

RESEARCH COMMUNICATION

Risk Factors for Oesophageal Cancer in Linzhou, China: a Case-Control Study

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Abstract

Linzhou City has one of the highest incidences of oesophageal cancer in China, and in the world. A case-control study was here conducted to investigate potential risk factors in this area. Linzhou Cancer Registry was used to identify cases of oesophageal cancer, aged between 30 and 75, diagnosed between January 1998 and April 1999. Three neighbourhood controls were selected for each case, matched according to age, sex and village of residence. A total of 211 cases and 633 controls were interviewed. A strong association was found between socio-economic status and the risk of oesophageal cancer. Increased income, residential space and education were all significantly associated with a decreased risk (OR 0.54, 0.36 and 0.30 respectively). Using a drinking water source other than tap water was significantly associated with an increased risk (OR 5.49). The consumption of beans, vegetables and vinegar all showed a protective effect with odds ratios of 0.37, 0.44 and 0.37 respectively. Preferences for a low salt diet or a high salt diet were both associated with an increased risk. It can be concluded that in Linzhou, oesophageal cancer is a disease related to poverty. Having a drinking water source other than tap water increases the risk of oesophageal cancer. As in other populations, a high consumption of vegetables and beans are associated with a decreased risk and a preference for a high salt diet is associated with an increased risk.

Key Words: Oesophageal cancer - risk factors - Linzhou, China - case-control

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Introduction

Oesophageal cancer is one of the most common cancers in the People's Republic of China (Li et al., 1997) and Linzhou City of Henan province is a region with a particularly high incidence and mortality of this cancer. Previous research has shown that dietary factors are associated with the occurrence of oesophageal cancer in this region (Lu et al., 2000; Li et al., 1989; Guo et al., 1994), in other areas of China (Gao et al., 1994; Cheng et al., 1992), and in western populations (Tavani et al., 1994; Tzonou et al., 1996; Brown et al., 1998; Sharp et al., 2001).

Linzhou City (formerly LinXian County) is situated in the northwest of Henan province in the Taihang Mountain area. The area, which has a high incidence of oesophageal cancer, also includes the southwest of Shanxi province and the south of Hebei province. It is a rural area with 90 per cent of the population working in agriculture. The climate

is arid with a low rainfall. The traditional diet mainly consists of wheat, maize and other cereals.

According to the Linzhou Cancer registry, the annual average age-standardized incidence rate/100,000 (ASIR per 100,000 world standard population) of oesophageal cancer was 121 for men and 80 for women in the period 1993 to 1997. During the same period, the annual average mortality rate (age-standardized by 100,000 world standard population) of this cancer was 108 for men and 71 for women.

The present paper reports a case-control study that was conducted to investigate potential risk factors in Linzhou City, China between August 1999 and June 2000.

Materials and Methods

Linzhou Cancer Registry is population-based and has collected data on all incident cancers diagnosed in residents

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of the Linzhou City area of Henan province (population 1.06 million) since 1987. Between 1959 and 1986, the Registry collected data only on oesophageal cancer and cancer of the gastric cardia.

The Registry was used to identify all cases of oesophageal cancer, aged between 30 and 75 years old, diagnosed between 1st January 1998 and 30th April 1999. Cases were only included if they were alive at the time of inquiry, August 1999 to June 2000 and if the diagnosis was confirmed by histopathology.

Three neighbourhood controls were selected for each case of oesophageal cancer, matched according to age (within 5 years), sex and village of residence. The controls were selected by choosing the fifth residence along from the residence of the index case, in three different directions. Controls were eligible for inclusion in the study if they had not had a diagnosis of cancer before 30th April 1999 and if they had not had a disease associated with oesophageal cancer, such as epithelioid hyperplasia of the oesophagus. Cases and controls were excluded if they had not lived in Linzhou for the last ten years.

A questionnaire was designed to obtain information on demographic and socio-economic status, characteristics of the residence, and dietary habits. Trained village doctors visited the residences of cases and controls to administer the questionnaire.

