Original Article

TP53 Polymorphisms in Smokers' and Nonsmokers' Pericoronal Follicles of Asymptomatic Impacted Third Molars

E Burhanoğlu, MÇ Aksoy[1], PA Kosar[2]

Private Practice, Oral Maxillofacial Surgeon, Balıkesir, [1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, [2]Department of Medical Biology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey

Abstract

Background and Purpose: The investigators designed and implemented a prospective cohort study composed of smoking and nonsmoking patients with asymptomatic fully impacted mandibular third molars. The objective of the paper was to evaluate 21 single-nucleotide polymorphisms (SNP) on the *TP53* gene in smokers' (S) and nonsmokers' (NS) pericoronal follicles of asymptomatic impacted third molars. **Materials and Methods:** Matrix-assisted desorption/ionization time of the flight mass spectrometry was used for SNP analysis of 21 regions in the *TP53* gene. Descriptive statistics and Chi-square tests were computed with a *P* value of 0.05. **Results:** Ten of the 21 SNPs related to oral pathologies according to NCBI dbSNP, were detected; in these, the genotypic frequencies showed no differences between the S and NS groups ($P > 0.05$). The results showed a high ratio of SNPs without correlation between smoking and *TP53* gene status. **Conclusion:** Further studies should examine the entire *TP53* gene to elucidate how smoking affects it in larger study populations.

Keywords: *Dental follicle, matrix-assisted desorption/ionization time of flight mass spectrometry, single-nucleotide polymorphism, smoking, TP53*

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Introduction

The extraction of impacted teeth is the most common surgical procedure performed in oral surgery, but the extraction of asymptomatic impacted teeth remains controversial. Studies on asymptomatic fully impacted teeth have focused on the histopathologic and immunohistochemical findings in their follicles. Dentigerous cysts, odontogenic keratocystic tumors, odontomas, and ameloblastomas are some of the pathologies that may arise from the follicles of asymptomatic impacted teeth. Although rare, malignancies have been reported as arising from these follicles.[1]

Cigarette smoke is comprised of approximately 5000 chemicals, of which 81 are classified "carcinogenic" by the International Agency for Research on Cancer;[2] free radicals and the chemicals in cigarette smoke form DNA adducts and cause DNA damage.[3,4]

Human cells have various protective mechanisms that can prevent damaged DNA from replicating itself,[5] and p53 is one of the most well-known tumor suppression proteins.[6] In healthy tissues, p53 protein is found in low levels, but because of its short half-life (6–20 min), it cannot be detected in routine immunohistochemical procedures.[7] In cases of cellular stress or DNA damage, its transcription increases and it arrests cells in the G1 phase of the cell cycle to provide time for DNA repair.[8] If the damage is irreparable, then it directs the cell to apoptosis.[9]

Studies investigating p53 in tissue have found that p53 staining was more common and intense in the smoking group than the control group, which suggested that one effect of smoking could be some kind of mutation in the *TP53* gene that leads to the increased transcription of the mutated and more stable p53 protein, leading to its accumulation in tissues.[1]

Address for correspondence: Dr. MÇ Aksoy,
Department of Oral and Maxillofacial Surgery,
Faculty of Dentistry, Süleyman Demirel University,
32260 Çünür, Isparta, Turkey.
E-mail: mugecina@hotmail.com

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TP53 mutation is the most common genetic mutation encountered in human cancers; there is an accompanying *TP53* mutation in 50% of squamous cell carcinomas. Smoking is a major etiologic factor for squamous cell carcinoma of the head-and-neck regions, and it has been suggested that the repetitive exposure of squamous epithelial cells in the oral cavity to carcinogens in cigarette smoke can cause neoplastic transformations. However, the exact mechanism of how cigarette smoke causes neoplastic changes still requires elucidation.[3]

