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ORIGINAL RESEARCH

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Effect of CDH1 and CDH2 genes polymorphisms in oral squamous cell carcinoma susceptibility in a sample of Iranian population: A case-control study

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Abstract

Background and Aims: Oral squamous cell carcinoma (OSCC) is a global malignant epithelial neoplasm affecting the oral cavity. Cadherins, as an adhesion molecule, are involved in cell–cell interaction. We aim to study the effect of two cadherin polymorphisms on OSCC risk in southeast of Iran.

Methods: In this case-control study, 94 individuals (47 OSCC cases and 47 controls), that referred to the Department of Oral Pathology, Faculty of Dentistry, Zahedan University of Medical Sciences, Iran were included. Cadherin single nucleotide polymorphisms CDH1 (rs16260) and CDH2 (rs11564299) were genotyped by the tetra-Amplification Refractory Mutation System—PCR technique.

Results: N-cadherin genotyping showed that the AA, AG, and AG + GG were presented 78.7%, 17%, 21.3% versus 66%, 29.7%, 34% in the cases and the control group, respectively. AG genotype was more common in control than case (OR = 0.47, 95% CI: 0.17–1.29, $p = 0.14$). G allele was more prevalent in control (19.1%) than the case group (12.8%) (OR = 0.61, 95% CI: 0.27–1.36, $p = 0.23$). In E-cadherin, AC, AA, and AC + AA genotypes frequency were 17%, 12.8%, and 29.8% in case versus 8.5%, 8.5%, and 17% in the control group. Allele A was more common in the case than the control group (OR = 1.84, 95% CI: 0.84–4.03, $p = 0.12$). Also, AA and CC, the codominant genotypes were common in CDH2 and CDH1 respectively in all histopathological grades, and no statically significant association was observed between OSCC different histopathological grades and cadherin genotypes ($p = 0.39$ in N-cadherin, $p = 0.74$ in E-cadherin).

Conclusion: Our results showed a lack of association between CDH1 and CDH2 gene polymorphisms with OSCC risk in a population of Southeastern of Iran.

KEYWORDS

E-cadherin, N-cadherin, oral cavity, polymorphism, squamous cell carcinoma

1 | INTRODUCTION

Oral cancer is the sixth most prevalent cancer affecting the oral cavity, salivary glands, and pharyngeal areas worldwide.[1] Oral squamous cell carcinoma (OSCC) accounts for at least 80%–90% of oral malignancies' neoplasms.[2] The estimated annual incidence of oral cancer is 443,000 new cases and approximately 241,450,000 deaths in the world.[3] The prevalence of OSCC in Iran is 20–36.3 in 100,000 people, which stands alongside some countries in the southern region of Asia such as India, Bangladesh, and Pakistan.[4] Also, the mean survival rate is 5 years in about half of the patients. The main risk factors include heavy use of tobacco and alcoholic beverages, infection by high-risk HPV genotype, and diet.[5] However, OSCC is considered a multifactorial disorder; genetic susceptibility, environmental, and occupational factors may promote oral carcinogenesis.[6] Although the molecular mechanism of tumorigenesis is not clear yet, the accumulation of genetic defects in the cell's DNA cycle, proto-oncogenes, and tumor suppressor genes may lead to oral malignancies in several processing steps.[7]

Cadherin is a large family of cell surface protein that plays a critical role in cell differentiation, adhesion, and solid tissue formation.[8] Cadherin's down regulation in multicellular assemblies is correlated with adhesive properties and metastasis potential enhancement.[9] These proteins are classified into three groups: type I, type II, and type III. Type I contains neural (N), epithelial (E), retinal (R), and placental (P) cadherins which are expressed in the mammary gland. Type II cadherin includes cadherin five, which is identified with vascular endothelial cadherin and has an essential role in blood vessels' integrity. Cadherin 11 is expressed in osteoblasts to help bone and joint maintenance. Type III cadherin, which is related to the mammary gland, includes cadherin 13 and 15.[10]

