RESEARCH COMMUNICATION

Risk Factors for Esophageal Cancer: a Case-control Study in South-western China

Chun-xia Yang[1,3], Hua-yu Wang[2], Zhi-ming Wang[4], Hui-zhang Du[2], De-ming Tao[2], Xiao-yan Mu[2], Huai-gong Chen[1], Yan Lei[1], Keitaro Matsuo[3], Kazuo Tajima[3]

Abstract

Esophageal cancer is a crucial cancer in China. Yanting in Sichuan Province was a key area with highest esophageal cancer mortality in China, but little evidence on esophageal cancer risk factors has been reported for this area and the etiology remains unclear. To clarify risk factors, a 1:1 matched case-control study was conducted. Totals of 185 eligible esophageal cancer patients and 185 healthy residents matched for sex and age were recruited. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for possible risk/ protective factors. All ORs were adjusted by family history of esophageal cancer and occupation, and then further adjusted by other possible confounding factors. Our results showed that smoking and alcohol drinking were risk factors for esophageal cancer with dose-response. The ORs (95% CI) compared with never smokers and drinkers were 4.06 (1.55-10.6) and 2.49 (1.06-5.85), respectively. The OR was further increased to 8.86 (95%CI, 3.82-20.5) for both smoking and drinking in combination. Eating food rapidly (OR=5.84, 95%CI, 2.05-16.7), drinking shallow ground water (OR=4.18, 95%CI, 1.30-13.4) and frequent intake of picked vegetables (OR=2.12, 95%CI, 1.00-4.49) appeared to increase the risk, while frequent intake of fresh fruit (OR=0.42, 95%CI, 0.19-0.89), fresh vegetables (OR= 0.62, 95%CI, 0.32-1.17) and eggs (OR=0.59, 95%CI, 0.25-1.39) decreased the risk. In conclusion, smoking and alcohol drinking are common in Yanting and main contributors to esophageal cancer. Consumption of fresh fruit and eggs are not common and high consumption of these two foods as well as fresh vegetables may decrease the risk of esophageal cancer in this area. In addition, drinking shallow ground water and eating food rapidly, as well as frequent intake of pickled vegetables, are also factors increasing the risk.

Key Words: Esophageal cancer- case control study- risk factors- South western China.

Asian Pacific J Cancer Prev, **6**, 48-53

Introduction

The incidence and mortality of esophageal cancer ranked the eighth and fifth, respectively, over the world in 1996. The prognosis is generally poor with five-year survival rates of only 5-10%. The majority of incident cases occur in the developing world and China is one of the highest risk countries, accounting for about half of the world's esophageal cancer cases (IARC, 1997). According to the China National Survey of Mortality Spectrum and Type Composition of Malignant Tumours in 1990-1992, mortality rates of esophageal cancer in the countryside were $27.5/10^5$ for males, and $14.1/10^5$ for females, ranking the fourth causes of cancer deaths (Li et al., 1997). It is crucial to clarify the major risk factors to prevent this lethal disease in view of its poor prognosis.

Epidemiological studies in Western countries have shown that smoking and alcohol drinking are important risk factors for esophageal cancer in low incidence areas (Brown et al., 2002; Castelletto et al., 1994; Kinjo et al., 1998). However, the etiological factors in high risk areas such as in China are less clear and the contributors may be quite different among different areas and could be changing with time. Some previous studies conducted in Linxian, North China, showed the major risk factors in this high risk area to be intake of nitrosamines and their precursors contained

[1]*Department of Epidemiology, Huaxi Public Health School, Sichuan University, Chengdu 610041, China.* [2]*Yanting Cancer Research Institute, Sichuan, China.* [3]*Division of Epidemiology and Prevention, Aichi Cancer Center, Nagoya, Japan.* [4]*Huaxi Public Health School, Sichuan University, Chengdu 610041, China.*
Correspondence to Kazuo Tajima. Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Fax: +81-52-763-5233. E-mail: ktajima@aichi-cc.jp

in pickled vegetables, mouldy food and water, rather than smoking or alcohol drinking (Yang et al., 1980). However, a relatively recent nested case-control study with large samples in Linxian showed different results: tobacco smoking was associated with a significantly elevated risk, with a two fold increase among long-term smokers. Furthermore, high consumption of eggs or fresh vegetables was associated with 20% reduction in risk, but intake of pickled vegetables and mouldy foods were not associated with the risk (Guo et al, 1994). Evidence from Shanghai, East China, showed smoking and alcohol drinking to contribute to the risk of esophageal cancer (Gao et al, 1994) and a study in Chaoshan area, South China, found fermented fish sauce to be an important risk factor (Ke et al., 2002). Although a number of epidemiological studies on esophageal cancer have thus been conducted in China, little has been reported for Sichuan, in South-western China.

