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Impact of MT-MMPS and E2F2 gene polymorphism and Environmental Factor in Oral Cancer Development and Malignancy in Western Uttar Pradesh

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ABSTRACT

Objectives: To identify the role of environmental factors and polymorphisms in the development of malignancy of oral cancer in western Uttar Pradesh. **Methodology:** The study involved 400 participants, with 200 individuals comprising the experimental group diagnosed with oral squamous cell carcinoma (OSCC), while the remaining 200 participants formed the control group. Polymerase chain reaction-restriction fragment length polymorphism genotyping and haplotype-base analysis were used to investigate three single nucleotide polymorphisms (SNPs) in the MT-MMP and E2F2 genes. **Results:** Oral cancer risk was shown in MMP7 gene smokers. Risk was double in-between smokers and non-smokers due to heterozygous genotype (RQ) in MMP9 (Q279R) A/G (p=0.048; OR=2.18; 95%CI= l.0I-4.71). Minor allele frequencies for E2F2-rs2742976 oral cancer patients were 23.6%, controls were 22.7%, and the controls shared minor allele frequencies. **Conclusion:** The E2F2-rs2742976, heterozygous genotype (RQ) in MMP9 (Q279R) A/G, and MMP7 smoker's gene polymorphism may contribute to predict OSCC susceptibility and pathological progression.

1. Introduction

Oral squamous cell carcinoma (OSCC) constitutes over 90% of oral malignancies and poses a significant public health issue. OSCC patients have an elevated likelihood of developing concurrent tumours, particularly within the oral cavity, owing to a heightened genetic susceptibility of mucosal cells to carcinogenic agents (Rao, Mejia, Roberts-Thomson, & Logan, 2013). The tongue, oral mucosa (the lining of the mouth and gums), the floor of the mouth (the region below the neck), and the sides and base of the tongue are the usual regions where oral cancer occurs (Chi, Day, & Neville, 2015). It is the fourth most frequent kind of cancer in men and the fourth worst killer cancer (Tsai, Huang, Su, & Tang, 2014). Oral cancer affects around 11 out of every 100,000 persons each year. Males are more probable than females to get an oral cancer diagnosis (Sarode et al., 2020). Despite being treated with surgery, chemotherapy, and radiation, OSCC still has a dismal prognosis and death rate (Xie et al., 2015). Multiple genetic changes that have accumulated over time and impacts from environmental carcinogen exposure are what cause OSCC to emerge. There are evidence that drinking alcohol, smoking cigarettes, eating betel nut, chronic inflammation, and viral infection are risk factors for OSCC (Chang et al., 2005; Chen et al., 2008; Ajila et al., 2015). The most frequent kind of DNA sequence variation, single-nucleotide polymorphisms (SNPs), affects a person's vulnerability to illness, gene expression, and protein function. Previous studies suggest that Single Nucleotide Polymorphisms (SNPs) may have the potential to predict the risk of oral cancer (Chien et al., 2013; Lin et al., 2013; Yang et al., 2016). Despite reports that there is a connection between genetic variants and environmental carcinogens, identifying the key genes linked to OSCC susceptibility is crucial for disease early identification (Huang et al., 2009; Chien et al., 2012). This study aimed to determine the frequency of "exposure (genotype)" and "environmental factors" in the development and malignancy of oral cancer, respectively.

2. Methodology

2.1 Study design

This "case-control" prospective research was carried out at Subharti University's medical and dentistry college on the people of Western Uttar Pradesh, mostly in Meerut and surrounding areas. The Subharti Medical Institutional Ethics Committee in Meerut gave its approval to this project. The inclusion criteria include age between 18 and 80 years, a history of consuming tobacco, smoking, betal quid, and alcohol, and a positive family history. Oral cancer has also been established by pathology finding. Additionally, the exclusion criteria include additional metastatic malignancies, being under 18 years old, and the patient declining further examination.

2.2 Sample collection

The pathology departments of the dental and medical schools at Subharti University provided information on individuals with mouth cancer that had been definitively diagnosed. Interviews were used to gather each participant's demographic data, which included age, sex, place of residence, ethnicity, and smoking patterns. Only seasoned research professionals collected the data to guarantee that the study's quality standards were satisfied. We made sure that individuals in the experimental group shared a number of crucial traits, such as age (within 5 years), sex, location (rural/urban), smoking status, and ethnicity, in order to minimize the possibility of bias.

