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Risk factors for esophageal and gastric cancers in Shanxi Province, China: A case-control study

Ying GAO¹, Nan HU¹, Xiao You HAN², Ti DING², Carol GIFFEN³, Alisa M GOLDSTEIN¹, and Philip R TAYLOR¹

¹Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20852, USA,

²Shanxi Cancer Hospital, Taiyuan, Shanxi 030013, PRC

³Information Management Services, Inc., Silver Spring, MD 20904, USA

Abstract

Objective—Smoking and alcohol consumption explain little of the risk for upper-gastrointestinal (UGI) cancer in China, where over half of all cases in the world occur.

Methods—We evaluated questionnaire-based risk factors for UGI cancers in a case-control study from Shanxi Province, China, including 600 esophageal squamous cell carcinomas (ESCC), 599 gastric cardia adenocarcinomas (GCA), 316 gastric noncardia adenocarcinomas (GNCA), and 1514 age- and gender-matched controls.

Results—Ever smoking and ever use of any alcohol were not associated with risk of UGI cancer; only modest associations were observed between ESCC risk and highest cumulative smoking exposure, as well as GNCA risk and beer drinking. While several associations were noted for socioeconomic and some dietary variables with one or two UGI cancers, the strongest and most consistent relations for all three individual UGI cancers were observed for consumption of scalding hot foods (risk increased 150% to 219% for daily vs never users) and fresh vegetables and fruits (risk decreased 48% to 70% for vegetables and 46% to 68% for fruits, respectively, for high vs low quartiles).

Conclusion—This study confirms the minor role of tobacco and alcohol in UGI cancers in this region, and highlights thermal damage as a leading etiologic factor.

Correspondence to: Dr. Ying Gao, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, 6120 Executive Blvd., EPS 7110, Bethesda, MD 20892-7236, USA. gaoying@mail.nih.gov.

Coauthors' email address:

Nan Hu, nhu@mail.nih.gov

XiaoYou Han, han_xiaoyou@yahoo.com.cn

Carol Giffen, giffenc@imsweb.com

Ti Ding, dingti@yahoo.com

Alisa M. Goldstein, goldstea@mail.nih.gov

Philip R. Taylor, ptaylor@mail.nih.gov

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Keywords

smoking; alcohol; socioeconomic status; diet

Introduction

Upper gastrointestinal (UGI) cancers, including esophageal and gastric cancer, are among the most common causes of cancer death in the world, with an estimated 562 000 esophageal and 883 000 gastric cancer deaths annually[1]. Shanxi Province in north central China has among the highest esophageal cancer rates in the world [2]. However, to date, no single dominant environmental risk factor has been identified for esophageal or gastric cancer in this region.

Tobacco smoking is consistently reported as an important risk factor of esophageal cancer [3; 4; 5; 6; 7], especially for squamous cell carcinoma, and gastric cancer [4; 8; 9] in the West, but appears to incur little or no effect for these cancers in Asian countries [9; 10; 11; 12]. Our group previously reported that tobacco smoking was only a modest risk factor for esophageal cancer, and did not increase risk for gastric cardia adenocarcinoma (GCA) or gastric noncardia adenocarcinoma (GNCA) in Linxian, Henan Province[9], which is geographically adjacent to Shanxi Province.

Similar to smoking, alcohol consumption is considered a dominant risk factor for esophageal squamous cell carcinoma (ESCC) in the West [13; 14; 15], but has not been associated with risk in Linxian or Shanxi Province [9; 16].

Among different lifestyle factors, dietary factors may play an important role in the carcinogenesis of esophageal cancer. Some specific dietary elements, like pickled vegetable juice and moldy food, have been reported to be associated with esophageal cancer risk in north China [9; 16]. Nutrition-related deficiencies in vitamins, minerals, and other micronutrients have also been linked to the elevated risk of esophageal and gastric cancer in these areas [17; 18].

To explore the role of these risk factors in esophageal cancer in detail, we conducted a large case-control study in Shanxi Province. Because cancers of the esophagus and stomach are anatomically adjacent, may share common etiologies, and occur at very high rates in this region of north central China, we also evaluated risk factors for gastric cancer, including GCA and GNCA.

Materials and Methods

Study population

This study was based on a case-control study of upper gastrointestinal (UGI) tract cancers conducted in Shanxi Province, China[19; 20]. Briefly, the recruiting criteria for cases include: 1. Males or females over 20 years old; 2. Residents from Taiyuan, Linfen, Jinzhong, Changzhi, and Xinzhou; 3. Recently diagnosed for cancer of the esophagus or stomach without previous treatment; 4. Had surgical treatment for tumor at the Shanxi Cancer Hospital; 5. Diagnoses were histologically confirmed by pathologists at the Shanxi Cancer Hospital and the National Cancer Institute in the United States. Esophageal cancer cases were limited to esophageal squamous cell carcinoma (ESCC), which is the dominant type in Shanxi Province. Gastric adenocarcinoma (GCA) included gastric cancers located in the top three centimeters of the stomach, while gastric noncardia adenocarcinomas (GNCA) were gastric cancers located in the remainder of the stomach. One control was recruited for each

case matched on age (± 5 years), gender, and neighborhood of residence. Interviews for controls were completed within six months of matched cases. To identify potential controls, each case was asked to identify a neighbor of approximately the same age and gender. When the initial suggested neighbor could not be enrolled (ie, unavailable, ineligible, or refused), that neighbor, other neighbors, or the village doctor were asked to suggest another neighbor of the same age and gender. Potential controls were asked if they had any cancer or UGI disease, and were considered ineligible if they reported affirmatively to either question. Ninety-five percent of available and eligible controls (ie, the ones actually invited) were enrolled. The primary reason for non-enrollment among available/eligible controls was refusal to give a blood sample.

