Abstract. Background/Aim: This study aimed to determine the relationship between the relative leukocyte telomere length (RLTL) and gene polymorphisms involved in its regulation with the occurrence of oral squamous cell carcinoma (OSCC). Patients and Methods: Patients with OSCC and healthy subjects were examined. Genotyping and RLTL measurement were carried out using rPCR. Results: The OSCC group had longer telomeres than controls (p=0.001). Minor allele T at TERF1rs1545827 may increase RLTL shortening (p=0.047). TNKS2 rs10509639 A/G and A/G+G/G genotypes were associated with a 2.6-fold increased odd (p=0.012) and a 2.4-fold increased odd (p=0.019) of RLTL elongation compared to A/A genotype. The A/G genotype was associated with a 2.6-fold increased odd (p=0.011) compared to the A/A+G/G genotypes. Each G allele was associated with a 2.1-fold increased odd of longer RLTL (p=0.036). Conclusion: Longer telomeres were found in patients with OSCC than in controls. The TERF1 rs1545827 and the TNKS2 rs10509639 polymorphisms were associated with an increase in RLTL.

Oral squamous cell carcinoma (OSCC) accounts for 20% of all head and neck squamous cell carcinoma (HNSCC) cases worldwide, which makes it one of the most common types of malignant tumors of this anatomical region. This broad prevalence can be associated with risk factors, such as the use of tobacco products and alcohol consumption that are also associated with the development and progression of various chronic diseases. Early cancer diagnosis (stage I-II), rises the patient survival rate up to 70-90%. For this purpose, new molecular biological markers could be of service in diagnosing the disease at its early stages (1). Molecular markers are indicators of normal biological, pathological and pharmacological molecular responses, which can provide useful information for diagnosis and prognosis (2).

Lately, the attention has been focused on telomeres and telomere length regulating genes, due to their importance in aging and the development of chronic diseases and malignant tumors. The name telomere itself originates from the Greek word “telos”, which means the end, and “meros”, which means a part (3). The main function of telomeres is to protect the ends of chromosomes from degradation and end-to-end fusions (4). There is also a telomere protein complex, called shelterin, that is incredibly important for the protection of the ends of chromosomes and the regulation of telomere length (5). Although telomeres in the human generative cells and embryotic stem cells are kept active by the help of telomerasers, telomeres become shorter when somatic cells divide, because of insufficient telomerase expression (4). There is also a telomere protein complex, called shelterin, that is incredibly important for the protection of the ends of chromosomes and the regulation of telomere length (5).

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in cancer cells, resulting in unlimited replication potential and growth of the tumor (11). It is particularly important to understand the mechanisms regulating telomere length and the relation between telomere length changes and various diseases. Discovery of new molecular markers is required to diagnose tumorous diseases, identify the risk groups for disease development, predict the response to treatment and carry out patients’ observations in order to apply personalized treatment. For this reason, we assessed the associations of \( \text{TERT} \) rs2736098, \( \text{TERT}\text{-CLPTM1} \) rs401681, \( \text{TRF1} \) rs1545827, rs10107605, \( \text{TNKS2} \) rs10509639 and \( \text{TERF2} \) rs251796 gene polymorphisms and telomere length with OSCC.

**Materials and Methods**

All the procedures used in this study were approved by the Kaunas Regional Ethics Committee for Biomedical Research, Lithuania in compliance with ethical standards (permission number is BE-2-34). The study was conducted at the Department of Otorhinolaryngology, and Ophthalmology Laboratory of Neuroscience Institute, Lithuanian University of Health Sciences, Kaunas, Lithuania.

**Study group.** The current study included 47 patients (35 males and 12 females with a mean age of 59.5 years old) with a diagnosis of OSCC and 204 healthy control group subjects (144 males and 60 females, with a mean age of 62.02 years old) (Table I).

The patients included in the study had OSCC with no additional diseases, their general health status was good, and they had provided a written informed consent for participation in the study. The final diagnosis of OSCC was confirmed following histopathological investigation after a biopsy or surgery. Subjects chosen to participate as a control group did not have any oncological diseases, their general health status was good, and they provided a written informed consent for inclusion in the study.

