

ASSOCIATION OF THE TP53 PIN3 16-BP DUPLICATION POLYMORPHISM WITH ORAL SQUAMOUS CELL CARCINOMA RISK AND PROGNOSIS

Antunović Marija^{1,2}

¹ University of Montenegro, Faculty of Medicine, Podgorica, Montenegro

² Clinical Center of Montenegro, Department for Oral Surgery, Podgorica, Montenegro

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Abstract: Background/Aim: Oral squamous cell carcinoma (OSCC) is associated with multiple risk factors, including genetic variations such as the TP53 PIN3 16-bp duplication polymorphism. This study aimed to assess the association between this polymorphism and susceptibility to OSCC in the Montenegrin population and to evaluate its influence on OSCC prognosis and progression.

Materials and Methods: Genomic DNA extracted from 60 patients with OSCC and 71 cancer-free controls was analyzed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique to identify TP53 PIN3 genotypes and allele frequencies. Clinical and pathological data, along with three-year follow-up outcomes, were also analyzed.

Results: During the follow-up period, 12 patients (20%) experienced local recurrence of disease and 6 patients (10%) developed regional metastases, with no distant metastases detected. No significant associations were observed between the PIN3 16-bp duplication polymorphism and patient age, tumor site, grade, disease recurrence, or metastasis ($p > 0.05$). A significant association between TP53 genotypes and advanced stage of disease was found ($p = 0.006$). There were no significant differences in disease-free survival among genotypes: A1A1 (28.26 ± 1.70 months), A1A2 (35.00 ± 0.94 months), and A2A2 (30.00 ± 5.20 months) ($p = 0.38$). Additionally, no significant differences in allele or genotype frequencies between patients and controls were observed ($p > 0.05$).

Conclusion. The TP53 PIN3 16-bp duplication polymorphism cannot be considered a risk factor for OSCC development in the Montenegrin population. Furthermore, this polymorphism does not modulate susceptibility to OSCC progression.

Keywords: TP53, PIN3 16-bp polymorphism, oral cancer.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is ranked as the 11th most common type of cancer worldwide (1). Carcinogenesis is a complex, multifactorial process influenced by environmental factors and genetic alterations in oncogenes and tumor suppressor genes (2).

The tumor suppressor gene TP53 is the most frequently altered gene across human cancers. It encodes the TP53 protein, a central transcriptional regulator that maintains genomic stability by controlling genes involved in cell cycle arrest, DNA damage response, apoptosis, and cellular senescence (3, 4). Therefore, disruption of TP53 function through either somatic mutations or inherited polymorphic variants can promote malignant transformation and tumor progression, including in OSCC (2).

To date, more than 200 polymorphisms (SNPs) have been identified in both exonic and intronic regions of TP53 (5). Among them, the 16-bp duplication polymorphism (rs17878362) within intron 3 has been widely investigated for cancer susceptibility due to its potential influence on TP53 transcriptional regulation and post-transcriptional processing (3). Accordingly, the insertion allele of this polymorphism has been associated with decreased TP53 expression, possibly through altered splicing efficiency, leading to an increased risk of cancer development (6).

Over the last two decades, a number of studies have shown that the TP53 PIN3 16-bp duplication polymorphism is associated with an increased risk of various malignant tumors, most often breast (5), colon (6), and lung cancer (7). However, data regarding its role

in oral carcinogenesis remain limited and inconsistent. Additionally, the relationship between the TP53 PIN3 16-bp duplication polymorphism and the risk of oral squamous cell carcinoma has not been evaluated in our population.

Therefore, we conducted the present study to investigate the association between the TP53 PIN3 16-bp duplication polymorphism and the risk of OSCC in the Montenegrin population and to evaluate the impact of this polymorphism on OSCC prognosis and progression.

