PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• ESOPHAGEAL CANCER •

Relationship of tobacco smoking, CYP1A1, GSTM1 gene polymorphism and esophageal? cancer in Xi'an

An-Hui Wang, Chang-Sheng Sun, Liang-Shou Li, Jiu-Yi Huang, Qing-Shu Chen

An-Hui Wang, Chang-Sheng Sun, Liang-Shou Li, Jiu-Yi Huang, Department of Epidemiology, Faculty of Preventive Medicine, Fourth Military Medical University Xi'an 710033, Shaanxi Province, China
Qing-Shu Chen, Department of Thoracic Surgery, Tangdu Hospital, Fourth Military Medical University, Xi'an 710038, Shaanxi Province, China
Supported by National Natural Science Foundation of China, No.39670651
Correspondence to: An-Hui Wang, Department of Epidemiology, Faculty of Preventive Medicine, Fourth Military Medical University Xi'an 710032,Shaanxi Province, China. wanganhui@hotmail.com
Telephone: +86-29-3374871
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Abstract

AIM: **To analyze the association of tobacco smoking, polymorphism of CYP1A1 (7th exon) and GSTM1 genotype and esophageal cancer(EC) in Xi'an.**

METHODS: **A hospital based case-control study, with molecular epidemiological method, was carried out. Polymorphism of CYP1A1 and GSTM1 of samples from 127 EC cases and 101 controls were detected by PCR method.**

RESULTS: **There were no significant difference of age and gender between cases and controls. Tobacco smoking was the main risk factor(OR=1.97 ;95% CI=1.12-3.48) for EC in Xi'an. The proportions of CYP1A1 *Ile/Ile, Ile/Val* and *Val/Val* gene types in cases and controls was 19.7%,45.7%,34.6% and 30.7%,47.5%, 21.8% respectively(*P*=0.049).Individuals with CYP1A1 *Val/Val* genotype compared to those with CYP1A1 *Ile/Ile* genotype had higher risk for EC increased (OR=2.48, 95%CI=1.12-5.54). The proportions of GSTM1 deletion genotype in cases and controls were 58.3% and 43.6% (OR=1.81, 95%CI=1.03-3.18,*P*=0.028). Analysis of gene-environment interaction showed that tobacco smoking and CYP1A1 *Val/Val* genotype; tobacco smoking and GSTM1 deletion genotype had synergism interaction respectively. Analysis of gene-gene interaction did not find synergistic interaction between these two genes. But in GSTM1 deletion group,there was significant difference of distribution of CYP1A1 genotype between cases and controls (*P*=0.011).**

CONCLUSION: **CYP1A1 *Val/Val* and GSTM1 deletion genotypes are genetic susceptibility biomarkers for EC. The risk increases, when person with CYP1A1 *Val/Val* and/or GSTM1 deletion genotype. And these two-metabolic enzymes seem to have interactions with tobacco smoking, in which the mechanism still needs further study.**

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INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors of human being. The incidence of EC varies in different countries. China is the country with highest incidence and mortality rate of EC. Research showed that risks for EC in different countries or different places were different[1-6].In western countries alcohol intake and tobacco smoking were studied deeply[7-12]. It was thought that besides tobacco smoking and alcohol drinking, nutrition factors, life style, viruses infection, heredity or exposure to nitrosamines, fungi or AFB1 maybe involved in the process of EC[1,3,13-19]. In China, researches showed risks for EC were different in areas with different incidence[1-5,16,18,20,21]. The mortality rate of EC of Xi'an city in Shaanxi province is about 24 per 100,000, which ranks first in all cancer mortalities. Previous studies showed that both of tobacco smoking and family history of EC were main risk factors for EC in Xi'an city[2,22,23].

EC is a multi-etiology disease; environmental risks exposures and genetic susceptibility may take the role part[2,22-24]. Almost all of the environmental carcinogens (procarcinogens) are activated to be ultimate carcinogens before initiate the process of carcinogenesis. Some metabolic enzymes are closely related to the activation and detoxification of procarcinogens. Alterations of the key oncogene or tumor suppress gene can disturb the cycle of cell proliferation, which can also initiate the process of carcinogenesis[23,25,26]. Susceptibility of cancer is associated with the genetics polymorphism of related metabolic enzymes. Both certain susceptibility related biomarkers and certain environmental carcinogens perhaps are indispensable factors for EC[20,23,27,28]. To explore the bio-basis of genetic susceptibility of EC in Xi'an, we carried out a hospital based case- control study to analyze the associations of tobacco smoking, CYP1A1, GSTM1 gene polymorphism and EC.