Epithelial cadherin is a 120 kDa transmembrane glycoprotein with three functional domains: cytoplasmic, transmembrane, and extracellular.[11] The E-cadherin gene (CDH1) is encoded of E-Cad that is located in 16p22.1 chromosomal position.[12] This calcium-dependent adhesion molecule controls signal events such as differentiation, polarity, and cell migration.[13] The loss of CDH1 expression has been linked with the invasiveness of epithelial neoplasm and tumor progression, including oral carcinomas.[12]

Neural cadherin (CDH2) has a large extracellular domain which is primarily found in neuronal tissues and fibroblasts,[14] and mediates calcium-dependent hemophilic interaction between cadherins. N-cadherin is located in the 18q11.2 chromosomal position. The CDH2 expression has an essential role in neural cells' migration in embryonic development.[15,16] Domenico et al. indicated that N-cadherin expression had a worse outcome and was related to reduced survival and increased invasiveness in OSCC patients.[17] Furthermore, Pyo et al. demonstrated that loss of E-cadherin expression was associated with metastasis and malignant behavior in oral SCC.[18]

Regarding the role of E-cadherin in tumor invasion suppression in human epithelial cancer, it has been suggested that cadherin polymorphism may be related to malignancies.[19] Polymorphism in this gene could be associated with increased oral cancer susceptibility and may be a predictive factor for invasiveness. The role of CDH1 and CDH2 promoter polymorphisms in oral carcinomas has been studied in various populations. However, there has been no report of cadherin genotypes in OSCC susceptibility in the south-east of Iran. The current research aimed to investigate the impact of these polymorphisms on OSCC risk in an Iranian population.

2 | MATERIALS AND METHODS

2.1 | Sample collection

In the current case-control study, after approval of the local Ethics Committee (IR.Zaums.REC.1394.380), 47 patients with OSCC from Dentistry Faculty of Zahedan University of Medical Science, Iran were included. Forty-seven healthy controls without any history of neoplastic conditions were voluntarily included. Informed written consent was obtained from each person. All patients and healthy participants were matched for age, gender, and ethnicity. Histopathological slides of OSCC patients were reviewed by oral and maxillofacial pathologist for diagnosis confirmation and for classification of histopathological grading according to International Histological Classification of Tumors. All samples were categorized into well differentiated, moderately differentiated, and poorly differentiated.[20]

2.2 | Nucleic acid isolation

Genomic DNA was extracted from formalin-fixed paraffin-embedded tissue in the patient group by standard isolation protocol, and also blood sampling was performed for the healthy group. The paraffin removal was done by xylene, 100% alcohol, 80% alcohol, and 50% alcohol and then incubated overnight in H_2O at 4°C. Nucleic acid lysis buffer and proteinase K enzyme were utilized for protein digestion. Precipitation of protein was carried out using 6 M NaCl, and then 100% ethanol was added to the supernatant. At last, the DNA pellet was solved in a TE buffer.

2.3 | Polymorphism genotyping

Cadherin single nucleotide polymorphisms CDH1 (rs16260) and CDH2 (rs11564299) were genotyped using polymerase chain reaction followed by tetra-Amplification Refractory Mutation System PCR technique. The outer and inner primers' sequences were summarized in Table 1. PCR was carried out according to the following protocol: initial denaturation at 95°C for 5 min, followed by 30 cycles of 95°C for 1 min, annealing step at 69°C (CDH1) and 60°C (CDH2) for 1 min, extension at 72°C for 1 min, and final extension at 72°C for 5 min. We used 2% agars for DNA fragment separation, safe stain (Cinna Gen), and DNA was visualized by UV light (Cleaver).

TABLE 1 Primers sequencing for *CDH1* and *CDH2* polymorphisms.