MATERIAL AND METHODS

The study population comprised 60 patients with histopathologically confirmed oral squamous cell carcinoma involving the lower lip, tongue, or floor of the mouth, who underwent surgical treatment at the Clinic for Maxillofacial Surgery, Clinical Center of Montenegro, between 2005 and 2009. The research adhered to the standards of the Declaration of Helsinki (2002 version) and was conducted with the consent of the institutional Ethical Committee.

Patients were followed for three years after surgical treatment, and survival time was measured from the end of primary treatment to the first detection of local recurrence or regional recurrence (nodal metastasis), defined as the disease-free interval (DFI).

The KAPA Express Extract Kit (Kapa Biosystems, Inc., Wilmington, MA, USA) was used for DNA isolation from 60 formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. DNA isolated from peripheral blood samples of 71 healthy individuals, age- and gender-matched to OSCC patients, was used for the association study. The concentration of DNA isolated from blood samples and OSCC tissue was determined spectrophotometrically.

TP53 PIN3 Ins16bp genotyping was performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The reaction mixture (25 μ l) for detection of the PIN3 Ins16bp polymorphism consisted of the following components: 2.5 μ l of 10 \times PCR buffer (MBI Fermentas, Lithuania), 1.5 μ l of MgCl₂, 0.2 mM dNTPs, 0.375 μ M of each primer, 200 ng of DNA isolated from OSCC samples or peripheral blood of healthy individuals, and 1 unit of Taq DNA polymerase.

The PIN3 Ins16bp duplication was amplified using the following primers: 5'-CTGGTAAGGACAA-GGGTTGG-3' and 5'-TCATCTGGACCTGGGTCT-TC-3'. PCR products were 185 bp or 201 bp in length and were resolved on an 8% polyacrylamide gel.

Restriction digestion was performed using the MspI enzyme (MBI Fermentas, Lithuania). The A1A1

genotype was identified by a single fragment of 185 bp, the A1A2 genotype by two fragments of 185 bp and 201 bp, and the A2A2 genotype by a single fragment of 201 bp.

Statistical analyses were conducted using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was applied to evaluate correlations between the PIN3 Ins16bp duplication polymorphism and clinicopathological parameters. The relationship between the TP53 PIN3 Ins16bp duplication polymorphism and the risk of OSCC development was evaluated by calculating odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. Survival analysis was performed using Kaplan–Meier curves and the log-rank test. A p value < 0.05 was considered statistically significant.

RESULTS

The study included 60 patients with OSCC, comprising 13 females (21.7%) and 47 males (78.3%), aged 37–86 years (mean age: 62 years) (Table 1). Among the 60 patients, the majority of cases (two-thirds) were in the early stages (I and II) of the disease. The A1A1 and A1A2 genotypes were approximately equally distributed among the age groups 40–60 years and over 60 years.

During the three-year follow-up period, 12 patients (20%) experienced local recurrence of disease and 6 patients (10%) developed regional (nodal) metastases, with no distant metastases detected. Accordingly, 18 patients (12 + 6; 30.0%) developed disease progression, whereas 42 patients (70.0%) remained recurrence- and metastasis-free.

No significant associations were observed between the TP53 PIN3 Ins16bp duplication polymorphism and clinicopathological features, including patient age, gender, tumor site, grade, disease recurrence, or metastasis ($p > 0.05$). However, a significant association between TP53 genotypes and disease stage was found ($p = 0.006$), with the A2A2 genotype being significantly more frequent in advanced stages of disease (III and IV).

Kaplan–Meier analysis showed no significant differences in disease-free survival among genotypes: A1A1 (28.26 \pm 1.70 months), A1A2 (35.00 \pm 0.94 months), and A2A2 (30.00 \pm 5.20 months) ($\chi^2 = 1.95$; $p = 0.38$; Figure 1). Cox regression analysis confirmed that PIN3 Ins16bp genotypes were not predictive of disease recurrence or metastasis (-2 log likelihood = 132.65; $\chi^2 = 1.64$; $p = 0.44$).