All subjects signed informed consents and all study interviews were conducted by trained study nurses using a standardized, interviewer-administered questionnaire. Cases were interviewed in the hospital at the time of their admission for the diagnosis and treatment of their cancer (but before their surgery), while controls were interviewed in their homes within six months of the diagnosis of their matched control. Interviews obtained information on demographics and lifestyle during the most of the lives before they became ill for cases and before their interview for controls. Questionnaire-based information on tobacco smoking (cigarettes per day, tobacco amount [grams] per month for pipe smoking, age started and quit smoking); frequency (ie, daily, weekly, monthly, seldom, not at all) of alcohol use (ie, beer, wine, and liquor use separately); socioeconomic status (SES) (occupation for most of life, education, household size, household income, and refrigerator usage); and frequency (ie, daily, weekly, monthly, seldom, not at all) of dietary intake before illness (scalding hot food, moldy food, vinegar, pickled vegetable or pickled vegetable juice, pork, beef, lamb, fish, chicken, eggs, 16 kinds of vegetables, and 12 kinds of fruits) were collected. To capture the impact of the Chinese economic reformation in the late 1970s on food and drink consumption, we asked about frequency of alcohol and dietary intake before and after 1984. For beer, consumption frequency in summer and winter was also asked.

This study was approved by the institutional review boards of the Shanxi Cancer Hospital in Taiyuan, Shanxi Province, China, and the National Cancer Institute in Bethesda, Maryland, USA.

Statistical analysis

Odds ratios (*OR*) and 95% confidence intervals (*CI*) were calculated from unconditional logistic regression models adjusted for the three matching factors, including age (continuous), gender, and geographic region (as a proxy of neighborhood). To increase power, all 1514 controls were analyzed together.

As very few women ever smoked (10%) either cigarettes or a pipe, analysis of smoking was restricted to males. Since only 3% of controls were exclusively pipe smokers, we combined these tobacco exposures in most of our analysis; intensity of pipe smoking (grams/month) was expressed as cigarettes/day equivalents (1g tobacco = 1 cigarette), and cumulative lifetime tobacco exposure (pack-year equivalents) was calculated as the product of intensity (packs/day) and duration (years). Intake frequencies of meat and legumes were combined when the number of subjects in frequency categories was small. Consumptions of red meat, chicken, fish, eggs, and soy products were adjusted for each other to control for the effect of substitution; similarly, consumptions of corn, millet, wheat, rice, and sorghum were adjusted for each other. The frequencies of total vegetable and total fruit consumption were calculated as the sum of the number of times per year each food item was eaten. As very few women reported ever drinking any alcohol (8.6%), analysis of alcohol consumption was restricted to males.

For exposure variables that showed significant relations with cancer in analyses controlled for matching factors only, we further assessed their independence in analyses adjusted for additional potential confounders (ie, occupation, education, household size, household income, refrigerator usage, ever smoking, and ever alcohol drinking). Since results of these additional analyses did not alter the magnitude or significance of the basic findings, we only report results adjusted for matching factors here. All *P* values were two-sided and a *P* value < 0.05 was considered statistically significant. We used SAS 9.1 for all statistical analyses.

Results

A total of 600 ESCC, 599 GCA, and 316 GNCA cases and their 1514 matched controls were included in the current analyses. Among ESCC cancers, 7% were anatomically located in the upper third of the esophagus, 70% in the middle, and 23% in the lower third. Gender, age, and geographic region distribution of study subjects are shown in Table 1. Overall, nearly three-quarters of cases were males and the median age of all cases was 59 years.

Tobacco (cigarettes and pipe) smoking among males

Among the 85% of male controls who ever smoked tobacco, 19% smoked both cigarettes and pipes, 3% smoked pipes only, and 63% smoked cigarettes only (Table 2). Ever tobacco smoking (vs. never) was not associated with risk of any of the three UGI cancers studied here. Based on small numbers (9% of controls and 5% of cases), current pipe smoking was associated with decreased risk of all three UGI cancers. Neither former nor current cigarette smoking status was associated with UGI cancer risk. Compared with never smokers, higher quartiles of cumulative lifetime exposure (pack-year equivalents) were associated with a monotonically increased risk for ESCC (*P* for trend=0.009), and men with over 40 pack-year smoking exposure had a 1.5-fold increased risk (*OR*=1.51, 95% *CI* = 1.01-2.24).

Alcohol consumption among males

Among male controls, about 66% reported ever use of any alcohol, including 43% ever consumption of beer, 23% ever consumption of wine, and 63% ever consumption of liquor (Table 3). Beer was consumed more frequently in summer than winter, while both beer and liquor were consumed by more people after 1984 than before. Ever consumption of any alcohol (versus never) was not associated with risk at any UGI cancer site. Persons who reported ever consuming beer (vs. never) had higher risk for GNCA (*OR*=1.53, 95% *CI* = 1.14-2.05); this association was consistent for consumption in both summer and winter, and both before 1984 and after. Wine usage did not show any association with the risk of UGI cancer. Ever use of liquor was unassociated with risk of UGI cancer, but analysis of risk by frequency showed that weekly usage of liquor was associated with increased risk of GCA, for use both before 1984 (*OR*=2.39, 95% *CI*=1.30-4.40) and after 1984 (*OR*=1.64, 95% *CI*=1.02-2.65). However, this one usage group with elevated risks was based on small numbers (2% of controls versus 4% of GCAs before 1984; 5% of controls versus 7% of GCAs after 1984), and no dose-response for increasing frequency was observed overall.

Socioeconomic status

Compared to farmers, office workers had 50% and 130% increased risks for GCA and GNCA, respectively (Table 4). Persons with the highest level of education (more than 10 years) showed increased risk at all three cancer sites, reaching significant levels for GCA (*OR*=1.98, 95% *CI*=1.49-2.64) and GNCA (*OR*= 1.50, 95% *CI*=1.05-2.13). Larger household size (more than 4 family members) also appeared to increase risk for ESCC (*OR*=1.29, 95% *CI*=1.06-1.58) and GCA (*OR*=1.31, 95% *CI*=1.07-1.59). Longer refrigerator ownership was associated with decreased risk for ESCC (*OR*=0.62, 95% *CI* =0.46-0.84 for ≤ 8 years ownership versus none).