**DNA extraction, genotyping, relative leukocyte telomere length measurement and statistical analysis.** DNA extraction, genotyping and measurement of the relative leukocyte telomere length (RLTL) methods, as well as statistical analysis, have been described in detail in our previous studies (12, 13).

**Results**

OSCC patients had statistically significantly longer telomeres than healthy controls [median (IQR): 1.5 (3.34) vs. 0.95 (1.43), \( p = 0.001 \), respectively. Results are shown in Figure 1.

After analyzing patients’ relative leukocyte telomere length in relation to the stage of the disease, we determined that OSCC patients with stage IV cancer had longer relative leukocyte telomere length than those with stage I [median (IQR): 1.952 (3.573) vs. 0.560 (-), \( p = 0.047 \)] (Table II). Analogous analysis was performed with different G status (tumor differentiation grade) groups of OSCC patients, but no statistically significant results were acquired (Table III).

We also determined statistically significant differences between telomere lengths of healthy control group individuals and OSCC patients with different stages of the disease (control group stage is marked with 0). OSCC patients with stage II and IV disease had longer relative leukocyte telomere length than controls (\( p = 0.014 \) and \( p = 0.003 \), respectively. Results are shown in Table IV.

\( \text{TERT} \) rs2736098, \( \text{TERT}\text{-CLPTM1} \) rs401681, \( \text{TRF1} \) rs1545827, rs10107605, \( \text{TNKS2} \) rs10509639 and rs10509637,
TERF2 rs251796 matched the Hardy-Wainber equilibrium (HWE) \((p>0.001)\) (Table V). After analyzing these SNPs' distribution, no statistically significant differences were found between the OSCC patients and control groups (Table VI).

Analysis of the SNPs \((TERT \text{ rs}2736098, \ TERT-CLPTM1 \text{ rs}401681, \ TERF1 \text{ rs}1545827, \text{ rs}10107605, \ TNKS2 \text{ rs}10509639 \text{ and rs}10509637, \ TERF2 \text{ rs}251796)\) and binary logistic regression association with the age and gender of patients with OSCC and healthy controls, did not reveal any statistically significant differences.

The relative leukocyte telomere length of the healthy control group individuals and OSCC patients was analyzed in relation to the SNPs \((TERT \text{ rs}2736098, \ TERT-CLPTM1 \text{ rs}401681, \ TERF1 \text{ rs}1545827, \text{ rs}10107605, \ TNKS2 \text{ rs}10509639 \text{ and rs}10509637, \ TERF2 \text{ rs}251796)\). This analysis showed no statistically significant results (Table VII). We also searched for an association between the control group subjects and OSCC patients’ leukocyte telomere length and SNP genotypes. Analysis showed that at least one rare allele at \(TERF1, \text{ rs}1545827\), increased the possibility of telomere shortening \((p=0.047)\) in the healthy control group. Analysis of the other polymorphisms showed no statistically significant results. Results are given in Table VIII and Table IX.

For further analysis, subjects were divided in two groups according to telomere length: short and long telomere groups. The \(TNKS2 \text{ rs}10509639\) genotype rate was found to be statistically significantly different between the short and long telomere groups \((p=0.022)\). Also, \text{rs}10509639 G allele was more common in subjects who had long telomeres \((p=0.036)\) (Table X).

| Stage | \(p\)-Value* |
|-------|-------------|
| 0 vs. I | 0.418       |
| 0 vs. II | 0.014      |
| 0 vs. III | 0.246      |
| 0 vs. IV | 0.003      |

*Mann-Whitney U-test.
Binary logistic analysis was performed in order to evaluate the effect of TERT rs2736098, TERT-CLPTM1 rs401681, TRF1 rs1545827, rs10107605, TNKS2 rs10509637 and rs10509639, TERF2 rs251796 on the length of telomeres. Based on the analysis, the TNKS2 rs10509639 polymorphism A/G genotype and the A/G and G/G genotypes together increased the odd of telomere lengthening 2.0-fold (OR=2.555; 95%CI=1.227-5.318; \( p = 0.012 \)), and 2.4-fold (OR=2.358; 95%CI=1.152-4.827; \( p = 0.019 \)), respectively, in comparison to A/A genotype. Also, the odds ratio of telomere length was increased 2.6-fold by the A/G genotype, in comparison to A/A and G/G genotypes together (OR=2.578; 95%CI=1.239-5.366; \( p = 0.011 \)) and each G allele increased the odd 2.1-fold (OR=2.090; 95%CI=1.050-4.160; \( p = 0.036 \)) (Table XI).

