

RESEARCH ARTICLE

CYP1A1 Genetic Polymorphisms and Risk for Esophageal Cancer: a Case-control Study in Central China

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Abstract

The purpose of this study was to evaluate the associations of *CYP1A1* genetic polymorphisms with the risk of developing esophageal cancer (EC). A case-control study was carried out in a Chinese population in which 157 hospital based EC cases and 157 population based healthy controls with 1:1 match by age and sex were included. PCR based restriction fragment length polymorphisms (PCR-RFLP) were used to detect genotypes in case and control groups. For the *CYP1A1* Ile/Val polymorphism, comparing with wild genotype Ile/Ile, both the heterozygote genotype Ile/Val and the combined variant genotype Ile/Val+Val/Val increased the risk of esophageal cancer (OR: 2.05, 95% CI: 1.19-3.54, OR: 1.86, 95% CI: 1.11-3.12). No significant association was found between the *CYP1A1* MspI polymorphism and EC. According to analysis of combined genotypes, the TC/AG combined genotype which contained both variant alleles of these two polymorphisms increased the risk of developing EC (OR: 2.12, 95% CI: 1.16-3.85). Our results suggested that genetic polymorphisms of *CYP1A1* may increase the susceptibility to EC.

Keywords: Polymorphisms - *CYP1A1* - esophageal cancer - susceptibility - Central China

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Introduction

Esophageal cancer (EC) is one of the most common malignant diseases worldwide and the sixth leading cause of cancer death, with the majority of cases occurring in developing countries (Parkin et al., 2005). Research showed that risks for EC in different countries or different places were various (Zhuo et al., 1999; Lu et al., 2000; Zhang et al., 2000; Li et al., 2001). China, with about 250,000 cases diagnosed yearly, lies in the "esophageal cancer belt" (Parkin et al., 1988), and contributes to about half of the world's cases (Yang et al., 2003). The ratio in incidence between high- and low-risk areas could be as great as 500:1 (Xing et al., 2003). The high incidence in special areas suggests that the importance of environmental factors in esophageal cancer is developing (Mao et al., 2011). However, only a small part of individuals can develop esophageal cancer under the similar environmental conditions in the high-risk areas, indicating that host susceptibility factors such as the polymorphisms of phase I metabolism enzyme gene *CYP1A1*, may be risk factors in increasing risk for esophageal cancer.

Esophageal cancer is a complex disease likely resulting from multiple interacting genetic polymorphisms and gene-environment interactions. Most of environmental carcinogens are pre-carcinogens which have carcinogenicity after activated by phase I enzymes. The *CYP1A1* gene is closely associated with the metabolism of polycyclic aromatic hydrocarbons (PAHs) carcinogens, which code in the aryl hydrocarbon hydroxylase (AHH) enzyme (Kopf et al., 2010). The enzyme *CYP1A1* is involved in the activation of major classes of tobacco procarcinogens, such as polyaromatic hydrocarbons and aromatic amines, and is present in many epithelial tissues (Bartsch et al., 2000). Evidence suggests (Hiyama et al., 2007) that genetic polymorphisms of *CYP1A1* may influence the balance between metabolic activation and detoxification of toxicants and thus are related to individual susceptibility to esophageal cancer.

Recently, many investigators have reported association between *CYP1A1* polymorphisms and cancers (Dai et al., 2009; Atinkaya et al., 2012; Lopez-Cima et al., 2012; Sergeantanis et al., 2012; Ding et al., 2013), especially for two main functional polymorphic sites of *CYP1A1* gene (*MspI* and Ile/Val) and cancer susceptibility. Previous

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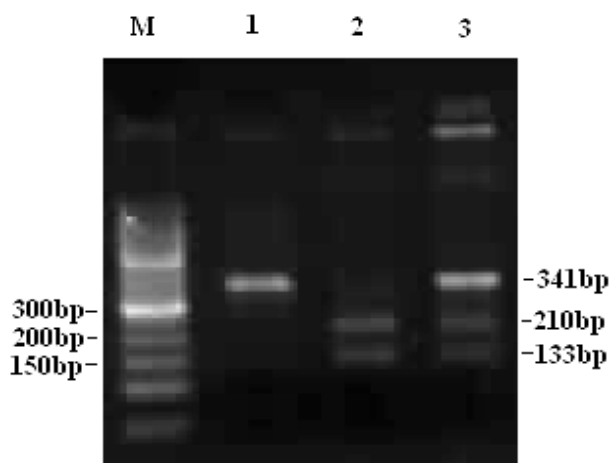