Dietary factors

Intake frequencies of primary staple foods (not mutually exclusive) and meat and legumes were evaluated for the time periods both prior to and after 1984 (Table 5A). The primary staple cereal foods in controls shifted from corn (86% reported corn as a primary staple food) and sorghum (44%) before 1984, to wheat (98%) and rice (37%) after 1984. Corn as a primary staple food before 1984 was associated with lower GNCA risk ($OR=0.68$, 95% $CI=0.42-0.86$); while rice as a primary staple after 1984 was associated with decreased GCA risk ($OR=0.78$, 95% $CI=0.63-0.98$). Further adjustment for SES, smoking, and alcohol drinking did not alter these findings (data not shown).

Intake of meat and legumes was rare before 1984: among controls, the median frequency of red meat consumption per year was 3; the median category of frequency of chicken, fish, eggs, and beans/soy consumption was “seldom”. After 1984, consumption of red meat increased dramatically (median frequency of 54 times per year), as did eggs (median category of frequency “daily”) and beans/soy (median category of frequency “weekly”). However, the median category of consumption remained unchanged for chicken and fish (“seldom”) (data not shown). Intake frequencies of these food items before 1984 were not associated with UGI cancer risk (Table 5A). After 1984, frequent intake of red meat (pork, beef, and lamb) was associated with increased risk of all three cancers. The most frequent eaters of fish (daily) had a 50% lower risk of ESCC, while persons who ate beans or soy most often (daily) had a 37% decreased risk of GNCA.

Consumption of fresh vegetables (median among controls, 1000 times/year) was more frequent than fruit (median among controls, 65 times/year) in our study population (Table 5B). Compared with the lowest intake quartiles, higher intakes of fresh vegetables and fruits were associated with monotonically decreased risk for all three cancers. Adjustment for potential confounders did not alter the findings. In contrast, persons who reported ever using milk or dairy products had 56% to 108% higher risk for UGI cancers than never users.

Table 5C shows the intake frequencies of specific dietary factors in Shanxi Province. Intake of scalding hot food was associated with a monotonically increased risk for all three cancers. Daily consumption of scalding hot food was reported by 25% of controls and was a particularly strong risk factor for ESCC ($OR=2.74$, 95% $CI=2.06-3.65$), GCA ($OR=2.50$, 95% $CI=1.88-3.32$), and GCNA ($OR=3.19$, 95% $CI=2.10-4.84$). Moldy food intake was also associated with a greater than 50% increased risk for all three cancers. Consumptions of salted meat and pickled vegetables and pickled vegetable juice were associated with 20% to 40% increased risks for GCA and GNCA. Vinegar and seasoning use were both associated with monotonically decreased risks for all three cancers.

Discussion

We evaluated lifestyle factors and risk of three UGI cancers in this relatively large case-control study (significant risk factors are summarized in Table 6). Tobacco smoking and alcohol drinking conferred little or no increased risk for these UGI cancers, while several SES and dietary factors showed significant associations for one or more of the UGI cancers. The strongest and most consistent risk factors across all three UGI cancer sites were the increased risk in persons who consumed scalding hot foods and the decreased risk observed in those who ate vegetables and fruits most frequently.

Smoking is a dominant risk factor for ESCC in the West [3; 13; 21; 22; 23], and some parts of Asia [24; 25]. However, smoking exposures confer little risk for ESCC in the areas of the world where this disease occurs in epidemic proportions with rates in excess of 100 per 100,000 (ie, the Taihang mountain region of north central China which includes Shanxi and

Linxian; northern Iran around the Caspian Littoral) [9; 16; 26]. Analytic epidemiologic studies from the West show that tobacco smoking is associated with a 3- to 7-fold increased risk of ESCC in current smokers [27]; in contrast, increased ESCC risk from smoking is minimal in north central China and Iran, with ORs of only ~1.5 [27]. In these high-risk areas, women have rates that are as high as men (ie, northern Iran) [28] or nearly as high as men (Taihang mountain region of China) [29], despite the fact that the women are virtually all non-smokers.

Consistent with previous studies of ESCC in high-risk regions [27], we found only limited evidence of an association between tobacco and risk, with a 50% elevated risk among men in the highest quartile of cumulative lifetime tobacco exposure. Further adjustment for potential confounders did not alter our findings. The most likely explanation for these results is that people in the high-risk region of Shanxi are exposed to carcinogens similar to those found in tobacco (ie, polycyclic aromatic hydrocarbons [PAHs], nitrosamines) through alternative environmental exposures, such as general outdoor air pollution or indoor air pollution resulting from cooking or heating practices, and that the effect of these alternative environmental exposures overwhelms any effect of tobacco.

Alcohol consumption is also a dominant risk factor for ESCC in the West where studies consistently show a 3 to 5-fold increased risk [13; 27]. Similar to tobacco, however, previous studies of alcohol in Linxian and Shanxi have also shown little or no association with risk for UGI cancers [9; 16; 30]. In the present study we found no association with ever use of alcohol for any UGI cancer site; our only notable finding was for beer consumption, where GNCA risk was consistently elevated by about 50% regardless of season or year of consumption. Confounding did not explain these findings either, as further adjustment for multiple covariates did not change these results. The apparent discrepancy for the role of alcohol in UGI cancers between the West and high-risk areas of the world may be due to the consumption rate, which is high in the West [31] but relatively low in rural areas of Asia as well as other high-risk areas that have religious proscription of alcohol, such as Iran. It is also possible that acetaldehyde, the putative carcinogen formed by the metabolism of alcohol, is still responsible for elevated risk in high-risk populations as a result of alternative non-alcoholic sources of exposure (eg, yogurt).

