Review Article Open Acces

MMP-2 is tightly regulated at the transcriptional and post-transcriptional levels. Functional single nucleotide polymorphism (SNP) in the promoter region of MMP-2 has been reported, that may in uence gene transcription and expression level in potentially malignant and malignant lesions. MMP-2 SNP is located at -1306 upstream of the transcriptional site and contains either a cytosine (C) or thymidine (T) [13]. e C/T transition located at nucleotide -1306 abolishes the Sp1-binding site and consequently diminishes promoter activity [6].

Studies on the MMP-2 -1306 promoter polymorphism have been carried out in cancers of lungs, breast, esophagus and colorectum and have demonstrated its inconsistent association in subjects with di erent ethnicity [14-17]. We investigated the association of -1306 promoter polymorphism in MMP-2 with susceptibility to develop OSCC in Indian population. We also investigated the distribution of MMP-2 promoter genotypes in patients with potentially malignant oral diseases namely OSMF and OLP.

Materials and Methods

Selection of cases and controls

Total one hundred newly diagnosed, previously untreated patients with OSCC (n=40), OSMF (n=40) and OLP (n=20) from the Department of Oral and Maxillofacial Pathology, Government Dental College and Hospital at Nagpur, India were recruited between November 2010-May 2011. ose with second primary Head and Neck Squamous Cell Carcinoma, primaries of the nasopharynx or sinonasal tract or primaries outside the upper aerodigestive tract and cervical metastasis of unknown origin were excluded. e diagnosis was con rmed by histopathological examination. Twenty control subjects were selected from people who came to the hospital for routine physical checkups or had non-neoplastic operations in the same hospital, and frequency-matched to the cases by age (± 5 years), sex, and tobacco/alcohol use status. e frequency matching was used to evaluate the main e ect of the polymorphisms. ose with previous diagnosis of any cancer type, autoimmune disorders, and blood diseases were excluded from the control group. All subjects were ethnically homogenous Indians and from the same region of India. All enrolled subjects were consented and were investigated by author with designed standard protocol that involved history, clinical and histopathological examination. e study was approved by Research and Ethics Committees of Maharashtra University of Health Sciences (MUHS), Nashik (ECM/8344-53).

MMP-2 genotyping

enzyme (New England Biolabs, USA) and separated on a 2.5% agaros gel stained with ethidium bromide to determine genotype.

Statistical analysis

e distribution of genotypes in all groups was tested deviation of Hardy-Weinberg Equilibrium. e Chi square test was applied to examine di erences in genotypic and allelic distribution between patients and controls. Moreover, the Odd's ratio and 95% con dence interval (95% CI) were calculated by unconditional logistic regression. A p value <0.05 was considered statistically signi cant.

Results

Amongst 40 cases of OSCC, the allele frequencies for the MMP-2 -1306 C and -1306 T were 81.25% and 18.75% in OSCC patients compared with 57.5% and 42.5% in controls (p=0.0042) (Table 1). e frequencies of the CC genotype was signi cantly higher in OSCC patients than in controls (72.5% versus 20%; p=0.0001).

By using logistic regression analysis, we evaluated the association between the MMP-2 -1306C/T polymorphism and risk of head and neck cancer. Because the MMP-2 -1306TT homozygotes were extremely rare, this genotype was combined with the MMP-2 -1306CT genotype for estimation of oral cancer risk. We found that subjects with the MMP-2 CC genotype was associated with signi cantly increased risk [adjusted OR, 10.54; 95% con dence interval (95% CI), 2.88-38.57] for developing HNSCC compared with those with the variant T allele, suggesting that the C allele could be the risk allele (Table 2).

Data presented as n (%) unless otherwise stated
[a]SD: Standard Deviation
[b]T: primary tumour
[c]N: regional lymph node
[d]SCC: Squamous Cell Carcinoma

Table 1: Clinical characteristics of cases and controls.