Some continuous variables, such as consumption of rice, were grouped into categories by combining the frequency and amount consumed. The data were analysed statistically using conditional logistic regression analysis. The odds ratio associated with a given risk factor or level of a categorical variable was estimated, along with its 95% confidence interval. The reference category was selected as the no-exposure or low exposure group, or an intermediate group with high prevalence.

Results

A total of 211 cases and 633 controls were interviewed. Of the 211 oesophageal cancers, 176 (83.4%) were squamous cell carcinomas and 35 (16.6%) were adenocarcinomas. The general characteristics of cases and controls are shown in Table 1. Men accounted for 58.8% of the total (124 cases and 372 controls) and women accounted for 41.2% (87 cases and 261 controls). The mean age was 58.3 years for cases and 57.9 years for controls. 170 (80.6%) cases and 522 (82.5%) controls were married. The majority of the cases and controls (95.7% and 92.4% respectively) were farmers.

The results of the conditional logistic regression analysis of factors relating to socio-economic status are shown in Table 2. Univariate analysis showed the odds ratios for increasing per capita income 10 years ago were 0.48, 0.35 and 0.46 (p for trend = 0.01) respectively, using less than 38 yuan/month as the reference group. After adjusting for other socio-economic characteristics, multivariate analysis produced slightly attenuated odds ratios of 0.53, 0.38 and 0.54 (p for trend = 0.06). For residential space, people with

10-20 square metres had an adjusted odds ratio of 0.46 and those with more than 20 square metres had an adjusted odds ratio of 0.36 (p for trend <0.01), compared with people with residential space below 10 square metres. The adjusted odds ratio for the group with the highest educational level versus the group without any education was 0.30 (95% CI 0.15 to 0.61). The associations with residential space and education level were highly statistically significant and insensitive to statistical adjustment for other socio-economic variables. Using a refrigerator was unrelated to the risk of oesophageal cancer (OR 1.30; 95% CI 0.57 to 2.97).

Table 3 shows the results of analysis of oesophageal cancer risk in relation to environmental risk factors. Using a drinking water source other than tap water (such as well, surface and cellar water) ten years ago was significantly associated with a more than five-fold increase in risk of oesophageal cancer in multivariate analysis (OR 5.49; 95% CI 1.43 to 21.1). Using firewood as the most common fuel ten years ago was significantly associated with an increased risk of oesophageal cancer in univariate analysis (OR 3.97; 95% CI 1.17 to 13.6). This association was no longer significant after adjustment for age, income, residential space and educational level. A similar pattern was seen for the presence of soot and the feeling of irritation on eyes or throat by soot: both factors showed statistically significant associations in univariate analysis (p for trend 0.02 and <0.01 respectively) but these associations were attenuated after adjusting for age, income, resident space and educational level (p for trend 0.13 and 0.08).

Table 4 shows the risk of oesophageal cancer in relation to dietary factors. No association was found between the risk of oesophageal cancer and the consumption of staple foods (rice, wheat flour, maize and other food grain) or animal proteins (pork, egg and milk). The consumption of animal oils or vegetable oils was not associated with the

Table 1. General Characteristics of Cases and Controls

Variable	211Cases %	633 Controls %
Sex		
Male	58.8	58.8
Female	41.2	41.2
Agegroup		
<40	9.5	10.4
45-49	16.1	11.7
50-54	14.2	16.6
55-59	10.1	11.5
60-64	20.4	16.1
65-69	18.5	17.7
70+	11.4	16.0
Marriage		
Married	85.5	82.5
Divorce	0.5	0.5
Widow or widower	19.0	16.7
Never married	0.0	0.3

Table 2. Risk of Oesophageal Cancer in Relation to Socio-economic Status

Risk factors	Distribution of cases %	Univariate OR (95%CI)	Multivariate* OR (95%CI)
Per capita income at 10 years ago (yuan/month)			
<38	31.3	1.00	
38-69	24.2	0.48 (0.29-0.82)	0.53 (0.30-0.93)
70-123	20.4	0.35 (0.20-0.62)	0.38 (0.21-0.71)
124+	24.2	0.46 (0.26-0.85)	0.54 (0.29-1.03)
P-value for trend		P=0.01	P=0.06
Per capita residential space at 10 years ago (square metres)			
<10	32.2	1.00	1.00
10-20	33.2	0.44 (0.20-0.69)	0.46 (0.28-0.74)
20+	34.6	0.33 (0.18-0.59)	0.36 (0.20-0.65)
P-value for trend		P<0.01	P<0.01
Educational level			
No education	32.23	1.00	1.00
Primary	48.82	0.46 (0.28-0.77)	0.54 (0.32-0.90)
Middle or higher	18.96	0.31 (0.18-0.59)	0.30 (0.15-0.61)
P-value for trend		P<0.01	P<0.01
Using refrigerator			
No	95.7	1.00	1.00
Yes	4.3	1.09 (0.49-2.41)	1.30 (0.57-2.97)