Previous studies have shown that workers with occupational exposure to toxic substances have higher risk of UGI cancers when compared to office workers [32; 33]. Similarly, lower education has also been associated with increased risk for these cancers [9; 34]. In the present study, however, we found the opposite: both office workers and persons with higher education were at increased risk of UGI cancer. Although these characteristics are correlated, mutual adjustment for both factors (as well as other potential confounders) showed that they were independent risk factors. The reason our results differ from earlier reports is not clear and may be due to unknown or unmeasured confounding factors (eg, physical activity [35]), or the role of chance; another possibility is that our use of neighborhood controls may have resulted in over matching for certain factors (such as SES) and reduced our ability to observe differences for these factors. Larger family sizes have been associated with increased esophageal and gastric cancer risk in several previous studies [36; 37; 38]. We also observed increased UGI cancer risk among individuals with larger families, which may potentially be due to an infectious etiology enhanced by a crowded environment [39]. Studies have suggested that *Helicobacter pylori* (Hp), Epstein-Barr virus, human papilloma virus, and some fungi may be related to UGI cancers [40; 41; 42]; however, at this time only Hp is an established human carcinogen for gastric cancer [40]. Unfortunately, we do not have specific information on infections in the subjects in the current study.

China experienced an economic reformation from the late 1970s to the early 1980s, which resulted in dramatic economic development. The impact of this reformation was relatively rapid, over a matter of a few years, and improved dietary intake was one important benefit of this development. As a result, we observed major shifts in the primary staple foods from corn and sorghum before 1984 to wheat and rice after; moreover, the frequencies of meat and legumes also increased greatly after 1984. Though hard, scratchy, and starchy staple foods, like maize and sorghum, have reportedly been associated with increased esophageal cancer risk due to the physical irritation and/or nutritional deficiencies [43; 44; 45], we found an association opposite: corn as primary staple food before 1984 was associated with decreased GNCA risk. In addition, persons who reported rice as a primary staple after 1984 had lower risk of GCA. Neither of these results related to primary staple grains was significant or consistent across all three cancer sites, suggesting that further study is needed to sort out these interesting but inconsistent findings.

Parallel to the shift in staple foods, consumption of animal protein was considerably improved after 1984. Numerous studies have reported positive associations between red meat intake and UGI cancers [46; 47; 48], and we also observed consistently elevated risk for all three UGI cancers among red meat consumers after 1984, including after adjustment for SES, smoking, alcohol, and other potential confounding factors. The most frequently suggested mechanistic explanation for this association is that carcinogenic compounds were generated from high temperature cooking (eg, N-nitroso compounds, heterocyclic amines, and PAHs), as well as free radicals from heme iron [49]. Before 1984, the intake of meat was as low as that observed in Linxian during the same time period [9], and no associations with risk of UGI cancer were observed there either.

Though not consistent, some studies have reported positive associations between intake of dairy products and gastric cancer risk [50; 51]. Intake of milk or dairy products was associated with increased risk of all three UGI cancers studied here. Adjustment for other covariates did not diminish these effects. Possible explanation for these associations may relate to inflammation due to lactose intolerance, or carcinogen contamination of the milk products [52].

Fresh vegetable and fruit consumption are well-established protective factors for UGI cancer [53]. As expected, cancer risk decreased monotonically with increased intake of fruits and vegetables across all three of the UGI cancer sites studied here. Modulation of xenobiotic-metabolizing genes and anti-oxidation from the vitamins and phytochemicals in fruits and vegetables are often cited as potential mechanisms [54].

Consumption of hot foods and beverages has consistently been associated with increased risk for esophageal cancer (reviewed by Islami et al) [55]. We observed markedly increased risk for all three UGI cancers studied here, which adds evidence to the thermal damage etiologic hypothesis. Importantly, daily consumption of scalding hot food was reported by 25% of this population, thus making this practice a target for risk reduction by education and behavior modification.

Other special foods and food practices, like consumption of moldy food, salted meat, pickled vegetables, and pickled vegetable juice, have also been associated with elevated risk for UGI cancers in previous reports [30; 56; 57; 58; 59]. We observed similar positive associations between consumption of these foods and risk for UGI cancers. Contamination by N-nitroso compounds and mycotoxins are the most frequently proposed link between these food items and increased risk of UGI cancers [60]. In contrast, we observed protective effects in persons who most frequently consumed vinegar and seasonings typical of Chinese cuisine (eg, black pepper, spicy pepper, garlic, ginger, cinnamon); these findings are

consistent with previous reports [45; 58; 61; 62; 63]. The active phytochemicals in these foods may underline their presumptive cancer preventive action.

There are several notable advantages to our study: we had a relatively large sample size with exclusively histologically-confirmed cancer cases, participation rates for both cases and controls were very high, and we employed neighborhood-matched controls. These advantages allowed us to obtain unbiased estimates of modest effects not captured by small studies. The detailed frequency and duration information on cigarettes and pipe smoking allowed us to estimate cumulative lifetime smoking exposure. The dietary patterns captured for both before and after 1984 provided better estimates for the effects of these factors. Our study collected information on specific dietary elements consumed in Shanxi, which provided an opportunity to evaluate important lifestyle factors specific to this population. In addition, we were able to simultaneously evaluate relations with cancers at three adjacent but anatomically different sites using identical study methods.

Some limitations to our study are also evident: susceptibility to recall bias is inherent in the case-control approach; the use of neighborhood controls may have resulted in over matching for selected risk factors; we did not collect information on all known potential confounders (eg, physical activity); our dietary questionnaire was not validated, and information was not collected on portion size or cooking practices, which may have resulted in residual confounding; and we recruited only cases who had surgery as their initial and primary therapy, so our results may not be generalizable to all UGI cancer cases.

Conclusions

This large case-control study of UGI cancers corroborated prior results that showed that tobacco and alcohol have only minor roles in these cancers in north central China, where rates of esophageal and gastric cancer are among the highest in the world. The study also confirmed the protective role for vegetable and fruit consumption, and highlighted the importance of thermal damage as a strong risk factor for UGI cancer.

