RESEARCH ARTICLE

Interaction of Tobacco Smoking and Chewing with Angiotensin Converting Enzyme (Insertion/Deletion) Gene Polymorphisms and Risk of Lung Cancer in a High Risk Area from Northeast India

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Abstract

Background: Association of *angiotensin converting enzyme* (*ACE*) gene polymorphisms with lung cancer susceptibility remains uncertain and varies with ethnicity. Northeast India represents a geographically, culturally, and ethnically isolated population. The area reports an especially high rate of tobacco usage in a variety of ways of consumption, compared with the rest of the Indian population. Materials and Methods: We conducted a population based case control study in two major high risk region for lung cancer from Northeast India. A total of 151 consecutive lung cancer cases diagnosed histopathologically and equal numbers of controls were recruited with record of relevant sociodemographic information. Blood samples were collected and processed to identify *ACE* gene polymorphism. Results: Significantly higher (40.4 % *vs* 29.1%, OR=1.97, CI=1.04-3.72; p=0.037) prevalence of the *ACE II* genotype was observed among lung cancer cases. Smoking was significantly associated with increased risk of lung cancer (OR=1.70, CI=1.02-2.81; p=0.041). An enhanced risk was also observed for interaction of *ACE II* genotype with tobacco smoking (OR=4.09, CI=1.51-11.05; p=0.005) and chewing (OR=3.68, CI=1.22-11.13; p=0.021). Conclusions: The present study indicates significant association s of the *ACE II* genotype with lung cancer in high risk Northeast India.

Keywords: Angiotensin converting enzyme - bradykinin - lung cancer - polymorphisms

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Introduction

Polymorphisms of gene encoding Angiotensin Converting Enzyme (*ACE*) and the risk of development of lung cancer have gained special attention in current years (Nacak et al., 2010). *ACE* gene located in chromosome 17q23, presents either Insertion (I) or Deletion (D) of 287 base pairs of intron 16 resulting in ID polymorphisms (Li et al., 2014). *ACE* is a membrane-bound dipeptidyl carboxypeptidase enzyme of the renin angiotensin system (RAS) (Goto et al., 2005). It acts as an important regulator of blood pressure and cardiovascular homeostasis by converting angiotensin *I* into the potent vasoconstrictor angiotensin *II* and inactivating the known vasodilator bradykinin (BK) (van der Knaap et al., 2008; Pei and Li, 2012).

Polymorphisms of gene encoding (*ACE*) has been implicated in the pathogenesis of a number of cancers including lung cancer, breast cancer, gastric cancer, oral cancer (Zhang et al., 2011; Devic et al., 2012; Pei and Li, 2012; Liu et al., 2013). However, the observed associations of these studies were inconsistent, plausibly due to inadequate sample size, or varied ethnicity of the study population.

Northeastern parts of India have a very high incidence of cancer of all anatomical sites (Sharma et al., 2014). Population based cancer registries in India revealed a high incidence of lung cancer in Mizoram, North East India (AAR -28.3 per 100,000 in males and AAR -28.7 per 100,000 in females) (NCRP, 2013).

Northeastern population especially from Mizoram reveals a unique distribution pattern of *ACE* genotype (Borah et al., 2011). Moreover, there is a high consumption of tobacco smoking and chewing and a unique dietary habit among the population of North East India (Chaturvedi et al., 2003; Phukan et al., 2005; Saikia et al., 2014; Phukan et al., 2014). Considering the extensive role of *ACE* in the pathogenesis of cancers and a very high incidence of lung cancer in North East, the present study was conducted to explore the association of *ACE* polymorphisms and its interaction with tobacco smoking and chewing and risk of lung cancer.

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Materials and Methods

The basic design of present study was an age (±5 years), sex and ethnicity matched population based case-control study. The work was carried out by Regional Medical Research Centre (RMRC), Indian Council of Medical Research (ICMR), N.E. Region; India in collaboration with Population based Cancer Registry (PBCR), Imphal, Manipur, India and Civil Hospital, Aizawl, Mizoram, India. The study duration was from June 2009-May 2012. Histopathologically confirmed cases of no evidence of pulmonary inflammation or benign lung tumors and only lung as their primary site of cancer were included in the study. Cases too aged to be interviewed elaborately and who refused to be interviewed were excluded from this study. Cancer free controls with age (±5 years), sex and ethnicity matched were selected from the community population of both the states. In order to reduce potential bias in our study, none of the controls had consanguinity with the cases or had any non-communicable diseases. Information of sociodemographic characteristics, smoking and chewing of tobacco were recorded in a structured pre-designed questionnaire. All subjects were provided written informed consent for participation in the study which was designed under a protocol approved by institutional ethical committee of Regional Medical Research Centre, Northeast region (Indian Council of Medical Research). Of 155 lung cancer cases collected, 4 cases were excluded because they had a missing histology and blood sample. Hence, a total of 151 lung cancer cases and 151 controls matched for (±5 years), sex and ethnicity were enrolled in the study.

