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NOT *PON1 L55M* BUT *ACE* I/D VARIANT MIGHT BE A RISK FACTOR FOR OSCC IN THE TURKISH POPULATION

TÜRK POPÜLASYONUNDA ACE I/D VARYANTI OSCC İÇİN BİR RİSK FAKTÖRÜ OLABİLİR FAKAT PON1 L55M RİSK FAKTÖRÜ DEĞİLDİR

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ABSTRACT

Objective: Oral squamous cell carcinoma (OSCC) covers more than 90% of the malignant neoplasms in the mouth. It has been shown that angiotensin-converting enzyme (*ACE*) and paraoxonase (*PON1)* gene variants were associated with several cancers. Therefore, we investigated the possible association between *ACE* insertion/deletion (I/D)-*PON1* L55M variants and OSCC development risk in a Turkish population.

Material and Methods: A total of 155 people (104 healthy controls and 51 OSCC patients) made up the study population. These variants were genotyped using polymerase chain reaction (PCR) and/or restriction fragment length polymorphism (RFLP) assays.

Results: *ACE* I/D allele frequencies were significantly different between patients and controls. The *ACE* D allele was higher in the patient group compared to the control group, while the I allele was more prevalent in controls than patients (*p<0.0000001*). When the patients and controls were examined based on the II+ID vs. DD genotype and II: ID vs. DD, a statistically significant correlation was found (*p = 0.0000001* and *p = 0.008691,* respectively). The genotype and allele distribution of *PON1* L55M did not significantly differ between the groups.

Conclusion: In conclusion, our study showed that the *ACE* I/D variant D allele is a risk factor for the development of OSCC in Turkey. This study contributes to more studies to confirm that *ACE* I/D plays a role as a genetic risk factor for OSCC.

Keywords: Oral squamous cell carcinoma, angiotensin-converting enzyme, paraoxonase, variant

ÖZ

Amaç: Oral skuamöz hücreli karsinom (OSCC), ağızdaki malign neoplazmların %90'ından fazlasını kapsar. Anjiyotensin dönüştürücü enzim (ACE) ve paraoksonaz (PON1) gen varyantlarının birçok kanserle ilişkili olduğu gösterilmiştir. Bu nedenle, Türk popülasyonunda ACE I/D-PON1 L55M varyantları ile OSCC gelişim riski arasındaki olası ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışma popülasyonu toplam 155 bireyden oluşmaktaydı (51 OSCC hastası ve 104 sağlıklı kontrol). ACE I/D - PON1 L55M varyantları, PCR ve RFLP analizleri kullanılarak genotiplendi.

Bulgular: ACE I/D alel frekansları hastalar ve kontroller arasında anlamlı şekilde farklılık göstermiştir. ACE D aleli, hasta grubunda kontrol grubuna kıyasla daha yüksek iken, I aleli kontrollerde hastalara kıyasla daha fazlaydı (p<0,0000001). Hastalar ile kontroller, II+ID vs. DD genotipine (p=0,0000001) ve II: ID vs. DD'ye (p=0,008691) göre karşılaştırıldığında istatistiksel olarak anlamlı bir ilişki gözlendi. PON1 L55M genotipi veya alel dağılımı açısından hastalar ve kontroller arasında anlamlı bir fark bulunamadı (p>0,05).

Sonuç: Sonuç olarak çalışmamız ACE I/D varyant D alelinin Türkiye'de OSCC gelişimi için risk faktörü olduğunu gösterdi. Bu çalışma, ACE I/D'nin OSCC için genetik bir risk faktörü olarak rol oynadığını doğrulamak amacıyla yapılacak daha fazla araştırmaya katkı sağlamaktadır.

Anahtar Kelimeler: Anjiyotensin dönüştürücü enzim, oral skuamöz hücreli karsinom, paraoksonaz, varyant

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) covers more than 90% of the malignant neoplasms in the mouth (1). Risk factors for OSCC include tobacco and alcohol consumption, chronic inflammation, viral infection, and betel quid chewing (2). Despite being administered with surgery, radiation, and chemotherapy, OSCC is still considered to have a poor prognosis (3). Multiple genetic alterations cause OSCC because of chronic exposure to environmental carcinogens. There has been an association between common polymorphisms in inflammation, angiogenesis, and thrombosis-related genes and a higher risk of OSCC.