**Discussion**

Despite the development of modern medical technologies and the increasing number of diagnostic methods, the survival rate of patients with advanced (III-IV stage) HNSCC, as well as with OSCC, has increased only up to 65% (14). In order to increase the survival rate of patients, research is focused on identifying new markers such as telomere length and gene polymorphisms regulating telomere length (TERT rs2736098, TERT-CLPTM1 rs401681, TRF1 rs1545827, rs10107605, TNKS2 rs10509637, TERF2 rs251796), which could be useful for diagnosis and treatment.

Results from analyses of telomere length in cancer patients are scarce and inconsistent. Our results revealed that OSCC patients had statistically significantly longer telomeres than healthy controls [median (IQR): 1.5 (3.34) vs. 0.95 (1.43), \( p=0.001 \), respectively]. A number of studies have examined associations between telomere length and cancer, but only few studies have focused on head and neck cancer, telomere length and telomere length regulating gene polymorphisms. Zhang et al. have demonstrated that short telomere length in peripheral blood mononuclear cells (PBMCs) was strongly associated

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**Table V. Hardy-Weinberg equilibrium analysis.**

| SNP            | Allele rate | Gene distribution | HWE p-Value |
|----------------|-------------|-------------------|-------------|
| TERT rs2736098 | C 0.73      | 17/77/110         | 0.50        |
| TERT rs401681  | C 0.62      | T 0.27            |             |
| TERT rs251796  | A 0.92      | G 0.08            | 0.22        |

SNP: Single-nucleotide polymorphism.

**Table VI. TERT rs2736098, TERT-CLPTM1 rs401681, TRF1 rs1545827, rs10107605, TNKS2 rs10509637 and rs10509639, TERF2 rs251796 genotype polymorphisms and alleles’ frequencies in OSCC patients and control group individuals.**

| SNP            | Genotype | Control group N (%) | Floor of the mouth cancer N (%) | p-Value* |
|----------------|----------|---------------------|-------------------------------|---------|
| TERT rs2736098 | CC       | 110 (53.9)          | 24 (51.1)                     | 0.936   |
| TERT rs401681  | CT       | 77 (37.7)           | 19 (40.4)                     |         |
| TERT rs401681  | TT       | 17 (8.3)            | 4 (8.5)                       |         |
| TERT-CLPTM1 rs401681 | C       | 251 (61.5)          | 63 (67.0)                     |         |
| TERT-CLPTM1 rs401681 | T       | 157 (38.5)          | 31 (33)                       |         |
| TRF1 rs1545827 | CC       | 105 (51.5)          | 28 (59.6)                     | 0.447   |
| TRF1 rs1545827 | TT       | 32 (15.7)           | 8 (17.0)                      |         |
| TNKS2 rs10509637 | A       | 137 (67.2)          | 34 (72.5)                     | 0.749   |
| TNKS2 rs10509637 | G       | 34 (17.7)           | 11 (23.4)                     |         |
| TERF2 rs251796 | A        | 172 (84.3)          | 36 (76.6)                     | 0.070   |
| TERF2 rs251796 | G        | 32 (15.7)           | 10 (21.3)                     |         |

SNP: Single-nucleotide polymorphism; *Pearson’s \( \chi^2 \) test.
with a moderately increased risk of oropharyngeal squamous cell carcinoma; however, not with an increased risk of oral cavity cancer. Associations between telomere length and a higher risk of HPV16-positive oropharyngeal carcinoma and tumor HPV16 status have also been revealed (15). Bau et al. have observed that short leukocyte telomere length was associated with an increased risk of developing oral premalignant lesions and precursors of OSCC (16). A study performed by Alves-Paiva et al. has also found that RLTL was significantly shorter in patients with head and neck cancer (HNC) in comparison to healthy controls \((p=0.0003)\). Patients with shortest RLTL had an increased risk of developing HNC \((p<0.0001)\). No significant correlation was observed between RLTL and patients’ clinical features and personal habits (17).

