PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

ELSEVIER

World J Gastroenterol 2005;11(38):6056-6060
World Journal of Gastroenterology ISSN 1007-9327

• *BRIEF REPORTS* •

Interaction models of *CYP1A1*, *GSTM1* polymorphisms and tobacco smoking in intestinal gastric cancer

Jing Shen, Run-Tian Wang, Yao-Chu Xu, Li-Wei Wang, Xin-Ru Wang

Jing Shen, Yao-Chu Xu, Xin-Ru Wang, Department of Epidemiology and Biostatistics, School of Public Health, Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Jing Shen, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032, USA
Run-Tian Wang, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100083, China
Li-Wei Wang, Yang Zhong Cancer Research Institute, Yang Zhong City Municipal Hospital, Yang Zhong 212200, China
Supported by the National Natural Science Foundation of China, No. 30170827 and 30070671
Correspondence to: Dr. Jing Shen, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 701 West 168th Street (Room 505), New York, NY 10032, USA. js2182@columbia.edu
Telephone: +1-212-3058158 Fax: +1-212-3055328
Received: 2005-01-07 Accepted: 2005-04-02

Abstract

AIM: To explore the interaction models of the cytochrome P-450 (CYP) *1A1 Val* variant and glutathione S-transferase (GST) *M1* null polymorphisms with tobacco smoking in the occurrence of intestinal gastric cancer.

METHODS: A community-based case-control study was conducted in Yangzhong. Subjects included 114 intestinal types of gastric cancer with endoscopic and pathological diagnosis during January 1997 and December 1998, and 693 controls selected from their spouse, siblings or siblings-in-law who had no history of digestive system cancer. Logistic regression was used to estimate the interaction models.

RESULTS: The frequency of the *CYP1A1 Val* variant allele in cases did not differ from that in controls. The OR of *GSTM1* null genotype was 2.0 (95% confidence interval [95%CI]: 1.2-3.1, $P<0.01$). It showed a significant type 2 form of interaction model when both *CYP1A1 Val* variant allele and former tobacco smoking existed (i.e., among the multiplicative effects, the disease risk is increased by the tobacco exposure alone but not by the *CYP1A1* variant alone). The interaction index γ was 2.8, and OR_{eg} (95%CI) was 5.0 (1.9-13.4). *GSTM1* null genotype and former tobacco smoking were significant in a type 4 interaction model (i.e., the disease risk is increased by *GSTM1* null genotype or tobacco exposure alone among the multiplicative effects). The interaction index γ and OR_{eg} (95%CI) were 3.4 and 8.4 (3.4-20.9), respectively.

CONCLUSION: Different interaction models of *CYP1A1 Val* variant allele and *GSTM1* null genotype with tobacco smoking will contribute to understanding carcinogenic mechanism, but there is a need to further investigate in larger scale studies.

Key words: Interaction models; *CYP1A1*; *GSTM1*; Tobacco smoking; Intestinal gastric cancer

Shen J, Wang RT, Xu YC, Wang LW, Wang XR. Interaction models of *CYP1A1*, *GSTM1* polymorphisms and tobacco smoking in intestinal gastric cancer. *World J Gastroenterol* 2005; 11(38): 6056-6060
http://www.wjgnet.com/1007-9327/11/6056.asp

INTRODUCTION

Worldwide, gastric cancer is the second in rank overall (798 000 new cases per year), and ranks second in males, fourth in females. It remains the most common malignancy in many countries of the world[1,2], though the frequency of incidence and mortality is declining in almost all populations. Thirty-eight percent of gastric cancer cases occurred in China, where it remains to be most common and is the leading cause of cancer death in both sexes[1]. Yangzhong is among the areas with the highest gastric cancer mortality and incidence rate in south-east of China[3]. The crude mortality rate of gastric cancer changed from 96.9 to 110.9/100 000 during 1991 and 1997, and the average adjusted incidence rate in the same period was over 115/100 000 (unadjusted rate is 155.5/100 000). Previous studies have shown that high incidence rate of gastric cancer is associated with exposure to environmental factors (tobacco, alcohol consumption, and *H pylori* infection), and individual susceptibility[2,4].