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Table 1

Demographic characteristics of subjects

		ESCC	GCA	GNCA
		Controls	Cases	Cases
Age *		N = 1514	N = 600	N = 316
	All	59(52-65)	58(51-64)	57.5(50-63)
	Male	60(53-65)	59 (52-64)	58(51-63)
	Female	57(50-63)	57(50.5-63)	54(44-63)
Gender	Male (%)	1107(73)	376(63)	239(76)
	Female (%)	407(27)	224(37)	77(24)
Geographic regions				
	Taiyuan (%)	524(35)	212(35)	113(36)
	Linfen (%)	266(18)	94(16)	54(17)
	Jinzhong (%)	294(19)	153(26)	37(12)
	Changzhi (%)	274(18)	90(15)	63(20)
	Xinzhou (%)	156(10)	51(8)	49(15)

* Median (inter quartile range)
ESCC: esophageal squamous cell carcinoma
GCA: gastric cardia adenocarcinoma
GNCA: gastric noncardia adenocarcinoma

Table 2
Tobacco (cigarette + pipe) smoking and risk for upper gastrointestinal cancer (males only) (cigarette equivalents)

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Ever tobacco							
Never	169(15)	48(13)	1	93(19)	1	32(13)	1
Ever	938(85)	328(87)	1.19(0.84-1.69)	399(81)	0.80(0.60-1.06)	207(87)	1.12(0.74-1.69)
Ever tobacco							
Never	169(15)	48(13)	1	93(19)	1	32(13)	1
Cigarettes only	696(63)	249(66)	1.22(0.85-1.73)	303(62)	0.83(0.62-1.10)	162(68)	1.18(0.78-1.80)
Pipes only	37(3)	5(1)	0.53(0.19-1.47)	13(3)	0.60(0.30-1.23)	5(2)	0.57(0.20-1.62)
Cigarettes and pipes	205(19)	74(20)	1.22(0.80-1.86)	83(17)	0.74(0.52-1.08)	40(17)	1.004(0.60-1.68)
Tobacco smoking status							
Never	169(16)	48(13)	1	93(22)	1	32(15)	1
Former ^a	165(15)	64(17)	1.37(0.89-2.12)	92(19)	0.99(0.69-1.42)	41(18)	1.47(0.88-2.48)
Current	742(69)	256(70)	1.17(0.82-1.67)	289(61)	0.74(0.56-0.998)	161(69)	1.05(0.69-1.60)
Cigarette smoking status							
Never	206(19)	53(14)	1	106(21)	1	37(15)	1
Former ^a	193(17)	72(19)	1.43(0.94-2.15)	107(22)	1.06(0.76-1.49)	45(19)	1.51(0.92-2.46)
Current	708(64)	251(67)	1.28(0.91-1.80)	279(57)	0.81(0.61-1.06)	157(66)	1.18(0.80-1.76)
Pipe smoking status							
Never	865(78)	297(79)	1	396(80)	1	194(81)	1
Former ^a	144(13)	62(16)	1.21(0.87-1.69)	73(15)	1.10(0.80-1.50)	33(14)	1.08(0.71-1.64)
Current	98(9)	17(5)	0.54(0.30-0.94)	23(5)	0.45(0.27-0.74)	12(5)	0.45(0.23-0.87)
Tobacco intensity ^b (cigarettes/day)							
Never smoker	169(17)	48(16)	1	93(22)	1	32(15)	1
1-9	253(25)	39(13)	0.56(0.35-0.89)	53(13)	0.39(0.26-0.57)	42(20)	0.84(0.50-1.30)
10-19	184(18)	55(18)	1.04(0.67-1.62)	77(19)	0.80(0.55-1.15)	39(19)	1.08(0.64-1.80)
20-29	324(32)	135(44)	1.40(0.96-2.06)	152(37)	0.90(0.65-1.25)	75(36)	1.17(0.74-1.85)
30-70	77(8)	30(10)	1.28(0.75-2.19)	37(9)	0.96(0.60-1.53)	20(10)	1.33(0.71-2.48)
P for trend			<0.01		0.13		0.14

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Tobacco duration ^b (years)	Never smoker	169(17)	1	93(22)	1	32(15)	1
	1-26	203(20)	1.08(0.68-1.70)	64(16)	0.70(0.47-1.05)	54(26)	1.22(0.73-2.05)
	27-33	192(19)	1.20(0.78-1.85)	89(22)	0.97(0.67-1.41)	46(22)	1.20(0.73-2.00)
	34-41	233(23)	1.10(0.72-1.66)	101(24)	0.81(0.57-1.15)	52(25)	1.18(0.73-1.92)
	42-58	206(20)	0.92(0.58-1.45)	65(16)	0.51(0.35-0.76)	23(11)	0.65(0.36-1.17)
	<i>P</i> for trend		0.89		0.01		0.38
Total tobacco exposure ^c (pack-years)	Never smoker	169(17)	1	93(22)	1	32(15)	1
	0.5-14	209(21)	0.75(0.48-1.18)	73(18)	0.73(0.51-1.05)	52(25)	1.24(0.77-2.02)
	15-26	217(22)	1.09(0.72-1.65)	72(17)	0.74(0.52-1.06)	39(19)	0.88(0.53-1.45)
	27-39	216(22)	1.39(0.93-2.08)	90(22)	0.90(0.64-1.27)	44(21)	1.14(0.70-1.86)
	40-157	192(19)	1.51(1.01-2.24)	84(20)	0.84(0.60-1.18)	40(19)	1.25(0.76-2.04)
	<i>P</i> for trend		< 0.01		0.7769		0.5515

[#] Adjusted for age (continuous), geographic region (5 classes); *OR*: odds ratio; *CI*: confidence interval

^a Former smokers were defined as persons who stopped smoking for at least 2 years

^b Intensity (average usual tobacco per day, cigarette equivalent), and duration (years of tobacco) among smokers