**Table VII.** Association between relative leukocyte telomere length and SNP genotypes.

| SNP       | 22 Median (IQR) | 11+12 Median (IQR) | p-Value* | 12+22 Median (IQR) | 11 Median (IQR) | p-Value* |
|-----------|-----------------|--------------------|----------|--------------------|-----------------|----------|
| TERT rs2736098 | 1.176 (2.05)    | 0.977 (1.51)      | 0.313    | 1.11 (1.85)        | 0.964 (1.27)   | 0.297    |
| TERT-CLPTM rs401681 | 0.883 (1.19)    | 1.012 (1.82)      | 0.224    | 1.052 (1.54)       | 0.881 (1.68)   | 0.294    |
| TRF1 rs1545827  | 1.007 (1.25)    | 0.997 (1.63)      | 0.6      | 0.933 (1.44)       | 1.057 (1.82)   | 0.061    |
| TRF1 rs10107605 | 0.745 (1.58)    | 1.017 (1.59)      | 0.258    | 0.965 (1.13)       | 1.007 (1.81)   | 0.497    |
| TNKS2 rs10509637 | 1.298 (1.52)    | 0.99 (1.57)       | 0.458    | 1.010 (2.04)       | 1.003 (1.39)   | 0.557    |
| TNKS2 rs10509639 | 0.857 (1.81)    | 1.028 (1.6)       | 0.668    | 0.94 (1.61)        | 1.112 (1.59)   | 0.588    |

11-homozygotes, who have the more frequent allele, 12-heterozygotes, 22-homozygotes, who have the rarer allele; SNP: single-nucleotide polymorphism; *Mann-Whitney U-test.

**Table VIII.** Association between healthy control group individuals’ relative leukocyte telomere length and SNP genotypes.

| SNP       | 22 Median (IQR) | 11+12 Median (IQR) | p-Value* | 12+22 Median (IQR) | 11 Median (IQR) | p-Value* |
|-----------|-----------------|--------------------|----------|--------------------|-----------------|----------|
| TERT rs2736098 | 0.878 (1.9)     | 0.959 (1.39)      | 0.709    | 0.967 (1.84)       | 0.933 (1.2)    | 0.453    |
| TERT-CLPTM rs401681 | 0.937 (1.16)    | 0.947 (1.62)      | 0.596    | 1.003 (1.37)       | 0.858 (1.72)   | 0.478    |
| TRF1 rs1545827  | 0.832 (1.43)    | 0.957 (1.5)       | 0.552    | 0.825 (1.29)       | 1.043 (1.75)   | 0.047    |
| TRF1 rs10107605 | 0.745 (1.58)    | 0.957 (1.44)      | 0.347    | 0.954 (1.19)       | 0.94 (1.57)    | 0.781    |
| TNKS2 rs10509637 | 1.175 (1.51)    | 0.933 (1.43)      | 0.84     | 0.883 (1.66)       | 0.959 (1.33)   | 0.818    |
| TNKS2 rs10509639 | 0.731 (1.61)    | 0.963 (1.42)      | 0.75     | 0.88 (1.41)        | 1.005 (1.54)   | 0.714    |

11-homozygotes, who have the more frequent allele, 12-heterozygotes, 22-homozygotes, who have the rarer allele; SNP: single nucleotide polymorphism; *Mann-Whitney U-test.

**Table IX.** Association between relative leukocyte telomere length and SNP genotypes in OSCC patients.

| SNP       | 22 Median (IQR) | 11+12 Median (IQR) | p-Value* | 12+22 Median (IQR) | 11 Median (IQR) | p-Value* |
|-----------|-----------------|--------------------|----------|--------------------|-----------------|----------|
| TERT rs2736098 | 4.172 (5.1)     | 1.479 (3)         | 0.159    | 1.952 (4.09)       | 1.432 (2.07)   | 0.448    |
| TERT-CLPTM rs401681 | 0.693 (-)      | 1.562 (3.76)     | 0.147    | 1.782 (4.9)        | 1.21 (1.67)    | 0.095    |
| TRF1 rs1545827  | 1.21 (4.58)     | 1.782 (3.21)     | 0.773    | 1.5 (3.78)         | 2.014 (3.09)   | 0.56     |
| TRF1 rs10107605 | 1.5 (3.34)      | 1.5 (3.34)       | -        | 1.21 (2.01)        | 1.782 (4.26)   | 0.385    |
| TNKS2 rs10509637 | 4.862 (-)       | 1.479 (3.02)     | 0.22     | 3.531 (4.2)        | 1.277 (2.17)   | 0.147    |
| TNKS2 rs10509639 | 1.103 (4.27)    | 1.625 (3.67)     | 0.577    | 1.31 (4.12)        | 1.562 (2.24)   | 0.715    |