SNP	Primers sequencing	Product size (bp)
N. cadherin (rs11564299)	F-outer:5′-CCAACAGTTTTTGATCCTTTAAGTAAG-3′	Outers:298
	R-outer:5′-TAGGTATGGTATTACTGAGGTAAAGCTG-3′	
	F-inner:5′-AATAAATAATAGGCCTATGATTACACGA-3′	Inner G:203 Inner T:153
	R-inner:5′-ACAGCATGATTTTAGACTAGACTATTCATC-3′	
E. cadherin (rs16260)	F-outer:5′-AGTTCGAGGCTGCAGTGAGCTGTGA-3′	Outers:441
	R-outer:5′-CTCACAGGTGCTTTGCAGTTCCGAC-3′	
	F-inner:5′-GACCCTAGCAACTCCAGGCTAGAGGGTTAA-3′	Inner C:269 Inner A:222
	R-inner:5′-CCGGCCTCGCATAGACGTGG-3′	

2.4 | Statistical analysis

All statistical analyses were carried out with SPSS software version 23 (SPSS Inc.). The allelic and genotypes distribution was estimated by the χ^2 test. The univariate association among the E-cadherin and N-cadherin polymorphisms and OSCC susceptibility was calculated using odds ratios (OR) of 95% and confidence interval (CI) in the patient and healthy group. $p < 0.05$ was considered significant.

3 | RESULTS

In the current study, 94 individuals (47 OSCC patients and 47 healthy subjects) were included. The mean age of OSCC patients and control individuals were 56.08 ± 15 and 58.36 ± 15, respectively. The percentage of female and male participants in OSCC patients were 30 (63.8%) and 17 (36.2%), respectively; and 29 (61.7%) females and 18 (36.3%) males for the control group. There was no statistically significant distribution in mean age and gender between OSCC patients and healthy controls.

Genotyping for N-cadherin showed that the AA genotype was 72.3%, AG genotype 23.4%, and GG genotype were 4.3% in all studied populations. The results have been given by the case and control group in Table 2. AG genotype was more common in control than case (OR = 0.47, 95% CI: 0.17–1.29, $p = 0.14$). No statically significant distribution was found in N-cadherin ($p = 0.31$). G allele was more prevalent in control than case group (OR = 0.61, 95% CI: 0.27–1.36, $p = 0.23$).

No statically significant distribution was found in E-cadherin ($p = 0.33$). The distribution of genotypes frequency was 76.5%, 12.8%, and 10.6% in AA, AC, and CC, respectively, in the studied population, as detailed in Table 2. Allele A was more common in the case than the control group ($p = 0.12$). Moreover, most OSCC patients expressed the dominant homozygote genotypes in all histopathological grades; however, there was no significant relationship between OSCC grade and cadherin polymorphisms (Table 3).

TABLE 2 Cadherin genotypic and allelic frequency for CDH1 and CDH2 in OSCC patients and controls.

Genotype	Case *N* (%)	Control *N* (%)	*p* Value	OR	95% CI
N-cadherin (rs11564299)					
AA	37 (78.7)	31 (66.0)		Ref:1	
AG	8 (17.0)	14 (29.7)	0.14	0.47	0.17–1.29
GG	2 (4.3)	2 (4.3)	0.86	0.83	0.11–6.29
AG + GG	10 (21.3)	16 (34.0)	0.17	0.52	0.20–1.31
A allele	82 (87.2)	76 (80.9)		Ref:1	
G allele	12 (12.8)	18 (19.1)	0.23	0.61	0.27–1.36
E-cadherin (rs16260)					
CC	33 (70.2)	39 (83.0)		Ref:1	
AC	8 (17.0)	4 (8.5)	0.19	2.36	0.65–8.55
AA	6 (12.8)	4 (8.5)	0.40	1.77	0.46–6.80
AC + AA	14 (29.8)	8 (17.0)	0.14	2.06	0.73–5.53
C allele	74 (78.7)	82 (87.2)		Ref:1	
A allele	20 (21.3)	12 (12.8)	0.12	1.84	0.84–4.03

Abbreviations: CI, confidence interval; OSCC, oral squamous cell carcinoma.

4 | DISCUSSION

OSCC is a multistage malignancy with unknown etiology. Despite the achievements regarding various diagnoses and treatments of OSCC, the mortality rate is extremely high. Therefore, this challenge encourages the researchers to find the novel prognostic marker for tumor progression. They believe that the synergy effect of genetic and environmental factors could trigger the disorder. Among genetic causes, different reports showed cadherin genotypes and cancer susceptibility in several populations.[5,21] Although various research have been carried out on this subject, the controversial study in a different geographic area with diverse genetic backgrounds encouraged us to pursue the role of cadherin variation in OSCC patients in the Sistan-Baluchistan population.