MATERIALS AND METNODS

Seletion of patients and controls

All cases with esophageal cancer (confirmed by pathological diagnosis) came from inpatients of Tandu Hospital during half a year period (December, 1999 to April, 2000). All controls were stratified randomly selected from non-cancer inpatients from different department of the same hospital during the same period. Both cases and controls were confined to residents with long-term living in Xi'an (with similar proportion of gender and age).

Collected data

Trained interviewers using a structured questionnaire interviewed cases and controls in the hospital. The questionnaire obtained detailed information on residence, occupation, tobacco smoking habit and so on. Here tobacco smoking was defined as smoking at least one cigarette per day and persisting for more than one year. 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 had been stored at -70℃ before started DNA extraction.

PCR methods to detect polymorphism of CYP1A1 and GSTM1

Digested by Proteinase K, DNA genomes were extracted from blood

clot of cases and controls with hydroxybenzene, chloroform method in a uninterrupted period. CYP1A1 and GSTM1 polymorphisms were identified by polymerase chain reaction (PCR) before which DNA samples were stored at 4℃. Primers for GSTM1(P1:5'-GTA CCC TAC TTG ATT GAT GGG-3'; P2:5' -CTG GAT TGT AGC AGA TCA TGC-3') and for 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 Shenggong bio-technical company of Shanghai. PCR condition for GSTM1 as follows, 50μL solution including 10×buffer 5μL, Mg^{2+} 2μL, P1,P2 1μL respectivly, template DNA1.5μL, dDNTPs 1μL and Taq DNA polymerase 3^{U}. After denaturation at 94℃ for 10 min, Taq DNA polymerase was added,followed by 30 cycles with 94℃ 1min, 60℃ 1min, and 72℃ 1min.20g·L^{-1} agar was used to electrophoresis PCR production, then observed under the violate light. GSTM1 exist genotype was characterized as had a 273bp fragment; while GSTM1 deletion genotype had no fragment (Figure 1).

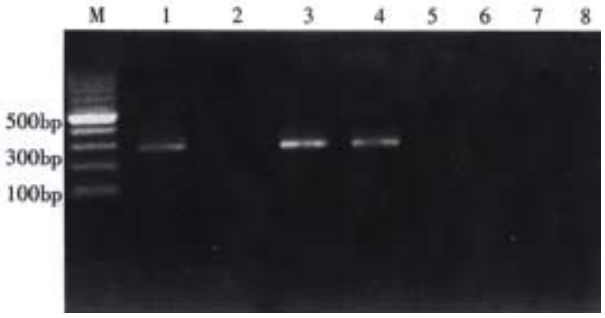

Figure 1 Identify the GSTM1 genotype
M:100bp DNA ladder, 3,4 were GSTM1 exist 2,5 were GSTM1 deletion; 1 positive control,6 negative control,7 was blank control (without DNA template)

We used two pairs of primers to detect the polymorphism of CYP1A1 (7^{th} 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 were the same:50μL solution including 10×buffer 5μL,Mg^{2+} 2μL, P3,P5 (or P4,P5) 1μL, template DNA 1.5μL, dDNTPs 1μL and Taq DNA polymerase 3^{U}, then 94℃ 10min followed by 94℃ 1min,55℃ 1min, 72℃ 1min, 35 cycles,72℃ extending 10 min. PCR products were observed. The PCR was conducted to detect the mutation of A-G in CYP1A1 7^{th} exon, the mutation can leads to change of one amino acid (Ile to Val). If there was only tube A had the specifically fragment (200bp), 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 with both tube A and tube B had the fragment (Figure 2).

Quality control

DNA extraction and PCR were conducted in different period and places. The genotypes of DNA samples were identified blindly. Every PCR had were set controls as blanket control (without DNA template), positive control and negative control, and when any one of these controls was failure, PCR wasre-conducted.

Statistical analysis

Data were input into computer, then the values of χ^2, odds ratio (OR) and OR95% CI (confidence intermediate) were calculated. And ORs of gene-environment and gene-gene interaction were also estimated.