2.3 Sample size

According to the prevalence rate, 200 cancer patients with a history of using tobacco, smoking, betal quid, and alcohol were examined.

2.4 Solutions and Buffers

Solutions were produced using Millipore water, and all plastic and glassware used in this study was autoclaved for sterilization.

- **1M Tris-HCl (pH 7.6):**

700ml dH2O dissolved 121.1g Tris. Concentrated HCl lowered pH to 7.6 and increased volume to 1L. The autoclave-sterilized solution was stored at 40º C.

- **0.5M EDTA (pH 8):**

Dihydrate EDTA, 186.1 g sodium, was dissolved in 700 mL dH2O. Dissolving EDTA with 20g of NaOH raised the pH to 8.0. Volume was 1 L. Autoclaving and 4º C sterilized the solution.

- **Lysis Buffer (pH 8):**

800 ml of distilled water was mixed with 10mm of 1Mole Tris HCl, 109.54 grams of sugar, 0.47 grams of MgCl, and 10milliliter of Triton X 100, pH to 8.0. Distilled water increased capacity to 1000 milliliters. Autoclaves sterilized the reagent. Before Triton X 100, pH was corrected.

- **Reagent B of pH 8:**

8.76 gram of NaCl, 120 ml of 0.5 mol EDTA, and 400 ml of 1 mol Tris HCl were added. Distilled water lowered the volume to 1000ml. After autoclaving the reagent, 10g SDS was added.

- **5M Sodium perchlorate:**

80 ml distilled water dissolved 70g of sodium per chlorate. Distilled water increased capacity to 100 mm. Avoid autoclaving reagent.

- **TE buffer (pH 7.6):**

2ml 0.5M EDTA and 10millitre 1M tris HCl (pH 8.0) were added, 7.6 was pH. The capacity was 1000millitre with distilled water. Autoclaving sterilized the reagent.

- **20% SDS:**

At 65º C, 20g of SDS were dissolved in 80 ml of DDW and raised to 100 ml with distilled H2O.

- **Tris-saturated Phenol:**

A magnetic bead stirred 500 mm of phenol and 500 mm of 0.5M Tris for an hour to form two layers. Wrap the foil-wrapped beaker at room temperature.

- **Chloroform: isoamyl alcohol (24:1):**

24 ml chloroform was mixed with 1 ml isoamyl alcohol.

80% ethanol

Absolute ethanol and 20 ml distilled water were chilled.

- **10X TAE Buffer:**

The volume was adjusted to 1000ml with filtered water after adding 48.4 Tris Base, 20ml of 0.5M Ethylenediamine Tetraacetic Acid (pH 8.0), and 11.402ml of glacial acetic acid. The reagent underwent autoclaving.

- **Absolute ethanol:**

Refrigerated pure ethanol was bought.

- **Agarose:**

Agarose was acquired.

- **DNA Loading Dye – 6X:**

60mM EDTA, 0.03 percent xylene cyanol, 60% glycerol, 0.03 percent bromophenol blue, and 10mM Tris-Hydrogen chloride (pH 7.6) were added throughout processing.

- **Ethidium bromide:**

To dissolve 10mg of Ethidium bromide in 10 mL of sterile double-distilled water, a magnetic stirrer was used. After that, the solution was stored in an airtight container with aluminum foil.

- **100 base pair DNA Ladder (0.1µg/µl):**

Ready-to-load at 0.1 g/l. The marker and 6X loading buffer are pre-mixed. The 100 bp Sharp DNA Ladder separates polymerase chain reaction products on agarose gels quickly. The DNA 'ladder' included "2000, 1500, 1000, 900, 800, 700, 600, 500, 400, 300, 200, and 100" base pairs.

2.5 Genotyping assays (E2F2 gene)

Applied Biosystems utilized allelic discrimination to genotype five E2F2 gene single nucleotide polymorphisms (SNPs): "rs6667575, rs3218121, rs2742976, rs3218123, and rs3218148." This process involved the application of primers, probes, and a design strategy to accurately determine the genetic variations present at these specific SNP loci.