A zinc metallopeptidase in the cell surface, angiotensin-converting enzyme (ACE), is the renin-angiotensin system (RAS) system enzyme that plays the physiologic role of converting angiotensin I (Ang I) into angiotensin II (Ang II) and inactivating bradykinin. Ang II has been shown to have proliferative, angiogenic, and promitotic effects and therefore plays a role in the growth and proliferation of the tumour cells through the Ang II type 1 receptor (4). ACE may promote tumor cell proliferation, angiogenesis, migration, and metastatic behavior (5). There are 25 introns and 26 exons in the *ACE* gene (17q23.3 locus), which encode the ACE enzyme (6). Intron 16 contains a functional polymorphism as the deletion (D allele) and/or insertion (I allele) (7). *ACE* I/D variant (rs1799752) may affect Ang I-converting enzyme function and *ACE* gene expression. There is an association between the D allele presence, higher production of angiotensin II, and higher activity of the ACE enzyme than the I allele. Several studies have been recently conducted on the role of the *ACE* I/D variant in the risk of several cancers, but the results of these studies are contradictory.

Paraoxonase-1 (PON1) has strong lipophilic antioxidant properties and is an antioxidant enzyme maintain the antioxidant-oxidant balance. Human PON1 is related to a family of three serum paraoxonase, including PON3 and PON2. However, PON1 continues to be the most famous member of this family (8). At the same time, PON1 binds to involve high-density lipoprotein (HDL) an esterase in scavenging reactive oxygen species. Studies have found the participation of oxidative stress in the proliferation of cells and the malignant transformation process, damaging DNA and other biological molecules, leading to the occurrence of the tumour (9). The *PON1* gene is located on the seventh chromosome and the short arm at the q21-q22 locus. Replacing 55 leucines (L genotype) with methionine (M genotype) at the third exon caused 55 *PON1*-L55M (rs854560). The *PON1*-55M allele was shown to be associated with increased PON1 activity compared with the *PON1*-55L allele (10). This variant was associated with multiple cancer development.

Thus, the objective was to investigate the potential association between the risk of developing OSCC and ACE I/D-PON1 L55M variations in a Turkish population.

MATERIAL AND METHODS

Study population

ACE and *PON1* variants were studied in 51 OSCC patients (mean age: 61.51±13.07 years) pathologically confirmed and 105 age-matched healthy individuals (mean age: 59.50±9.39 years) with no disease history as a control group. This study obtained samples from the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Hitit University. All patients underwent oral examination, detailed medical history, and pathological diagnosis in the study. All patients underwent oral examination, detailed medical history, and pathological diagnosis in the study. Our study's control group consisted of people without a history of cancer at any site, leukoplakia, erythroplakia, or any oral precancerous diseases. In compliance with the 2008 Declaration of Helsinki's ethical guidelines, all patients and subjects gave their written informed consent before taking part in the study. The Hitit University ethics commission gave the study its clearance (Date: 19.12.2017, No: 2017/200).

Genotyping

We used the DNA Isolation Kit (PureLink Genomic DNA Mini Kit; Invitrogen) to isolate the genomic DNA from the peripheral cells. As previously mentioned, these variations were genotyped using PCR and/or the restriction fragment length polymorphism (RFLP) approach (11, 12). *ACE* I/D genotypes were determined by PCR. Forward 5'-CTGGAGACCACTCCCATCCTTTTTTTT-3' and reverse 5'-GATGTGGCCATCACATTCGTCAAGT-3' were used for the reactions. Reactions were set up in a volume of 25 µL containing 1.5 µL of each primer, 12.5 µL master mix, 7.5 µL H2O, and 2 µL deoxyribonucleic acid (DNA). After initial denaturation at 95°C for 7 min (min) and 94°C for 45 seconds (sec), the reaction mixtures were subjected to 35 cycles of 60°C for 30 s, 72°C for 45 s, and a final extension at 72°C for 7 min. After staining with ethidium bromide, we examined the PCR products on 2% agarose gels and observed them using a UV transilluminator. PCR revealed the variant as a roughly 490-bp fragment when the insertion (I) allele was present and as a roughly 190-bp fragment when the insertion (D) allele was absent. With the forward: 5'-GAA GAG TGA TGT ATA GCC CCA G-3' and reverse: 5'-TTT AAT CCA GAG CTA ATG AAA GCC-3' primers, the *PON1* L55M variant was amplified. In order to digest the amplified 170 bp product, NlaIII was used. The L allele remained intact, but the M allele was digested into 126- and 44-bp fragments.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 20.0 for Windows (IBM SPSS Corp., Armonk, NY, USA) was used for data analysis. The standard deviation and mean were used to present the continuous quantitative variables. The relationships between ACE I/D and PON1 L55M variants and the patients' demographic/clinical characteristics were analysed with the $\chi 2$ test, analysis of variance (ANOVA) statistics, or Fischer exact test. The associations between the genotypes of these variations and the allele distribution were determined using odds ratios (ORs) and 95% confidence intervals (CIs). A p-value of 0.05 was considered statistically significant.