The aim of this article is to investigate the *TP53* status in the dental follicles of asymptomatic impacted lower third molar teeth in smoking and nonsmoking patients and to assess whether a relationship exists between *TP53* status and smoking.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and the study design was approved by the Local Ethical Committee (Süleyman Demirel University Faculty of Medicine Ethical Committee, Decision No. 125). The study was supported by the Süleyman Demirel University Scientific Research Projects Coordination Department (Project No. 3608-D2-13). The inclusion criteria were patients aged 18 or above who were systemically healthy, had not used antibiotics or analgesic drugs for a minimum of 1-month before the surgical procedure, and had a clinically asymptomatic fully impacted lower third molar teeth with pericoronal radiolucency narrower than 2.5 mm on a panoramic radiograph.[10] Patients who were younger than 18 years, had accompanying systemic disease, had used antibiotics or analgesic drugs in the previous month, and/or had clinically symptomatic impacted lower third molar teeth with a pericoronal radiolucency wider than 2.5 mm on a panoramic radiograph were excluded from the study.

The patients' sociodemographic characteristics, smoking habits for the smoker group (smoking duration, daily consumption, and packs/year), the status of bone retention in the teeth, and the position of the teeth according to Winter's classification were recorded. The widest region of the pericoronal radiolucencies was measured with the Planmeca Romexis (Planmeca Oy, Helsinki, Finland) software.

Routine surgical extraction procedures were performed under local anesthetic by experienced surgeons. The follicles were separated from the teeth with the help of a lancet and kept in saline solution at 4°C. Specimens were sent to a private laboratory with a cold chain for single-nucleotide polymorphism (SNP) analysis. Before the polymerase chain reaction (PCR), the quantification of genomic DNA was confirmed with ultraviolet spectrophotometer measurements of 260–280-nm wavelength results at 1.8–2.0. After quantitation, most of the DNA was diluted to a stock concentration of 50 ng/μl. For the analysis, a matrix-assisted desorption/ionization time of flight mass spectrometry (MALDI-TOF MS; Sequenom, San Diego, USA) procedure was carried out on 21 regions of the *TP53* gene (selected from the NCBI dbSNP database) (*TP53* dbSNP 2015). Nucleic acid changes were detected by amplifying target regions using the genomic software of MassARRAY® TYPER 4.0 (Agena Bioscience Inc., San Diego, USA) and specially designed primer pairs. Unconnected deoxynucleotide triphosphates in the amplification products were neutralized with shrimp alkaline phosphatase. These products were then subjected to elongation reaction with iPLEX (Agena Bioscience Inc., San Diego, USA). The iPLEX reaction products were treated with a cationic exchange resin to remove ions such as Na+, K+, Mg+, and to minimize the background contamination, and then centrifuged. SNPs that are classified as either pathologic or likely pathologic in the database and associated with oral pathologies were included in the study. Furthermore, some SNPs were eliminated and replaced with SNPs in the kit design [Figure 1].

Chi-square test for independence was used for the statistical analysis of the relationship between SNP occurrence and smoking, and a *Z*-test was used to compare the two ratio's critical values.

Results

One hundred follicles were examined in the paper and the main reason for extraction being prophylactic followed by orthodontic treatment. The study group consisted of the follicles from 50 smoking participants and the control group consisted of those from the 50 nonsmoking participants. Out of the 100 follicles, 58 were from female and 42 were from male patients, and ages were in the range 18–50 (22.9 ± 5.9). Patients' gender and smoking status, bone retention status, and angulation according to the Winter's classification of the impacted teeth were as given in Table 1.

The shortest duration of smoking habit was 7 months, while the longest was 33 years. The mean duration of smoking habit was 7.7 ± 6.4 years. The number of cigarettes consumed varied between two cigarettes a month to 30 cigarettes a day. The mean cigarette consumption was 12.5 ± 7.5 cigarettes each day. In terms of packs per year, the mean cigarette consumption was 4.9 ± 5.1 (varying between 0.1 and 25).

