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• ESOPHAGEAL CANCER •

Genetic susceptibility and environmental factors of esophageal cancer in Xi'an

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Abstract

AIM: To analyse the role of genetic susceptibility and environmental factors in the process of esophageal cancer (EC) formation in Xi'an, China.

METHODS: A hospital based case-control study, combined with molecular epidemiological method, was carried out. A total of 127 EC cases and 101 controls were interviewed with questionnaires containing demographic items, habit of tobacco smoking, alcohol drinking, and family history of EC. Polymorphism of CYP1A1 and GSTM1 of 127 EC cases and 101 controls were detected by PCR method. The interactions between genetic susceptibility and environmental factors were also discussed.

RESULTS: Tobacco smoking, alcohol drinking and a family history of EC were risk factors for EC with an OR of 2.04 (95% CI 1.15-3.60), 3.45(95% CI 1.74-6.91), 3.14 (95% CI 1.28-7.94), respectively. Individuals carrying CYP1A1 *Val/Val* genotype compared to those with CYP1A1 *Ile/Ile* genotype had an increased risk for EC (OR 3.35, 95% CI 1.49-7.61). GSTM1 deletion genotype was a risk factor for EC (OR1.81, 95% CI 1.03-3.18). Gene-environment interaction analysis showed that CYP1A1 *Val/Val* genotype, GSTM1 deletion genotype had synergetic interactions with tobacco smoking, alcohol drinking and family history of EC.

CONCLUSION: Tobacco smoking, alcohol drinking and a family history of EC are risk factors for EC. CYP1A1 *Val/Val* and GSTM1 deletion genotypes are genetic susceptibility biomarkers for EC. There are synergic interactions between genetic susceptibility and environmental factors.

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INTRODUCTION

China is a country with high incidence and mortality rate of EC. Risks for EC vary in different countries or different places[1-6]. Studies have shown that tobacco smoking, alcohol drinking[7-13], nutrition factors (fruit and vegetable consumption), life style, virus infection, heredity or exposure to nitro amines, fungi or AFB1 may be involved in the process of EC[1,3,14-24]. In China, the risks for EC were different among areas with different incidences[1-5,17,19,25,26]. The mortality rate of EC is about 24 per 100 000 in Xi' an, and it ranks first of all cancer mortalities. Previous studies showed that tobacco smoking and a family history of EC were risk factors for EC in Xi' an[2,27,28].

Environmental risks and genetic susceptibility may play the main role in the process of EC[2,27-37]. Susceptibility and environmental carcinogens exposure are indispensable factors for EC[25,28,37]. To explore the bio-basis of genetic susceptibility to EC in Xi' an, we carried out a hospital based case- control study to analyze the role of tobacco smoking, alcohol drinking, family history of cancer, family history of EC, CYP1A1, and GSTM1 gene polymorphism in the process of EC, and possible susceptibility –environmental risk interaction.

MATERIALS AND METHODS

Selection of patients and controls

Cases of esophageal cancer (confirmed by pathological diagnosis) came from inpatients of Tangdu Hospital, during Dec 1999 to May 2000. Controls were randomly selected from non-cancer inpatients from different wards of the same hospital during the same period. Both cases and controls were confined to Xi' an area residents.

Data collection

Trained interviewers using a structured questionnaire interviewed cases and controls in the hospital. The questionnaire contained information of residence, occupation, tobacco smoking habit, alcohol intake, family history of EC, *etc*. 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 twice a week with more than 50 gram every time and persisting for more than one year. Totally 127 cases (male 97, female 30) and 101(male 78, female 23) controls were included. Blood samples were also collected for extraction of DNA genome. All blood samples were stored at -70 ℃ before DNA extraction.

Detection of polymorphism of CYP1A1 and GSTM1 by PCR methods

DNA genomes were extracted from blood clots by proteinase K digestion, hydroxybenzene, and chloroform method. Polymerase chain reaction (PCR) was used to identify their CYP1A1 and GSTM1 polymorphisms.