DNA extraction and genotyping of ACE gene polymorphisms

Four ml. of blood was collected from all the subjects in EDTA vials. DNA was isolated by using standard phenol chloroform method and stored at -80ºC until further analysis (Sambrook and Russel, 2001). *ACE* gene *ID* polymorphisms was determined by polymerase chain reaction (PCR) using the following oligonucleotide primers: 5'-GCC CTG CAG GTG TCT GCA GCA TGT-3' (forward) and 5'-GGA TGG CTC TCC CCG CCT TCT CTC-3' (reverse) to amplify D and *I* alleles (Borah et al., 2012), of 319 and 597 bp products. PCR amplification used 25.0 µl reaction volumes and consisted of 10 pmol of each primer (Sigma), 10mM Tris-HCL, pH 9.0 (Roche), 10mM dNTPs, 1U of Taq. DNA polymerase (Roche) and 50-100 ng of genomic DNA. Amplification cycle was carried on Gene Amp PCR System 9700: Version 3.08 thermal cycler (Applied Biosystems, USA) following standard protocol. Amplified PCR products were run on 2% agarose gel electrophoresis with ethidium bromide and were visualized in a gel documentation system (Cell Biosciences). Insertion *(I)* or Deletion *(D)* of 287 bp Alu repeat in intron 16 resulting in one of the three genotypes viz. insertion homozygous *(II)*, deletion homozygous *(DD)* or insertion-deletion *(ID)* heterozygous and was detected. Thus, each DNA sample revealed one of the three possible patterns after electrophoresis: a 597 bp band (*II* genotype), a 319 bp band (*DD* genotype) or both 597 bp and 319 bp bands (*ID* genotype) (Figure 1). Samples with *DD* genotype were again processed to a second PCR amplification with insertion-specific primer (5` TTT GAG ACG GAG TCT CGC TC 3`) to evade *DD* mistyping (Shanmugam et al., 1993).

Statistical analysis

Differences in the consumption of dietary habits, distribution of sociodemographic characteristics and genotype frequencies between cases and controls were evaluated using the Chi Square (χ^2) test. Estimates of lung cancer risk, imparted by genotypes and other covariates as tobacco smoking and chewing were determined by

Table 1. Distribution of Demographic Characteristic, ACE Genotype and Risk of Lung Cancer

Category		Case n (%)	Control n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Sex	Male	82 (54.3)	82 (54.3)	---	---	---	---
	Female	69 (45.7)	69 (45.7)	---	---	---	---
Age	Range	33-85	34-82	---	---	---	---
	Means±SD	59.01±10.35	58.49±10.22	---	0.659#	---	---
Type of Cancer							
	Non-small squamous	95 (62.9)	---	---	---	---	---
	Non-small adenocarcinoma	34 (22.5)	---	---	---	---	---
	Small cell carcinoma	22 (14.6)	---	---	---	---	---
Tobacco smoking†							
	Never smoker	45 (29.8)	65 (43.0)	Reference		Reference	
	Smoker	106 (70.2)	86 (57.0)	1.78 (1.11-2.86)	0.017	1.70 (1.02-2.81)	0.041*
Tobacco chewing†							
	Never chewer	41 (27.2)	55 (36.4)	Reference		Reference	
	Chewer	110 (72.8)	96 (63.6)	1.54 (0.94-2.51)	0.084	1.59 (0.96-2.64)	0.073
ACE‡							
	II	61 (40.4)	44 (29.1)	1.93 (1.04-3.59)	0.038	1.97 (1.04-3.72)	0.037*
	ID	62 (41.1)	68 (45.1)	1.27 (0.70-2.30)	0.431	1.42 (0.77-2.63)	0.264
	DD	28 (18.5)	39 (25.8)	Reference		Reference	

#For independent samples T-test; †Adjusted OR were estimated by adjusting education, occupation and alcohol consumption in conditional multiple logistic regression model; ‡Adjusted OR were estimated by adjusting education, occupation, tobacco chewing, tobacco smoking and alcohol consumption in conditional multiple logistic regression model; *Significant