MALDI-TOF MS analysis detected 10 SNPs on the *TP53* gene [Table 2]: rs2287497, rs2287498, rs2287499, rs2909430, rs8079544, rs9895829, rs12947788,

Figure 1: The schematic view of the *TP53* gene and the localization of the detected SNPs on the gene. Empty boxes represent noncoding exons, blue boxes represent coding exons, and the lines connecting boxes represent introns

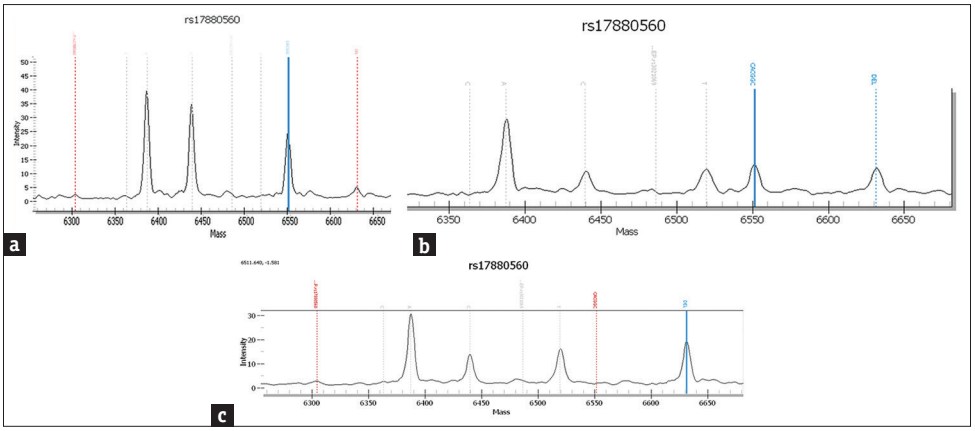

Figure 2: Matrix-assisted desorption/ionization time of flight mass spectrometry analysis results of rs17880560 and the image of three different genotypes: (a) healthy homozygote genotype, (b) heterozygote genotype, and (c) polymorphic homozygote genotype

Table 1: Gender and smoking status of the patients and classifications of the impacted teeth

	n (%)
Gender	
Female	58 (58)
Male	42 (42)
Smoking status	
Yes	50 (50)
No	50 (50)
Bone retention	
Fully	70 (70)
Partially	30 (30)
Angulation (according to Winter's classification)	
Distoangular	2 (2)
Vertical	55 (55)
Mesioangular	17 (17)
Horizontal	26 (26)

rs12951053, rs17551157, and rs17880560 [Figure 2a-c]. Four of these SNPs (rs2287497, rs2287498, rs2287499, and rs17551157) were on the *WRAP53* gene, which is a 5' flanking gene and a negative regulator of *TP53*.

According to the Chi-square analysis results, the Chi-square test statistic calculated between the base sequence of the rs2287497 gene region and smoking status was found to be 3.8, which was not statistically significant. Furthermore, as a result of the *Z*-test, the difference between the C base rate (38/50-0.8) and the C base rate (45/50-0.9) among the nonsmokers (NS) in the rs2287497 gene was not statistically significant.

The Chi-square test statistic calculated between the base sequence of the rs2287498 gene region and smoking status was found to be 1.5, which was not statistically significant. In the rs2287498 gene, the difference between the prevalence of the G base rate (29/50-0.6) in NS and the prevalence of G in smokers (33/50-0.7) was not statistically significant.

The Chi-square test statistic calculated between the base sequence of the rs2287499 gene region and smoking status was found to be 3.3, which was not considered statistically significant. In the rs2287499 gene area, the difference between the prevalence of the G base incidence in NS (43/50-0.9) and in smokers (48/50-1) was not statistically significant.

The Chi-square test statistic that is calculated between the base sequence of the rs2909430 gene region and smoking status was found to be 1.7, that between the base sequence of the rs8079544 gene region and smoking status was found to be 1.9, that between the base sequence of the rs9895829 gene region and smoking status was found to be 1.9, that between the base sequence of the rs12947788 gene region and smoking status was found to be 1, and that between the base sequence of the rs12951053 gene region and smoking status was found to be 1, none of which are statistically significant.

