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A Nested Case-Control Study of Oesophageal and Stomach Cancers in the Linxian Nutrition Intervention Trial

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Background. Rates of oesophageal/gastric cardia cancer in Linxian, a rural county in north central China, are among the world's highest, but the risk factors are not well understood.

Methods. A nested case-control study of oesophageal and stomach cancers was conducted within a cohort of 29 584 adults who participated in a randomized nutrition intervention trial. Information on participant characteristics collected during interviews before the trial began was compared between individuals who subsequently developed cancers of the oesophagus (N = 640) or stomach (N = 539), mainly cardia, and individually matched controls (control/case ratio = 5). Analyses were performed separately for oesophageal and stomach cancers using conditional logistic regression.

Results. For oesophageal cancer, tobacco smoking was associated with a significantly elevated risk, with a twofold increase among long-term smokers. Alcohol consumption was uncommon and not related to risk. High consumption of eggs or fresh vegetables was associated with 20% reductions in risk, and risk significantly declined as pre-trial body mass index (BMI), an indicator of long-term nutritional status, increased. No increases in risk were associated with intake of pickled vegetables or mouldy foods, although consumption levels at the start of the trial were low. Excess risks of 40–80% were found among individuals who had reported a history of cancer, notably of the oesophagus and stomach, in parents or sibs. For stomach cancer, only low BMI was significantly associated with elevated risk.

Conclusions. This study indicates that several risk factors for oesophageal and stomach cancers in Linxian, including smoking, nutritional deficiency, and familial cancer occurrence, resemble those in other areas of the world and contribute partly to the remarkably elevated rates in this area of China.

Linxian is a rural county in Henan province located on the border of Henan, Hebei and Shanxi provinces. It has one of the world's highest rates of oesophageal/gastric cardia cancer.[1] The mortality rates of this cancer exceed the Chinese national average levels by 10-fold and the levels among white Americans by 100-fold.[2] Although previous studies of oesophageal/gastric cardia cancer in China have provided a number of aetiological clues, no dominant risk factors responsible for the clusters of extremely high rates have been identified.[3] To further evaluate aetiological factors for these cancers, we conducted a nested case-control study within a cohort of the Linxian general population who participated in a randomized nutrition intervention trial.

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METHODS

Details of the study protocol for the intervention trial are presented elsewhere.[4,5] Briefly, approximately 30 000 residents aged 40–69 without disabilities or cancer were recruited in 1985 from the general population in four of Linxian's northern communes. All participants were interviewed, using a structured questionnaire, to obtain information related to usual dietary intake of several foods in the past 12 months, lifetime use of tobacco and alcohol, history of cancer in parents, siblings, children and spouses, prior medical conditions and other factors. Physical examinations, including blood pressure, height and weight, were conducted at the same time. All subjects were randomized into treatment groups according to a one-half replicate of a 2^4 factorial design.[4] Supplementation of micronutrients started in March 1986 and continued through May 1991.

During the study period, mortality from all causes and incidence of all cancers were ascertained, with little or no

TABLE 1 *Per cent distributions of study subjects according to sex, age, and education*

	Oesophagus		Stomach	
	Cases (N = 640)	Controls (N = 3200)	Cases (N = 539)	Controls (N = 2695)
Sex				
Male	49.8	49.8	63.1	63.1
Female	50.2	50.2	36.9	36.9
Age				
<50	18.6	19.0	14.3	15.1
50–54	21.4	21.2	18.2	17.5
55–59	21.6	22.3	25.4	26.7
60+	38.4	37.5	42.1	40.7
Education				
No formal schooling	53.8	52.3	51.2*	45.9
Primary school	42.1	43.0	45.2	49.2
≥High school	4.1	4.8	3.6	4.9

*$P = 0.10$

loss to follow up.[4,5] Diagnostic materials for cancers, including X-ray films and cytological, pathological and surgical specimens, were collected from local hospitals or from a study medical team which provided clinical and diagnostic services. They were reviewed by a panel of senior Chinese and American radiologists, cytologists, pathologists and surgeons. All those with cancers of the oesophagus (640 cases) and stomach (539 cases, with 435 arising in the gastric cardia and 104 elsewhere in the stomach) newly diagnosed during the 1986–1991 study period were enrolled as cases. Nearly all oesophageal cancers were squamous cell carcinomas, while the gastric cancers were adenocarcinomas. For each case, five controls were randomly selected from cohort members alive and free of cancer at least 90 days after the date the index case was diagnosed. The controls were matched to the index case on sex and age (± 1 year). Information obtained from the baseline interview and examination in 1985 was then compared between the cases and their matched controls.

Statistical analyses were performed separately for oesophageal and stomach cancers. Initial analyses examined cardia cancers separately from non-cardia cancers, but the two were combined because the results tended to be similar. Conditional logistic regression was employed to derive the odds ratio (OR) and 95% confidence interval (CI) after adjustment for potential confounders as well as vitamin/mineral intervention

TABLE 2 *Odds ratios for cancers of the oesophagus and stomach associated with tobacco use among men*