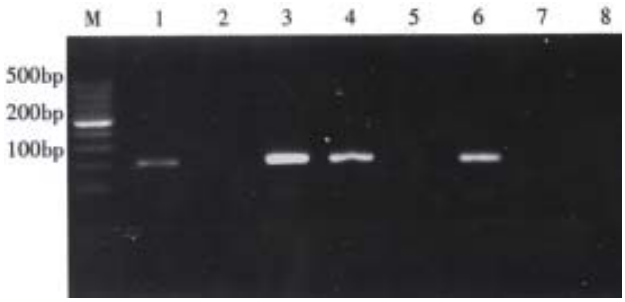

Figure 2 Identified the genotypes of CYP1A1
M: 100bp DNA ladder; 1(A),2(B) represent Ile/Ile genotype; 3(A),4(B) represent Ile/Val genotype; 5(A),6(B) represent Val/Val genotype; 7(A),8(B) as blank control(without DNA template).

RESULTS

Comparability between cases and controls

The age and gender in cases and controls were comparable(Table 1).

Table 1 Comparability of age and gender in cases and controls

Factor	Case	Control	χ^2	*P*
Age(year)				
<50	28	16		
50-	38	44		
⩾60	61	41	4.73	0.094
Gender				
Male	97	78		
Female	30	23	0.02	0.80

Risk factors for EC

The proportions of tobacco smoking, *GSTM1* deletion genotype and *CYP1A1* genotype (*Val/Val*) in cases and controls were significantly different ($P<0.05$) (Table 2).

Table 2 Distributions of smoking, GSTM1 deletion and CYP1A1 genotypes

Factors		Case	Control	OR	OR95%CI	χ^2	*P*
Smoking	Yes	69	38	1.97	1.12-3.48	6.28	0.012
	No	58	63				
GSTM1							
Deletion		74	44	1.81	1.03-3.18	4.85	0.028
Exist		53	57				
CYP1A1							
Ile/Ile		25	31	1.00		1.00	
Ile/Val		58	48	1.50	0.74-3.03	1.48	0.22
Val/Val		44	22	2.48	1.12-5.54	5.93	0.015

Interaction of tobacco smoking and GSTM1 deletion genotype or CYP1A1 Val/Val genotypes

Analysis showed that there was synergistic interaction between tobacco smoking and GSTM1 deletion genotype (Table 3).

Table 3 Interaction of smoking and GSTM1 deletion genotype.

Smoking	GSTM1 deletion	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	25	37	1.00			
Yes	No	28	20	2.07	0.90-4.80	3.48	0.062
No	Yes	33	26	1.88	0.86-4.13	2.93	0.087
Yes	Yes	41	18	3.37	1.49-7.69	10.29	0.0013

SIA=3.37/(1.88+2.07-1.00)=1.14

Tobacco smoking and CYP1A1 *Val/Val* genotype also appeared synergistic interaction(Table 4).

Table 4 Interaction of tobacco smoking and CYP1A1 Val/Val genotype

Smoking	CYP1A1(*Val/Val*)	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	36	47	1.00			
Yes	No	47	32	1.92	0.98-3.76	4.18	0.04
No	Yes	22	16	1.80	0.77-4.20	2.18	0.14
Yes	Yes	22	6	4.79	1.62-14.83	10.30	0.0013

SIM=4.79/(1.92×1.80)=1.39

But CYP1A1 mutation genotypes(*Val/Val, Ile/Val*)and GSTM1deletion genotype did not show significant interaction (Table 5).

Table 5 Interaction of CYP1A1mutation genotypes(Val/Val, Ile/Val)and GSTM1deletion genotype

GSTM1 deletion	CYP1A1 mutation	Case	Control	OR	OR95%CI	χ^2	*P*
No	No	10	20	1.00			
No	Yes	43	37	2.32	0.89-6.14	3.61	0.057
Yes	No	15	11	2.73	0.81-9.42	3.28	0.070
Yes	Yes	59	33	3.58	1.39-9.38	8.66	0.0033

OR of individuals with CYP1A1 mutation genotype and GSTM1deletion genotype was greater than those with of any other forms of the two genotypes. But there did not show any synergistic interaction between CYP1A1 mutation genotypes and GSTM1deletion genotype.

Stratified with GSTM1 deletion genotype to analyze the distributions of CYP1A1 genotypes in cases and controls. Results showed that there were significant different in cases and controls (*P*=0.011) in GSTM1 exist genotype CYP1A1 genotypes, whereas there were no significant difference (*P*=0.83) between cases and controls in GSTM1 deletion genotype (Table 6).