Primers for GSTM1(P1: 5' -GTA CCC TAC TTG ATT GAT GGG-3' ; P2: 5' -CTG GAT TGT AGC AGA TCA TGC-3') and CYP1A1 (P3: 5' -CGG AAG TGT ATC GGT GAG ACC **A** -3' , P4: 5' -CGG AAG TGT ATC GGT GAG ACC **G** -3' ; P5: 5' -GTA GAC AGA GTC TAG GCC TCA-3') were synthesized by Shengong Bio-technology Company of Shanghai. PCR condition for GSTM1: 50 μL solution containing 10×buffer 5 μL, Mg^{2+} 2 μL, P1,P2 1 μL, template

DNA1.5 μL, dDNTPs 1 μL and *Taq* DNA polymerase 3u. PCR consisted of denaturation first at 94 ℃ for 10 min, followed by addition of *Taq* DNA polymerase, and then at 94 ℃ for 1 min, at 60 ℃ for 1 min, at 72 ℃ for 1 min with 30 cycles. After 20 g/L agar was used for electrophoresis, PCR products were observed under violet light. GSTM1 genotype was characterized by 273 bp fragment, while GSTM1 deletion genotype had no fragment.

Two pairs of primers were used to detect the polymorphism of CYP1A1 (7th exon). For each DNA sample two sets of PCR were carried out using P3, P5 (marked as tube A) and P4, P5 (marked as tube B) respectively. PCR conditions for tube A and tube B were the same: 50 μL solution containing 10×buffer 5 μL, Mg^{2+} 2 μL, P3, P5 (or P4, P5) 1 μL, template DNA1.5 μL, dNTPs 1 μL and *Taq* DNA polymerase 3u. PCR was carried out at 94 ℃ for 10 min, followed by at 94 ℃ for 1 min, at 55 ℃ for 1 min, at 72 ℃ for 1 min, for a total of 35 cycles, at last extension at 72 ℃ for 10 min. After 20 g/L agar was used for electrophoresis, PCR products were observed under the violet light. If only tube A had the specific fragment (200 bp), the DNA was regarded as CYP1A1 *Ile*/*Ile* genotype (pure wild genotype). If only tube B had the positive fragment, CYP1A1*Val*/*Val* genotype (pure mutation) was considered, and CYP1A1 *Ile*/*Val* genotype was identified when both tube A and tube B had the fragment.

Quality control

DNA extraction and PCR were conducted in different times and places. The genotypes of DNA samples were identified blindly. Controls were set up within every PCR operation as blank control (without DNA template), positive control and negative control and when any one of these controls failed, PCR needed to be re-conducted.

Statistical analysis

Data were checked and input into the computer. The values of chi-square, odds ratio (OR) and OR 95% CI (confidence interval) were calculated. And interactions between genetic susceptibility-environmental factors were also estimated.

RESULTS

Test of comparability between cases and controls showed that the age and gender in cases and controls were comparable.

Risk factors for EC

Tobacco smoking, alcohol drinking, a family history of EC, *GSTM1* deletion genotype and *CYP1A1* genotype (*Val*/*Val*) were risk factors of EC (Table 1).

Analysis of genetic susceptibility-environmental factor interaction

GSTM1 deletion genotype had synergic interactions with tobacco smoking ,alcohol drinking and family history of EC (Tables 2,3,4).

CYP1A1 *Val/Val* genotype had synergic interactions with tobacco smoking, alcohol drinking, and family history of esophageal cancer (Tables 5, 6, 7).

Table 1 Risk factors for esophageal cancer

Risk factors		Case	Control	OR	OR95%CI	χ^2	*P*
Tobacco smoking	Yes	70	38	2.04	1.15-3.60	6.88	0.009
	No	59	63				
Alcohol drinking	Yes	50	16	3.45	1.74-6.91	15.08	0.000
	No	77	85				
FHEC	Yes	27	8	3.14	1.28-7.94	7.67	0.006
	No	100	93				
GSTM1	Deletion	74	44	1.81	1.03-3.18	4.85	0.028
	Existed	53	57				
CYP1A1	*Ile / Ile*	21	31	1.00			
	Ile / Val	56	48	1.72	0.83-3.58	2.50	0.114
	Val / Val	50	22	3.35	1.49-7.61	10.33	0.001

FHEC: family history of esophageal cancer.