2.6 DNA Isolation

Phenol-chloroform removed DNA from each sample. Cell Lysis Buffer-Proteinase K, 0.01M Tris HCl, 320mM sucrose, 5mM MgCl2, and 1% Triton X 100—resuspended blood samples. Samples were centrifuged at 3000 rpm for 10 minutes after an hour incubation. Discarding supernatant broke the particle. 1.25 ml of reagent C (5M Sodium per chlorate) and 5 ml of reagent B (5 ml of Lysis Buffer II: 0.4M Tris hydrogen chloride; 150 mM sodium chloride; 0.06M Ethylenediamine tetra acetic acid; 1% SDS) were mixed well. After adding 3 ml of Tris-saturated phenol, mixing gently, and centrifuging at 3000 rpm for 10 minutes, 3 ml of chloroform-isoamyl alcohol (24:1) were added. Utilizing a three-layered system consisting of phenol, chloroform, and water, the aqueous phase was collected using a blunt-ended tube. Proteins precipitated at the interface of the aqueous and organic layers. The resulting aqueous aliquot underwent centrifugation at 3000 rpm for 5 minutes, employing 3 ml of chloroform-isoamyl alcohol. Post-centrifugation, the aqueous phase was carefully separated into a new tube, where

DNA precipitation was induced by adding 2 liters of ice-cold 100% alcohol. The mixture showed DNA precipitate. After centrifuging at 10,500 rpm for 10 minutes at 4°C, DNA precipitated.

After centrifugation, the "supernatant" was removed, and the pellet cleaned in ice-cold 70% ethanol before being centrifuged again for 10 min at 10,500 rpm at 4 degrees Celsius. After centrifugation, the pellet was "air-dried" until the tube was ethanol-free and the supernatant discarded. The pellet was resuspended in 100 L of pH 7.6 Tris-EDTA buffer overnight at 4°C. -20°C DNA samples were used at 4°C.

2.7 Genomic DNA quantification using a spectrophotometric technique.

The DNA concentration was assessed using the NanoDrop ND-1000 Spectrophotometer, a product of Thermo Scientific NanoDrop Technologies based in Wilmington, DE. This spectrophotometer enables the quantification of DNA samples without the need for a standard curve. The measurements included the UV spectrum, DNA concentration expressed in ng/µl, and DNA absorbance at 260 and 280 nm, all conducted in accordance with the manufacturer's V3.1.0 User's guidelines. To ensure accuracy, the NanoDrop pedestal was cleaned with distilled water before each concentration measurement. A blank measurement was obtained using 2 µl of distilled water. The same approach measured samples (2 µl). The program showed sample concentration. The nucleic acid's purity was determined using the 260/280 ratio, which is the ratio of OD values at 260 and 280 nm. Pure DNA ratios were 1.8, but RNA and protein (or phenol) contamination ratios were greater and lower, respectively.

2.8 Agarose gel electrophoresis for the quality control of genomic DNA

Using 0.8% agarose, a Medox horizontal agarose gel electrophoresis equipment evaluated DNA samples. It was added to 100 mL of 0.5x TAE buffer, pH 8.3, in conical flasks sealed with aluminum foil to prevent buffer leakage. Microwaved and magnetized, the conical flask's slurry dissolved all agarose grains. Heterogeneous cooling was avoided via 60°C off-bench cooling. Ethidium bromide was added and then appropriately diluted to achieve a concentration of 0.5 g/L. 70% ethanol cleaned mold, plastic tray, and comb as agarose gel heated. The plastic tray was put in the mold on a horizontal bench with the comb 0.5–1.0 mm above the plate to create a full well while pouring agarose. The pipette tip removed air bubbles under and between the comb's teeth before pouring the heated agarose solution into the mold. 20–40 minutes at room temperature hardened the gel.

The gel tank was given 2000 mL of 0.5x TAE buffer. The gel in the plastic tray was gently removed from the comb and placed in the electrophoresis tank with slots towards the negative pole-cathode. The gel

was 1 mm deep in 0.5x TAE buffer. A micropipette mixed 4 L DNA (40 ng) and 1 L gel loading buffer. Mixture slowly filled gel slots. 80 V provided 5 V/cm. Gel documentation took a photo after 45 minutes and UV-visible ethidium bromide staining.

2.9 Genes analyzed

This research seeks genetic variants that might predict oral cancer in high-risk patients. A highly penetrant gene mutation increases oral cancer risk. The polymorphic configuration of the 12 possible SNPs in the four detoxification pathway genes determined each person's genotype. Each polymorphism has three genotypes: heterozygote variation, wild type, or variant (PQ, PP, & QQ respectively).