Figure 1. CYP1A1 MspI Genotype. Lane M: 50bp marker; Lane 1: T/T genotype; Lane 2: C/C genotype; Lane 3: T/C genotype

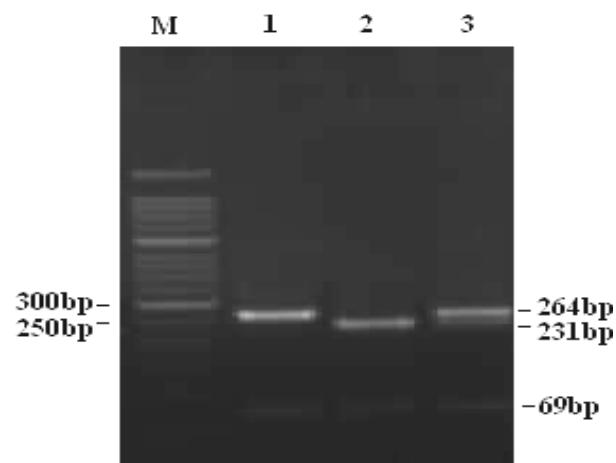


Figure 2. CYP1A1 Ile/Val Genotype. Lane M: 50bp marker; Lane 1: Val/Val genotype; Lane 2: Ile/Ile genotype; Lane 3: Ile/Val genotype

studies (Kawajiri et al., 1990; Nakachi et al., 1991; Hayashi et al., 1992; Xu et al., 1996) have suggested that variant allele of *CYP1A1 MspI* polymorphisms is associated with malignancies, particularly lung cancer. No association was identified between *CYP1A1 MspI* and *Ile/Val* polymorphisms with esophageal cancer risk in a series of studies done on populations of Caucasians and Japanese (Lucas et al., 1996; Hori et al., 1997; Morita et al., 1997; van Lieshout et al., 1999). However, Nimura et al. (1997) reported that heavy smokers with *Val/Val* genotype of *CYP1A1 Ile/Val* had a three-fold risk of developing esophageal cancer as compared to those with *Ile/Ile* genotype in a case-control study in Chinese population. Roth et al. (2000) carried out a study in Linxian, a region of high esophageal cancer risk in China, and did not find any significant effect between *CYP1A1 Ile/Val* polymorphism and esophageal cancer. A recent study by Wang et al. (2002a) found that individuals with the *CYP1A1 Val/Val* genotype had a higher risk of developing esophageal cancer than those with *Ile/Ile* (*OR*:2.48, *95%CI*:1.12-5.54) in 127 esophageal cancer cases and 101 controls.

Thus, the present study was undertaken to assess the association of genetic polymorphisms of *CYP1A1* with esophageal cancer susceptibility in Henan province, the highest incidence area of EC in China.

Materials and Methods

Study population

We recruited 157 patients with pathologically proven esophageal squamous cell carcinoma before undergoing any treatment at the First Affiliated Hospital of Zhengzhou University, during March 2008 to September 2008. 157 healthy population controls with 1:1 matching by age (± 5 years) and sex were selected from a census of digestion diseases carried out in Xinxiang County and Xin'an County of Henan Province. All cases were newly diagnosed and primary esophageal squamous cell carcinoma patients. Controls were required to be free of any digestion diseases, having no cancer history and related clinical signs. All of the subjects were unrelated individuals.

Data collection

Uniform trained investigators using a special questionnaire interviewed cases and controls by face to face. The special questionnaire contained information of age, sex, tobacco smoking, alcohol drinking, family history of cancer, etc. The venous blood obtained from the subjects was collected in an EDTA tube and stored at -80°C for extraction of DNA genome. Tobacco smoking was defined as smoking at least one cigarette per day and persisting for more than one year. Alcohol intake was defined as drinking at least once a week with more than 100 gram every time and persisting for more than six months. We used the medians (18 pack-year) of lifetime consumption of tobacco of control cigarette smokers in distinguishing the moderate and medium heavy smokers.

