due to cancer type, selection criteria, ethnic differences and size of the studied population.

In conclusion, XRCC3 Thr241Met polymorphism does not correlate with the development of laryngeal cancer in Turkish population. Moreover, carrying mutant allele was not associated with the risk of the disease. On the other hand, smoking and chronic alcohol consumption were associated with the risk of laryngeal cancer cases but there is no association between Thr241Met, smoking and chronic alcohol consumption in laryngeal cancer cases. Although no significant relation was identified in our studied group, the association of a polymorphism with cancer susceptibility can differ due to several factors such as cancer type, selection criteria, ethnic differences and size of the studied population.

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