* Mutually adjusted and adjusted for age

Table 3. Risk of Oesophageal Cancer in Relation to Residential Environment

Risk factors	Distribution of cases %	Univariate OR (95%CI)	Multivariate* OR (95%CI)
Main type of drinking water at 10 years ago			
Tap water	32.7	1.00	1.00
Other water	67.3	9.24 (2.69-34.6)	5.49 (1.43-21.1)
Most common used fuel at 10 years ago			
Coal	91.9	1.00	1.00
Firewood	8.1	3.97 (1.17-13.6)	1.94 (0.57-7.01)
The situation of soot at home when cooking			
No	14.7	1.00	1.00
A little	64.9	1.52 (0.74-3.13)	1.18 (0.51-2.74)
More	20.4	2.72 (1.14-6.50)	1.98 (0.73-5.35)
P-value for trend		P=0.02	P=0.13
Irritation on eyes or throat by soot			
No	11.4	1.00	1.00
Occasional	43.6	2.24 (0.96-5.20)	1.95 (0.75-5.31)
Some time	40.3	4.03 (1.61-10.1)	2.97 (1.05-8.71)
Often	4.7	3.98 (1.16-13.7)	2.95 (0.47-8.06)
P-value for trend		P<0.01	P=0.08

* Mutually adjusted and adjusted for age, income, resident space and educational level.

Table 4. Risk of Oesophageal Cancer in Relation to Dietary Habits (consumption per week 10 years ago)

Risk factors	Distribution of cases (%)	Multivariate*	P-value for trend
	<i>Low→High intake</i>	Odds Ratio	
Rice	19, 26, 21, 34	1.00, 0.98, 1.06, 0.92	0.81
Wheat flour	23, 16, 41, 20	1.00, 0.98, 1.72, 0.78	0.60
Maize	16, 22, 29, 33	1.00, 1.81, 2.08, 1.77	0.41
Other food grain	19, 27, 28, 26	1.00, 1.80, 1.81, 1.87	0.19
Bean or bean's products	34, 19, 24, 23	1.00, 0.61, 0.69, 0.37	0.03
Vegetable	29, 30, 17, 24	1.00, 0.51, 0.28, 0.44	0.01
Pickled or salted vegetable	62, 5, 20, 12	1.00, 0.79, 1.97, 1.32	0.17
Pork	22, 38, 23, 17	1.00, 1.04, 1.35, 1.66	0.28
Eggs	47, 20, 10, 23	1.00, 1.26, 1.46, 0.93	0.98
Milk	90, 10	1.00, 1.24	–
Animal oils	88, 12	1.00, 0.81	–
Vegetable oils	44, 29, 12, 15	1.00, 1.41, 1.26, 1.85	0.17
Deep-fry food	15, 22, 30, 33	1.00, 1.86, 1.22, 1.57	0.57
Hot flavour food	76, 24	1.00, 1.19	–
Vinegar	16, 14, 20, 12	1.00, 0.58, 0.87, 0.37	0.03
Spring onion or garlic	15, 15, 35, 35	1.00, 1.18, 0.81, 0.65	0.19
Person's taste for salt	20, 59, 21	2.14, 1.00, 1.91	–

* Mutually adjusted and adjusted for age, income, resident space and educational level.

risk of oesophageal cancer and neither was the intake of deep-fried or hot flavoured food.