The study subjects were given the written informed consent before participating in the study.

Genotyping analysis

Genomic DNA was extracted from the blood specimen using the phenol chloroform method for genotyping. All genotyping analyses were PCR-based, with a total volume of 20 μl for each reaction containing 10 μl 2 \times Tap PCR MasterMix, 0.8 μM each primer, 100 ng DNA, 7.4 μl deionized water. Digestive products were electrophoresed on 3% agarose gel, and photographed. And all assays were repeated at least one time by the same individual to verifying the genotyping results. Genotypes were validated by sequencing through biological technology company.

PCR-RFLP analysis was used to detect the *MspI* polymorphism, using primer sequences as reported (Wang et al., 2003). Primer sequences used were: 5'-CAGTGAA GAGGTGTAGCCGCT-3' for forward primer and 5'-TAG GAGTCTTGTCTCATGCCT-3' for reversed primer. After an initial denaturation at 94°C for 3 min, the samples underwent 30 cycles for 30 s at 94°C , 30 s at 55°C and 1 min at 72°C , followed by the final extension at 72°C for 5 min. The digestion system contained 5 μl PCR products, 1 μl 10 \times T buffer, 1 μl 0.1% BSA, 0.6 μl *MspI*, 2.4 μl double distilled water.

The PCR products were digested by restriction endonuclease at 37°C overnight. The digested products

Table 1. Characteristics of Esophageal Cancer Cases and Controls

Variables	Case N (%) [*]	Control N (%)	P
Mean age	61.29±10.85	60.22±10.79	0.38
Gender			
Male	105 (66.8)	105 (66.8)	
Female	52 (33.2)	52 (33.2)	1.00
Smoking			
Non-smokers	62 (56.9)	102 (65.0)	
Smokers	47 (43.1)	55 (35.0)	0.18
Moderate smokers	15 (13.8)	27 (17.4)	0.80
Medium and heavy smokers	32 (29.3)	28 (17.6)	0.04
Drinking			
Non-drinkers	83 (76.2)	124 (79.0)	
Drinkers	26 (23.8)	33 (21.0)	0.58
Family history of cancer			
No	90 (82.6)	151 (96.2)	
Have	19 (17.4)	6 (3.8)	0.00

^{*}Because of the failure data collection, the cases number for some factors was less than 157

were separated by 3% agarose gel electrophoresis then visualized under ultraviolet light. A single band of 343bp represented *MspI* T/T genotype, two bands of 210bp, 133bp represented *MspI* C/C genotype, three bands of 343bp, 210bp, 133bp represented *MspI* T/C genotype (Figure 1). For *Ile/Val* polymorphism, three bands of 231bp, 69bp, 32bp represented *Ile/Ile* genotype, two bands of 264bp, 69bp represented *Val/Val* genotype, four bands of 264bp, 231bp, 69bp 32bp represented *Ile/Val* genotype (Figure 2).

Statistical analysis

χ^2 test was used to detect whether there were significant ($\alpha = 0.05$) differences in frequencies between cases and controls.

Online software <http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl> was used to assess Hardy-Weinberg equilibrium for genotype frequency of control group.

Odds ratios (OR) and 95% confidence intervals (95%CI) from logistic regression models were used for detecting the associations between these two polymorphisms and EC risk. Each analysis was also adjusted for confounding factors (age, gender, smoking,

drinking and family history of cancer).

Haplotypes for each individual were inferred using the SNP2.0 software.

All analyses were conducted using SPSS12.0 software. All tests were two sided and *P* values <0.05 was considered statistically significant.

Results

Subject characteristics

Table 1 shows the distribution characteristics of 157 EC patients and 157 controls. The distributions of medium and heavy smoking (*P*=0.04) and family history of cancer (*P*=0.00) had significant differences between cases and controls groups.

The relationship between CYP1A1 polymorphisms and esophageal cancer

The frequencies of wild genotype, heterozygous genotype, and homozygous genotype of *MspI* and *Ile/Val* polymorphisms among controls were both not departure from Hardy-Weinberg equilibrium (*P*=0.42 and *P*=0.14).