Table 2 Synergic interactions of tobacco smoking and GSTM1 deletion genotype

Tobacco smoking	GSTM1 deletion	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	24	37	1.00			
No	Yes	33	26	2.96	0.89-4.33	3.28	0.07
Yes	No	29	20	2.24	0.97-5.19	4.24	0.04
Yes	Yes	41	18	3.51	1.55-8.05	10.89	0.001

SIA=3.51 / (2.24+1.96-1.00)=1.10. SIA: Synergic index of addition.

Table 3 Synergic interactions of alcohol drinking and GSTM1 deletion genotype

Alcohol drinking	*GSTM1* deletion	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	35	48				
No	Yes	42	37	1.56	0.80-3.04	1.95	0.16
Yes	No	18	9	2.74	1.01-7.55	4.85	0.03
Yes	Yes	32	7	6.27	2.30-17.72	16.91	0.00

SIM=6.27 / (1.56×2.74)=1.47 SIM: Synergic index of multiplication.

Table 4 Synergic interaction of GSTM1 deletion genotype and family history of esophageal cancer

ECFH	*GSTM1*deletion	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	44	53	1.00			
No	Yes	56	40	1.69	0.92-3.11	3.24	0.07
Yes	No	9	4	2.71	0.69-12.76	2.59	0.11
Yes	Yes	18	4	5.42	1.60-23.34	9.47	0.00

SIM=5.42 / (1.69×2.71)=1.18.

Table 5 Interaction of tobacco smoking and CYP1A1 *Val* / *Val* genotype

Smoking	*CYP1A1* (*Val/Val*)	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	33	47	1.00			
No	Yes	24	16	2.14	0.92-4.99	3.73	0.05
Yes	No	44	32	1.96	0.99-3.90	4.29	0.04
Yes	Yes	26	6	6.17	2.14-20.10	14.54	0.00

SIM=6.17 / (2.14×1.96)=1.47.

Table 6 Interaction of alcohol drinking and C*YP1A1Val/Val* genotype

Alcohol drinking	*CYP1A1 Val/Val*	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	50	67	1.00			
No	Yes	27	18	2.01	0.94-3.43	3.86	0.05
Yes	No	27	12	3.02	1.31-7.03	8.16	0.00
Yes	Yes	23	4	7.71	2.39-32.16	15.71	0.00

SIM=7.71 / (2.01×3.02)=1.27.

Table 7 Interaction of *CYP1A1 Val/Val* genotype and a family history of esophageal cancer

ECFH	*CYP1A1 Val/Val*	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	65	74	1.00			
No	Yes	35	19	2.10	1.04-4.24	5.05	0.03
Yes	No	12	5	2.73	0.84-10.38	3.42	0.06
Yes	Yes	15	3	5.69	1.50-31.72	8.47	0.00

SIA=5.69 / (2.73+2.10-1.00)=1.49.

DISCUSSION

Under similar environmental carcinogens exposure, different individuals respond to environmental exposures differently. The different liability to cancer was called genetic susceptibility to cancer. Genetic susceptibility can affect in every step of carcinogenesis, including modifying the effect of environmental carcinogens[29,38-44]. Oncogenes and tumor suppressor genes can also affect individual' s susceptibility to cancer[34-36,45]. Cancer susceptibility genes include type I, type II metabolism enzyme genes, DNA repair gene and those affecting cell proliferation rate. In recent years the evidence has been accumulated to support the hypothesis that cancer susceptibility genes may be of importance in determining individual susceptibility to cancer[43,46-59].

EC is a multi-factor determined disease, including environmental risk factors and genetic factors. In recent years, more and more researchers considered environmental and genetic susceptibility factors and their interactions in evaluating the risks of cancer[2,18,53,60-63]. Investigations showed the mortality rate of EC in Shanxi province was not decreased during the latest 20 years, and risk factors for EC in Xi' an city were discussed in several researches[2,27,28,33]. In the present hospital based case- control study, it was revealed that tobacco smoking was a risk factor, and also had interactions with GSTM1deletion genotype and CYP1A1 *Val*/*Val* genotype.