2.10 Genotyping

Real-time and visible PCR were used. RT-PCR measures DNA. TaqMan genotyped this research. Dye-labeled DNA probe fluorescence detects TaqMan allelic discrimination mutations and PCR. Fast polymorphism detection. Gold-Taq DNA PCR's 5'-3' nuclease emits a fluorescent reporter for direct detection. Two target-allele-specific TaqMan probes. 5'-reporter/3'-quencher probe, Tetramethylrhodamine (TAMRA), a "3'-quencher dye", and carboxyfluorescein VIC and FAM, 5'-reporters, identify alleles. 20–24-mer SNP-PCR probes hybridize. "5'-exonuclease" inhibits reporter fluorescence. Taq DNA polymerase stretches the primer and copies the template to the probe's edge to cleave. Cycle-independent PCR. Finally, the Applied Biosystem 7900's laser light will penetrate the allelic discrimination plate to detect fluorescence signals. Mixed VIC/FAM/TET signals suggest heterozygosity. Foster City's Applied Biosystems contributed SNPs. DNA analysis followed assays and real-time PCR. 384-well optical reaction plates assessed samples after a successful pilot. Each experiment utilized 5 µL DNA (10 g/µL), 1.375 L distilled water, 2.5 µL TaqMan® Universal PCR Master Mix, and 0.125 L SNP Genotyping Assay. SNP genotypes had positive controls. The plate featured two DNA-free negative water controls.

PCR and allelic discrimination simplified genotyping. 7900 Real-Time PCR performed PCR and allelic discrimination. 60 cycles of 92 °C for 15 seconds and 60 °C for 1 minute followed by two initial stays of 50 °C for 2 minutes and 95 °C for 10 minutes. Allelic discrimination followed each PCR. Poor fluorescence required genotyping reanalysis.

2.11 Statistical analysis

- **HWSIM tool**

HWSIM used "one-degree-of-freedom X2 test and a Monte Carlo simulation test" to determine whether the "allele frequency spectrum" strayed from "Hardy-Weinberg equilibrium".

- **Hardy-Weinberg exact test**

A "Hardy-Weinberg exact test" was performed on each marker to assess the genotype frequency distribution's equilibrium assumption. This might imply genotyping issues or that the SNP or gene needs more study to determine the variation mechanism. SNPs that failed the polymorphism test or Hardy-Weinberg equilibrium were removed from the research.

- **Logistic regression**

Logistic regression predicts genotype-clinical outcomes. Logistic regression analyzes polymorphisms and illness status using parametric statistics. Oral cancer candidate gene polymorphisms were examined using binary logistic regression.

- **Fisher exact test**

Fisher exact test examined genotype-clinopathological parameter correlations, demographic variables, smoking, and other case group traits.

3. Result and discussion

3.1 Demographical Details

Table 1 shows subjects' demographics, 200 cancer-free individuals and controls were studied. Patients and controls were unrelated, age, gender, and ethnicity matched. All Patients were Indian (58.5±12.4, 75male:25female) and controls (58.8±10.8, 79 male:2 female) had similar mean age and gender distribution. Questionnaires and interviews captured smoking behaviors.

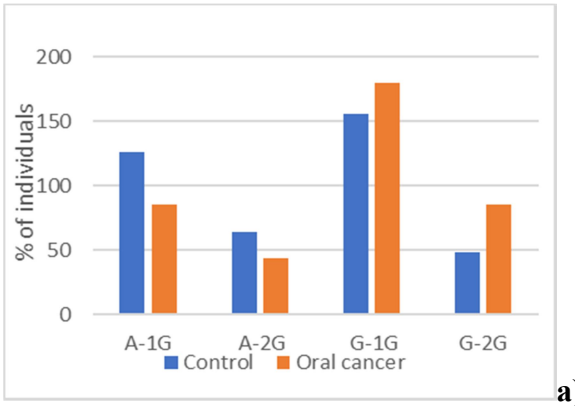
Table 1. Demographical characteristics

Variable	Cases n = 200(%)	Controls N=200(%)	Chi-square-value
Sex			
Female	30(15)	27(13.5)	0.520
Male	170(85)	173(86.5)	