For *CYP1A1 MspI* polymorphism, the distributions of genotypes were not significantly different between the cases and controls groups ($\chi^2_{0.05,2}=5.784$, *P*>0.05). The individuals with T/C genotype had an increased risk for EC, compared with wild genotype T/T (OR: 1.68, 95%CI: 1.04-2.72). But after adjusting for age, gender, smoking, drinking and family history of cancer, there was no significant association between *CYP1A1 MspI* polymorphism and esophageal cancer.

For *CYP1A1 Ile/Val* polymorphism, both *Ile/Val* genotype and *Ile/Val+Val/Val* combined variant genotype showed increased risk of esophageal cancer (OR: 1.87, 95%CI: 1.17-3.01 and OR:1.76, 95%CI:1.12-2.76), compared with wild genotype *Ile/Ile*. And after adjusting for age, gender, smoking, drinking and family history of cancer, there was also significant association between *Ile/Val* genotype, *Ile/Val+Val/Val* combined variant genotype and esophageal cancer (OR:2.05,95%CI:1.19-3.54 and OR:1.86,95%CI:1.11-3.12). The distribution of minor allele G had significant difference between the cases and controls groups (OR: 1.43, 95%CI; 1.00-2.04). But no

Table 2. CYP1A1 Genotypes and Esophageal Cancer

Genotypes	Case N (%)	Control N (%)	P	OR (95%CI)	P *	OR (95%CI)*
<i>MspI</i>						
T/T	47 (29.9)	62 (39.5)		1		
T/C	98 (62.4)	77 (49.0)	0.03	1.68 (1.04-2.72)	0.13	1.53 (0.88-2.67)
C/C	12 (7.7)	18 (11.5)	0.76	0.88 (0.39-2.00)	0.55	0.74 (0.28-1.97)
T/C+C/C	110 (70.1)	95 (60.5)	0.08	1.53 (0.96-2.44)	0.24	1.39 (0.81-2.39)
T	192 (61.1)	201 (64.0)		1		
C	122 (38.9)	113 (36.0)	0.46	1.13 (0.82-1.56)	0.77	1.06 (0.73-1.54)
<i>Ile/Val</i>						
Ile/Ile	73 (46.5)	95 (60.0)		1		
Ile/Val	72 (45.9)	50 (31.9)	0.01	1.87 (1.17-3.01)	0.01	2.05 (1.19-3.54)
Val/Val	12 (7.6)	12 (7.6)	0.55	1.30 (0.55-3.06)	0.82	1.12 (0.41-3.04)
<i>Ile/Val+ Val/Val</i>	84 (53.5)	62 (39.5)	0.01	1.76 (1.12-2.76)	0.02	1.86 (1.11-3.12)
A	218 (69.8)	240 (76.4)		1		
G	96 (30.2)	74 (23.6)	0.05	1.43 (1.00-2.04)	0.08	1.43 (0.96-2.15)

*Adjusted for age, gender, smoking, drinking and family history of cancer

significant difference was observed after adjusting for age, gender, smoking, drinking and family history of cancer.

Haplotype analysis

There were totally four possible haplotypes and the most common haplotype TA containing both major alleles was taken as the reference. As shown in Table 3, the distribution of CG haplotype genotype between the cases and controls reached statically significant difference ($P < 0.05$). But significant difference was null after adjusting for age, gender, smoking, drinking and family history of cancer.

Combined genotypes analysis of MspI and Ile/Val

There were totally nine combination genotypes of *MspI* and *Ile/Val*, which were shown in Table 4. The combination genotype TT/AA with wild genotypes of two polymorphisms was taken as referent genotype, and its frequency was 25.5% in cases and 31.2% in controls. The individuals carrying the combined genotype TC/AG including two heterozygosis genotypes showed two-fold increased risk for esophageal cancer ($OR: 2.12, 95\%CI: 1.16-3.85$). And after adjusting for age, gender, smoking, drinking and family history of cancer, there was also significant association between combined genotype TC/AG and esophageal cancer ($OR: 2.01, 95\%CI: 1.02-4.00$). There were no associations between the other seven combined genotypes and esophageal cancer susceptibility.