TABLE 3 Distribution of CDH1 and CDH2 polymorphisms in OSCC patients, according to histopathological grades.

Genotype	Grade I *N* (%)	Grade II *N* (%)	Grade III *N* (%)	*p* Value
N-cadherin (rs11564299)				
AA	16 (66.7)	14 (93.3)	7 (87.5)	0.39
AG	6 (25)	1 (6.7)	1 (12.5)	
GG	2 (8.3)	0 (0)	0 (0)	
E-cadherin (rs16260)				
CC	16 (66.7)	10 (66.7)	7 (87.5)	0.74
AC	5 (20.8)	3 (20.0)	0 (0.0)	
AA	3 (12.5)	2 (13.3)	1 (12.5)	

Abbreviation: OSCC, oral squamous cell carcinoma.

In this study, results indicated that no statically significant association was observed in genotypes frequency of rs16260 in patients and healthy individuals, while the AC (17% vs. 8.5%) and AA (12.8% vs. 8.5%) genotypes were common in the case than the control group (OR = 2.36 and OR = 1.77, respectively) also, OR -160A allele carriers were 1.8 times versus the -160C allele. The -160A allele frequency was reported differently in several ethnic, geographic regions. The -160AA homozygote variant frequency ranges from 3.4% in the United Kingdom to 18.9% in Italy and from 0% in Japan to 44% in China.[22] Moreover, the A-allele frequency in Europe ranges from 23.3% in the United Kingdom to 43.4% in Italy. In Asia, this frequency ranges from 14.3% in Korea to 61.0% in China.[22] Meta-analysis studies demonstrated no significant correlation between genotypic and allelic frequency of CDH1 C-160A polymorphism and esophageal and gastric cancer risk than the control group.[22,23]

According to evidence from a meta-analysis, demonstrated that the CDH1-160C/A polymorphism might lead to breast cancer susceptibility.[24] Also, in an Iranian population (Kurdish), has been reported that the A allele of CDH1 -160C/A may be a risk factor for breast cancer. In their study, the A allele was correlated to high grade, stage IV, and metastatic tumors in the groups.[25] It has been reported that CDH1-160C/A polymorphism is associated with decreased colorectal cancer risk.[26] Therefore the CDH1-160C/A polymorphism might have a different effect on each tumor, and this diversity can be due to different carcinogenic mechanisms.[24]

Another report (2006) indicated that the 160AA homozygote significantly increased the urothelial tumor's risk, and it is also a significant susceptibility factor for lung tumors.[27] It has been reported that SNPs in the E-cadherin gene promoter region caused individual alteration in the E-cadherin production that leads to susceptibility to cancer.[28] To date, no confirmative report has been performed for rs16260 SNP in OSCC Iranian patients.

In India, from 60 oral cancer patients, 10%–13% and 30%–46% showed AA and CA genotypes, respectively, indicating a correlation between cadherin gene variation and oral cancer risk.[29] This polymorphism is located within the promoter's regulatory area and can affect E-cadherin transcription by altering transcription factor binding. It inhibits the transcription factor's binding at the E-cadherin promoter and leads to reduced gene transcription; therefore, this event elevated tumorigenesis in several neoplasms.[30] This displacement could have a significant effect on cancer development.[31]

Results of another study showed that persons with at least one varied GA allele of CDH1-347 polymorphic genotypes or combinations of the CDH1-160 CA/-347 GGA, CDH1-160 CC/-347 GGA, or CDH1-160 CC/-347 GAGA genotypes had a higher risk for oral cancer, whereas persons with CDH1-160 C/A or A/A had a lower risk of oral cancer development than those with wild-type genotypes. This study also found that the CDH1-347 polymorphisms but not the 160 gene polymorphism of CDH1 may be a significant factor for lymph node metastasis in patients above 60 years.[32]

Geng et al. suggest that genetic polymorphism of CDH1 was correlated with endometrial cancer (EC) susceptibility. They found that three htSNPs (rs17715799, rs6499199, and rs13689) were correlated with increased EC susceptibility and three htSNPs (rs12185157, rs10431923, and rs4783689) with decreased EC risk. In this study, rs10431923 (G>T) was the most important Independent protective factor for EC risk in the Chinese population.[33]