The Chi-square test statistic calculated between the base sequence of the rs17551157 gene region and smoking status was found to be 2.2 and was not statistically

Table 2: Base substitutions of observed single nucleotide polymorphisms (SNPs) and reference SNP Number

Reference SNP number (SNP500 cancer ID)	Base substitution
rs2287497 (*WRAP53-07*)	C>T
rs2287498 (*WRAP53-08*)	Ex^2+19C>T
rs2287499 (*WRAP53-11*)	Ex1-230C>G
rs2909430 (*TP53-66*)	IVS4-91G>A
rs8079544 (*TP53-09*)	IVS1-112C>T
rs9895829 (*TP53-65*)	IVS4-125A>G
rs12947788 (*TP53-10*)	IVS7+72G>A
rs12951053 (*TP53-11*)	IVS7+92T>G
rs17551157	C>DEL
rs17880560	delCACGGC

SNP=Single-nucleotide polymorphism

Table 3: Allele frequencies of different rs regions in smoking and nonsmoking patients

	Smoking	Genotype			χ^2
	Smoking (+) Nonsmoking (-)	AA	Aa	aa	
rs2287497	+	0.900	0.100	0	3.840
	-	0.760	0.220	0.020	
rs2287498	+	0	0.340	0.660	1.501
	-	0.020	0.400	0.580	
rs2287499	+	0	0.040	0.960	3.275
	-	0.020	0.120	0.860	
rs2909430	+	0.020	0.260	0.720	1.670
	-	0.020	0.380	0.600	
rs8079544	+	0.980	0.020	0	1.895
	-	0.920	0.080	0	
rs9895829	+	0.980	0.020	0	1.895
	-	0.920	0.080	0	
rs12947788	+	0.860	0.140	0	1.012
	-	0.840	0.140	0.020	
rs12951053	+	0.860	0.140	0	1.012
	-	0.840	0.140	0.020	
rs17551157	+	0	0.060	0.940	2.178
	-	0.020	0.120	0.860	
rs17880560	+	0.120	0.340	0.540	1.890
	-	0.060	0.280	0.660	

AA=Homozygote major allele; Aa=Heterozygote allele; aa=Homozygote minor allele; += Positive means Smoking; -= Negative means non smoking

significant. The difference between the C-based deletion rate (43/50-0.9) in NS in the rs17551157 gene region and the C-based deletion rate (47/50-0.9) in smokers was not statistically significant.

The Chi-square test statistic between the base sequence of the rs17880560 gene region and smoking status was found to be 1.9 and was not statistically significant. According to the results of the present study, the base sequences of the rs2287497, rs2287498, rs2287499, rs2909430, rs8079544, rs9895829, rs12947788, rs12951053, rs17551157, and rs17880560 gene regions are independent from cigarette smoking. The allele frequencies are given in Table 3.

Statistical analysis showed no correlation between smoking and SNP occurrence. The Chi-square values for each SNP and smoking habit were in the range 1.0–3.8.

Discussion

The extraction of impacted teeth is the most common surgical procedure in oral surgery, but the prophylactic extraction of asymptomatic fully impacted teeth remains controversial. Studies on these teeth have focused on histopathological changes and immunohistochemical stainings as seen on the dental follicles of such teeth. The term "asymptomatic" refers to impacted teeth that show no signs of illness, including radiographic findings, and studies involving these teeth should have pericoronal radiolucencies no wider than 2.5 mm; this limit can be extended to 3 mm if analog radiographs are used to account for magnification errors.[11]

In immunohistochemistry, p53 is one of the most commonly investigated proteins, which is a tumor suppressor protein found at very low levels in healthy tissue.[8] In cases, in which cellular stress causes DNA damage in cells, p53 expression increases and arrests the cell cycle in the G1 phase to allow time for DNA repair.[8] If the damage is irreparable, then p53 directs the cell to apoptosis and prevents the proliferation of damaged DNA.[9] This very important protective function has afforded p53, the honor of being called the "guardian of the genome."[12]