Discussion

The important phase I enzyme *CYP1A1* plays an essential role in the metabolic activation of major classes of procarcinogens such as benzo[a]pyrene, a prototypic polycyclic aromatic hydrocarbon, thus affecting the metabolism of the environmental carcinogens and

altering the susceptibility of esophageal cancer. Generally, variation of *CYP1A1* gene can alter efficiency of its enzymes which could enhance toxicity of the extraneous stimulating factors that directly influence tissues, thus increasing susceptibility to carcinoma. Two major relevant polymorphic sites of the *CYP1A1* gene (*MspI* and *Ile/Val*) have been suggested to be associated with several types of cancer. The former is located in the 3'-flanking region of the gene (T6235C position) in which the presence of C has been linked with genetic susceptibility to lung cancer. The latter, A4889G, located in the heme-binding region of *Ile/Val* at codon 462, alters the protein structure by replacing an isoleucine for a valine, making the carriers more susceptible to some cigarette smoking-associated diseases (Wang et al., 2002b).

A case-control study with molecular epidemiology methods was used in the present study to analyze the relationship between *CYP1A1* polymorphisms and esophageal cancer risk. Our data showed that the heterozygosis genotype T/C of *MspI* can increase the risk of esophageal cancer. But associations were null after adjusting for age, gender, smoking, drinking and family history of cancer. This result is consistent with the study of Wu et al. (2002). Guo et al. (2005) found that individuals with the *MspI* T/C or C/C genotype had a higher risk of developing esophageal cancer than those with the T/T genotype ($OR: 1.93, 95\%CI: 1.01-3.84$). However, the study results of Wang et al. (2003) suggested that the genotype of *MspI* T/C ($OR: 0.41, 95\%CI: 0.17-0.99$) or (T/C+C/C) ($OR: 0.41, 95\%CI: 0.17-0.99$) might be protective factor for developing esophageal cancer. The heterozygosis genotype T/C of *CYP1A1 MspI* genetic polymorphism was found to be associated with elevated esophageal cancer risk in the study of van Lieshout et al. (1999). A study of Casson et al. (2003) on Canada population reported no association between the genotype of *MspI* (T/C+C/C) and risk of esophageal cancer. These different results may be related to sample size, ethnicity and other factors. Therefore, further and large population studies should be carried out to analysis the relationship of *CYP1A1 MspI* genetic polymorphism and esophageal cancer.

For *CYP1A1 Ile/Val* polymorphism, most studies of the contribution of *CYP1A1 Ile/Val* polymorphism to risk of esophageal cancer have provided inconsistent results. The results of our study showed that the *Ile/Val* (or *Ile/Val+Val/Val*) genotype can increase the risk of esophageal cancer ($OR: 1.87, 95\%CI: 1.17-3.01$) (or $OR: 1.76, 95\%CI: 1.12-$

Table 3. CYP1A1 Haplotype Analysis

Haplotypes	Case N (%)	Control N (%)	OR (95%CI)	OR (95%CI)*
TA	175 (55.7)	181 (57.6)	1	1
TG	17 (4.4)	20 (6.4)	0.88 (0.45-1.73)	1.04 (0.50-2.18)
CA	43 (13.7)	60 (19.1)	0.74 (0.48-1.16)	0.72 (0.43-1.22)
CG	79 (25.2)	53 (16.9)	1.54 (1.03-2.31)	1.46 (0.92-2.31)
Total	314 (100.0)	314 (100.0)		