Table 5 shows the detailed results for dietary factors that were statistically significantly associated with the risk of oesophageal cancer in univariate and/or multivariate analysis. Consumption of beans or beans' products and the consumption of vegetables both showed a protective effect, with odds ratios of 0.37 (95% CI 0.61 to 0.82) and 0.44 (95% CI 0.21 to 0.95), respectively in the highest group of consumption. The trend was significant in both the univariate and multivariate analyses. High intake of pickled or salted vegetables showed an association with a moderately increased risk of oesophageal cancer (p trend=0.02) in univariate analysis, but the trend was no longer significant in multivariate analysis (p =0.17). The consumption of vinegar was significantly associated with a decreased risk, with an odds ratio of 0.37 (95% CI 0.16 to 0.86) for the highest group of consumption. The consumption of spring onion or garlic had a protective effect in univariate analysis (p trend=0.02) but this association was attenuated in multivariate analysis (p trend=0.19). A preference for a highly salted diet was associated with an increased risk (OR 1.91). Conversely, preference for a low salt diet was also associated with an increased risk (OR 2.14), compared with people with moderate salt preference.

Discussion

Previous studies have shown that the consumption of vegetables is associated with a decreased risk of oesophageal cancer (Gao et al., 1994; Tavani et al., 1994; Tzonou et al., 1996; Brown et al., 1998; Sharp et al., 2001; Cheng et al., 1995; Terry et al., 2001). Our data confirmed the protective effect of vegetable consumption. In this population, vegetables are the main source of vitamins. Vitamin C and

E can inhibit synthesis of N-nitroso compounds and stop the formation of a tumour (Steinmetz and Potter et al., 1991; Mirvish et al., 1986). In this study a protective role of vinegar consumption was found. This may be contributing to the function of vitamin C, because vinegar is made from some fruit such as persimmon in local area.

The present study shows a strong association between low socio-economic status and an increased risk of oesophageal cancer, which has been shown previously. Lu Jianbang et al (Lu et al., 2000) reported that high income was associated with a reduced risk of oesophageal cancer (OR=0.61) in the same area. In Zimbabwe, research showed that low socio-economic status conferred increased risks of oesophageal cancer in comparison with men of high socio-economic status (OR=1.5; 95% CI: 1.0 to 2.1) (Vizcaino et al., 1995). A case-control study in USA (Gammon et al., 1997) reported that risk of oesophageal cancer was higher among those with low income or education. In the present data, three out of four variables that were used to express socio-economic status were associated with the risk of oesophageal cancer. People with high income, large residential space and higher educational level had a decreased risk of the cancer.

A number of residential environmental factors were associated with an increased risk of oesophageal cancer. Drinking non-tap water was a strong risk factor (OR 5.57, 95% CI 1.45 to 21.4 in multivariate analysis). It was hypothesised that non-tap water may contain more nitrate, nitrite and ammonia nitrogen as well as micro-organisms, which could create carcinogenic compounds such as nitrosamines. Previous studies suggested that N-nitroso compounds and their precursor were associated with risk for oesophageal cancer (Lu et al., 1984) and some nitrosamines, such as N-nitroso-N-methylbenzylamine, is carcinogenic in human oesophageal epithelium in this area

Table 5. Detailed Analysis of Risk of Oesophageal Cancer in Relation to Dietary Habits (consumption per week 10 years ago)