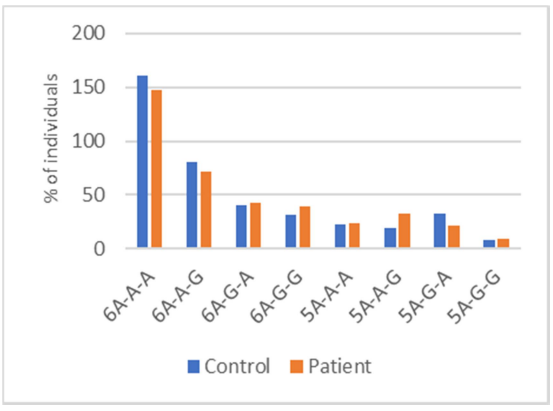
Age (years)			
Mean age ± SD	54.9±10.9	53.5±9.8	0.113
Smoking			
Never smokers	45(29.2)	150(73.5)	<0.001
Smoker	106(67.9)	43(20.5)	

3.2 Haplotype analysis of MMP gene polymorphisms in Oral cancer

MMP1 (-519 AIG) frequencies-controlled AA 50.5%, AG 34.7%, and GG 11.0%. MMP1 (-1607 1G/2G) controls had 25.5% lG/lG, 40.5% 1G/2G, and 29.1% 2G/2G genotypes. 1n regulates MMP3(11 71) allele 6A, heterozygous 35.0% of the time. 2.5% were homozygous 5A. Genotypic frequency distribution and logistics analysis demonstrated no mouth cancer risk from MMP3(116J) or MMP3(5356) AIG. MMP9 (Q279R) (QQ) genotype increased oral cancer risk (p=0.048; OR=0.92; 95%CI=1.0-3.66). The variant allele (R) of MMP9(P574R) G/C was higher in cases than controls (31.8% vs 18.5% and 56.0% vs 32.5%, respectively) and substantially associated with oral cancer risk (p<0.001, OR=2.05; 95%CI=l.47-2.85 and OR=2.59; 95%CI=l.72-3.91). Additionally, the MMP polymorphisms have been associated with an increased risk of oral cancer, according to research by Pereira et al., 2012 (Pereira, do Carmo, da Silva, & Rosa, 2012). A SNP in the MMP-1 promoter (1607 bp) was shown to be related with OSCC susceptibility in a Chinese population, according to Cao et al., 2004 report (Cao & Li, 2006).



a)



b)

Figure 1. Haplotype analysis of MMP I & MMP3 gene polymorphisms and oral cancer risk. a) (G-1 G Pc=0.012 and G-2G Pc=0.004) & (5A-A-G Pc=0.176).

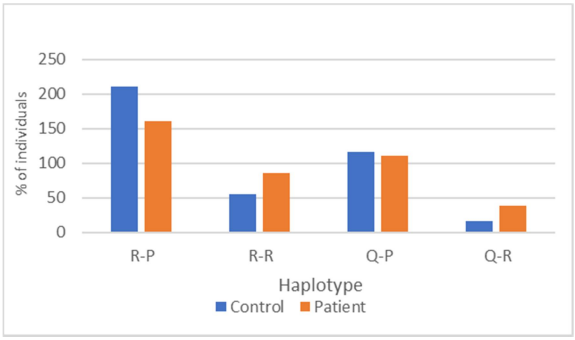
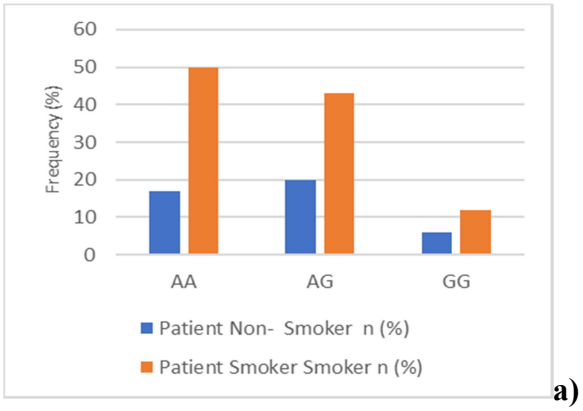