Table 2. Interaction of ACE Genotype with Tobacco Chewing and Tobacco Smoking Habits

Model	Interaction Parameters		Case n (%)	Control n (%)	Crude OR (95% CI)	p-value	Adjusted# OR (95% CI)	p-value
1†ACE	II	Never smoker	13 (8.6)	17 (11.3)	1.63 (0.54-4.92)	0.39	1.85 (0.59-5.73)	0.29
Tobacco	II	Smoker	48 (31.8)	27 (17.9)	3.78 (1.44-9.90)	0.007	4.09 (1.51-11.05)	0.005
smoking	ID	Never smoker	24 (15.9)	31 (20.4)	1.65 (0.61-4.45)	0.327	2.00 (0.72-5.59)	0.186
	ID	Smoker	38 (25.2)	37 (24.5)	2.18 (0.84-5.67)	0.109	2.35 (0.87-6.37)	0.092
	DD	Smoker	20 (13.2)	22 (14.6)	1.93 (0.69-5.44)	0.213	2.05 (0.71-5.96)	0.187
	DD	Never smoker	8 (5.3)	17 (11.3)	Reference		Reference	
2‡ ACE	II	Never chewer	16 (10.6)	14 (9.3)	2.48 (0.74-8.26)	0.14	2.91 (0.84-10.1)	
Tobacco	II	Chewer	45 (29.7)	30 (19.9)	3.25 (1.11-9.49)	0.031	3.68 (1.22-11.1)	0.092
chewing	ID	Never chewer	19 (12.6)	28 (18.5)	1.47 (0.48-4.55)	0.504	1.74 (0.54-5.57)	0.021*
	ID	Chewer	43 (28.5)	40 (26.5)	2.33 (0.81-6.72)	0.118	2.89 (0.96-8.72)	0.352
	DD	Chewer	22 (14.6)	26 (17.2)	1.83 (0.60-5.63)	0.29	2.17 (0.68-6.87)	0.059
	DD	Never chewer	6 (4.0)	13 (8.6)	Reference		Reference	0.19

#Adjusted OR were estimated through conditional multiple logistic regression model; †Education, occupation, tobacco chewing and alcohol consumption were adjusted to estimate adjusted OR in each model; ‡Education, occupation, tobacco smoking and alcohol consumption were adjusted to estimate adjusted OR in each model; *Significant

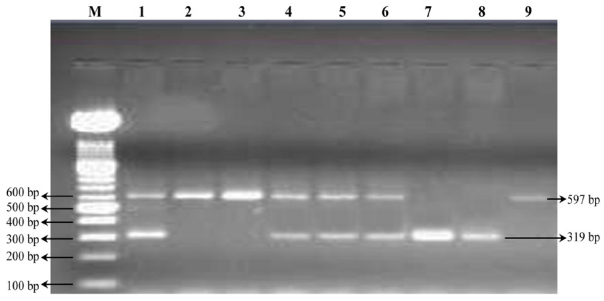

Figure 1. Photograph of 2% Agarose Gel Electrophoresis for ACE Gene Polymorphisms. Lane M represents 100 bp DNA Ladder. Lane 1, 4, 5 and 6 characterized by presence of both 597 and 319 bp represents *ACE ID* genotype. Lane 7 and 8 characterised by 319 bp represents *ACE DD* genotype. Lane 2, 3 and 9 characterised by 597 bp represents *ACE II* genotype

deriving the odds ratio (OR) and its corresponding 95% confidence interval (95%CI) using multivariable conditional logistic regression after adjusting with potential confounders. For all tests a two sided p≤0.05 was considered statistically significant. All statistical analysis were done using SPSS version 17.0.

Results

The genotype distribution of cases (χ^2=2.85, p=0.09) and control (χ^2=1.46, p=0.22) population were in Hardy-Weinberg equilibrium (HWE) (p>0.05). Mean age for cases and control were 59.01±10.35 and 58.49±10.22 and result was statistically insignificant (p=0.659) Table 1.

The frequencies of *ACE* genotype of lung cancer cases and control are shown in Table 1. Prevalence of *ACE II* genotype were significantly higher among cases than control groups (40.4% *vs* 29.1%; OR=1.97, CI=1.04-3.72; p=0.037) after adjusting with potential confounders. Interaction combinations of *ACE* genotype with tobacco smoking and chewing are outlined in Table 2. Interestingly an enhanced risk was observed for interaction of *ACE II* genotype with tobacco smoking (OR=4.09, CI=1.51-11.05; p=0.005) and chewing (OR=3.68, CI=1.22-11.13; p=0.021).