Genetic polymorphisms in cytochrome P-450 (CYP) *1A1* and glutathione S-transferase (GST) *M1* genes that metabolize known and potentially carcinogenic environmental exposures may affect enzymatic activities and alter an individual's ability to metabolize pro-carcinogenic and related compounds, which may change the biologic effect of exposures[5]. A large number of studies have examined the role of polymorphisms in *CYP1A1*, *GSTM1*, and cancer risk, including gastric cancer[6-10], but the results are equivocal[11–14]. The interaction between *GSTM1* null genotype and tobacco smoking for the risk of gastric cancer has only been explored in three studies, with inconsistent evidence of departure from a

multiplicative model, possibly because of the small size (70, 91, and 136 gastric cancer cases, respectively), and the gene-environmental interaction (GEI) models best describing the risk of gastric cancer is not clear[6,11,14]. For this reason, we conducted a community-based case-control study in a Chinese population. Genetic polymorphisms in *CYP1A1* and *GSTM1* were analyzed to test the hypothesis that these genotypes have different interaction models with tobacco smoking in the development of intestinal gastric cancer.

MATERIALS AND METHODS

Subjects

All gastric cancer patients and controls in this study are Han ethnic Chinese selected from Yangzhong County. Gastric cancer was prevalent in cases diagnosed according to International Classification of Diseases for Oncology IX, code = 151, and classified by the criteria of Laurén[15]. One hundred and fourteen intestinal gastric cancer patients (76 men and 38 women; mean age and SD 59.4±9.9 years) were identified by endoscopic and pathological diagnosis in Yangzhong City Municipal Hospital from January 1997 to December 1998. To reduce misclassification of the histological types, two pathologists reviewed and confirmed all diagnosed cases. Controls were selected from case's siblings (150 male and 140 female) and non-blood relatives (403 spouses and the siblings-in-law, 160 male and 243 female) without digestive tract cancers. Both kinds of controls differed slightly in demographic features, and their results were combined to increase the sample size and decrease type I error. The study was approved by the regional ethics committees of Yangzhong. All participants were given an explanation of the study and informed consent was obtained. Study subjects completed a questionnaire administered by specially trained interviewers through a face-to-face interview. The questionnaire was designed to elicit detailed information on tobacco smoking habit, alcohol drinking habit, family history of cancer, and occupational exposures. Cigarette smokers were defined as subjects who reported smoking of at least one cigarette per day for 1 year or more, or whose accumulated tobacco cigarette consumption was over 18 packs per year. Former smokers were those who had stopped smoking for one or more years before the interview. Cumulative smoking exposure (pack years) was defined as one pack per day for 1 year equals 1 pack years.

CYP1A1 and GSTM1 genotypes

DNA extraction was performed using Puregene DNA isolation kits (Gentra Systems, Minneapolis, MN, USA). PCR-RFLP approach was used to detect the 7th *CYP1A1 Ile/Val* variant at position 4 889. PCR was used to amplify the transcription regulatory region of *CYP1A1* that includes the restriction enzyme recognition site for *Hin*cII. The two allele-specific primers are respectively F5'-TCCT ACCTG-AACGGTTTCTCACCC-3' (T_m = 63.0) and R5'-TTTTTT-TTTTTGAAAGACCTCCCAGG GGTCA-3' (T_m = 65.1) modified from those previously reported[16]. The homozygous null polymorphism of *GSTM1* was determined using a PCR approach as previously reported[16].