To determine whether the TP53 PIN3 16-bp polymorphism modulates the risk of oral cancer development in the studied population, genotype distributions

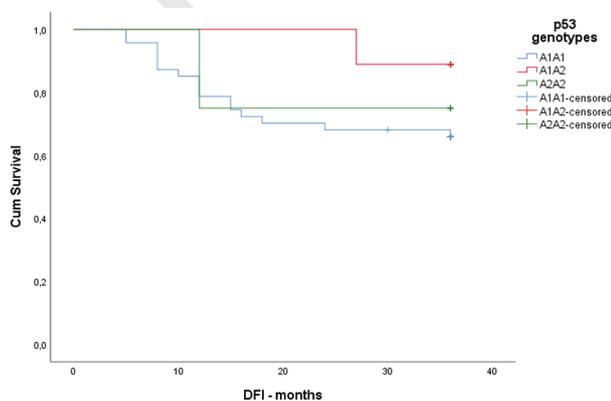
Table 1. Correlation of PIN3 Ins16bp duplication polymorphism of TP53 with clinicopathological parameters in OSCCs

Category	Variable	Patients n (%)	PIN3 Ins16bp genotype n (%)			P-value
			A1A1	A1A2	A2A2	
		60	47 (78.3)	9 (15.0)	4 (6.7)	
Age	≤ 40	2 (3.0)	2 (100.0)	0.0	0.0	0.752
	> 40 < 60	27 (45.0)	22 (81.5)	5 (18.5)	0.0	
	≥ 60	31 (52.0)	23 (74.0)	4 (13.0)	4 (3.0)	
Gender	Female	13 (22.0)	10 (77.0)	2 (15.0)	1 (8.0)	0.867
	Male	47 (78.0)	37 (79.0)	7 (15.0)	3 (6.0)	
Stage	I + II	36 (60.0)	26 (72.0)	9 (25.0)	1 (3.0)	0.006*
	III + IV	24 (40.0)	21 (87.5)	0.0	3 (12.5)	
Tumor differentiation	Well	35 (58.0)	26 (74.3)	5 (14.3)	4 (11.4)	0.520
	Moderately	23 (38.0)	20 (87.0)	3 (13.0)	0.0	
	Poorly	2 (4.0)	1 (50.0)	1 (50.0)	0.0	
Localisation (site)	Lip	28 (47.0)	22 (79.0)	4 (14.0)	2 (7.0)	0.977
	Tongue	18 (30.0)	14 (78.0)	3 (17.0)	1 (5.0)	
	Floor of mouth and tongue	14 (23.0)	11 (79.0)	2 (14.0)	1 (7.0)	
Disease recurrence	+	12 (20.0)	11 (92.0)	1 (8.0)	0.0	0.209
	-	48 (80.0)	36 (75.0)	8 (17.0)	4 (8.0)	
Metastasis (node)	+	6 (10.0)	5 (83.0)	0.0	1 (17.0)	0.916
	-	54 (90.0)	42 (78.0)	9 (17.0)	3 (5.0)	

Table 2. Genotype and allele frequencies of the PIN3 16-bp polymorphism among OSCC cases and control subjects and their associations with the risk of OSCC

Genotype/ allele	OSCCs n = 60 (%)	Controls n = 71 (%)	OR	95% CI	p
A1A1	47 (78.0)	56 (79.0)	1.00	Reference	
A1A2	9 (15.0)	13 (18.0)	0.83	0.32-2.10	0.322
A2A2	4 (7.0)	2 (3.0)	2.38	0.42-13.6	0.800
A1A2+A2A2	13	15	1.03	0.45-2.38	0.342
A1A1+A1A2	56	69	2.46	0.43-13.97	0.452
A1	103 (86.0)	125 (88.0)	1.00	Reference	
A2	17 (14.0)	17 (12.0)	1.21	0.59-2.49	0.598

OR – odds ratio; CI – confidence interval; p – probability; n – number of individuals

**Figure 1.** Kaplan-Meier survival plot regarding TP53 genotypes in oral carcinoma

among OSCC patients and healthy controls were analyzed (Table 2).