TP53 is the most frequently mutated gene in human cancers,[3,13] and there is a *TP53* mutation in more than 50% of cancers in the head-and-neck regions.[14] While smoking is a major etiological factor in cancer development, it also causes specific mutations in the *TP53* gene by forming DNA adducts in hotspot regions.[15]

In the presented paper, the researchers investigated 21 SNPs in the *TP53* gene using MALDI-TOF MS, of which 10 were detected (rs2287497, rs2287498, rs2287499, rs2909430, rs8079544, rs9895829, rs12947788, rs12951053, rs17551157, and rs17880560). The allele frequencies of the SNPs in this paper population were in concordance with previous studies except for rs17880560 and rs2287499.

Rs2287497 is an intronic change that takes place in the 5' flanking gene of *TP53*; *WRAP53* is a negative regulator of *TP53* and partly overlaps with it.[16] In this SNP, a

thymine (T) nucleotide is substituted for a cytosine (C) nucleotide. This SNP has been linked with ovarian cancer.[16,17] The genotype frequencies of the paper population were 0.8 (C/C), 0.2 (C/T), and 0 (T/T) and the frequencies were 0.9, 0.1, and 0 in the smoker group and 0.8, 0.2, and 0 in the NS group. These results are in agreement with those of Mędrek *et al*.[17] and Pineda *et al*.[18] Pineda *et al*.[18] reported a healthy homozygote genotype ratio of 0.8, a heterozygote genotype ratio of 0.2, and a polymorphic homozygote ratio of 0 in European races in their study of *TP53* variants in urothelial bladder cancer. In patients diagnosed with such cancer, the rates that were found were 0.8, 0.2, and 0. Therefore, they suggested that variations in the rs2287497 region in the European race were not associated with bladder cancer.

rs2287498 is an exonic change in the second exon of *WRAP53*. In this SNP, a silent mutation takes place with a guanine (G) to adenosine (A) nucleotide exchange that does not affect the coding of the phenylalanine amino acid.[19] Although this is a silent mutation, it has been reported that the SNP in rs2287498 is related to ovarian and breast cancer.[17,20] The allele frequencies in the presented study population were 0 (A/A), 0.4 (A/G), and 0.6 (G/G), and these results are in concordance with the paper of Mędrek *et al*.[17] Garcia-Closas *et al*.[20] reported that a healthy homozygote genotype in healthy Polish and Norwegian populations was found to be 0.8, whereas in individuals with breast cancer, this ratio was found to be 0.9. On comparing subgroups of breast cancer, there was an increased risk of estrogen-receptor-negative breast cancer in the presence of SNP in the rs2287498 region.

rs2287499 is in the first exon of the *WRAP53* gene.[21] A G nucleotide is substituted for a C nucleotide, which results in glycine amino acid coding.[22] Garcia-Closas *et al*.[20] reported that SNPs in rs2287499 may be associated with estrogen-receptor-negative breast cancer. The study population's allele frequencies were found to be 0 (C/C), 0.1 (C/G), and 0.9 (G/G), which are in accordance with previous studies that reported high frequencies of the C/C genotype.[20,23] Bonab *et al*.[23] reported a healthy homozygote genotype ratio of 0.7, a heterozygote genotype ratio of 0.3 and a homozygous polymorphic genotype ratio of 0.1 in the control group of Iran's Azeri population; meanwhile, these ratios were respectively reported as 0.7, 0.3, and 0 in the patient group. Thus, they suggested that SNPs in the rs2287499 region were not associated with breast cancer. Garcia-Closas *et al*.[20] reported that the rate of the homozygote healthy genotype incidence was 0.8 in the healthy population and 0.5 in the patient population; the heterozygote genotype incidence was 0.3 in the healthy group, 0.2 in the patient group; the homozygote polymorphic genotype was found to be 0 in both the healthy and patient groups.