In the present study, the AA genotype distribution in CDH2 had more frequency in OSCC patients than the control group (78.7% vs. 66%). G allele frequencies were 19.1% and 12.8% in the control and the case group, respectively. The OR G versus A allele was 0.6. The A and G allele frequencies were 74% and 26% in the United States of America, 78% and 22% in Europe, and 86% and 14% in South Asia, respectively.[34] Rudel et al. have been reported a statistical association between CDH2 promoter and osteoarthritis susceptibility, and they indicated that the minor allele of CDH2 had a protective role on German osteoarthritis patients.[35] This SNP is located upstream of the CHD2 transcription start site and can affect on mRNA gene expression. The promoter's strong activity of the CDH2 gene in the carrier allele can be led to a novel allele-specific transcription factor binding site.[35,36] Also, Shang et al. showed that G allele or GG genotype of CDH2 gene rs11564299 polymorphism might be a risk factor for knee osteoarthritis susceptibility in the Chinese population.[37]

The CDH2 is a remarkable biomarker for cancer and can be conducted to trans-endothelial migration to poor differentiation.[38] There is new evidence suggesting that N-cadherin plays an important role in hematologic malignancies consisting of leukemia and multiple myeloma. Upregulation of the N-cadherin gene (CDH2) expression in multiple myeloma patients with high-risk t(4;14)(p16;q32) translocation is reported.[39] Also, in Yu et al.' study, *CDH2* rs643555C>T was correlated to prostate cancer biochemical recurrence and tumor aggressiveness through increasing expression of *CDH2*. CDH2 develops prostate cancer cells epithelial–mesenchymal transition,

stemness, and ability to metastasize through activating the ErbB signaling pathway.[40]

The reduction of E-cadherin expression in OSCC cases improved metastatic cells and malignancy behavior.[18] In Lopez-Verdin et al.'s study, E-cadherin mRNA expression was significantly decreased in the early clinical stage of OSCC, and it no changed in advanced stages.[41] Studies indicated that cytoplasmic N-cadherin expression has increased in neoplastic tissue compared to the normal epithelium, so that this protein can have a crucial role in OSCC prognostic stratification.[17]

In the present study, we found no significant association between E-cadherin (CDH1) and N-cadherin gene (CDH2) polymorphisms and OSCC susceptibility in our population. This result can be due to the small sample size in our study. Other carcinogenic mechanisms, such as environmental exposure, dietary habit, race, or family history, affect the result.

In this study, most of the patients showed AA and CC genotypes in N-cadherin and E-cadherin in all histopathological grades of OSCC. Still, no statically significant association was observed between histopathological grades of OSCC samples and cadherin genotypes. However, Kaur et al. demonstrated that loss of E-cadherin had an essential role in OSCC dedifferentiation; this protein's lack of expression could lead to OSCC invasion and progression.[42] Other reports showed that the tumor stage was related to E-cadherin expression.[43] However, oral SCC is a revolute disorder; therefore, cadherin's role needs to be more studied for clarification.

5 | CONCLUSION

According to the present study, the G allele of N-cadherin and Allele A of E-cadherin were more prevalent in control than the OSCC group, but this distribution was not statistically significant. Moreover, most of the OSCC patients expressed the dominant homozygote genotypes in all histopathological grades of OSCC. Since the alternation of E and N-cadherin expression was related to cancer invasion, we suggest that further studies should be conducted in larger populations of this region. Also, different ethnicities and lifestyle risk factors should be studied to produce more valid results.

AUTHOR CONTRIBUTIONS

Hamideh Kadeh: Conceptualization; investigation; writing—original draft. **Negin Parsamanesh**: Formal analysis; methodology; writing—original draft. **Ebrahim Miri-Moghaddam**: Formal analysis; methodology; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting and findings of this study are available within the article. Ebrahim Miri-Moghaddam takes responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

The ethical committee approved the study of Zahedan University of Medical Sciences (IR.Zaums.REC.1394.380).

TRANSPARENCY DECLARATION

The lead author (Ebrahim Miri-Moghaddam) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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