Risk factors	Distubution of Cases %	Univariate OR (95% CI)	Multivariate* OR (95% CI)
Bean or bean's products(g/w)			
No	34.1	1.00	1.00
<25	18.5	0.87 (0.48-1.59)	0.61 (0.27-1.36)
25-79	24.2	0.72 (0.42-1.24)	0.69 (0.35-1.37)
80+	23.2	0.46 (0.26-0.90)	0.37 (0.16-0.82)
P-value for trend		P=0.02	P=0.03
Vegetable (g/w)			
<700	29.4	1.00	1.00
700-799	29.9	0.61 (0.36-1.06)	0.51 (0.26-1.01)
800-1399	17.1	0.36 (0.20-0.63)	0.28 (0.13-0.59)
1400+	23.7	0.49 (0.27-0.91)	0.44 (0.21-0.95)
P-value for trend		P<0.01	P=0.01
Pickled or salted Vegetables (g/w)			
No	62.1	1.00	1.00
<10	5.2	1.07 (0.46-2.48)	0.79 (0.29-2.18)
10-39	20.4	2.00 (1.11-3.67)	1.97 (0.98-4.01)
40+	12.3	1.73 (0.94-3.21)	1.32 (0.62-2.84)
P-value for trend		P=0.02	P=0.17
Vinegar (g/w)			
No	15.6	1.00	1.00
<10	13.7	0.71 (0.33-1.53)	0.58 (0.21-1.58)
10-39	42.2	0.88 (0.46-1.67)	0.87 (0.39-1.96)
40+	28.4	0.42 (0.22-0.81)	0.37 (0.16-0.86)
P-value for trend		P=0.01	P=0.03
Onion or garlic (g/w)			
No	14.7	1.00	1.00
<10	15.2	1.21 (0.61-2.39)	1.18 (0.49-2.86)
10-39	35.1	0.76 (0.42-1.36)	0.81 (0.38-1.70)
40+	35.1	0.57 (0.31-1.04)	0.65 (0.29-1.42)
P-value for trend		P=0.02	P=0.19
Person's taste for salt			
Low salt	19.9	1.85 (1.17-2.92)	2.14 (1.24-3.74)
Moderate salt	58.8	1.00	1.00
More salt	21.3	1.91 (1.22-2.99)	1.91 (1.13-3.17)

* Mutually adjusted and adjusted for age, income, resident space and educational level

(Lu et al., 1991). In Cixian of Hebei province, which is another high incidence area of oesophageal cancer in the same Taihang Mountain area as Linzhou, one ecological study showed that the well water polluted with nitrogen compounds was significantly related to the high incidence of oesophageal cancer (Yoshiharu et al., 1999). Both the presence of soot in the home and the feeling of irritation on eyes or throat by soot were associated with an increased risk, but the statistical significance disappeared after adjusting for socio-economic status. It means that the socio-economic status can influence the degree of pollution of the indoor air. In general less domestic air pollution is mostly associated with a higher socio-economic status.

The traditional staple foods in Linzhou are wheat, maize and other grains; the intake of animal protein is low. The staple foods and animal protein, which were reported to be

associated with oesophageal cancer in other studies (Mayne et al., 2001; De Stefani et al., 1999; Terry et al., 2001), were not found to be risk factors in Linzhou. High cereal fibre consumption is ubiquitous and consumption of animal proteins is too rare in the local diet for these associations to be detected. A high consumption of beans, which is the main source of protein in this area, showed a protective effect for oesophageal cancer. The same result was reported in Uruguay (De Stefani et al., 1999).

Another strong risk factor for oesophageal cancer in our study was an individual's taste for salt, with preference for a high salt intake (compared with moderate taste) being associated with an increased risk. Studies of correlation in China and Japan showed that salt intake was positively related to the mortality rate of oesophageal cancer (Lu and Qin et al., 1987; Nagai et al., 1982). This association was

also found in a previous case-control study in Linzhou (Lu et al., 2000) but not in other studies in China (Guo et al., 1994; Hu et al., 1994). Epidemiological evidence has supported an association between the risk of developing gastric cancer and the intake of salt and salted-preserved foods (Riboli and Norat et al., 2001; Tuyns et al., 1998). Salt can damage the gastric mucosa, increase DNA synthesis and cell proliferation. Salt is also co-carcinogenic and stomach cancer-promoting in experimental animals (Joossens and Geboers et al., 1986). Salt might play a similar role on oesophageal epithelia, in company with N-nitrosocarcinogens and nutrient deficiency, and promote occurrence of oesophageal cancer. In the present data an unexpected increased risk with preference of a little salt was observed. This may be due to the part of cases changed dietary habit before diagnosis. Some persons of high-risk population for oesophageal cancer, such as those with epithelioid hyperplasia and family history of carcinoma, may be more influenced by stories in the media about the relation between salt and health than the normal population. This can cause some bias.

In conclusion, oesophageal cancer is a disease related to poverty. High consumption of vegetables and beans are associated with decreased risk of oesophageal cancer and preference for a high salt diet is associated with increased risk. Our results also find an increased risk associated with having a main drinking water source other than tap water and a decreased risk associated with a high intake of vinegar.

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