rs2909430 is an intronic change in *TP53*'s fourth intron. This SNP, in which an A nucleotide is substituted for a G nucleotide, is associated with a decreased risk of invasive breast cancer in women younger than 50.[24] Mechanic *et al*.[25] reported an increased risk of lung cancer with a worse prognosis in the African–American population with this SNP and accompanying SNPs in rs1042522, rs9895829, rs1625895, and rs12951053. However, this was not the case for the Caucasian population.[25] The allele frequencies in the study population were 0.7 (A/A), 0.3 (A/G), and 0 (G/G), which are in concordance with previous studies.[18,20] Pineda *et al*.[18] reported that SNPs commonly found in the *TP53* gene were not associated with bladder cancer.

rs8079544 is found in the first intron of *TP53*, where a T nucleotide is substituted for a C nucleotide. Few studies have focused on this SNP, and no association has yet been established with any cancer type. The allele frequencies were 1 (C/C) and 0.1 (C/T), but no T/T homozygosity was detectable in the study group. These results are in agreement with the NCBI dbSNP CAUC1 population.[26] Pineda *et al*.[18] reported that a healthy homozygote genotype ratio of 0.9, a heterozygote genotype ratio of 0.1, and a homozygote polymorphic genotype ratio of 0 in a healthy population among Spanish races. These rates were no different from those seen in patients who had been diagnosed with bladder cancer.

rs9895829 is an intronic polymorphism in the *TP53* gene's fourth intron where a G nucleotide has been substituted for an A nucleotide. In patients with bladder cancer, the G allele was found in higher frequencies than in the healthy group.[27] In the present paper, allele frequencies were reported as 1 (A/A) and 0.1 (A/G), but no G/G homozygosity was detected; these results concur with the NCBI dbSNP CAUC1 population.[26]

rs12947788 is an A-to-G nucleotide exchange in intron 7. Studies have associated this SNP with malign pleural mesothelioma and lung cancer.[28] In this paper, the respective frequencies of A/A, A/G, and G/G genotypes were 0, 0.1, and 0.9, which were again in concordance with the NCBI db SNP CAUC1 population.[26] Sprague *et al*.[24] reported that *TP53* polymorphisms were associated with an increased risk of breast cancer. In another study comparing colorectal cancer cases with a healthy control group, it was reported that the T allele, which is a minor allele, was seen less often in patients with colorectal cancer, but the difference was not statistically significant.[29]

rs12951053 is an A-to-C nucleotide exchange in intron 7. In the literature, studies have related this SNP with invasive breast cancer, lung cancer, malign pleural mesothelioma, and cervical cancer.[16,24,25,28] However,

instead of an A-to-C exchange, these studies investigated a T-to-G exchange. The genotype frequencies of the study population were 0.9 (A/A), 0.1 (A/C), and 0 (C/C).

SNP in rs17880560 is the addition/deletion of 6 base pairs (bps) in the sequence of the 3'-untranslated region of the *TP53* gene. Very few studies have investigated this SNP, although Sagne *et al*.[30] investigated the addition of 6 bps to the sequence and found that, if seen together with another germline mutation in the *TP53* gene, this SNP was associated with later cancer onset. The study population's allelic frequencies were 0.1 (CACGGC/CACGGC), 0.3 (CACGGC/delCACGGC), and 0.6 (delCACGGC/delCACGGC).

rs17551157 is an intronic change in the *WRAP53* region of the *TP53* gene.[26] Little is known about this SNP and no association with any disease has been established for it. The allele frequencies of the study group were 0 (C/C), 0.1 (C/delC), and 0.9 (delC/delC).

There are very few studies on the possible roles of these SNPs in various cancer types,[28] and although some SNPs have been associated, the results were inconclusive.[16,17,19,20] The reasons for this uncertainty are population-based genotypic frequency discrepancies, the distinct effects of specific SNPs in different populations, and difficulties determining the possible interactions between SNPs (phenotypic affect).