Statistical analysis

The relative associations between cases and controls were assessed by crude odds ratio (OR), interaction OR_{eg} and the corresponding 95%CI. Unconditional logistic regression analysis was performed to assess the association between the *CYP1A1 Ile/Val* and *GSTM1* null polymorphism and intestinal gastric cancer after adjusting for confounding factors. All models included as co-variables: gender, age (entered as a continuous variable), living areas (relative lower or higher incidence areas in Yangzhong), education level (years), former tobacco smoking, former alcohol drinking, BMI (weight [kg]/height [m^2]) and family history of cancer. Test of trend was calculated through logistic models based on semi-continuous and dummy variables. A common way to describe the interaction between the effect of an environmental agent and a genetic risk factor is to use a term called interaction index (γ), which is determined by coefficient (β) in a multiple logistic regression model. The coefficient of this interactive term was calculated according to the method of Taioli *et al*.[17]. If the types of interaction belong to multiplicative effects suggested by Khoury and Ottman[18-20], it included several types of interactions. Such as type 1 interaction which means that the disease risk is increased only in the presence of the genotype and the environmental exposure. Type 2 interaction: the disease risk is increased by the environmental exposure alone but not by the genotype alone. Type 3 interaction: the disease risk is increased by the genotype in the absence of the environmental exposure but not by the environment alone. Type 4 interaction means that the disease risk is increased by genotype or environmental exposure alone[18-20]. False positive report probability (FPRP) was used as an index for judging the noteworthy or not noteworthy results at the 0.5 FPRP level among significant GEI results[21]. All data analysis was performed with the SAS package Genmod (SAS Institute, Cary, NC, USA) for the personal computer.

RESULTS

CYP1A1, GSTM1 polymorphisms and risk of intestinal gastric cancer

Compared with controls, patients were significantly older (median age 59 years for cases and 53 years for controls) and with a BMI less than 20. Former tobacco smoking is significantly associated with the risk of intestinal gastric cancer (OR = 2.4, 95%CI: 1.0-5.8). A significant dose-response was observed in relation to increasing gastric cancer risk, especially in 20 pack-years or more smokers (Table 1). The frequencies of *CYP1A1 Ile/Val* and *Val/Val* genotypes in controls were 33.4% and 5.6%, respectively, which showed no significant difference from that in cases (32.1% and 5.4%, respectively). The homozygote null *GSTM1* genotype was observed in 63.4% of cases, which was significantly higher than that in controls (53.5%). The adjusted OR was 2.0 (95%CI: 1.2-3.1).

Interaction models of CYP1A1 and GSTM1 polymorphisms with former tobacco smoking

Among former tobacco smokers with *CYP1A1 Ile* or *GSTM1* present genotypes, the OR_{eg} of intestinal gastric