Yanting of Sichuan Province, a rural county, is one of the areas with the highest esophageal cancer mortality in China (Yang, 1989; Kou et al., 2003). The average age-adjusted mortality of esophageal cancer by world population was $99.6/10^5$ during 1969-1998 in Yanting (Chen et al., 2000). The lifestyles of people in Yanting may be different from those of other areas in China. Therefore, the risk factors contributing to esophageal cancer may also be different between Yanting and other areas of China. To clarify the risk/ protective factors in Yanting, we therefore conducted the present case-control study.

Materials and Methods

Subjects

Esophageal cancer cases were collected from the hospital of the Yangting Cancer Research Institute during July 2003 to July 2004. All the cases were histologically diagnosed within half a year. One particular doctor interviewed every case and filled in one questionnaire which included the basic demographic items, information on esophageal cancer such as the location, stage, histological type, the time diagnosed, and family history of esophageal cancer, smoking and alcohol drinking history, and dietary habits over the recent five years. A total of 185 eligible cases (179 with squamous cell carcinomas and 6 with adenocarcinomas) in the age range of 35-85 years were recruited for the study.

The same number of controls matched to each case for sex and age (within 5 years) were collected from residents in Yanting and interviewed in March or August of 2004 by epidemiological workers. The questionnaire included the same items as that for cases except information on esophageal cancer.

Statistical Analysis

Statistical analyses were performed using the STATA statistical package (version 8, Stata, College Station, TX). Odds ratios (ORs) and their 95% confidence intervals (95%CIs) were used to estimate the risk of each item for esophageal cancer. Conditional logistic regression was employed to calculate ORs and their 95%CIs. First, we calculated the OR and its' 95%CI for each possible risk/ protective factor adjusting for family history of esophageal cancer and occupation, and then by further adjusting for other possible confounding factors, including smoking, drinking, eating hot food, eating speed, vegetables, fruit, pickled vegetables, fresh meat, processed meat, eggs, tea and water supply. We also estimated the combined risk of smoking and alcohol drinking or smoking and vegetable consumption.

Table 1. Characteristics of Cases and Controls

	Cases n=185	Controls n=185
Age:		
age<=40	3 (1.6%)	3 (1.6%)
41-59	102 (55.1%)	102 (55.1%)
age>=60	80 (43.2%)	80 (43.2%)
Mean age(SD)	58.1 (8.5)	57.9 (8.8)
Sex:		
Male	119 (64.3%)	119 (64.3%)
Female	66 (35.7%)	66 (35.7%)
Family History of Esophageal Cancer:		
Negative	125 (67.6%)	140 (75.7%)
Positive	60 (32.4%)	45 (24.3%)
Occupation:		
Peasant	172 (93.0%)	177 (95.7%)
Non-peasant	13 (7.0%)	8 (4.3%)

Results

The average ages of the cases and controls were 58.1 and 57.9, respectively. The males accounted for 64.3% in both cases and controls. The basic characteristics were shown in Table 1. Over 90% of the cases and controls were peasants, and 32.4% of cases as well as 24.3% of controls had a family history of esophageal cancer. The basic characteristics did not significantly differ between cases and controls.

Findings for the association between smoking, alcohol drinking and esophageal cancer are shown in Table 2. The smoking and alcohol drinking proportion among cases were 57.3% and 53.0%, respectively, which were significantly higher than in controls, 34.0% and 29.9%. The ORs for smokers and alcohol drinkers compared with the abstinent groups were 6.13 (95%CI, 2.97-12.7) and 4.02 (95%CI, 2.19-7.41), respectively. After further adjusted by other possible confounding factors, the odds ratios were 4.06 (95%CI, 1.55-10.6) and 2.49 (95%CI, 1.06- 5.85), respectively. A dose-response relationship was also detected for both smoking and alcohol drinking ($P<0.01$). Almost all the alcohol drinkers had been drinking hard liquor containing ethanol over 48% in this area and the main tobacco type was the cigarette (not listed in Table 2).