In this paper, the researchers standardized study specimens by collecting dental follicles from patients who had asymptomatic fully impacted lower third molars and had not been administered analgesics or antibiotics for a month before surgery. The adverse effects of smoking were assessed by comparing the study group of smoker patients and the control group of NS patients.

The results of this paper show a high ratio of SNPs without any correlation between smoking and *TP53* gene status. Furthermore, there were no correlations between gender, tooth angulation, tooth developmental stage, and *TP53* status, and so the researchers can assume that these SNPs were not a result of smoking but rather other environmental causes or perhaps ethnic characteristics of the study population. It is common knowledge that the rates of genotypes in different populations may vary. A major limitation of this paper was that only one part of the *TP53* gene was examined. Further studies should be carried out on larger populations and total gene sequence analysis should be carried out to help assess the possible effects of smoking on the *TP53* gene.

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Conflicts of interest

There are no conflicts of interest.

References

1. Toptaş O, Baykul T, Başak K. Does smoking affect the Ki67 and p53 expressions in asymptomatic fully impacted lower third molar follicles? J Oral Maxillofac Surg 2015;73:819-26.
2. Smith CJ, Perfetti TA, Garg R, Hansch C. IARC carcinogens reported in cigarette mainstream smoke and their calculated log *P* values. Food Chem Toxicol 2003;41:807-17.
3. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P, *et al.* Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene 2002;21:7435-51.
4. Yoshitomi T, Kuramochi K, Binh Vong L, Nagasaki Y. Development of nitroxide radicals-containing polymer for scavenging reactive oxygen species from cigarette smoke. Sci Technol Adv Mater 2014;15:035002.
5. Pagès V, Fuchs RP. How DNA lesions are turned into mutations within cells? Oncogene 2002;21:8957-66.
6. Brázda V, Hároníková L, Liao JC, Fojta M. DNA and RNA quadruplex-binding proteins. Int J Mol Sci 2014;15:17493-517.
7. Nasser W, Flechtenmacher C, Holzinger D, Hofele C, Bosch FX. Aberrant expression of p53, p16INK4a and Ki-67 as basic biomarker for malignant progression of oral leukoplakias. J Oral Pathol Med 2011;40:629-35.
8. Bourdon JC. P53 family isoforms. Curr Pharm Biotechnol 2007;8:332-6.
9. Ferraiuolo M, Verduci L, Blandino G, Strano S. Mutant p53 protein and the hippo transducers YAP and TAZ: A Critical oncogenic node in human cancers. Int J Mol Sci 2017;18. pii: E961.
10. Villalba L, Stolbizer F, Blasco F, Mauriño NR, Piloni MJ, Keszler A, *et al.* Pericoronal follicles of asymptomatic impacted teeth: A radiographic, histomorphologic, and immunohistochemical study. Int J Dent 2012;2012:935310.
11. Farah CS, Savage NW. Pericoronal radiolucencies and the significance of early detection. Aust Dent J 2002;47:262-5.
12. Nguyen D, Liao W, Zeng SX, Lu H. Reviving the guardian of the genome: Small molecule activators of p53. Pharmacol Ther 2017;178:92-108.
13. Nakayama M, Sakai E, Echizen K, Yamada Y, Oshima H, Han TS, *et al.* Intestinal cancer progression by mutant p53 through the acquisition of invasiveness associated with complex glandular formation. Oncogene 2017;36:5885-96.
14. De Oliveira SR, Da Silva IC, Mariz BA, Pereira AM, De Oliveira NF. DNA methylation analysis of cancer-related genes in oral epithelial cells of healthy smokers. Arch Oral Biol 2015;60:825-33.
15. Feng Z, Hu W, Hu Y, Tang MS. Acrolein is a major cigarette-related lung cancer agent: Preferential binding at p53 mutational hotspots and inhibition of DNA repair. Proc Natl Acad Sci U S A 2006;103:15404-9.
16. Schildkraut JM, Iversen ES, Wilson MA, Clyde MA, Moorman PG, Palmieri RT, *et al.* Association between DNA damage response and repair genes and risk of invasive serous ovarian cancer. PLoS One 2010;5:e10061.
17. Mędrek K, Magnowski P, Masojć B, Chudecka-Głaz A, Torbe B, Menkiszak J, *et al.* Association of common WRAP 53 variant