Table 6 Analysis of CYP1A1 genotypes in cases and controls with Stratified GSTM1deletion

CYP1A1 genotype	GSTM1 deletion		existing GSTM1	
	Case	Control	Case	Control
Ile/Ile	15	11	10	20
Ile/Val	35	19	23	29
Val/Val	24	14	20	8
χ^2	0.39		9.04	
P	0.83		0.011	

DISCUSSION

Under similar environmental carcinogens exposure only a few of individuals get neoplasm, for there were individual difference to environmental exposure. The different liability to cancer was called genetic susceptibility of cancer. Genetic susceptibility can affect on every step of carcinogenesis, including modify the effect of environmental carcinogens[24,29-35].Oncogenes and tumor suppressor genes can also affect individual's susceptibility to cancer.Cancer susceptibility genes includes typeI, typeII metabolism enzyme gene,DNA repair gene and those affect cell proliferation rate gene. In recent years evidence has accumulated to support the hypothesis that cancer susceptibility gene may be of importance in determining individual susceptibility to cancer[34,36-46].

EC is a multi-factor determined disease; including environmental risk factors and genetic factors. In recent years, more and more researches considered environmental and genetic susceptibility factors and their interactions in evaluating the risks of cancer[2,17,43,47-50]. Investigations showed the mortality rate of EC in Shaanxi province did not decreased during the late 20 years, and risks factors for EC in Xi'an city were discussed in several researches[2,22,23]. In this hospital based case- control study, the results showed that tobacco smoking was a risk factor;and tobacco smoking had interactions with GSTM1deletion genotype and CYP1A1 *Val/Val* genotype.

Most chemical carcinogens in environment are pro-carcinogens. And aromatic hydrocarbons (AHs) in tobacco smoking are pro-carcinogens, they need to be activated to reactive electrophilic forms by type ¢ñ metabolic enzymes (CYP450s), then initiate the carcinogenesis. On the other hand the reactive electrophilic forms of carcinogen can be detoxified and excreted by typeI metabolic enzymes such as GSTM1. Although theoretically the increase of activity of type II metabolic enzymes and/or decrease of activity of typeI metabolic enzymes can increase the risk for cancer, there were different results in different researches, some supported this hypothesis and others did not[27,34,35,37,40-42,51-56]. Our results showed that individuals with the GSTM1 deletion genotype or/and CYP1A1 *Val/Val* genotype had increased risks for EC.

P450 CYP1A1 gene located in chromosome 15q22 mainly metabolizes pro-carcinogens. There are three kinds of polymorphism of CYP1A1: MspI site, 7th exon (Ile-Val) and AA polymorphism. *MspI* polymorphism include three genotypes: without MspI enzyme cleavage site allele gene m1(*m1/m1*)as A genotype;having MspI cleavage site allele (*m2/m2*)as C genotype and *m1/m2* as B genotype. In different populations the distribution of these three genotypes were different. CYP1A1 Ile-Val polymorphism caused by 7th exon 4889th base difference (A or G), transition of A to G results in 462th amino turned from isoleucine to valine[13],then form three kinds of genotypes: homozygote wild genotype(*Ile/Ile*), mutation genotype(*Val/Val*)and heterozygote *Ile/Val* genotype. Polymorphism of 7th exon correlated with polymorphism of *Msp*I in Asia and Caucasian populations, and in Americans from Africa these two kind of CYP1A1 polymorphism were independent, CYP1A1 7th exon polymorphism and *Msp*I site were incomplete linkage. Research showed CYP1A1 *Val/Val* genotype have higher ability to activate pro-carcinogen than CYP1A1 *Ile/Ile* genotype. PAH-DNA adducts in leukocyte were higher in heavy smoking population with CYP1A1 *Val/Val* genotype than those with CYP1A1 Ilel/Val or Ile/Ile genotype. AA polymorphism was new special *MspI* polymorphism, which still under discussion.

Although evidence showed that CYP1A1 mutation genotype (*Val/Val*) had the strongest ability to activate pro-carcinogens, the associations between CYP1A1 genotype and susceptibility to cancers were varied[30-33,37,57,58]. Data from Guandong province in China showed that MspI C correlated with no-smoking population's lung cancer susceptibility[52]. Study in Shanghai and Haerbin no significant relation was discovered between CYP1A1 (*Ile-Val*) polymorphism and lung cancer susceptibility in non-smoking female patients[51].CYP1A1 *Val/Val* genotype only appear about 3.2%~5% in white population,while in Japanese it was about 19.8%,in Chinese it was 22.3%. Our study showed that distributions of CYP1A1 genotypes in cases and controls were different (*P*=0.049), CYP1A1 *Val/Val* genotype was associated with EC (OR= 2.48,95%CI=1. 12-5.54) and there was interaction of tobacco smoking and CYP1A1 *Val/Val* genotype.