^c Total exposure was calculated as the product of intensity and duration (pack-year equivalent); 1 pack-year equals 20 cigarettes per day for 1 year

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma

Table 3

Alcohol consumption and risk for upper gastrointestinal cancer (males only)

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Ever alcohol	Ever vs. never	731(66)	270(72)	1.23(0.95-1.60)	319(65)	1.01(0.80-1.27)	1.29(0.94-1.76)
Beer							
<1984 summer	Any vs. never	299(27)	119(32)	1.17(0.90-1.52)	135(27)	1.10(0.86-1.40)	1.58(1.17-2.14)
<1984 winter	Any vs. never	169(15)	67(18)	1.15(0.84-1.57)	89(18)	1.30(0.98-1.73)	1.65(1.16-2.33)
>1984 summer	Any vs. never	465(42)	185(49)	1.25(0.98-1.60)	203(41)	1.06(0.85-1.33)	1.56(1.16-2.09)
>1984 winter	Any vs. never	181(16)	72(19)	1.16(0.85-1.57)	92(19)	1.25(0.95-1.66)	1.74(1.25-2.44)
Ever beer	Ever vs. never	474(43)	186(49)	1.23(0.96-1.56)	206(42)	1.05(0.84-1.32)	1.53(1.14-2.05)
Wine							
<1984	Any vs. never	221(20)	83(22)	1.05(0.78-1.40)	101(20)	1.10(0.84-1.45)	1.31(0.93-1.84)
>1984	Any vs. never	251(23)	98(26)	1.11(0.84-1.46)	112(23)	1.07(0.83-1.39)	1.23(0.88-1.71)
Ever wine	Ever vs. never	253(23)	99(26)	1.11(0.84-1.46)	112(23)	1.06(0.82-1.37)	1.22(0.87-1.69)
Liquor							
<1984	Never	533(48)	160(42)	1	234(47)	1	1
	<Weekly	456(41)	172(46)	1.19(0.92-1.53)	197(40)	1.03(0.82-1.30)	1.24(0.92-1.68)
	weekly	23(2)	14(4)	1.90(0.95-3.81)	22(4)	2.39(1.30-4.40)	1.95(0.87-4.36)
	Daily	95(8)	30(8)	0.99(0.63-1.56)	39(8)	0.95(0.63-1.43)	1.23(0.72-2.12)
>1984	Never	421(38)	121(32)	1	194(39)	1	1
	<Weekly	421(38)	156(42)	1.23(0.94-1.63)	177(36)	0.96(0.75-1.24)	1.34(0.96-1.86)
	weekly	51(5)	20(5)	1.26(0.71-2.21)	33(7)	1.64(1.02-2.65)	1.88(1.04-3.40)
	Daily	214(19)	79(21)	1.18(0.84-1.65)	88(18)	0.94(0.69-1.28)	1.23(0.81-1.88)
Ever liquor	Ever vs. never	700(63)	258(69)	1.20(0.93-1.55)	306(62)	1.01(0.81-1.27)	1.30(0.96-1.77)

[#] Adjusted for age (continuous), geographic region (5 classes); OR: odds ratio; CI: confidence interval

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma

Table 4

Socioeconomic status and risk for upper gastrointestinal cancer

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Occupation							
Farmer	760(50)	306(51)	1	275(46)	1	141(45)	1
Industrial worker	390(26)	137(23)	0.94(0.59-1.22)	142(24)	0.98(0.76-1.26)	66(21)	1.04(0.74-1.48)
Office worker	239(16)	108(18)	1.29(0.97-1.72)	147(24)	1.54(1.18-2.02)	83(26)	2.30(1.63-3.24)
Other	125(8)	48(8)	0.85(0.59-1.22)	35(6)	0.88(0.58-1.32)	26(8)	1.20(0.74-1.93)
Education							
0-5 years	650(47)	228(41)	1	228(41)	1	97(33)	1
6-9 years	561(40)	244(44)	0.75(0.60-0.94)	202(36)	0.90(0.71-1.13)	133(46)	0.69(0.52-0.93)
≥ 10 years	174(13)	83(15)	1.12(0.82-1.51)	128(23)	1.98(1.49-2.64)	61(21)	1.50(1.05-2.13)
Household size							
0-3	806(53)	284(47)	1	292(49)	1	145(46)	1
>=4	708(47)	316(53)	1.29(1.06-1.58)	307(51)	1.31(1.07-1.59)	171(54)	1.20(0.93-1.55)
Household income (Yuan/month)							
0-259	378(25)	159(26)	1	145(24)	1	61(19)	1
260-499	288(19)	107(18)	0.90(0.67-1.20)	116(19)	1.11(0.82-1.48)	71(22)	1.42(0.97-2.08)
500-999	429(28)	164(27)	0.92(0.70-1.20)	155(26)	0.99(0.75-1.31)	84(26)	1.16(0.80-1.69)
>=1000	419(28)	170(28)	0.99(0.75-1.30)	183(30)	1.21(0.92-1.60)	100(32)	1.42(0.98-2.06)
Own refrig years							
0	948(63)	397(66)	1	370(62)	1	193(61)	1
1-7 years	276(18)	121(20)	1.03(0.80-1.33)	107(18)	1.00(0.77-1.31)	58(18)	1.06(0.75-1.48)
≥ 8 years	289(19)	82(14)	0.62(0.46-0.84)	122(20)	1.13(0.86-1.49)	65(20)	1.14(0.80-1.62)

[#] Adjusted for age (continuous), gender, geographic region (5 classes); OR: odds ratio; CI: confidence interval

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma

Table 5A

Dietary factors and risk for upper gastrointestinal cancer Cereal and meat and legumes intake and upper gastrointestinal cancer risk