The ORs for food consumption are shown in Table 3. Eating food rapidly, frequent intake of pickled vegetables and drinking shallow ground water were associated with increased risk. On the other hand, frequent intake of fresh vegetables, fruit and eggs appeared to decrease the risk of esophageal cancer, while drinking tea, and fresh meat and

Table 2. Smoking, Alcohol Drinking and Esophageal Cancer

	Cases n=185	Controls n=185	OR1 (95%CI)	OR2 (95%CI)
Smoking:				
Never	79 (42.7%)	122 (66.0%)	Reference	Reference
Ever	106 (57.3%)	63 (34.0%)	6.13 (2.97-12.7)	4.06 (1.55-10.6)
Age Beginning to Smoke Tobacco				
>=20	61 (57.6%)	45 (71.4%)	Reference	Reference
<20	45 (42.3%)	18 (28.6%)	1.73 (0.73-4.08)	0.81 (0.14-4.63)
Tobacco Dose				
Never Smoking	79 (42.7%)	122 (66.0%)	Reference	Reference
<10 cigarettes/day	19 (10.3%)	13 (7.0%)	5.36 (2.02-14.2)	3.29 (0.94-11.5)
10-20 cigarettes/day	23 (12.4%)	19 (10.3%)	4.27 (1.76-10.4)	2.65 (0.81-8.69)
>20 cigarettes/day	64 (34.6%)	31 (16.8%)	8.45 (3.66-19.5)	6.05 (1.99-18.4)
P for Trend			<0.01	<0.01
Alcohol Drinking:				
Never	87 (47.0%)	188 (70.2%)	Reference	Reference
Ever	98 (53.0%)	80 (29.9%)	4.02 (2.19-7.41)	2.49 (1.06-5.85)
Age Beginning to Drink Alcohol				
>=20	63 (64.3%)	40 (74.1%)	Reference	Reference
<20	35 (35.7%)	14 (25.9%)	1.12 (0.45, 2.78)	0.52 (0.13-2.20)
Alcohol Dose				
Never drinking	87 (47.0%)	128 (69.2%)	Reference	Reference
<50ml/day	17 (9.2%)	22 (11.9%)	1.44 (0.63-3.32)	0.85 (0.28-2.54)
50-100ml/day	24 (13.0%)	13 (7.0%)	5.72 (2.13-15.4)	5.92 (1.45-24.1)
>100ml/day	57 (30.8%)	22 (11.9%)	8.10 (3.44-19.1)	6.71 (1.92-23.4)
P for Trend			<0.01	<0.01

*: OR1 was adjusted by family history of esophageal cancer and occupation; OR2 was farther adjusted by other possible confounding factors

processed meat consumption, as well as eating hot food, demonstrated no clear relationship with esophageal cancer risk in this area.

Tables 4 and 5 show the combined risk of smoking and drinking or smoking and vegetables, respectively. It was obvious that alcohol drinking markedly increased the risk of esophageal cancer among smokers. The OR was only 2.26 for smokers compared with non-smokers among never drinkers, while the OR increased to 8.86 in drinkers. On the other hand, high intake of vegetables decreased the risk of esophageal cancer among smokers. The OR was 10.6 for smokers with a low intake of vegetables compared with non-smokers with high vegetables consumption. However, the OR of smokers was reduced to 4.5 in individuals consuming a high amount of vegetables.

Discussion

Esophageal cancer is modulated by not one single factor, but rather a large number of factors such as smoking, alcohol drinking and food consumption. The particular contributions of these factors to esophageal cancer may differ among areas or countries along with variation in exposure levels, both individually and in combination.

Smoking has been proved to be a major risk factor for several cites cancer such as nasal, oral and lung cancers. Processed tobacco contains over 3,000 compounds including 30 carcinogens. Polyaromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), and aromatic amines are three major classes of carcinogens responsible for tobacco-associated cancers (Bartsch et al., 2000). Our results also showed habitual smoking to be an important risk factor in Yanting, consistent with previous studies in Western countries (Brown et al., 2002; Castelletto et al., 1994; Kinjo et al., 1998) and also investigations in China (Guo et al., 1994; Gao et al., 1994; Wang et al., 2004). Especially, when smokers also drink alcohol, the OR was further increased since alcohol can dissolve the carcinogens in tobacco and facilitate their absorbtion. In contrast, a high intake of fresh vegetables was here found to decrease the risk among smokers. Over half of the risk could be prevented by a high intake of vegetables (the OR reduced to 4.5 from 10.6 among smokers).