with ovarian cancer risk in the Polish population. Mol Biol Rep 2013;40:2145-7.
18. Pineda S, Milne RL, Calle ML, Rothman N, López de Maturana E, Herranz J, *et al.* Genetic variation in the TP53 pathway and bladder cancer risk. A comprehensive analysis. PLoS One 2014;9:e89952.
19. Schildkraut JM, Goode EL, Clyde MA, Iversen ES, Moorman PG, Berchuck A, *et al.* Single nucleotide polymorphisms in the TP53 region and susceptibility to invasive epithelial ovarian cancer. Cancer Res 2009;69:2349-57.
20. Garcia-Closas M, Kristensen V, Langerød A, Qi Y, Yeager M, Burdett L, *et al.* Common genetic variation in TP53 and its flanking genes, WDR79 and ATP1B2, and susceptibility to breast cancer. Int J Cancer 2007;121:2532-8.
21. Lan Q, Zhang L, Shen M, Jo WJ, Vermeulen R, Li G, *et al.* Large-scale evaluation of candidate genes identifies associations between DNA repair and genomic maintenance and development of benzene hematotoxicity. Carcinogenesis 2009;30:50-8.
22. Saintigny P, Zhang L, Fan YH, El-Naggar AK, Papadimitrakopoulou VA, Feng L, *et al.* Gene expression profiling predicts the development of oral cancer. Cancer Prev Res (Phila) 2011;4:218-29.
23. Sedaie Bonab A, Pouladi N, Hosseinpourfeizi MA, Ravanbakhsh Gavgani R, Dehghan R, Azarfam P, *et al.* Single-strand conformational polymorphism analysis of a common single nucleotide variation in WRAP53 gene, rs2287499, and evaluating its association in relation to breast cancer risk and prognosis among Iranian-Azeri population. Med Oncol 2014;31:168.
24. Sprague BL, Trentham-Dietz A, Garcia-Closas M, Newcomb PA, Titus-Ernstoff L, Hampton JM, *et al.* Genetic variation in TP53 and risk of breast cancer in a population-based case control study. Carcinogenesis 2007;28:1680-6.
25. Mechanic LE, Bowman ED, Welsh JA, Khan MA, Hagiwara N, Enewold L, *et al.* Common genetic variation in TP53 is associated with lung cancer risk and prognosis in African Americans and somatic mutations in lung tumors. Cancer Epidemiol Biomarkers Prev 2007;16:214-22.
26. TP53dbSNP; 2017. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=7157. [Last Retrieved on 2017 Jul 20].
27. Al-Delayme RM. The effect of cigarette smoking on the severity of pain, swelling and trismus after the surgical extraction of impacted mandibular third molar. J Clin Exp Dent 2013;5:e117-21.
28. Andujar P, Pairon JC, Renier A, Descatha A, Hysi I, Abd-Alsamad I, *et al.* Differential mutation profiles and similar intronic TP53 polymorphisms in asbestos-related lung cancer and pleural mesothelioma. Mutagenesis 2013;28:323-31.
29. Polakova V, Pardini B, Naccarati A, Landi S, Slyskova J, Novotny J, *et al.* Genotype and haplotype analysis of cell cycle genes in sporadic colorectal cancer in the Czech republic. Hum Mutat 2009;30:661-8.
30. Sagne C, Marcel V, Bota M, Martel-Planche G, Nobrega A, Palmero EI, *et al.* Age at cancer onset in germline TP53 mutation carriers: Association with polymorphisms in predicted G-quadruplex structures. Carcinogenesis 2014;35:807-15.