11-homozygotes, who have the more frequent allele, 12-heterozygotes, 22-homozygotes, who have the rarer allele; SNP: single-nucleotide polymorphism; *Mann-Whitney U-test.
The opposite results were revealed by Liu et al. who have reported that relative telomere length may be not important in HNSCC carcinogenesis (18). Oh et al., have suggested that the advancement of tumors may correlate with long telomere length and a poor prognosis (19). The authors stated that increased telomere length indicates that telomere maintenance may also be important for the progression of cancer.
HNSCC (20). Our results are inconsistent with previous studies, except for the study by Oh et al. Also, longer telomeres can increase the possibility of cancer development by stimulating cell immortality, and causing genome instability; the association between long telomeres and an advanced stage with lower survival rate has been found in colorectal and liver carcinoma patients (19, 21, 22).

Therefore, there are many studies suggesting that RLTL is associated with other types of cancer, and that both short and long telomeres can be associated with cancer development (23-27). However, a big meta-analysis performed by Weischer et al. has shown that RLTL is not associated with cancer risk (25). Da-Tian Bau et al. have stated that different cancers have different etiology, and pooling all cancer types together may mask the significant associations of RLTL with individual cancer types (16).

In our study, the TERT rs1545827 polymorphism was associated with an increased RLTL, while the TNKS2 rs10509639 polymorphism was associated with longer RLTL. Ying Bao et al. have found that the TERT rs401681 rarer allele (A) was statistically significantly associated with telomere shortening (p=0.023) in pancreatic cancer patients (28). Carriers of the C allele of the rs2736100 polymorphism were statistically significantly associated with longer telomeres and a higher risk of cancer, while the A allele carriers were associated with shorter telomeres (29). TERT rs2736098 polymorphism increases the risk of lung, heart, bladder cancer and other malignancies (30). Also, Liu et al. have found that TERT rs2736098 with TERT-CLPTM1 rs401681 genotype variants are statistically significantly associated with reduced chances of having HNSCC (p=0.048) (31). TERT2 rs251796 G variant increases the risk for lung cancer (p=0.03) (32). The TNKS2 rs10509637 rare allele G was associated with an increased risk of breast cancer (p=0.006) (33). Furthermore, several studies have examined the association of single nucleotide polymorphisms with telomere regulation. For example, in a metaanalysis performed in 2013, Bojesen et al. have found that the TERT gene rs7705526 polymorphism was associated with longer telomeres and a reduced risk of cancer (34, 35). Research on TNKS2 rs1340420 showed that the G/G and A/G genotypes reduced the risk of lung adenocarcinoma (p=0.03); whereas the TNKS2 rs1770474 rarer (T) allele increased the risk of lung squamous cell carcinoma in women 4.7 times (p=0.049) (36).

In order to evaluate TERT rs2736098, TERT-CLPTM1 rs401681, TERT rs1545827, rs10107605, TNKS2 rs10509639 and rs10509637, TERT2 rs251796 polymorphisms’ association with OSCC and telomere length changes, more subjects have to be analysed.

Conclusion

The relative telomere length was significantly higher in the group of OSCC patients compared to healthy controls. In OSCC patients, the TERTF1 rs1545827 and TNKS2 rs10509639 polymorphisms were associated with increased relative telomere length.

Conflicts of Interest

None of the Authors have any conflicts of interest related to this submission.

Authors’ Contributions

R.L., A.V., G.G., A.K., A.S., and V.U. designed research; Z.J., R.L., A.V., G.G., A.K., and V.U. performed research; A.V., G.G., Z.J., and V.U. analyzed data; and R.L., A.V., G.G., A.K., V.L., A.S., and V.U., wrote the paper.

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