Ethanol is not a carcinogen itself, but may promote carcinogenesis via: 1) generation of free radical products during its metabolism (Eskelson et al., 1993); 2) solvent effects on tobacco and other carcinogens; 3) induction of microsomal enzymes involved in carcinogen metabolism (Yokoyama et al., 2003); 4) metabolism to acetaldehyde which has proven to be a carcinogen in animal experiments (Woutersen et al., 1986; Feron et al., 1982). In this context, it is of interest that polymorphisms of ADH2 (ADH2 metabolizes alcohol to acetaldehyde) and ALDH2 (ALDH2 metabolizes acetaldehyde to acetate) have been shown to modify the risk of esophageal cancer through affecting the metabolism of acetaldehyde (Matsuo et al., 2001; Yokoyama et al., 2002; Hori et al., 1997). The importance of alcohol as a risk factor depends on the exposure level among studied

Table 3. Habitual Food Consumption and Esophageal Cancer

	Cases n=185	Controls n=185	OR1 (95%CI)	OR2 (95%CI)
Eating Hotfood:				
Rarely	22 (11.9%)	23 (12.4%)	Reference	Reference
Occasionaly	65 (35.1%)	89 (48.1%)	0.73 (0.36-1.48)	0.43 (0.17-1.09)
Often	98 (53.0%)	73 (39.5%)	1.24 (0.62-2.48)	0.40 (0.14-1.16)
P for Trend			0.1	0.17
Eating Speed:				
Slow	17 (9.2%)	34 (18.4%)	Reference	Reference
Usual	51 (27.6%)	79 (42.7%)	1.23 (0.59-2.55)	2.17 (0.87-5.44)
Rapidly	117 (63.2%)	72 (38.9%)	2.96 (1.47-5.98)	5.84 (2.05-16.7)
P for Trend			<0.01	<0.01
Vegetables:				
<=10meals/week	89 (48.1%)	67 (36.2%)	Reference	Reference
>10 meals/week	96 (51.9%)	118 (63.8%)	0.58 (0.38, 0.89)	0.62 (0.32-1.17)
Fruit:				
<=1 time/week	162 (87.6%)	121 (65.4%)	Reference	Reference
>1 time/week	23 (12.4%)	64 (34.6%)	0.24 (0.13, 0.43)	0.42 (0.19-0.89)
Picked Vegetables:				
<1meal/week	28 (15.1%)	45 (24.3%)	Reference	Reference
1-3 meals/week	29 (15.7%)	32 (17.3%)	1.48 (0.73-3.01)	1.94 (0.77-4.89)
>3 times/week	128 (69.2%)	108 (58.4%)	1.96 (1.12-3.41)	2.12 (1.00-4.49)
P for Trend			0.02	0.06
Fresh Meat:				
<=2 meals/week	114 (61.6%)	83 (44.9%)	Reference	Reference
3-7 meals/week	49 (26.5%)	77 (41.6%)	0.42 (0.25-0.70)	0.57 (0.29-1.11)
> 7 meals/week	22 (11.9%)	25 (13.5%)	0.50 (0.24-1.06)	1.51 (0.48-4.72)
P for trend			<0.01	0.69
Processed Meat				
<1meal/week	64 (34.6%)	53 (28.7%)	Reference	Reference
1-3 meals/week	45 (24.3%)	63 (34.1%)	0.62 (0.36-1.09)	0.65 (0.30-1.41)
>3 meals/week	76 (41.1%)	69 (37.3%)	0.89 (0.52-1.50)	0.66 (0.31-1.41)
P for Trend			0.83	0.33
Eggs:				
<=1time/week	163 (88.1%)	146 (78.9%)	Reference	Reference
>1time/week	22 (11.9%)	39 (21.1%)	0.39 (0.20-0.77)	0.59 (0.25-1.39)
Tea				
<=1time/week	100 (54.1%)	99 (53.8%)	Reference	Reference
2-4 times/week	21 (11.4%)	18 (9.8%)	1.20 (0.58-2.46)	0.45 (0.15-1.36)
>4 times/week	64 (34.6%)	67 (36.4%)	0.89 (0.51-1.55)	0.57 (0.25-1.31)
P for Trend			0.71	0.2
Water supply				
Well, Tap Water	159 (86.0%)	180 (97.3%)	Reference	Reference
Shallow Ground Water	26 (14.0%)	5 (2.7%)	5.08 (1.94-13.30)	4.18 (1.30-13.4)