Table 1 Characteristics of the interviewed subjects

	Characteristics	Gastric cancer cases (114)	Control subjects (693)	OR (95%CI)
Median age	yr±SD	59±10	53±10	1.1 (1.0-1.1) [1]
	Min (yr)	35	30	
	Max (yr)	82	78	
Gender	Female (%)	38 (33)	383 (55)	1.0 (Ref.)
	Male (%)	76 (67)	310 (45)	1.2 (0.7-2.1)
	F/M ratio	1:2	1:0.8	
Educational level	>5 yr	44 (38.6)	246 (35.5)	1.0 (Ref.)
	¡Ü5 yr	70 (61.4)	447 (64.5)	1.0 (0.6-1.7)
Occupation				
	Manual	51 (44.7)	375 (54.1)	1.0 (Ref.)
	Office	9 (7.9)	87 (12.6)	0.6 (0.2-1.3)
	Retired	54 (47.4)	231 (33.3)	1.2 (0.7-1.9)
Marriage status				
	Married	100 (87.7)	649 (94.7)	1.0 (Ref.)
	Divorce or bereft spouse	14 (12.3)	36 (5.3)	1.4 (0.6-3.0)
Family history of cancer				
	No	84 (76.4)	613 (90.3)	1.0 (Ref.)
	Yes	26 (23.6)	66 (9.7)	3.9 (2.1-7.3) [1]
BMI (kg/m^2)				
	<20	56 (49.1)	95 (13.7)	1.0 (Ref.)
	20-	44 (38.6)	254 (36.7)	0.3 (0.2-0.5)[1]
	23-	14 (12.3)	344 (49.6)	0.1 (0.03-0.12)[1]
Tobacco smoking habits				
	Never	51 (44.7)	437 (63.0)	1.0 (Ref.)
	Current	36 (31.6)	225 (32.5)	0.6 (0.3-1.3)
	Former	27 (23.7)	31 (4.5)	2.4 (1.0-5.8)[1]
Amount of former smoking (pack years)				
	No	87 (76.4)	662 (95.6)	1.0 (Ref.)
	1-19	7 (6.1)	10 (1.4)	2.6 (0.8-8.6)
	20-29	8 (7.0)	11 (1.6)	3.1 (1.1-9.0)[1]
	¡Ý30	12 (10.5)	10 (1.4)	4.4 (1.7-11.9)[1]
Alcohol drinking habits				
	Never	78 (68.5)	505 (72.9)	1.0 (Ref.)
	Current	11 (9.6)	156 (22.5)	0.2 (0.1-0.5)[1]
	Former	25 (21.9)	32 (4.6)	2.3 (1.2-4.7)[1]
Plasma *H pylori* CagA antibody				
	Negative	136 (82.4)	107 (49.3)	1.0 (Ref.)
	Positive	29 (17.6)	110 (50.7)	0.2 (0.1-0.3)[1]
CYP1A1 genotype				
	Ile/Ile	70 (62.5)	412 (61.0)	1.0 (Ref.)
	Ile/Val	36 (32.1)	226 (33.4)	0.9 (0.5-1.4)
	Val/Val	6 (5.4)	38 (5.6)	0.7 (0.2-1.8)
GSTM1 genotype				
	Present	41 (36.6)	314 (46.5)	1.0 (Ref.)
	Null	71 (63.4)	361 (53.5)	2.0 (1.2-3.1) [1]

[1]Showed significant difference after adjusting co-variables.

cancer were 1.8 and 3.5, respectively. With both exposure to tobacco smoking and the *CYP1A1 Val* allele or *GSTM1* null genotype, the OR_{cg} of suffering intestinal gastric cancer increased sharply, 5.0 (95%CI: 1.9-13.4) and 8.4 (95%CI: 3.4-20.9), respectively. The γ were 2.8 and 3.4, respectively, which showed multiplicative effects of type 2 GEI model for *CYP1A1* and type 4 model for *GSTM1* (Table 2).

Assessment of the probability of a potential positive result

A high FPRP (e.g., >0.5) could be a consequence of any combination of a low prior probability, low statistical power, or a relatively high *P* value[21]. We calculated FPRP to assess the probability that a positive result might be false using the observed *P* value or CI for the observed ORs, and to determine whether to consider a significant finding to be noteworthy with the specific prior probability (Table 3). The results showed that the FPRP was less than 0.5 for *GSTM1* null and former smokers, which indicated the most noteworthy finding in the present study even with a prior probability between 0.0001 and 0.00001.

DISCUSSION

A large number of molecular epidemiological studies completed in the past decade have identified the relative etiologic roles of the *CYP1A1 Val* variant allele and *GSTM1* null genotype for cancer risk (including gastric cancer), although some results indicate no overall associations, only specific relationships were found in subgroups, such as in smokers, *H pylori*-infected patients or low consumption of

Table 2 Interaction models of *CYP1A1* and *GSTM1* polymorphism with former smoker in intestinal gastric cancer

Genotype	Former smoker	Cases	Controls	OR_{eg}	95%CI
Ile[1]	No	57	391	1.0	Ref.
Val[2]	No	29	254	0.7	0.4-1.1
Ile	Yes	13	21	1.8	0.7-4.3
Val	Yes	13	10	5.0[5]	1.9-13.4
Present[3]	No	31	302	1.0	Ref.
Null[4]	No	54	345	1.9	1.1-3.1
Present	Yes	10	12	3.5	1.2-10.1
Null	Yes	17	16	8.4[6]	3.4-20.9