Genotype and allele frequencies of the PIN3 16-bp polymorphism showed no significant differences between the two groups. Carriers of the A2A2 genotype (homozygous for insertion of the 16-bp sequence in intron 3) were more frequent in the OSCC group; however, this difference was not statistically significant ($p = 0.800$).

Additionally, carriers of the A2A2 genotype showed a non-significant trend toward an increased risk of OSCC development ($OR = 2.38-2.46$). However, more definitive conclusions would require a larger study population.

DISCUSSION

Our results indicate that the TP53 PIN3 16-bp duplication polymorphism does not appear to influence disease risk or progression. No statistically significant associations between TP53 genotypes and clinicopathologic parameters were observed, suggesting that, within this cohort, this polymorphism does not affect clinical outcomes. Previous reports on the prognostic and predictive significance of this polymorphism in head and neck cancers, including OSCC, have reported limited results.

Some studies of breast cancer (5) have noted that patients with the A2A2 genotype were more likely to present with invasive ductal carcinoma histology, larger tumor size (T3), lymph node involvement, and absence of distant metastases compared to carriers of the A1A1/A1A2 genotypes. These authors observed a correlation between the TP53 genotype and histological type of breast cancer but found no correlations with other clinicopathological parameters.

Another study (8) in breast cancer confirmed that variation in the PIN3 16-bp polymorphism was not significantly associated with survival; however, within a subgroup of patients treated with chemotherapy without anthracycline, carriers of the A2A2 genotype exhibited significantly poorer overall survival compared with carriers of other genotypes. Similarly, survival assessment showed no significant association between TP53 polymorphism and overall survival in head and neck cancer patients (9).

The literature on the TP53 PIN3 16-bp polymorphism in cancer progression is inconsistent. In our study, carriers of the A2A2 genotype (homozygous for the 16-bp insertion in intron 3) were more frequent among OSCC patients, but these differences were not statistically significant. Furthermore, no correlation was found between this polymorphism and recurrence or metastasis within the 36-month follow-up period. Investigation of clinicopathological features, including age, tumor location, and histological grade, revealed no significant associations with PIN3 16-bp polymorphism genotypes. Additionally, the PIN3 16-bp polymorphism was not identified as a risk factor for the development of OSCC.

An interesting finding in our study is the association of TP53 PIN3 genotypes with disease stage: carriers of the A2A2 genotype were more frequently in the advanced stages (III and IV). This finding correlates with research on 106 gastric cancer samples (10), which also reported a statistically significant association between the A2A2 genotype and advanced disease stage. Overall, the presence of the A2A2 genotype may indicate a more aggressive biological behavior of malignancy.

Literature data regarding the contribution of TP53 polymorphism (rs17878362) to cancer susceptibility are also inconsistent. A meta-analysis including 25 published studies revealed that individuals homozygous for the duplicated allele (A2A2) exhibited a significantly elevated risk of cancer development compared with A1A1 individuals (11). Furthermore, by cancer site, increased susceptibility among A2A2 individuals was observed for breast and colorectal cancer, but no such association was observed for lung cancer. Some other reports have suggested that carriers of the PIN3 Ins16-bp allele (A2) and the A2A2 genotype are correlated with elevated risk for esophageal and gastric cancer (12).

In contrast, the TP53 PIN3 polymorphism has not been identified as a risk factor for breast cancer in the Azeri population (13), Chinese Han women (14), or the Moroccan population (15). Additionally, no significant correlations have been reported between this polymorphism and prostate cancer (16) or triple-negative breast cancer (17). Some studies have indicated that the A1A1 and A1A2 genotypes of this polymorphism, when combined with the Arg/Pro genotype at codon 72 (exon 4) of TP53, may have a protective role in oral cancer development (18).