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Before 1984							
Primary staple food ^a							
Corn	Yes	1305(86)	511(85)	0.93(0.68-1.27)	514(86)	239(76)	0.60(0.42-0.86)
Millet	Yes	196(13)	78(13)	1.06(0.77-1.47)	99(16)	44(14)	1.06(0.71-1.60)
Wheat	Yes	166(11)	65(11)	1.01(0.70-1.44)	83(14)	62(20)	1.46(0.97-2.19)
Rice	Yes	45(3)	17(3)	0.88(0.47-1.63)	16(3)	19(6)	1.11(0.59-2.11)
Sorghum	Yes	665(44)	268(45)	0.95(0.75-1.21)	242(40)	120(38)	0.88(0.64-1.21)
Other	Yes	21(1)	6(1)	--	5(1)	12(4)	-
Meat and legumes ^b							
Red meat	Any	1447(96)	568(95)	0.82(0.48-1.38)	578(96)	297(94)	0.73(0.39-1.37)
Chicken	Any	1255(83)	490(82)	1.23(0.81-1.84)	510(85)	251(79)	0.90(0.54-1.52)
Fish	Any	1198(79)	458(76)	0.76(0.53-1.10)	488(81)	239(76)	0.93(0.58-1.48)
Eggs	Any	1460(96)	586(98)	1.75(0.92-3.31)	588(98)	305(97)	1.22(0.60-2.50)
Beans or soy products	Weekly vs. less than weekly	478(32)	182(30)	0.94(0.78-1.17)	201(33)	104(33)	1.08(0.83-1.41)
After 1984							
Primary staple food ^c							
Corn	Yes	66(4)	16(3)	0.61(0.34-1.09)	31(5)	12(4)	0.94(0.48-1.82)
Millet	Yes	80(5)	32(5)	0.99(0.64-1.54)	49(8)	19(6)	1.20(0.69-2.06)
Wheat	Yes	1489(98)	595(99)	1.74(0.65-4.71)	584(98)	308(97)	0.72(0.31-1.67)
Rice	Yes	566(37)	206(34)	0.82(0.66-1.02)	185(31)	130(41)	1.19(0.90-1.57)
Sorghum	Yes	5(0.3)	2(0.3)	0.99(0.18-5.42)	5(1)	0	-
Other	Yes	7(0.5)	0	-	6(1)	3(1)	-
Meat and legumes ^d							
Red meat							
	Monthly/seldom/never	598(40)	231(38)	1	204(34)	1	101(32)
	Weekly	513(34)	203(34)	1.14(0.89-1.46)	214(36)	126(40)	1.62(1.18-2.24)

	ESCC		GCA		GNCA	
	Control (%)	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)
>Weekly	403(27)	166(28)	1.37(1.03-1.82)	181(30)	1.54(1.15-2.07)	89(28)
<i>P</i> for trend			0.04		<0.01	0.03
Chicken						
Never	149(10)	61(10)	1	50(8)	1	32(10)
Seldom	1140(75)	476(79)	1.37(1.03-1.82)	468(78)	0.90(0.55-1.47)	246(78)
Monthly	110(7)	33(6)	1.14(0.89-1.46)	36(6)	1.004(0.52-1.93)	20(6)
Daily/weekly	114(8)	30(5)	0.96(0.50-1.88)	45(8)	0.98(0.52-1.86)	18(6)
<i>P</i> for trend			0.32		0.72	0.18
Fish						
Never	179(12)	91(15)	1	59(10)	1	37(12)
Seldom	1056(70)	422(70)	0.59(0.39-0.88)	458(76)	1.29(0.82-2.03)	226(72)
Monthly	121(8)	40(8)	0.51(0.29-0.91)	25(4)	0.53(0.28-1.03)	24(8)
Daily/weekly	157(10)	47(8)	0.50(0.28-0.88)	57(10)	0.86(0.48-1.55)	29(9)
<i>P</i> for trend			0.06		0.06	0.83
Eggs						
Monthly/seldom/never	274(18)	105(18)	1	98(16)	1	63(20)
Weekly	429(28)	170(28)	1.04(0.77-1.41)	180(30)	1.10(0.81-1.49)	101(32)
Daily	811(54)	325(54)	1.12(0.84-1.49)	321(54)	0.95(0.71-1.28)	152(48)
<i>P</i> for trend			0.33		0.53	0.27
Beans or soy products						
Monthly/seldom/never	354(23)	138(23)	1	123(20)	1	78(25)
Weekly	754(50)	319(53)	1.10(0.86-1.42)	323(54)	1.16(0.89-1.50)	178(56)
Daily	406(27)	143(24)	0.88(0.65-1.20)	153(26)	0.96(0.70-1.30)	60(19)
<i>P</i> for trend			0.33		0.70	0.02

[#] Adjusted for age (continuous), gender, geographic region (5 classes); *OR*: odds ratio; *CI*: confidence interval

^a Primary staple food before 1984 were coded as yes or no consumption with not consumption as reference group. Primary staple foods were not mutual exclusive; 58% controls had more than one staple food before 1984. All these staple foods were adjust for each other

^b Red meat (pork, beef and lamb), chicken, fish, and eggs consumption before 1984 were coded as ever or never consumption with never as reference group; Red meat (pork, beef and lamb), chicken, fish, eggs, and soy products consumption before 1984 were adjusted for each other

^cPrimary staple food after 1984 were coded as yes or no consumption with not consumption as reference group. Primary staple foods were not mutual exclusive; 46% controls had more than one staple food after 1984. All these staple foods were adjust for each other

^dRed meat (pork, beef and lamb), chicken, fish, eggs, and soy products consumption after 1984 were adjusted for each other

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma

Dietary factors and risk for upper gastrointestinal cancer Dairy products, fruits and vegetable intake and upper gastrointestinal cancer risk