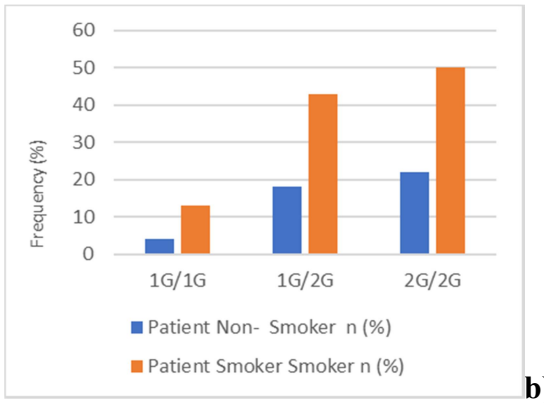
Figure 2. Haplotype analysis of MMP9 polymorphisms and oral cancer risk. (R-R Pc=0.004 and Q-R Pc=0.004).

3.3 Association of MMP Gene Polymorphisms with Smoking habits of patients

Smoking did not influence MMP1 and MMP3 without gene SNP polymorphisms and oral cancer risk. The genotype distribution between patients and controls in the study conducted by Hashimoto et al., 2004, explained MMP-3 polymorphism, did not vary significantly. The MMP-1 promoter polymorphism may be a cause of HNSCC, according to their findings (Hashimoto et al., 2004). The MMP7 gene smokers showed the risk for oral cancer. Heterozygous genotype (RQ) in MMP9 (Q279R) A/G doubled oral cancer risk between smokers and non-smokers (p=0.048; OR=2.18; 95%CI= 1.0I-4.71) whereas (PR) genotype protected MMP9 (P574R) G/C (p=0.008; OR=0.35; 95%CI=0.16-0.76). Many studies have indicated that the MMP gene increases the probability of an increase in the incidence of oral cancer (Hashimoto et al., 2004; Vairaktaris et al., 2008; Miao et al., 2003; Lin et al., 2004). While the increased incidence of oral cancer nowadays is due to smoking and several other environmental factors (Walker, Boey, & McDonald, 2003; Kaczmar et al., 2016; Kademani, 2007; Sinha et al., 2013; Chamoli et al., 2013).

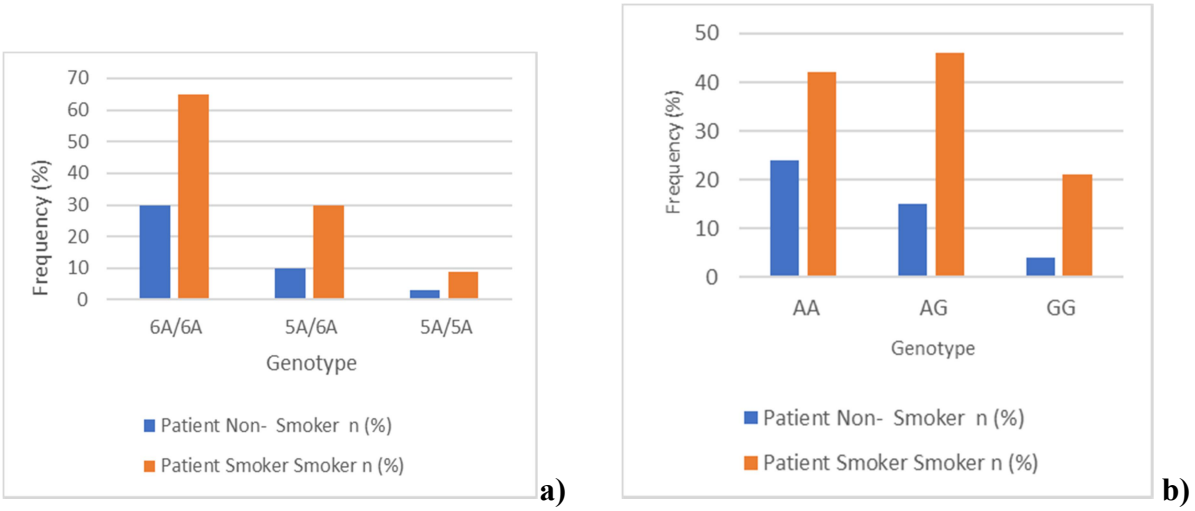


a)



b)

Figure 3. Graphical presentation of MMP 1 polymorphisms with smoking habit in oral cancer patients a) MMP1 (-519 AIG) b) MMP1 (-1607 1G/2G).



a) **b)**

Figure 4. Graphical presentation of MMP3 polymorphisms with smoking habit in bladder cancer patients a) MMP3(1171)5A/6A b) MMP3(1161) AIG.