RESULTS

The 51 OSCC patients and 105 controls were genotyped for *ACE* I/D and *PON1* L55M variants. Table 1 shows the participants' clinical and demographic characteristics. Table 2 shows the distributions of the genotype and allele of the *ACE* and

Table 1. Baseline clinical and demographic features of patients with OSCC

Characteristics	Controls (n=105)	Patients (n=51)
Gender, female/male, n (%)	35/70 (33.3/66.7)	18/33 (35.3/64.7)
Age, mean ± SD, years	59.50±9.39	61.51±13.07
Job		
Farmer, n (%)		11 (26.2)
Housewife, n (%)		12 (28.6)
Worker, n (%)		15 (36.7)
Officer, n (%)		3 (7.1)
Unemployed, n (%)		1 (2.4)
Smoking		
Yes, n (%)		5 (11.9)
No, n (%)		30 (71.4)
Ex-smoking, n (%)		7 (16.7)
Smoking Duration		
10-20 years, n (%)		2 (15.4)
20-30 years, n (%)		6 (46.2)
>30 years, n (%)		5 (38.5)
Daily cigarette consumption		
One package, n (%)		4 (33.3)
> One package, n (%)		8 (66.7)
Alcohol consumption, Yes/No, n (%)		8/34 (19/81)
Frequency of alcohol consumption		
Daily, n (%)		5 (62.5)
Social drinker, n (%)		3 (37.5)
Family history, Yes/No, n (%)		7/35 (16.7/83.3)
Response to treatment, Yes/No, n (%)		29/12 (70.7/29.3)
Patients status		
Alive, n (%)		35 (83.3)
Exitus, n (%)		7 (16.7)
Disease State		
Complete response, n (%)		27 (65.9)
Stable disease, n (%)		2 (4.9)
Metastatic disease, n (%)		12 (29.3)
Disease area		
Intra-oral, n (%)		3 (7.1)
Floor of the mouth, n (%)		3 (7.1)
Buccal, n (%)		1 (2.4)
Roof of the mouth, n (%)		3 (7.1)
Tongue, n (%)		12 (28.6)
Lip, n (%)		16 (38.1)
Oral mucosa, n (%)		1 (2.4)
Tonsil, n (%)		2 (4.8)
Cheek mucosa, n (%)		1 (2.4)

Table 2. Genotype and allele distribution of *ACE* I/D and *PON1* L55M variants in the groups

***ACE* I/D**			
	OSCC patients n = 51 (%)	**Control group n=105 (%)**	**p**
Genotypes			
I/I	4 (7.8)	27 (25.7)	
I/D	10 (19.6)	54 (51.4)	>0.05
D/D	37 (72.5)	24 (22.9)	
II + ID: DD	4+10:37	27+54:24	**0.0000001**
II: ID + DD	4:10+37	27:54+24	**0.008691**
Alleles			
I	18 (17.65)	108 (51.43)	**<0.0000001**
D	84 (82.35)	102 (48.57)	
***PON1* L55M**			
Genotypes	**OSCC patients n = 51 (%)**	**Control group n=105 (%)**	**p**
L/L	24 (47.1)	48 (45.7)	
L/M	19 (37.2)	47 (44.8)	>0.05
M/M	8 (15.7)	10 (9.5)	
MM + LM: LL	8+19:24	10+47:48	0.8744
MM: LM + LL	10:47+48	10:47+48	0.2593
Alleles			
L	67 (65.68)	143 (68.09)	0.6705
M	35 (34.32)	67 (31.91)	

The results that are statistically significant are shown in boldface

PON1 variants in the groups. The *ACE* I/D variant genotype distribution was not statistically different between the OSCC patients and controls (p>0.05). *The ACE* I/D D allele frequency significantly differed between the patients and controls. The patient group had a higher *ACE* I/D D allele than the control group, while the I allele was more prevalent in controls than patients (p<0.0000001). A statistically significant association was observed between II + ID vs. DD genotype and II: ID vs. DD (p=0.0000001, p= 0.008691, respectively). The OSCC patients and controls had no significant association regarding any allele or genotype frequency of the *PON1* L55M.

DISCUSSION

Several countries worldwide have seen the incidence of OSCC, which is a severe public health issue (13). Oral carcinogenesis is characterised by several epigenetic and genetic alterations as a complex pathological process, allowing the change of biologically healthy cells into functionally altered cells due to higher invasiveness, cell proliferation rates, and metastases. The RAS as a hormonal system causes increased cell proliferation through the active peptide Ang II signaling, stimulating neovascularization. Increasing evidence shows that vascular endothelial growth factor (VEGF)-mediated angiogenesis is promoted by ang signaling in malignancy by indirectly modulating the vascular cell growth during angiogenesis and directly impacting stromal cells and tumours (14). Matsushima-Otsuka et al. found an increase in the expression of Ang-II type 2 receptor (AGTR2) and Ang-I type 1 receptor (AGTR1) with the progression of OSCC (15). In contrast, AGTR2 exhibited a more pronounced increment than AGTR1, leading to a decrease in the AGTR1 to AGTR2 ratio in advanced-stage cases. Higher levels of ACE occurred in the mouth, larynx, and skin (16). Inhibition of ACE activity in in vitro and in vivo animal models results in suppression of tumor growth and angiogenesis. In addition, epidemiologic studies also found the reduced risk and mortality rate of cancers through ACE inhibitors (17).