Table 5B

	Control (%)	ESCC		GCA		GNCA	
		Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Milk or dairy products							
Ever vs. never	901(60)	415(69)	1.56(1.27-1.92)	455(76)	2.08(1.67-2.59)	222(70)	1.69(1.29-2.21)
<774	379(25)	194(32)	1	201(34)	1	107(34)	1
774-999	377(25)	181(30)	0.92(0.71-1.18)	174(29)	0.88(0.69-1.14)	100(32)	0.91(0.66-1.24)
Fresh vegetables^b							
1000-1229	377(25)	130(22)	0.64(0.49-0.83)	122(20)	0.62(0.47-0.81)	77(24)	0.70(0.51-0.98)
>=1230	381(25)	95(16)	0.46(0.35-0.62)	102(17)	0.52(0.39-0.69)	32(10)	0.30(0.19-0.45)
P for trend			<0.0001		0.0001		0.0001
Fresh fruits^c							
<17	375(25)	179(30)	1	199(33)	1	116(37)	1
17-64	382(25)	177(30)	0.92(0.71-1.18)	182(30)	0.92(0.72-1.18)	92(29)	0.74(0.54-1.01)
65-188	366(24)	132(22)	0.72(0.55-0.94)	112(19)	0.59(0.45-0.78)	66(21)	0.55(0.39-0.77)
>=189	391(26)	112(19)	0.53(0.40-0.71)	106(18)	0.54(0.40-0.71)	42(13)	0.32(0.22-0.47)
P for trend			<0.0001		0.0001		0.0001

[#] Adjusted for age (continuous), gender, geographic region (5 classes); OR: odds ratio; CI: confidence interval

^b Vegetable : potato, sweet potato, carrot, turnip, onion, bean pod, cabbage, cucumber, garlic bolt, gourds, squash, spinach, celery, rape, chives, green onion, tomato, eggplant; consumption was calculated as times per year

^c Fruit: apple, pear, grape, peach, apricot, watermelon, persimmon, hawthorn, orange, banana; consumption was calculated as times per year

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma

Dietary factors and risk for upper gastrointestinal cancer Special food intake habits and upper gastrointestinal cancer risk

Table 5C

	<u>ESCC</u>		<u>GCA</u>		<u>GNCA</u>		
	Control (%)	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]	Case (%)	OR (95% CI) [#]
Scalding hot food							
Never	369(24)	87(14)	1	93(16)	1	33(10)	
Monthly/seldom	647(43)	228(38)	1.46(1.11-1.94)	218(36)	1.39(1.05-1.83)	152(48)	2.60(1.74-3.87)
Weekly	125(8)	43(7)	1.46(0.96-2.23)	58(10)	1.92(1.30-2.84)	22(7)	1.90(1.07-3.40)
Daily	373(25)	242(40)	2.74(2.06-3.65)	230(38)	2.50(1.88-3.32)	109(34)	3.19(2.10-4.84)
<i>P</i> for trend			<0.0001		<0.0001		<0.0001
Moldy food							
Ever vs. never	461(30)	240(40)	1.55(1.27-1.89)	241(40)	1.53(1.26-1.87)	131(41)	1.66(1.29-2.14)
Salted meat							
Ever vs. never	570(38)	248(41)	1.20(0.98-1.46)	258(43)	1.24(1.02-1.51)	149(47)	1.46(1.14-1.87)
Pickled vegetable and pickled vegetable juice							
Ever vs. never	797(53)	322(54)	1.03(0.85-1.25)	351(59)	1.27(1.04-1.54)	190(60)	1.44(1.12-1.85)
Vinegar							
<Monthly	249(16)	121(20)	1	118(20)	1	83(26)	1
Weekly	116(8)	56(9)	0.98(0.66-1.45)	49(8)	0.90(0.60-1.34)	33(10)	0.88(0.55-1.40)
Daily	1149(76)	423(70)	0.75(0.59-0.96)	432(72)	0.78(0.61-0.997)	200(63)	0.54(0.40-0.72)
<i>P</i> for trend			0.0148		0.0406		<0.0001
Seasonings ^a							
Never	97(6)	47(8)	1	38(6)	1	26(8)	1
Monthly/seldom	580(38)	264(44)	0.93(0.64-1.36)	264(44)	1.20(0.80-1.80)	139(44)	0.93(0.58-1.49)
Weekly	333(22)	124(21)	0.77(0.51-1.16)	128(21)	1.01(0.65-1.55)	72(23)	0.83(0.50-1.37)
Daily	504(33)	165(28)	0.68(0.46-1.01)	169(28)	0.87(0.57-1.32)	79(25)	0.61(0.37-1.01)
<i>P</i> for trend			0.0035		0.0189		0.0053

[#] Adjusted for age (continuous), gender, geographic region (5 classes), OR: odds ratio; CI: confidence interval

^a Seasonings: black pepper, spicy pepper, garlic, ginger, cinnamon

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma
GNCA: gastric noncardia adenocarcinoma

Table 6

Summary of lifestyle factors and upper gastrointestinal cancer risk

	ESCC	GCA	GNCA
Smoking			
Current smoker	<i>o</i>	–	<i>o</i>
Higher intensity	<i>o</i>	<i>o</i>	<i>o</i>
Longer duration	<i>o</i>	–	<i>o</i>
Higher pack-years	+	<i>o</i>	<i>o</i>
Alcohol			
Beer	<i>o</i>	<i>o</i>	+
Socioeconomic status			
Office worker	<i>o</i>	+	+
Higher education	+	+	+
Larger household size	+	+	+
Refrigerator usage	–	<i>o</i>	<i>o</i>
Diet			
Scalding hot food	+	+	+
Moldy food	+	+	+
Salted meat	+	+	+
Pickled vegetables/ pickled vegetable juice	+	+	+
Vinegar	–	–	–
Seasonings	–	–	–
Milk and dairy products	+	+	+
Red meat >1984	+	+	+
Fish >1984	–	<i>o</i>	<i>o</i>
Beans and soy products >1984	<i>o</i>	<i>o</i>	–
Fresh vegetables	–	–	–
Fresh fruits	–	–	–

+ significantly increased risk

– significantly decreased risk

o no-significant association

ESCC: esophageal squamous cell carcinoma

GCA: gastric cardia adenocarcinoma

GNCA: gastric noncardia adenocarcinoma