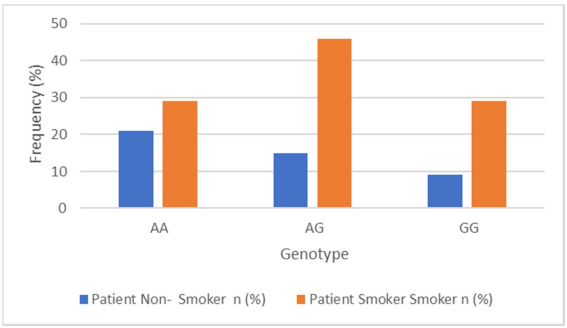


Figure 5. Graphical presentation of MMP7 (-181) AIG polymorphisms with smoking habit in oral cancer patients.

a) **b)**

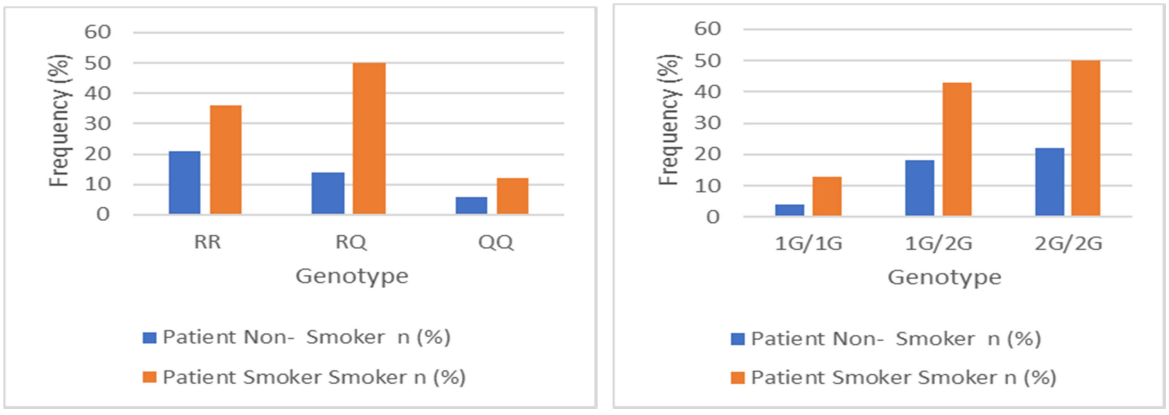


Figure 6. Graphical presentation of MMP9 polymorphisms with smoking habit in oral cancer patients a) MMP9(Q279R) AIG b) MMPJ (-1607 1G/2G).

3.4 EPHX1 gene polymorphisms and oral cancer

- **E2F2 -rs6667575, -rs3218121 & -rs2742976 polymorphism and oral cancer**

E2F2-rs6667575 showed oral cancer patients 35.4% minor allele frequency and controls 38.6%. E2F2-rs3218121 with 200 oral cancer controls yielded 67 GG, 53 GA, and 6 AA, 95GG, 46GA and 11AA. Both controls showed the presence of minor alleles. Specifically, in E2F2-rs2742976, oral cancer patients displayed a minor allele frequency of 23.6%, while controls exhibited a slightly lower frequency of 22.7%. It's noteworthy that the minor allele frequencies were comparable between the oral cancer patients and the controls.