[1][*Ile*]: *CYP1A1* homozygous (*Ile*/*Ile*) genotype; [2][*Val*]: *CYP1A1* heterozygous (*Ile*/*Val*)+homozygous (*Val*/*Val*) genotypes; [3][present]: present genotype for *GSTM1*; [4][null]: null genotype for *GSTM1*; [5]adjusted by age, gender, living areas, family history of cancer, and former alcohol drinking; $\chi^2_{trend} = 24.0$, df = 1, $P = 0.00$; $\gamma = 1.61/0.57 = 2.8$; [6]adjusted by age, gender, living areas, family history of cancer, and former alcohol drinking; $\chi^2_{trend} = 45.7$, df = 1, $P = 0.00$; $\gamma = 2.13/0.63 = 3.4$.

Table 3 FPRP values for interactions between GSTM1 and former tobacco smoking in intestinal gastric cancer

GSTM1	Former	Observed	Assuming	Prior probability					
genotype	Smoking	OR	OR	0.25	0.1	0.01	0.001	0.0001	0.00001
GSTM1 null	No	1.9	1.2	0.481[1]	0.736[2]	0.968	0.997	1.000	1.000
			1.5	0.151	0.348	0.854	0.983	0.998	1.000
			2.0	0.050	0.136	0.634	0.946	0.994	0.999
GSTM1 present	Yes	3.5	2.4	0.202	0.432	0.893	0.988	0.999	1.000
			3.0	0.137	0.322	0.840	0.981	0.998	1.000
			4.0	0.093	0.236	0.773	0.972	0.997	1.000
GSTM1 null	Yes	8.4	4.8	0.000	0.000	0.004	0.040	0.293	0.805
			6.0	0.000	0.000	0.002	0.020	0.168	0.669
			8.4	0.000	0.000	0.001	0.009	0.087	0.487

[1]Bold with gray fill color indicate "noteworthy at the 0.5 FPRP level"; [2]with no fill color indicate "not noteworthy at the 0.5 FPRP level".

fruit[6-10]. Other studies have reported contrary findings[11-14]. These inconsistent results might be contributed to ethnically diverse populations involved in studies, different histological subtypes of cases used, and different co-variables categorized the sub-population. Until now, only a few studies discussed interactions between tobacco smoking and the polymorphisms in the occurrence of gastric cancer[6,11,14]. In the present study, we observed some evidence of a relationship between *GSTM1* null genotype and a risk of gastric cancer. Both the *CYP1A1 Val* variant allele and *GSTM1* null polymorphism have statistically significant interactions with former tobacco smoking. The GEI model of *CYP1A1* with smoking belongs to type 2, and *GSTM1* with smoking belongs to type 4 as Khoury and Ottman described. Present study as most molecular epidemiology studies based on multiple comparison corrective procedures is relied on the standard *P* value criterion of 0.05 to define statistical significance without consideration of power or prior probability, which may create a lot of false positives[21]. We further calculated FPRP as one of indices to decide about whether a positive finding in association study can be called "a noteworthy finding" or "deserve of more attention". We confirmed that the interaction between *GSTM1* null and former smokers was the most noteworthy positive finding in the present study even with a prior probability less than 0.0001. The interaction between *CYP1A1 Val* variant allele and former smokers was also a possible noteworthy positive finding with a prior probability less than 0.01 (data not shown). These results suggest that the risk of intestinal gastric cancer was greatly dependent upon both tobacco smoking exposures and susceptibility genes. Only complete smoking cessation may decrease susceptibility to gastric cancer in persons carrying the *CYP1A1 Val* variant allele or *GSTM1* null genotype. The different types of GEI models indicated that the interactions between genes and environmental factors are neither simply gene specific, nor exposure specific, and must be related to the mechanism of action of the gene product and features of exposure leading to gastric cancer.