Discussion

Present study revealed significant association of *ACE II* genotype with lung cancer. The pathophysiological basis for association of *ACE* gene polymorphisms and risk of lung cancer may be related to its activity on BK. BK moderate mitogenic activity (Drube and Liebmann, 2000; Kramarenko et al., 2012). Such activities may be implicated in development of lung cancer. *ACE* inactivates BK (Kuoppala et al., 2000) and may reduce carcinogenic potential of this neuropeptide. Such inactivation may be genetically dependent because half of the interindividual difference in *ACE* levels may be explained by its polymorphisms (Gard, 2010) with highest concentration in DD genotype and lowest in *II* genotype. Subjects with *II* genotype with low concentration of *ACE* level have the less capacity to inactivate BK and therefore mitogenic potential of BK in these subjects may be enhanced. Frequency of the variant *II* genotype was significantly higher in the lung cancer patients than in control subjects (40.4 *vs* 29.1%; p=0.037). This may result from decreased inactivation of BK and thereby might increase mitogenic effects of BK in lung cancer. Another reason could be that inflammation induced by BK might be involved in the development of lung carcinogenesis.

For studying the role of gene-environment interaction that might modify susceptibility of lung cancers, potential interactions of *ACE* genotype with known risk factors were analysed. When analysed for *ACE* interaction with tobacco smoking and chewing for lung cancer, significantly enhanced risk was observed for *ACE II* genotype with both smoking and chewing. Thus, our results may indicate a tissue and carcinogen-specific modulation of cancer risk by *ACE* gene polymorphisms and is contrary to the classical roles assumed for the genetic variants of the genes. However, mechanistic explanation for association of variants with lung cancer might not be so clear and straight forward, genetic characterizations as linkage disequilibrium of the variants with certain functional polymorphisms could exist (Chung et al., 2013). Perhaps, investigating the mutational status of tumour and its correlations could possibly provide a better understanding.

Observations for association of *ACE* gene polymorphisms with any types of cancer were reported to be inconsistent in different ethnic and geographical regions. Study conducted by Cheon et al. (2000) found no significant difference between *ACE ID* polymorphisms and risk of lung cancer. However, contrary to this study, Pavlic et al. (2012) observed significant association for *ACE DD* Genotype for lung cancer. As for other cancers, including those of oral, breast, prostate and endometrium, associations with the *ACE ID* polymorphisms have been examined (Freitas-Silva et al., 2004; Yigit et al., 2007; Vairaktaris et al., 2007; Correa et al., 2009). Correa et al. (2009) reported that *ACE ID* might be more protective against breast cancer than DD and *II*, while Koh et al. (2003) have shown that *I* allele reduced the risk in Chinese and Haiman et al. (2003) have discovered that *II* had a marginally significant risk in African-Americans. The *ACE DD* posed a significantly higher risk genotype for prostate cancer (Yigit et al., 2007), whereas for oral cancer, *I* allele was significantly higher risk allele (Vairaktaris et al., 2007). In endometrial cancer, *I* allele carriers were at significantly higher risk among normotensive women aged 63 years or younger (Freitas-Silva et al., 2004).

Current study has several strengths and findings. It is a population based case control study and was carried out in a high risk area of lung cancer from Northeast India. Present study showed independent association of *ACE* polymorphisms with lung cancer. This information is new in the context that data related to *ACE* gene polymorphisms and the risk of lung cancer is not available for the South Asian population. Therefore, a comprehensive study may bring us with some interesting findings. Our study warrants need of understanding association of *ACE* polymorphisms with BK. The main limitation of our study is the lack of information of plasma *ACE* concentration of the study subjects in respect to *ACE* genotype.

Previous studies (Keavney et al., 1998; Chung et al., 2013) on segregation-linkage analysis suggested the existence of a functional mutation located within or close to the *ACE* locus, which might be in almost complete linkage disequilibrium with the *ACE ID* polymorphisms and accounts for half the variance of plasma concentration of *ACE*. Therefore, evaluation of both these markers at a time may not be required.

The present study indicates significant association of *ACE II* genotype with lung cancer in a high risk northeastern population. Our findings suggest role of ethnicity on *ACE* polymorphisms for lung cancer risk. Results of our study also indicate significant interaction of tobacco smoking and chewing with *ACE II* genotype. However, validation of results will require replication in a larger sample size. Taking into account other confounders such as dietary habits and environmental factors can give a more conclusive perspective.

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