GSTM1 can detoxify a number of reactive electrophilic compound substances, including the carcinogens PAHs. If

individuals with GSTM1 deletion genotype, the ability of detoxify the carcinogens decreased. Individuals with GSTM1 deletion can have the increased risk of cancers[24,43,46]. In China there were similar research on GSTM1 deletion genotype and the risks of lung cancer(OR=2.56)[53],and stomach cancer(OR=1. 90, 95%CI=1.01-3.56)[54].Researches showed that in Henan province, high incidence of EC in China, GSTM1 deletion gene polymorphisms had not significant relation with EC susceptibility[20]. Results of our study indicated GSTM1 deletion genotype was significant different in cases and controls (P=0.028) and the OR was 1.81(OR95%CI=1.03-3.18). GSTM1 deletion genotype had synergistic interaction with tobacco smoking.

In summary, we found tobacco smoking, CYP1A1 *Val/Val* genotype; GSTM1 deletion genotype had associations with EC in Xi'an area. Gene-environment interaction analysis showed that tobacco smoking had synergistic interactions with CYP1A1 *Val/Val* genotype, and with GSTM1 deletion genotype. Gene-gene interaction analysis did not find synergistic interaction between CYP1A1 mutation genotypes and GSTM1 deletion genotype, though individuals with these two genotypes had increased risk for EC. The synergistic interactions and their mechanisms of tobacco smoking with these two metabolic enzymes gene polymorphisms still need further study with large (population-based) samples and modified designs.

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REFERENCES

1 Zhang W, Bailey-Wilson JE, Li W, Wang X, Zhang C, Mao X, Liu Z, Zhou C, Wu M. Segregation analysis of esophageal cancer in a moderately high-incidence area of northern China. *Am J Hum Genet* 2000; 67: 110-119

2 Li LS, Sun CS, Zhang XL, Qiao GB, Xu DZ, Han CL, Yang WX, Chang GS, Yan MX, Wang Y, Zhang HY.A comparative molecular epidemiological study on esophageal cancer between Xi'an and Lizhou. *Jiefangjun Yufangyixue Zazhi* 1999; 17: 255-259

3 Zhou XG, Watanabe S. Factor analysis of digestive cancer mortality and food consumption in 65 Chinese countries. *J Epidemiol* 1999; 9: 275-284

4 Wang LD, Zou JX, Hong JY, Zhou Q, Deng CJ, Xie DW, Holly C. Identification of a novel genetic polymorphism of human O-6-alkyguanine -DNA alkyltransferase in patients with esophagus cancer. *Huren Xiaohua Zazhi* 1998; 6: 560-463

5 Lu JB, Lian SY, Sun XB, Zhang ZX, Dai DX, Li BW, Cheng LP, Wei JR, Duan WJ.A case-control study on the risk factors of esophageal cancer in Linzhou. *Zhonghua Liuxingbingxue Zazhi* 2000; 21: 434-436

6 Li WD, Wang XQ, Zhang CL, Han XY, Chen DQ, Zhang T, Pan XF, Jia YT, Mao XZ, Zhang R. Esophageal carcinoma in part of population of yangquan city. *Zhonghua Yixue Zazhi* 1998; 78: 203-206

7 Castellsague X, Munoz N, De Stefani E, Victora CG, Quintana MJ, Castelletto R, Rolon PA. Smoking and drinking cessation and risk of esophageal cancer (Spain). *Cancer Causes Control* 2000; 11: 813-818

8 Lagrgren J, Bergstrom R, Lindgren A, Nyren O.The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J cancer* 2000; 85: 340-346

9 Launoy G, Milan C, Faivare J, Pienkowski P, Gignoux M. Tobacco type and risk of squmous cell cancer of the oesophagus in males: a French multicentre case-control study. *Int J Epidemiol* 2000; 29: 36-42

10 Talamini G, Capelli P, Zamboni G, Mastromauro M, Pasetto M, Castagnini A, Angelini G, Basssi C, Scarpa A. Alcohol,smoking and papillomavirus infection as risk for esophageal squmous-cell papilloma and esophageal squamous-cell carcinoma in Italy. *Int J cancer* 2000; 86: 874-878