These discrepancies among studies may be attributable to several factors, including sample size, inclusion of tumors from different anatomical sites (e.g., oral cavity and oropharynx), and variability in therapeutic approaches (8). Additional contributing factors include regional environmental influences, ethnic differences, and genetic background (5).

Finally, to further validate the prognostic significance of the TP53 PIN3 16-bp polymorphism in OSCC, larger multicenter studies with increased sample sizes and detailed clinical follow-up data are necessary.

CONCLUSION

The TP53 PIN3 16-bp duplication polymorphism does not modulate susceptibility to oral squamous cell carcinoma in the Montenegrin population. This polymorphism does not appear to influence OSCC risk or progression in the studied cohort.

Abbreviations

OSCC - oral squamous cell carcinoma

DFI - disease-free interval

Note: This study is part of the PhD thesis of Marija Antunović (19).

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

ZNAČAJ PIN3 16-BP POLIMORFIZMA P53 GENA ZA RIZIK I PROGNOZU ORALNOG KARCINOMA

Antunović Marija^{1,2}

¹Univerzitet Crne Gore, Medicinski fakultet, Podgorica, Crna Gora

²Klinički centar Crne Gore, Odeljenje za oralnu hirurgiju, Podgorica, Crna Gora

Uvod: Oralni skvamocelularni karcinom (OSCC) je povezan sa više faktora rizika, uključujući i genetske faktore kao što je PIN3 16-bp polimorfizam p53 gena. Cilj ovog rada je bio da ispita ulogu PIN3 16-bp polimorfizma u nastanku OSCC u populaciji Crne Gore kao i njegov uticaj na prognozu/progresiju OSCC.

Materijal i metode: Istraživanje je obuhvatilo 60 pacijenata sa OSCC i 71 zdravog pojedinca kod kojih je metodom PCR-RFLP ispitivana frekvencija alela i genotipova PIN3 16-bp polimorfizma p53 gena. Analizirane su i kliničko-patološke varijable, a svi pacijenti su praćeni 3 godine.

Rezultati: U trogodišnjem periodu praćenja, 12 pacijenata (20%) je imalo recidiv bolesti, a 6 pacijenata (10%) je razvilo regionalne metastaze, bez udaljenih metastaza. Nije utvrđena povezanost između PIN3 16-bp polimorfizma i starosti pacijenata, lokalizacije tu-

mora, gradusa, recidiva bolesti i metastaza ($p > 0.05$). Utvrđena je statistički značajna povezanost PIN3 16-bp polimorfizma i stadijuma bolesti ($p = 0.006$). Nije utvrđena statistički značajna razlika u dužini vremenskog intervala bez ponovne pojave bolesti kod nosilaca različitih genotipova PIN3 16-bp polimorfizma: A1A1 (28.26 ± 1.70 mjeseci), A1A2 (35.00 ± 0.94 mjeseci) i A2A2 (30.00 ± 5.20 mjeseci) ($p = 0.38$). Takođe, nije bilo statistički značajnih razlika u frekvenciji alela i genotipova PIN3 16-bp polimorfizma između OSCC pacijenata i kontrolne grupe.

Zaključak: PIN3 16-bp polimorfizam p53 gena se ne može smatrati faktorom rizika za nastanak OSCC u populaciji Crne Gore. Takođe, polimorfizam PIN3 16-bp ne utiče na progresiju OSCC u ispitivanoj populaciji.

Ključne reči: TP53, PIN3 16-bp polimorfizam, oralni karcinom.

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Correspondence to/Autor za korespondenciju

Marija Antunović
Department for Oral Surgery, Clinical Center of Montenegro,
Faculty of Medicine, Podgorica, Montenegro
e-mail: antunovicmasa@gmail.com
phone no. + 382 69 494 943
ORCID: 0009-0000-3301-858X