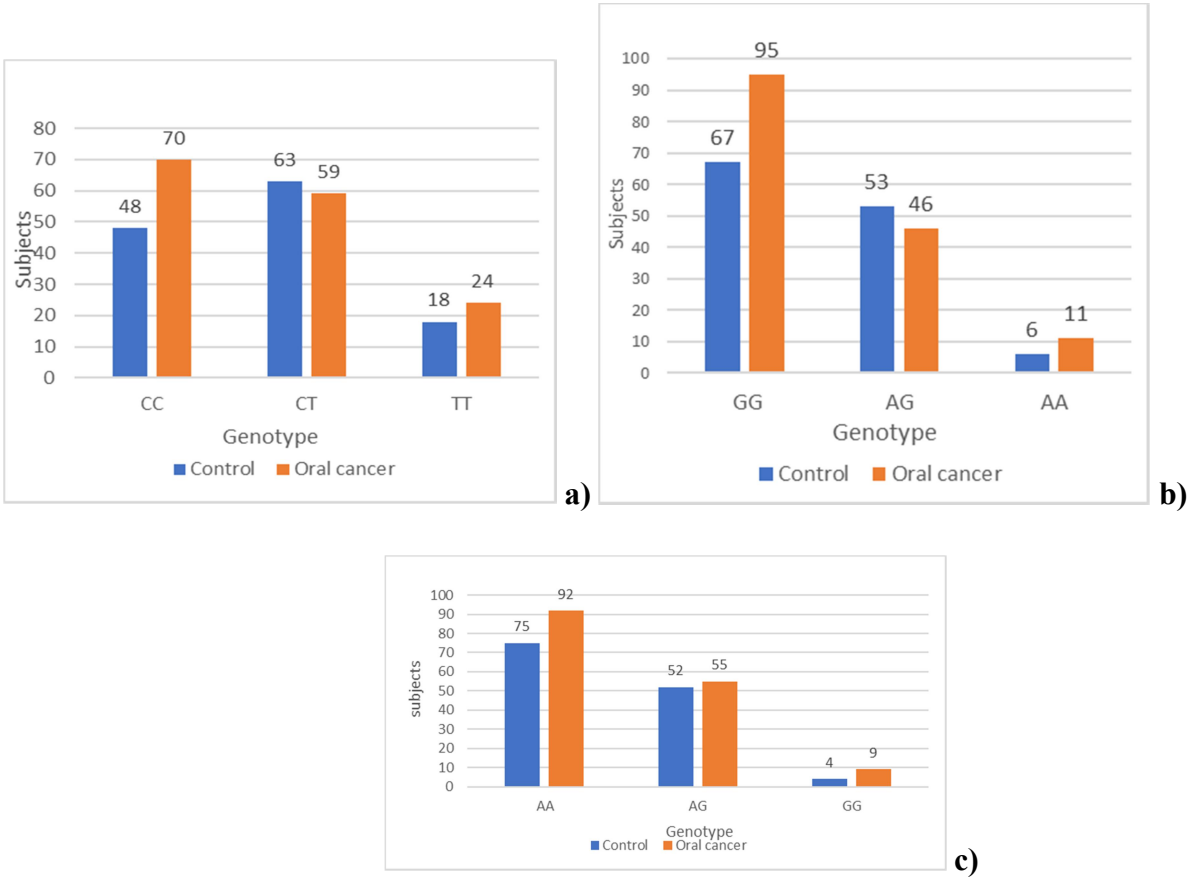


Figure 7. E2F2Gene haplotypes in oral cancer

All three SNPs and the two in the LD block are haplotyped in Table 2. Oral cancer and controls shared haplotypes. Haplotype phenotypic association showed no connection with oral cancer.

Table 2. Gene rs6667575, rs3218121, and rs2742976 haplotypes in oral cancer

Haplotype	Control	Case	OR (95%CI)	P value
TA	0.005	0.004	Reference	
TG	0.376	0.343	0.765(0.037-133.457)	0.858
CA	0.261	0.221	0.760(0.519-1.112)	0.156
CG	0.341	0.420	0.691(0.451-1.070)	0.101

4. Conclusion

In conclusion, our study revealed that smokers with the heterozygous genotype (RQ) in MMP9 (Q279R) A/G exhibited a doubled risk of oral cancer compared to non-smokers (p=0.048; OR=2.18; 95%CI=1.01-4.71). Additionally, the minor allele frequencies for E2F2-rs2742976 were found to be 23.6% in oral cancer patients and 22.7% in controls, with shared frequencies in controls. This emphasizes the role of E2Fs and MMP gene polymorphisms in regulating tumor development, growth, and aggressiveness in oral malignancies. The findings suggest the potential use of Mt-MMP and E2F2 as diagnostic and prognostic biomarkers due to their extensive expression in oral cancers and association with malignant development and poor prognosis. Further research, utilizing in vivo models and advanced molecular platforms, is necessary to elucidate the precise functions of different E2F2 and MT-MMP family members in oral carcinogenesis. Such efforts may lead to the identification of prospective therapeutic targets and the development of novel strategies for treating oral cancer.

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