11 Castellsague X, Munoz N, De Stefani E, Victora CG, Gastelletto R, Rolon PA, Quintana MJ. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer* 1999; 82: 657-664

12 Castellsague X,Munoz N, De Stefani E,Victora CG,Gastelletto R, Rolon PA. Influence of mate drinking,hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer* 2000; 88:658-664

13 Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD, Mayne ST, Stanford JL, Schoenberg JB, Ahsan H, Dubrow R, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Family history of cancer and risk of esophageal and gastric cancers in the Unitecd States. *Int J Cancer* 2001;93:148-152

14 Nayar D,Kapil U, Joshi YK, Sundara KR, Sriastava SP, Shukla NK,Tandon RK. Nutritional risk factors in esophageal cancer. *J Assoc Physicians India* 2000; 48: 781-787

15 Chang F, Syrjanen S, Shen Q, Cintorrino M, Santopietro R, Tosi P, Syrjanen K. Evaluation of HPV, CMV, HSV and EBV in esophageal squamous cell carcinomas from a high-incidence area of china. *Aticancer Res* 2000;20:3935-3940

16 Li T, Lu ZM, Chen KN, Guo M, Xing HP, Mei Q, Yang HH, Lechner JF, Ke Y. Human papillomavirus type 16 is an important infectious factor in the high incidence of esophageal cancer in Anyang area of China. *Carcinogenesis* 2001; 22: 929-934

17 Shi QL, Xu DZ, Sun CS, Li LS. Study on family aggregation of esophageal cancer in Linzhou city. *Zhonghua Yufang Yixue Zazhi* 2000; 34: 269-270

18 Shen YP, Gao YT, Dai Q, Hu X, Xu TL, Xiang YB, Tang ZL,Li WL. A case-control study on esophageal cancer in Huaian city, Jiansu province(I):role of the cigarette smoking and alcohol drinking. *Zhongliu* 1999; 19: 363-367

19 Lagergren J, Ye W, Lindgren A, Nyren O. Heredity and risk of cancer of the esophagus and GASTRIC cardia. *Cancer Epidemiol Biomarkers Prev* 2000; 9: 757-760

20 Lin DX, Tang YM, Lu SX, Kadlubar FF. Glutathione S-transferase M1, T1genetypes and risks of esophageal cancer: a case-control study. *Zhonghua Liuxingbing Zazhi* 1998;19: 195-199

21 Gao YT, Den J, Xiang YB, Ruan ZX, Wang ZX, Hu BY, Guo MR, Ten WK,Han JJ, Zhang YS.Smoking,related cancers, and other diseases in Shanghai:A 10-year prospective study. *Zhonghua Yufang Yixue Zazhi* 1999; 33: 5-8

22 Zhang HY, Sun CS, Li LS, Yan MX. CytochromeP450IA1 and the genetic susceptibility to esophageal carcinoma. *Zhonghua Yufang Yixue Zazhi* 2000; 34: 69-71

23 Wang AH, Zhang HY, Wang Y, Yan MX, Sun CS, Li LS, Huang JY, Cheng QS, Zhu YF. Molecular epidemiological study on esophageal cancer in Xi'an. *Disi Junyi Daxue Xuebao* 2001; 22: 61-63

24 Tan W, Song N, Wang GQ, Liu Q, Tang HJ, Kadlubar FF, Lin DX.Impact of genetic polymorphisms in cytochrome P450 2E1 and glutathione S-transferases M1, T1, and P1 on susceptibility to esophageal cancer among high-risk individuals in China. *Cancer Epidemiol Biomarkers Prev* 2000;9: 551-556

25 Hu N, Huang J, Emmert-buck MR, Tang ZZ, Roth MJ, Wang C, Dawsey SM, Li WJ, Wang QH, Han XY, Ding T, Giffen C, Goldstein AM, Taylor PR. Frequent inactivation of the TP53 gene in esophageal squamous cell carcinoma from a high-risk population in China. *Clin Cancer Res* 2001; 7: 883-891

26 Taniere P, Martel-Planche G, Puttawibul P, Casson A, Montesano R, Chanvitan A, Hainaut P. TP53 mutations and MDM2 gene amplification in squamous-cell carcinomas of the esophagus in south Tailand. *Int J Cancer* 2000; 88: 223-227

