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Original Research Article

The Relationship between Matrix Metalloproteinas- 2 Promoter Polymorphisms and the Risk of Lung Cancer

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Abstract:
Multiple cancer forms have been found to overexpress matrix metalloproteinases-2 (MMP2). However, it is debatable and has not yet been investigated in Bhubaneswar how different MMP2 genotypes may contribute to lung cancer. As a result, we examined how Bhubaneswar ese MMP2 genotypes relate to risk of lung cancer in the current study. In this hospital-based case-control investigation, the genotypic distributions of MMP2-1306 and MMP2- 735 were established by recruiting 358 lung cancer patients and 716 healthy controls who were matched for age and gender. Then, using a stratification analysis, their relationship with one's own smoking history was assessed as well as their correlation with lung cancer. The findings demonstrated that lung cancer patients had significantly lower percentages of variant CT and TT at MMP2-1306—17.3% and 1.7%, respectively—than did healthy controls—28.7% and 2.4%, respectively (P for trend = 0.0001). When compared to the wild-type C allele, the variant T allele at MMP2-1306 imparted a statistically significantly lower risk of developing lung cancer (adjusted odds ratio = 0.54, 95% confidence range = 0.41-0.72, P < 0.0001), according to the allelic frequency distribution analysis. The MMP2-1306 genotype clearly affected lung cancer risk among subpopulations of ever smokers, but not in nonsmokers. There was no such disparate distribution in the MMP2-735 genotypes' genotypic or allelic frequencies, or in the combinatorial effects of smoking status. In Bhubaneswar, the genotypes of MMP2-1306 may serve as a biomarker to identify an individual's vulnerability to lung cancer. The therapeutic practises for early diagnosis and prediction of lung cancer in Bhubaneswar should take into account the impact of MMP2 genotypes alone and its joint effects with personal cigarette smoking habit.

Keywords: Genotype, Lung Cancer, Matrix Metalloproteinase-2, Polymorphism, Smoking, Bhubaneswar.

Introduction

Lung cancer has long been the most prevalent and significant contributor to cancer-related deaths worldwide. [1] Despite the tremendous advancement of personalised therapy and medicine, the 5-year survival rate for patients with lung cancer is still dismal at around 20%.[1] In order to expose the unique lung aetiology, updated valuable predictive and prognostic markers may help to improve the current genomic prediction methods.

MMPs, also known as matrixins, are a class of proteins that control the extracellular matrix's (ECM) internal homeostasis. [2, 3, 4] The idea that MMPs are involved in a variety of cancer processes, including cell proliferation, differentiation, apoptosis, invasion, migration, metastasis, angiogenesis, and immune surveillance, was supported by growing evidence. [5] In recent years, a number of reports suggested that MMP genotypes, particularly those in the promoter regions of MMPs, may be related to determining interindividual variations of susceptibility to different types of cancer, [6-14], while other reports produced contradictory findings. [15-17]

The human MMP2 gene, which is situated on chromosome 16q21, and the protein it encodes are members of the endopeptidase family, which is present in many different tissues and cell types. [18-20] According to published research, changes in the expression levels of MMP2's mRNA and protein may be directly linked to how some solid tumours, such as breast, lung, esophageal, and colon cancers, behave when they metastatically spread. [8,21-23] For instance, it has been noted that MMP2 levels were increased in the tumour tissues of patients with oral cancer, especially in those who had lymph node metastases. [24] The

genotypic articles on MMP2's role in lung cancer are incredibly scarce. According to published research, the CT and TT variant genotypes at MMP2-1306 were nondifferentially distributed between the lung cancer group and the control group, preventing them from being used as a risk biomarker for lung cancer in a Turkish population. [25] The typical research that looked into the relationship between MMP2 genotypes and lung cancer has shown negative results that urgently need to be confirmed in other populations. [26,27]

Methods

Sample Collection: 358 lung cancer patients were histologically confirmed and enrolled at Hi Tech Medical College & Hospital, Bhubaneswar as previously described. The patients with a history of any other malignancy and pulmonary disorders, such as chronic obstructive pulmonary disease, pneumothorax, and asthma, were the instances that were excluded from the study, to put it briefly. In the same time frame, 716 healthy volunteers who were matched for age (differences 5), gender, and smoking habits were chosen from the database of the Hi-Tech Medical College & Hospital, Bhubaneswar Health Examination Cohort. Previous malignancy, metastasized cancer from other known or unknown origins, and any genetic or familial disorders were also excluded from the control group. All of the cases and controls are Bhubaneswar, and [Table 1] lists some of the recorded features for each group.

Table 1: Distribution of selected demographics of the 358 patients with lung cancer and the 716 matched controls

Characteristics	Controls (n=716), n (%)	Patients (n=358), n (%)	P[a]
Age (years), mean (SD)	64.8 (6.8)	64.0 (6.9)	0.5871
Gender			
Male	487 (68.1)	253 (70.9)	0.3642
Female	229 (31.9)	105 (29.1)	
Smoking status			
Even smokers	562 (78.6)	292 (81.8)	0.2282
Nonsmokers	154 (21.4)	66 (18.2)	
Histology			
Adenocarcinoma		217 (60.9)	
SCC		107 (29.6)	
Other		34 (9.5)	

[a]Based on Chi-square test, SCC: Squamous Cell Carcinoma, SD: Standard Deviation

Results

The frequency distributions of a few key demographic indicators, including age and gender, for the 358 lung cancer cases and the 716 healthy, non-cancer controls are compared and shown in [Table 1]. The histology of every patient in the group with lung cancer was also noted. As we used frequency matching in our methodology to select healthy non-cancer individuals as the control group, the results of the analysis revealed that there was no difference between the case and control groups in terms of the distributions of age and gender (P = 0.5871 and 0.3642, respectively) [Table 1]. About 358, or 35%, of the patients with lung cancer had the adenocarcinoma type, whereas 106, or 29.6%, had the squamous cell carcinoma kind.