Bioinformatic analyses showed that ACE inhibitors had therapeutic potential in OSCC (16). *The ACE* I/D variant, characterized by the absence or presence of a 287-bp Alu repetitive sequence, forms ~50% of the ACE levels. Half of the plasma ACE level may be displayed in homozygote II compared to the homozygote DD, while an intermediate level is displayed by heterozygote DI (17). Several studies have examined the contribution of this variant to the etiology of cancers among various organs, including the breast, lung, gastric, prostate, oral, and others (18). However, the results are contradictory. In a meta-analysis evaluating a total of 25 studies, it was found that in 3914 cancer patients, the *ACE* I/D variant was not related to all cancer risks (19). Also, several studies found *ACE* genotypes unrelated to various types of cancer, such as endometrial cancer and lung cancer (20, 21). However, a study found that the *ACE* D allele had a significant association with hepatocellular carcinoma risk in patients with HCV and a correlation with advanced stage and higher tumour growth (22). Furthermore, Yigit et al. showed an association between prostate tumour metastasis and the PSA level and genetic variation in the *ACE* I/D genotypes (23). Vairaktaris et al. found an association between *ACE* I/D and the progress of oral oncogenesis (17). In addition, Chung et al. found that *the ACE* D/D homozygous genotype was significantly higher in the subjects with oral precancerous lesions in Taiwanese subjects than in the controls (24).

It has been demonstrated that increased levels of reactive oxygen species (ROS) or free oxygen radicals during oxidative stress (OS) drive carcinogenesis by inducing metabolic dysfunction that damages biological macromolecules, including DNA. In this context, DNA bases are oxidated by ROS, forming chromosome aberrations and mutagenic lesions and activating the chemical carcinogens into highly reactive compounds (25). PON1, with its highly lipophilic antioxidant characteristics, is involved in eliminating ROS as an esterase enzyme. PON1 helps detoxify carcinogenic lipid-soluble ROS and organophosphate chemicals produced by lipid peroxidation in addition to its protective function against OS, which is believed to be involved in carcinogenesis (26). It has been reported that lower PON1 activity is associated with different disorders, including senile and diabetic cataracts (27), chronic renal failure (28), age-related macular degeneration (29), and hyperthyroidism (30). In a study measuring serum arylesterase and PON activity in OSCC patients and controls, it was shown that PON and arylesterase activities were decreased in OSCC patients (31). In addition, Metin et al. found that the serum PON1 activity levels were lower in OSCC patients than in controls (32). In a meta-analysis evaluating 19887 cases, 23842 controls, and 43 case-control publications, *PON1* L55M was significantly associated with the overall cancer risk (9). The stratified analyses of the cancer type showed the role of the *PON1*-L55M variant as a risk factor in the incidence of breast cancer, prostate cancer, and haematologic cancer (9). In another meta-analysis, it was found that there was a statistically significant difference between *PON1* L55M and cancer risk (33). The stratified analyses of ethnicity showed a statistically significant higher cancer risk in Caucasian populations. Santana et al. reported that *PON1* rs662 but not *PON1* L55M was associated with poor survival in patients with OSCC (34).

In this study, we evaluated whether *ACE* I/D and *PON1* L55M variants are risk factors for OSCC in the Turkish population. To the best of our knowledge, this is the first study to evaluate the relationship between these variants and the risk of OSCC in our population. We found an association between OSCC and the *ACE* I/D variant D allele. *ACE* D allele was higher in OSCC patients than in healthy controls (Table 2). Also, there was a significant association according to II + ID vs. DD genotype and II: ID vs. DD in comparison of the patients with the controls. The *PON1* L55M variant genotype distribution did not find any statistical difference between the OSCC patients and controls.

There are several limitations to this analysis. First, only two variants of these genes were evaluated. Second, the gene-gene and gene-environment interactions were not investigated for this variant due to a lack of original information. Finally, this study did not express the ACE and PON1 expression levels.

CONCLUSION

In conclusion, our research indicates that the *ACE* I/D variant D allele may be linked to an increased risk of developing OSCC in Turkish patients. This study adds to the body of research confirming the role of *ACE* I/D as a genetic risk factor for OSCC.

Ethics Committee Approval: This study was approved by Hitit University (Date: 19.12.2017, No: 2017/200).

Informed Consent: Written informed consent was obtained from all the participants of the study.

Peer Review: Externally peer-reviewed.

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