Although the mechanism for tobacco-related gastric cancer risk is not well understood, tobacco-specific nitrosamines and other nitroso-compounds, plus other carcinogens contained in tobacco and tobacco smoke, are swallowed and may thus be involved in the process of gastric carcinogenesis[22,23]. Among gastric cancer cases, smoking-related DNA-adduct levels were higher in smokers than in non-smokers[24], and a study in China found smoking to be a risk factor for intestinal metaplasia and gastric dysplasia arising from chronic atrophic gastritis[25]. The biological mechanisms responsible for different interaction models observed in our study were not known, but it was possible to speculate that these interaction effects might be a reflection for individuals with and without environmental susceptible genotypes. This analytical approach may be used to determine higher risk individuals and take further preventive measures to decrease cancer risks in these susceptible individuals.

One limit of the study is the small number of subjects in some cells when GEI models were analyzed. The models resulting from the present study might be affected by chance, and need to be identified by more large-scale molecular epidemiological studies. Another potential limit was the

selection of controls, which include case's siblings. This kind of selection might create over-matching because siblings were more likely to have the same genotypes as cases than non-related controls, therefore leading to some loss of statistical efficiency, i.e. larger sample sizes required to attain the same statistical precision[26]. But others consider that the use of sibling controls generally improves efficiency for GEI evaluations[27,28].

In conclusion, our studies identified two kinds of GEI models between the *CYP1A1 Val* variant allele, *GSTM1* null genotype and tobacco smoking. Although the proposed carcinogen metabolism pathway seems a plausible explanation of our findings, further large studies are required to replicate these observations.

ACKNOWLEDGMENTS

We thank Zhaoxi Wang for his excellent technical assistance; thank Professor Regina M Santella for editing the manuscript. We also thank all the doctors for their kind help in collecting the biological samples and epidemiological data. We thank all participants in our study for their cooperation.