In [Table 2], the distributions and frequencies of the MMP promoter-1306 (rs243865) and MMP promoter-735 (rs2285053) genotypes among the 358 patients with lung cancer (cases) and the 716 healthy individuals (controls) without cancer are shown and compared. First, according to the results of the PCR-RFLP genotyping, there were no differences in Bhubaneswarese citizens' genotypes of MMP2-735 between groups of individuals with lung cancer and those in the control group who were in good health [Table 2], bottom panel]. Second, there were differences in how the genotypes of MMP2-1306 were distributed between the two groups (P for trend = 0.0001) [Table 2], top panel]. Detail: When compared to the wild-type CC genotype, the MMP2-1306 homozygous variant TT and heterozygous variant CT did not reduce the risk of developing lung cancer (adjusted OR [aOR] =0.64 and 0.53, 95% CI = 0.26-1.73 and 0.41-0.71, P = 0.2829 and 0.0001, respectively). In the dominant analysing model, there was no difference in lung cancer risk between the CT + TT genotype of MMP2-735 and the CC wild-type genotype (aOR = 0.83, 95% CI = 0.63-1.09, P = 0.2363 [Table 2], bottom panel]). This supports the previous findings. However, compared to the CC wild-type genotype, there was a clear connection between the CT + TT genotype of MMP2-1306 with lung cancer risk in the dominant analysing model (aOR = 0.54, 95% CI = 0.39-0.74, P < 0.0001 [Table 2]).

Table 2: Distributions of matrix metalloproteinase-2 genotypes among lung cancer patients and healthy subjects

	Cases, n (%)	Controls, n (%)	aOR (95% CI)[a]	p[b]
MMP2-1306				
CC	290 (81.0)	493 (68.9)	1.00 (reference)	
CT	62 (17.3)	206 (28.7)	0.53 (0.41- 0.71)	0.0001
TT	6 (1.7)	17 (2.4)	0.64 (0.26-1.73)	0.2829
CT+TT	68 (19.0)	223 (31.1)	0.54 (0.39- 0.74)	0.0001*
P trend				0.0001*
P_{HWE}				0.4045
MMP2- 735				
CC	245 (68.4)	464 (64.8)	1.00 (reference)	
CT	101 (28.2)	219 (30.6)	0.86 (0.65- 1.15)	0.3468
TT	12 (3.4)	33 (4.6)	0.69 (0.43- 1.42)	0.2790
CT=TT	113 (31.6)	252 (35.2)	0.83 (0.63- 1.09)	0.2363
P trend				0.4009
P_{HWE}				0.2768

[a]Data have been adjusted for confounding factors age, gender and smoking, bBased on Chi-square test without Yates' correction, * and bolded, statistically significant. OR:Odds ratio, aOR:Adjusted OR, CI: Confidence interval, HWE: Hardy-Weinberg equilibrium, MMP2: Matrixmetalloproteinase-2

Discussion

In the current study, a representative group of 358 lung cancer patients and 716 age- and gender-matched healthy controls in Bhubaneswar was initially studied to determine the impact of the promoter region MMP2- 1306 and MMP2-735 genotypes to Bhubaneswar lung cancer risk. According to published research, changes at the two SNP loci for MMP2-1306 and MMP2-735 may impair Sp1's ability to bind to MMP2 mRNA, lowering transcription levels and ultimately lowering MMP2 production. [28] According to [Table 2]'s findings, there was no difference in the genotypic or allelic frequencies at MMP2- 735 between the studied case and control groups. The genotypes of MMP2- 1306, particularly the heterozygous variant CT genotype, are interesting and valuable because they may be used to predict an individual's susceptibility to lung cancer (aOR = 0.64, 95% CI = 0.41-0.71, P = 0.0001) [Table 2].

Our results are in line with a prior study's finding that lung cancer patients had a much greater frequency of the C allele at MMP2-1306 (91%) than healthy controls (83%).[29] Additionally, compared to individuals with the CT or TT genotypes, those with the CC genotype had a lung cancer risk that was 2.18 times higher. [29] Additionally, the stratified analysis showed that the odds ratios (ORs) for lung cancer were 2.38 (95% CI = 1.64-3.45), 4.26 (95% CI = 2.57-8.44), and 7.64 (95% CI = 4.74-12.33), respectively, among individuals with the CC genotype who smoked. In terms of smoking status, heavy smokers had a stronger and more noticeable joint impact than light smokers (OR = 10.25, 95% CI = 5.80-18.09 vs. OR = 5.55, 95% CI = 3.34-9.22). [29] In conclusion, results from both the current investigation and the study by Yu et al. showed a substantial relationship between the MMP2-1306C/T genotype and risk of lung cancer, either independently or in combination with a person's history of smoking.

Conclusion

The findings reveal that the susceptibility to lung cancer in Bhubaneswar may be influenced by the variation CT genotypes at MMP2 promoter-1306.

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