*Adjusted for age, gender, smoking, drinking and family history of cancer

Table 4. Combination Analysis of MspI and Ile/Val genotypes

Combined genotypes	Case N (%)	Control N (%)	P	OR (95%CI)	P*	OR (95%CI)*
TT/AA	40 (25.5)	49 (31.2)		1.00		
TT/AG	7 (4.5)	12 (7.6)	0.52	0.72 (0.26-1.99)	0.89	0.93 (0.30-2.82)
TC/GG	10 (6.3)	6 (3.8)	0.20	2.04 (0.68-6.10)	0.21	2.13 (0.65-6.96)
TC/AG	57 (36.3)	33 (21.0)	0.01	2.12 (1.16-3.85)	0.05	2.01 (1.02-4.00)
TC/AA	31 (19.8)	38 (24.2)	1.00	1.00 (0.53-1.88)	0.56	0.80 (0.37-1.71)
CC/GG	2 (1.3)	5 (3.2)	0.66	0.49 (0.09-2.66)	1.00	0.00
CC/AG	8 (5.1)	5 (3.2)	0.26	1.96 (0.60-6.46)	0.26	2.14 (0.57-8.06)
CC/AA	2 (1.2)	8 (5.1)	0.24	0.31 (0.06-1.52)	0.35	0.46 (0.09-2.36)
TT/GG	0 (0)	1 (0.7)	0.91	0.00	1.00	0.00
Total	157 (100.0)	157 (100.0)				

*Adjusted for age, gender, smoking, drinking and family history of cancer

2.76), which approximate the findings of van LieShout et al. (1999). And after adjusting for age, gender, smoking, drinking and family history of cancer, there was also significant association between *Ile/Val* genotype, *Ile/Val+Val/Val* combined variant genotype and esophageal cancer (*OR*:2.05,95%*CI*:1.19-3.54 and *OR*:1.86, 95%*CI*:1.11-3.12). In contrast, Wang et al. (2003) found cases with *CYP1A1 Ile/Val* polymorphism had no significant difference of developing esophageal squamous cell carcinoma compared to controls in Northern China. A study of Wang et al. (2002a) reported the distribution of the genotype *Val/Val* had significant difference between cases and controls ($P=0.049$), suggesting that the genotype *Val/Val* can increased susceptibility to EC. A meta-analysis of Dai et al. (2009) showed that genotype *Ile/Val* and combined genotype *Ile/Val+Val/Val* of *CYP1A1 Ile/Val* polymorphism, compared with wild genotype *Ile/Ile*, had association with ESCC risk (*OR*:1.34,95%*CI*: 1.11-1.61 and *OR*:1.43,95%*CI*:1.07-1.91). Current study had verified that the gene product of *CYP1A1 Val/Val* had higher catalytic and carcinogenic activity than that of *CYP1A1 Ile/Ile*, activating the original carcinogen, increasing individuals' susceptibility to cancers (Hayashi et al., 1991).

Tumorigenesis of esophageal cancer is a complex, multistep course that may be multifactorial. The analysis of haplotype and combined genotypes supplied a greater amount of information than a single SNP. According to analysis of haplotype, the CG haplotype was a risk factor of esophageal cancer (*OR*: 1.54, 95%*CI*: 1.03-2.31). But significant association was null after adjusting for age, gender, smoking, drinking and family history of cancer. According to analysis of combined genotype of these two polymorphisms, the TC/AG combined genotype, which contains two heterozygosis genotypes for both polymorphisms, can increase the risk to EC (*OR*: 2.12, 95%*CI*: 1.16-3.85), even after adjusting for age, gender, smoking, drinking and family history of cancer, there was also significant association between combined genotype TC/AG and esophageal cancer (*OR*: 2.01, 95%*CI*: 1.02-4.00). This approach can provide a theoretical basis for the etiology of EC.

Two polymorphisms of *CYP1A1 MspI* and *CYP1A1 Ile/Val* have been demonstrated in the *CYP1A1* gene: One is a T to C substitution in the 3' flanking region altering protein folding, the other one is an Ile to Val substitution may occur in the heme-binding region of *Ile/Val*. Both substitutions were considered to result in the enhancement of enzyme activity (Landi et al., 1994), but polymorphisms in the noncoding region of *CYP1A1* were unlikely to have direct functional consequences on *CYP1A1* activity (Bailey et al., 1998), even the variant of *CYP1A1 Ile/Val* was not sure to induce an increased enzyme activity (Zhang et al., 1996). These controversial reports suggested that the effect of *CYP1A1* polymorphisms on developing cancer remains to be test and verify.

In conclusion, the current study suggests that the polymorphic metabolic enzymes genes, *CYP1A1*, may be associated with the risk of esophageal cancer. Although the number of our study was sufficient to reach an adequate statistical power, our results need to be confirmed

further by a larger series of study. Future epidemiologic studies should also consider interactions between genetic polymorphisms and exposure to environmental carcinogens to make the tests results more objective and credible.

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