Aroma hydrocarbons (AHs) in tobacco smoking are pro-carcinogens. They need to be activated to reactive electrophilic forms by type I metabolic enzymes (CYP450s), then initiate cell carcinogenesis. On the other hand ,the reactive electrophilic forms of carcinogen can be detoxified and excreted by type II metabolic enzymes such as GSTM1. Although theoretically the increase of activity of type I metabolic enzymes and/or decrease of activity of type II metabolic enzymes can increase the risk for cancer, there were different results in different studies[43,44,47,50-52,64-69]. Our results showed that individuals carrying GSTM1 deletion genotype or/and CYP1A1 *Val*/*Val* genotype had increased risks for EC.

P450 CYP1A1 gene product metabolizes pro-carcinogens. There are three kinds of polymorphism of CYP1A1: *Msp*I site, 7th exon (Ile-Val) and AA polymorphism. CYP1A1 Ile-Val polymorphism is caused by a base difference (A or G) at 4 889 of 7th exon. The transition of A to G results changing of amino acid from isoleucine to valine at 462[14], thus forming three kinds of genotypes: homozygote wild genotype (*Ile*/*Ile*), mutation genotype (*Val*/*Val*) and heterozygote *Ile*/*Val* genotype. Researches showed CYP1A1 *Val*/*Val* genotype had a higher ability to activate pro-carcinogen than CYP1A1 *Ile*/*Ile* genotype. PAH-DNA adducts in leukocytes were higher in heavy smoking population with CYP1A1 *Val*/*Val* genotype than those with CYP1A1 *Ilel*/*Val or Ile*/*Ile* genotype.

The associations between CYP1A1 genotype and susceptibility to cancers were varied[39-42,47,70]. Data from Guangdong province of China showed that *MspI* C correlated with lung cancer susceptibility in no-smoking populations[65]. In studies in Shanghai and Haerbin, no significant relationship was discovered between CYP1A1 (*Ile*-*Val*) polymorphism and lung cancer susceptibility in non-smoking female patients[64]. CYP1A1 *Val*/*Val* genotype in white population only appeared about 3.2-5%, while in Japanese it was about 19.8%, in Chinese

22.3%. Our study showed that CYP1A1 *Val*/*Val* genotype was a genetic susceptibility risk factor for EC (OR 3.35, 95% CI 1.49-7.61). CYP1A1 *Val*/*Val* genotype had synergic interactions with tobacco smoking, alcohol drinking, and a family history of esophageal cancer.

GSTM1 can detoxify a number of reactive electrophilic compound substances, including the carcinogens PAHs. In individuals with GSTM1 deletion genotype, the ability of detoxifying the carcinogens decreased. Individuals with GSTM1 deletion could have increased risk of cancers[29,53,56]. In China there were similar researches on GSTM1 deletion genotype and the risks of lung cancer (OR=2.56)[66], and stomach cancer (OR 1.90, 95%CI 1.01-3.56)[67]. It was reported that in Henan province, a high incidence area of EC in China, GSTM1 deletion genotype did not show significant relation with EC susceptibility[25]. Results in our study indicated GSTM1 deletion genotype was a genetic susceptibility risk factor for EC (OR1.81, 95% CI 1.03-3.18), which interacted synergistically with tobacco smoking, alcohol drinking and family history of esophageal cancer.

In summary, we found that tobacco smoking, alcohol drinking, and a family history of EC were risk factors for EC in Xi' an area. CYP1A1 *Val/Val* genotype, GSTM1 deletion genotype were genetic susceptibility risk factors for EC. Gene-environment interaction analysis showed that CYP1A1 *Val/Val* genotype, GSTM1 deletion genotype synergetically interacted with tobacco smoking, alcohol intake, and family history of EC. Gene-gene interaction analysis did not show synergistic interaction between CYP1A1 mutation genotype and GSTM1 deletion genotype, although individuals carrying these two genotypes had increased risks for EC.

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