27 Shao GZ,Hu Z,Li EM,Li J,Wen BG. Relatyionship between the GSTM1 genetic polymorphisim and susceptibility to squamous cell carcinoma of esophagus. *Shantou DaxueYixueyuan Xuebao* 1999; 12: 1-3

28 Mizobuchi S, Furihata M, Sonobe H, Ohtsuki Y, Ishikawa T, Murakami H, Kurabayashi A, Ogoshi S, Sasaguri S. Association between p53 immunostaining and cigarette smoking in squamous cell carcinoma of the esophagus. *Jpn J Clin Oncol* 2000;30:423-428

29 van Lieshout EM, Roelofs HM, Dekker S, Mulder CJ, Wobbes T, Jansen JB, Peters WH.Polymorphic expression of the glutathione S-transferase P1 gene and its susceptibility to Barrett's esophagus and esophageal carcinoma. *Cancer Res* 1999;59: 586-589

30 Roth MJ, Dawsey SM, Wang G, Tangrea JA, Zhou B, Ratnasinghe D, Woodson KG, Olivero OA, Poirier MC, Frye

BL, Taylor PR, Weston A.Association between GSTM1*0 and squamous dysplasia of the esophagus in the high risk region of Linxian, China. *Cancer Lett* 2000; 156: 73-81
31 Morita S, Yano M, Tsujinaka T, Akiyama Y, Taniguchi M, Kaneko K, Miki H, Fujii T, Yoshino K, Kusuoka H, Monden M. Genetic polymorphisms of drug-metabolizing enzymes and susceptibility to head-and-neck squamous-cell carcinoma. *Int J Cancer* 1999; 80: 685-688
32 Butler WJ, Ryan P, Roberts-Thomson IC. Metabolic genotypes and risk for colorectal cancer. *J Gastroenterol Hepatol* 2001;16:631-635
33 Rojas M, Cascorbi I, Alexandrov K, Kriek E, Auburtin G, Mayer L, Kopp-Schneider A, Roots I, Bartsch H. Modulation of benzo [a] pyrene diolepoxide-DNA adduct levels in human white blood cells by CYP1A1, GSTM1 and GSTT1 polymorphism. *Carcinogenesis* 2000; 21: 35-41
34 Tanimoto K, Hayashi S, Yoshiga K, Ichikawa T. Polymorphisms of the CYP1A1 and GSTM1 gene involved in oral squamous cell carcinoma in association with a cigarette dose. *Oral Oncol* 1999; 35: 191-196
35 Sato M, Sato T, Izumo T, Amagasa T. Genetic polymorphism of drug-metabolizing enzymes and susceptibility to oral cancer. *Carcinogenesis* 1999; 20: 1927-1931
36 Xing DY, Tan W, Song N, Lin DX. Genetic polymorphism in hOGG1 and susceptibility to esophageal cancer in Chinese. *ZhonghuaYiue Yichuanxue Zazhi* 2000; 17: 377-380
37 Chen S, Xue K, Xu L, Ma G, Wu J. Polymorphisms of the CYP1A1 and GSTM1 genes in relation to individual susceptibility to lung carcinoma in Chinese population. *Mutat Res* 2001;458:41-47
38 Song C, Xing D, Tan W, Wei Q, Lin D. Methylenetetrahydrofolate reductase polymorphisms increase risk of esophageal squamous cell carcinoma in a Chinese population. *Cancer Res* 2001;61:3272-3275
39 Lee JM, Lee YC, Yang SY, Yang PW, Luh SP, Lee CJ, Chen CJ, Wu MT. Genetic polymorphisms of XRCC1 and risk of the esophageal cancer. *Int J Cancer* 2001;95:240-246
40 Chao YC, Wang LS, Hsieh TY, Chu CW, Chang FY, Chu HC. Chinese alcoholic patients with esophageal cancer are genetically different from alcoholics with acute pancreatitis and liver cirrhosis. *Am J Gastroenterol* 2000;95:2958-2964
41 Sato M, Sato T, Izumo T, Amagasa T. Genetically high susceptibility to oral squamous cell carcinoma in terms of combined genotyping of CYP1A1 and GSTM1 genes. *Oral Oncol* 2000;36: 267-671
42 Gsur A, Haidinger G, Hollaus P, Herbacek I, Madersbacher S, Trieb K, Pridun N, Mohn-Staudner A, Vetter N, Vutuc C, Micksche M. Genetic polymorphisms of CYP1A1 and GSTM1 and lung cancer risk. *Anticancer Res* 2001;21:2237-2242