*: OR1 was adjusted by family history of esophageal cancer and occupation; OR2 was farther adjusted by other possible confounding factors

Table 4. Tobacco Risk Elevation by Drinking

	Cases	Controls	OR	95% CI
Smoking (-) and Drinking (-)	72 (38.9%)	109 (58.9%)	Reference	
Smoking (-) and Drinking (+)	7 (3.8%)	13 (7.0%)	1.12	0.37-3.41
Smoking (+) and Drinking (-)	15 (8.1%)	19 (10.3%)	2.26	0.86-5.96
Smoking (+) and Drinking (+)	91 (49.2%)	44 (23.8%)	8.86	3.82-20.5

Table 5. Tobacco Risk Submission by Vegetables

	Cases	Controls	OR	95% CI
Smoking (-) and Vegetables (<=10 meals/week)	30 (16.2%)	47 (25.4%)	Reference	
Smoking (-) and Vegetables (>10 meals/week)	49 (26.5%)	75 (40.5%)	1.2	0.65-2.23
Smoking (+) and Vegetables (<=10 meals/week)	59 (31.9%)	20 (10.8%)	10.6	4.10-27.2
Smoking (+) and Vegetables (>10 meals/week)	47 (25.4%)	43 (23.2%)	4.5	1.85-11.1

populations. Since the alcohol consumption is different among areas of China and the levels of other risk factors also vary, alcohol has a different contribution to esophageal cancer among various areas of China. It has been found that alcohol play little role for risk of esophageal cancer in Linxian where alcohol drinking is uncommon (Guo et al., 1994; Yu et al., 1993; Yang et al., 1982). Studies in Cixian (Yokoyama et al., 1999), another high risk area in China as well as in Chaoshan area (Li et al., 2003), in Jiangshu province (Gao et al., 2002), also showed no association between alcohol drinking and esophageal cancer risk. However, studies in Shanghai (Gao et al., 1994), Helongjiang (Hu et al., 1994) and Xi'an (Wang et al., 2004) demonstrated a significant link. The OR was 1.4 among heavy drinkers in Shanghai (Gao et al., 1994), and 4.2 (95% CI, 2.1-8.6) for annual alcohol consumption greater than 114.5 litres compared with non-drinkers in Helongjiang and 3.45(95% CI 1.74-6.91) in Xi'an (Wang et al., 2004). A study in Shanxi province showed alcohol increased the risk in Yangchun, but not in Linfen (Wang et al., 1992). Our investigation found alcohol consumption to be common in Yanting, with most drinkers prefering hard liquor containing over 48% ethanol, and habitual drinking was highly associated with risk of esophageal cancer with a dose-response relationship.

Furthermore, eating food rapidly increased the risk, while frequent consumption of fresh fruit, fresh vegetables and eggs was associated with protection. Foods not chewed adequately could disrupt the mucosal lining of the oesophagus and cause cell proliferation, which could enhance both initiation of carcinogenesis and growth of lesions. Fresh fruit, fresh vegetables and eggs contain a lot of micronutrients and riboflavin which may help to repair the disrupted mucosal lining of esophagus or act as anti-carcinogens to prevent esophageal cancer. Indeed, fresh fruit and fresh vegetables have been identified as protective factors in many previous studies (Ke et al., 2003; Cheng et al., 1996; Launoy et al., 1998; Decarli et al., 1987; Yu et al., 1988). Our result showed high intake of vegetables can greatly decrease the risk of esophageal cancer among smokers, presumably because of the abundant vitamins in vegetables acting as anti-carcinogens. There is also some previous evidence on eggs playing a protective role against esophageal cancer. In an ecological study of 65 Chinese counties, the capital consumption of eggs was inversely associated with esophgeal cancer mortality (Zhuo et al., 1999). Other evidence of eggs' protective role was found in Linxian (Guo et al., 1994) and in Shanxi (Chang-Claude et al., 1991).