REFERENCES

1 **Parkin DM**. The global burden of cancer. *Seminars Cancer Biol* 1998; **8**: 219-235
2 **Stadtlander CT**, Waterbor JW. Molecular epidemiology, pathology and prevention of gastric cancer. *Carcinogenesis* 1999; **20**: 2195-2207
3 **Setiawan VW**, Zhang ZF, Yu GP, Lu QY, Li YL, Lu ML, Wang MR, Guo CH, Yu SZ, Kurtz RC, Hsieh CC. GSTP1 polymorphisms and gastric cancer in a high-risk Chinese population. *Cancer Causes Control* 2001; **12**: 673-681
4 **Zhang ZF**, Kurtz RC, Klimstra DS, Yu GP, Sun M, Harlap S, Marshall JR. *Helicobacter pylori* infection on the risk of stomach cancer and chronic atrophic gastritis. *Cancer Detect Prev* 1999; **23**: 357-367
5 **Nebert DW**, Ingelman-Sundberg M, Daly AK. Genetic epidemiology of environmental toxicity and cancer susceptibility: human allelic polymorphisms in drug-metabolizing enzyme genes, their functional importance, and nomenclature issues. *Drug Metab Rev* 1999; **31**: 467-487
6 **Tamer L**, Ates NA, Ates C, Ercan B, Elipek T, Yildirim H, Camdeviren H, Atik U, Aydin S. Glutathione S-transferase M1, T1 and P1 genetic polymorphisms, cigarette smoking and gastric cancer risk. *Cell Biochem Funct* 2005; 23: 267-272
7 **Gonzalez CA**, Sala N, Capella G. Genetic susceptibility and gastric cancer risk. *Int J Cancer* 2002; **100**: 249-260
8 **Parl FF**. Glutathione S-transferase genotypes and cancer risk. *Cancer Lett* 2005; **221**: 123-129
9 **Agundez JA**. Cytochrome P450 gene polymorphism and cancer. *Curr Drug Metab* 2004; **5**: 211-224
10 **Ng EK**, Sung JJ, Ling TK, Ip SM, Lau JY, Chan AC, Liew CT, Chung SC. *Helicobacter pylori* and the null genotype of glutathione-S-transferase-mu in patients with gastric adenocarcinoma. *Cancer* 1998; **82**: 268-273
11 **Deakin M**, Elder J, Hendrickse C. Glutathione S-transferase GSTT1 genotypes and susceptibility to cancer: studies of interactions with GSTM1 in lung, oral, gastric and colorectal cancers. *Carcinogenesis* 1996; **17**: 881-884
12 **Suzuki S**, Muroishi Y, Nakanishi I, Oda Y. Relationship between genetic polymorphisms of drug-metabolizing enzymes (CYP1A1, CYP2E1, GSTM1, and NAT2), drinking habits, histological subtypes, and p53 gene point mutations in Japanese patients with gastric cancer. *J Gastroenterol* 2004; **39**: 220-230
13 **Wu MS**, Chen CJ, Lin MT, Wang HP, Shun CT, Sheu JC, Lin JT. Genetic polymorphisms of cytochrome p450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. *Int J Colorectal Dis* 2002; **17**: 338-343
14 **Setiawan VW**, Zhang ZF, Yu GP, Li YL, Lu ML, Tsai CJ, Cordova D, Wang MR, Guo CH, Yu SZ, Kurtz RC. GSTT1 and GSTM1 null genotypes and the risk of gastric cancer: a case-control study in a Chinese population. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 73-80
15 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histoclinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49
16 **Morita S**, Yano M, Shiozaki H, Tsujinaka T, Ebisui C, Morimoto T, Kishibuti M, Fujita J, Ogawa A, Taniguchi M, Inoue M, Tamura S, Yamazaki S, Kikkawa N, Mizunoya S, Monden M. CYP1A1, CYP2E1 and GSTM1 polymorphisms are not associated with susceptibility to squamous-cell carcinoma of the esophagus. *Int J Cancer* 1997; **71**: 192-195
17 **Taioli E**, Zocchetti C, Garte S. Models of interaction between metabolic genes and environmental exposure in cancer susceptibility. *Environ Health Perspect* 1998; **106**: 67-70
18 **Khoury MJ**, James LM. Population and familial relative risks of disease associated with environmental factors in the presence of gene-environment interaction. *Am J Epidemiol* 1993; **137**: 1241-1250
19 **Khoury MJ**, Wagener DK. Epidemiological evalution of the use of genetics to improve the predictive value of disease risk factors. *Am J Hum Genet* 1995; **56**: 835-844
20 **Ottman R**. An epidemiologic approach to gene-environment interaction. *Genet Epidemiol* 1990; **7**: 177-185
21 **Wacholder S**, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004; **96**: 434-442
22 **Hecht SS**, Hoffmann D. The relevance of tobacco-specific nitrosamines to human cancer. *Cancer Surv* 1989; **8**: 273-294
23 **Hecht SS**. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 1999; **91**: 1194-1210
24 **Dyke GW**, Craven JL, Hall R, Garner RC. Smoking-related DNA adducts in human gastric cancers. *Int J Cancer* 1992; **52**: 847-850
25 **Kneller RW**, You WC, Chang YS, Liu WD, Zhang L, Xu GW, Fraumeni JF, Blot WJ. Cigarette smoking and other risk factors for progression of precancerous stomach lesion. *J Natl Cancer Inst* 1992; **84**: 1261-1266
26 **Thomas DC**, Witte JS. Point: population stratification: a problem for case-control studies of candidate-gene associations? *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 505-512
27 **Gauderman W**, Witte J, Thomas D. Family-based association studies. *Monogr Natl Cancer Inst* 1999; **26**: 31-37
28 **Witte JS**, Gauderman WJ, Thomas DC. Asymptotic bias and efficiency in case-control studies of candidate genes and gene-environment interactions: basic family designs. *Am J Epidemiol* 1999; **148**: 693-705

Science Editor Guo SY **Language Editor** Elsevier HK