43 Dong CH,Yu SZ,Chen GC,Zhao DM,Hu Y. Association of polymorphisms of glutathione S transferase M1 and T1 genotypes with elevated aflatoxin and increased risk of primary liver cancer. *Huaren Xiaohua Zazhi* 1998; 6: 463-466
44 Bian JC, Shen FM, Shen L, Wang TR, Wang XH, Chen GC, Wang JB. Susceptibility to hepatocellular carcinoma associated with genotypes of GSTM1 AND gstt1. *World J Gastroenterol* 2000; 6:228-230
45 Cai L,Yu SZ, Zhang ZF. Glutathione S-transferase M1, T1 genotypes and the risk of gastric cancer:a case-control study. *World J Gastroenterol* 2001;7:506-509
46 Cai L, Yu SZ. A molecular epidemiologic study on gastric cancer in Changle,Fujian province. *Shijie Huaren Xiaohua Zazhi* 1999; 7: 652-655
47 Lee JM, Lee YC, Yang SY, Shi WL, Lee CJ, Luh SP, Chen CJ, Hsieh CY, Wu MT. Genetic polymorphisms of p53 and GSTP1, but not NAT2, are associated with susceptibility to squamous-cell carcinoma of the esophagus. *Int J Cancer* 2000; 89: 458-464
48 Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev* 2000;9:3-28
49 Butkiewicz D, Cole KJ, Phillips DH, Harris CC, Chorazy M.GSTM1, GSTP1, CYP1A1 and CYP2D6 polymorphisms in lung cancer patients from an environmentally polluted region of Poland: correlation with lung DNA adduct levels. *Eur J Cancer Prev* 1999;8: 315-323
50 Liu G, Zhou Q, Wang LD, Hong JY, Deng CJ, Wang YY, Zou JX. Blood clot as a DNA source for studying genetic polymorphism of human carcinogen-metabolizing enzymes. *World J Gastroenterol* 1998; 4(Suppl 2): 108-109
51 Qu YH, Shi YB, Peter S, Zhong LJ, Sun L, Sun XW, Cheng JR, Lin YJ, Xian YB, Dai XD, Gao YT. The genotpyes of cytochrome P4501A1 and GST M1 in non-smoking female lung cancer. *Zhongliu* 1998; 18: 80-82
52 Hu YL, Zhang Q. Genetic Polymorphisms of CYP1A1and susceptibility of lung cancer. *Zhonghua YixueYichuangxue ZaZhi* 1999; 16: 26-28
53 Gao JR, Ren CL, Zhang Q. CYP2D6 and GSTM1 genetic polymorphism and lung cancer susceptibility. *Zhonghua Zhongliu Zazhi* 1998; 20: 185-186
54 Cai L, Yu SZ. Preliminary studies on cytochrome P4502E1 and glutathione stransferase M1 polymorphisms and susceptibility to gastric cancer. *Zhongguo Gonggong Weisheng* 1999; 15: 895-897
55 Olshan AF, Mark CW, Watson MA,Bell DA. GSTM1, GSTT1, GSTP1, CYP1A1and NAT1 Polymorphisms, Tobacco use, and the risk of head and neck cancer. *Cancer Epidemiol Biomarkers Prve* 2000; 9:185-191
56 London SJ, Yuan JM, Coetzee GA, Gao YT, Ross RK, Yu MC. CYP1A1 I462V genetic polymorphism and lung cancer risk in a cohort of men in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 2000;9:987-991
57 Murata M, Watanabe M, Yamanaka M, Kubota Y, Ito H, Nagao M, Katoh T, Kamataki T, Kawamura J, Yatani R, Shiraishi T. Genetic polymorphisms in cytochrome P450 (CYP) 1A1, CYP1A2, CYP2E1, glutathione S-transferase (GST) M1 and GSTT1 and susceptibility to prostate cancer in the Japanese population. *Cancer Lett* 2001; 165: 171-177
58 Shen J, Wang RT, Xing HX,Wang LW, Wang ZX, Wang BY, Li MS, Wang JM, Hua ZL, Guo CH, Wang XR, Xu XP. Research on the interaction models of cytochrome P450 1A1 polymorphism(s) in the agents of stomach cancer. *Zhonghua Yufang Yixue Zazhi* 2001;35:167-170

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