Many previous studies also suggested that pickled vegetables containing a quantity of nitrosamines increase risk of esophageal cancer (Yang et al., 1980; Chang-Claude et al., 1991; Takezaki et al., 2002), although no relationship was found in a recent large sample study in Linxian (Guo et al., 1994). This may suggest that the processed methods and stored period of pickled vegetables affect the contamination of nitrosamines and then determine the risk of esophageal cancer. Consumption of pickled vegetables is still common in Yanting and frequent intake of pickled vegetables here twice increased OR of esophageal cancer in our study. Therefore, reduction on pickled vegetables consumption may decrease the risk of esophageal cancer in this area. In addition, 14% of cases in Yanting took shallow ground water contaminated with harmful micro organisms and low quality of drinking water has proven to be a risk factor in previous studies in China (Yu et al., 1993; Yokoyama et al., 1999; Xibib et al., 2003; Tao et al., 1999; Zhang et al., 2001).

In conclusion, our study in Yanting showed smoking and alcohol drinking to be the major contributors to risk of esophageal cancer, while eggs, fresh vegetables and fruit intake were associated with protection. Other risk factors may be eating food rapidly and frequent intake of pickled vegetables, as well as drinking shallow ground water.

Acknowledgments

This research was funded partly by Sichuan University Youth Scientific Research Fund and partly by Sasakawa Classmate Association. The first author, Chun-xia Yang, was the recipient of a Japan-China Special Sasakawa Medical Fellowship during the period the paper was drafted.

References

Bartsch H, Nair U, Risch A, et al (2000). Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev*, **9**, 3-28.

Brown LM, Devesa SS (2002). Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*, **11**, 235-56.

Castelletto R, Castellsague X, Munoz N, et al (1994). Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol Biomarkers Prev*, **3**, 557-64.

Chang-Claude J, Wahrendorf J, Qiu SL, et al (1991). Epidemiological study of precursor lesions of oesophageal cancer among young persons in Huixian, China. *IARC Sci Publ*, 192-6.

Chen Jun-ze DX-h, Xie Zong-wei (2000). [Chronological change of esophageal cancer mortality in Yanting during 1969-1998]. *Zhongguo zhong Liu*, **9**, 171. (in Chinese)

Cheng KK, Day NE (1996). Nutrition and esophageal cancer. *Cancer Causes Control*, **7**, 33-40.

Decarli A, Liati P, Negri E, et al (1987). Vitamin A and other dietary factors in the etiology of esophageal cancer. *Nutr Cancer*, **10**, 29-37.

Eskelson CD, Odeleye OE, Watson RR, et al (1993). Modulation of cancer growth by vitamin E and alcohol. *Alcohol Alcohol*, **28**, 117-25.

Feron VJ, Kruysse A, Woutersen RA (1982). Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. *Eur J Cancer Clin Oncol*, **18**, 13-31.

Gao CM, Takezaki T, Wu JZ, et al (2002). Glutathione-S-transferases M1 (GSTM1) and GSTT1 genotype, smoking, consumption of alcohol and tea and risk of esophageal and stomach cancers: a case-control study of a high-incidence area in Jiangsu Province, China. *Cancer Lett*, **188**, 95-102.

Gao YT, McLaughlin JK, Blot WJ, et al (1994). Risk factors for esophageal cancer in Shanghai, China. I. Role of cigarette smoking and alcohol drinking. *Int J Cancer*, **58**, 192-6.

Guo W, Blot WJ, Li JY, et al (1994) . A nested case-control study of oesophageal and stomach cancers in the Linxian nutrition intervention trial. *Int J Epidemiol*, **23**, 444-50.

Hori H, Kawano T, Endo M, et al (1997). Genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and human esophageal squamous cell carcinoma susceptibility. *J Clin Gastroenterol*, **25**, 568-75.

Hu J, Nyren O, Wolk A, et al (1994). Risk factors for oesophageal cancer in northeast China. *Int J Cancer*, **57**, 38-46.

IARC (1997). Food, Nutrition and the Prevention of Cancer: A Global Perspective. American Institute for Cancer Research,119.