Amongst 40 cases of OSMF, the allele frequencies for the MMP-2 -1306 C and -1306 T were 76.25% and 23.75%, compared with 57.5% and 42.5% in controls (p=0.0189). e frequencies of the CC genotype was signi cantly higher in patients with OSMF than that of the controls (62.5% versus 20%; p=0.0014) [adjusted OR, 6.66; 95% con dence interval (95% CI), 1.87-23.71] (Table 3). Amongst 20 cases of OLP, the allele frequencies for the MMP-2 -1306 C and -1306 T were 70% and 30% in OLP patients, compared with 57.5% and 42.5% in controls (p=0.2013). e frequencies of the CC genotype was higher in patients with OLP than that of the controls (55% versus 20%; p=0.0128) [adjusted OR, 4.88; 95% con dence interval (95% CI), 1.19-19.94] (Table 4).

Discussion

Completion of the human genome project has revealed more than ten million single nucleotide polymorphisms; however, the signi cance of most of them in health and disease states is still elusive [19]. Genetic polymorphisms have emerged in recent years as important determinants of disease susceptibility and severity. Research considering genetic alterations jointly with environmental exposures could be relevant for a better understanding of HNC in the betel quid chewing area. Genetic polymorphism may play a signi cant role in person-to-person variability in cancer susceptibility, raising the intriguing possibility that some individuals could be predisposed to HNC development [20]. During the last few years, a number of polymorphisms in uencing the expression of genes encoding for factors implicated in tumor invasion and metastasis have been correlated with increased risk of developing oral malignancies [7].

MMP-2 is classi ed as gelatinase A. is gene is localized on 16q13. e gene is 17 kb long with 13 exons varying in size from 110 to 901 base pair (bp) and 12 introns ranging from 175 to 4350 bp [10]. e global role of functional genotype of MMP-2 for the risk of various neoplasms needs to be studied [21]. In the present study, we examined the relationship between the functional polymorphisms in the promoters of MMP-2 and oral cancer susceptibility in Indian population using PCR-RFLP.

e MMP-2 plays an important role in multiple stage carcinogenesis. e -1306 C/T transition in the promoter region of MMP-2 disrupts the Sp1 binding site and lead to a remarkable lower promoter activity [21]. e Sp1 is a ubiquitously expressed transcription factor that binds to GC/GT-rich elements and is critical for regulating MMP-2 in a constitutive or inducible manner. e CC allele binds substantially more Sp1 transcription factor and has signi cantly higher transcriptional activities than the CT or TT allele [6]. e presence of Sp1 consensus sequence at MMP-2 promoter may enhance transcription, which produces higher levels of MMP-2 in subjects carrying the CC genotype than those carrying the variants. us, it is reasonable to assume that subjects carrying germ line CC genotype would have increased expression of this enzyme for long period and they may be more susceptible to cancer [21].

Our data suggest that subjects carrying CC genotype were at a higher risk of developing OSCC in Indian population. is was in accordance with Lin SC et al. [21] and O-Charoenrat P and Khantapura [6] who demonstrated that subjects with the MMP-2 CC genotype was associated with signi cantly increased risk for developing OSCC compared with those with the variant genotype, in Taiwanese and ai population respectively. is could be interpreted by the fact that in these subjects there would be an increased MMP-2 promoter transcriptional activity leading to increased production of the enzyme.

Lin SC et al. [21] investigated the relative frequencies of MMP-2

In conclusion, the present study provides evidences for the rst time that -1306C/T polymorphism in MMP-2 promoter is a risk factor for oral carcinogenesis in Indian population, with the CC genotype being associated with the increase of risk. Also, it is the rst study to demonstrate an association of increased frequency of CC genotype in OSMF and OLP patients. To more precisely establish the contribution of the MMP-2 promoter polymorphism to oral cancer incidence, further examination of the prevalence of these variants in populations of other ethnic origin is required.