Ke L, Yu P, Zhang ZX (2002). Novel epidemiologic evidence for the association between fermented fish sauce and esophageal cancer in South China. *Int J Cancer*, **99**, 424-6.

Ke L, Ping Y, Ge H (2003). Protective action of fresh fruit and vegetable consumption on the synergic effect of alcohol and tobacco use on esophageal cancer in South China. *Nutrition*, **19**, 821.

Kinjo Y, Cui Y, Akiba S, et al (1998). Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol*, **8**, 235-43.

Kou Y, Zhang J, Chen G, et al (2003). Mutation of p53 gene in esophageal precancerous cells. *Sichuan Da Xue Xue Bao Yi Xue Ban*, **34**, 306-9. (in Chinese)

Launoy G, Milan C, Day NE, et al (1998). Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. *Int J Cancer*, **76**, 7-12.

Li K, Yu P (2003). Food groups and risk of esophageal cancer in Chaoshan region of China: a high-risk area of esophageal cancer. *Cancer Invest*, **21**, 237-40.

Li L, Lu F, Zhang S (1997). Analyses of variation trend and short-term detection of Chinese malignant tumor mortality during twenty years. *Zhonghua Zhong Liu Za Zhi*, **19**, 3-9. (in Chinese)

Matsuo K, Hamajima N, Shinoda M, et al (2001). Gene-environment interaction between an aldehyde dehydrogenase-2 (ALDH2) polymorphism and alcohol consumption for the risk of esophageal cancer. *Carcinogenesis*, **22**, 913-6.

Takezaki T, Gao CM, Wu JZ, et al (2002). hOGG1 Ser(326)Cys polymorphism and modification by environmental factors of stomach cancer risk in Chinese. *Int J Cancer*, **99**, 624-7.

Tao X, Zhu H, Matanoski GM (1999). Mutagenic drinking water and risk of male esophageal cancer: a population-based case-control study. *Am J Epidemiol*, **150**, 443-52.

Wang AH, Sun CS, Li LS, et al (2004). Genetic susceptibility and environmental factors of esophageal cancer in Xi'an. *World J Gastroenterol*, **10**, 940-4.

Wang YP, Han XY, Su W, et al (1992). Esophageal cancer in Shanxi Province, People's Republic of China: a case-control study in high and moderate risk areas. *Cancer Causes Control*, **3**, 107-13.

Woutersen RA, Appelman LM, Van Garderen-Hoetmer A, et al (1986). Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. *Toxicology*, **41**, 213-31.

Xibib S, Meilan H, Moller H, et al (2003). Risk factors for oesophageal cancer in Linzhou, China: a case-control study. *Asian Pac J Cancer Prev*, **4**, 119-24.

Yang CS (1980). Research on esophageal cancer in China: a review. *Cancer Res*, **40**, 2633-44.

Yang CS, Miao J, Yang W, et al (1982). Diet and vitamin nutrition of the high esophageal cancer risk population in Linxian, China. *Nutr Cancer*, **4**, 154-64.

Yang Y (1989). The relation between pathologic factors of esophagus cancer and prognosis of its sufferers: application of Cox's model. *Zhonghua Yu Fang Yi Xue Za Zhi*, **23**, 266-9. (in Chinese)

Yokokawa Y, Ohta S, Hou J, et al (1999). Ecological study on the risks of esophageal cancer in Ci-Xian, China: the importance of nutritional status and the use of well water. *Int J Cancer*, **83**, 620-4.

Yokoyama A, Kato H, Yokoyama T, et al (2002). Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. *Carcinogenesis*, **23**, 1851-9.

Yokoyama A, Omori T (2003). Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. *Jpn J Clin Oncol*, **33**, 111-21.

Yu MC, Garabrant DH, Peters JM, et al (1988). Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Res*, **48**, 3843-8.

Yu Y, Taylor PR, Li JY, et al (1993). Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. *Cancer Causes Control*, **4**, 195-202.

Zhang W, An F, Lin H (2001). [A case-control study on the risk factors of esophageal cancer in Jieyang City of Guangdong in China]. *Zhonghua Liu Xing Bing Xue Za Zhi*, **22**, 442-5. (in Chinese)

Zhuo XG, Watanabe S (1999). Factor analysis of digestive cancer mortality and food consumption in 65 Chinese counties. *J Epidemiol*, **9**, 275-84.