	Oesophagus			Stomach		
Smoking category	No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI
Never	69	1.0	—	95	1.0	—
Ever	249	1.8	1.4–2.4	244	1.1	0.8–1.4
Cigarette only	150	1.6	1.2–2.2	139	1.0	0.7–1.3
Cigarette and pipe	99	2.2	1.6–3.2	102	1.3	1.0–1.8
Years of smoking[b]						
<20	24	1.2	0.7–2.0	24	0.9	0.5–1.4
20–39	145	1.8	1.3–2.5	140	1.0	0.8–1.4
≥40	73	2.1	1.4–3.1	74	1.3	0.9–1.9
Trend test		$P < 0.01$			$P = 0.19$	
Average no. of cigarettes/day[b,c]						
<10	85	1.8	1.3–2.6	94	1.2	0.9–1.6
10–19	96	1.8	1.3–2.5	86	1.0	0.8–1.4
≥20	60	1.9	1.3–2.8	58	1.1	0.8–1.5
Pack-years[b,c]						
<10	54	1.5	1.0–2.2	60	1.0	0.7–1.5
10–19	84	2.1	1.5–3.1	69	1.0	0.7–1.4
20–29	43	1.6	1.0–2.4	47	1.1	0.8–1.7
≥30	60	2.0	1.4–3.0	62	1.2	0.9–1.8
Years since quitting smoking						
Current smokers	230	1.0	—	226	1.0	—
<3	13	1.1	0.6–2.2	8	1.0	0.4–2.3
≥3	6	0.5	0.2–1.2	10	0.8	0.4–1.7

[a]Odds ratios were adjusted for cancer history in first degree relatives.
[b]Odds ratios were compared to non-smokers.
[c]Tobacco smoked by pipe smokers was converted to cigarette equivalents.

TABLE 3 *Odds ratios for cancers of the oesophagus and stomach associated with intake of selected dietary items*

Indicator (times/month)	Oesophagus			Stomach		
	Cases	OR[a]	95% CI	Cases	OR[a]	95% CI
Fresh vegetables						
≤30	122	1.0	—	82	1.0	—
31–59	108	0.7	0.5–0.9	93	1.0	0.7–1.3
≥60	409	0.8	0.6–1.0	363	1.1	0.8–1.4
Trend test		$P = 0.08$				
Fresh fruits						
0	264	1.0	—	225	1.0	—
≥1	375	0.9	0.8–1.1	313	0.9	0.8–1.1
Meat						
0	230	1.0	—	189	1.0	—
≥1	409	0.9	0.7–1.1	349	0.9	0.7–1.1
Eggs						
0	292	1.0		226	1.0	—
≤5	267	0.8	0.7–1.0	236	1.0	0.8–1.2
>5	80	0.8	0.6–1.1	76	0.9	0.7–1.2
Trend test		$P = 0.05$				
Millet chaff						
0	614	1.0	—	518	1.0	—
≥1	25	1.5	0.9–2.3	20	1.3	0.8–2.1
Pickled vegetables						
0	597	1.0	—	499	1.0	—
≥1	42	0.9	0.6–1.2	39	0.9	0.7–1.3
Mouldy food						
0	619	1.0	—	514	1.0	—
≥1	20	0.8	0.5–1.3	24	1.1	0.7–1.8
Hot liquids						
0	176	1.0	—	125	1.0	—
≥1	463	0.9	0.7–1.0	413	1.0	0.8–1.3

[a]Odds ratios obtained from separate models for each variable and adjusted for years of smoking and cancer history in first degree relatives.

group.[6] To estimate cancer risks by tobacco intake, the amount of tobacco used by pipe smokers was converted to the equivalent number of cigarettes (1 g tobacco = 0.8 cigarettes). For dietary analyses the consumption frequency of each food was converted into a monthly intake and then categorized into three groups; if possible, usually based on the tertile distribution of intake among controls. Tests for trend across exposure levels for ordinal variables were performed using logistic regression by the level of the variable selected. All statistical tests were based on two-tail probabilities. Individuals with missing values for a variable of interest were excluded in the models examining that variable.

RESULTS

As expected by the study design, the age and sex distributions of the oesophageal and stomach cancer cases were similar to their matched controls (Table 1). Cases, however, were slightly less educated, but the difference was statistically significant for stomach cancer only.

Table 2 presents associations between tobacco use and risk of oesophageal and stomach cancers. Analyses were restricted to men since less than 2% of the female participants were smokers. An 80% significant excess risk of oesophageal cancer was found among individuals who reported ever regularly smoking cigarettes and/or pipes for 6 months or longer. The risks rose significantly with duration of smoking (trend test, $P < 0.01$), but were not influenced by amount smoked per day. No significant association was observed between stomach cancer and cigarette smoking, although the risk was of borderline significance among those smoking both cigarettes and pipes (OR = 1.3, 95% CI: 0.96–1.8).

Drinking alcoholic beverages was relatively uncommon, but reported by 22% of the cancer patients. No significant increases in risk of either oesophageal or stomach cancer were found among drinkers.

The frequency of consumption of several foods was related to subsequent risk (Table 3). Fresh vegetable and egg intakes were inversely associated with oesophageal

TABLE 4 *Odds ratios for cancers of the oesophagus and stomach associated with medical conditions and physical measurements at trial entry*

Indicators	Oesophagus			Stomach		
	Cases	OR[a]	95% CI	Cases	OR[a]	95% CI
Dysphagia	46	2.3	1.6–3.4	21	1.1	0.7–1.8
Chronic gastritis	49	1.2	0.9–1.6	43	1.4	1.0–2.0
Gastric ulcer	23	1.1	0.7–1.7	24	1.2	0.8–1.9
Duodenal ulcer	9	2.1	0.9–4.6	5	0.7	0.3–1.7
Bleeding gums	73	0.8	0.6–1.0	65	1.0	0.8–1.4
Inflammation at corners of mouth	138	1.0	0.8–1.2	114	1.1	0.9–1.4
Inflammation of tongue	148	0.9	0.7–1.1	134	1.1	0.9–1.4
White spots in mouth[b]	179	1.1	0.9–1.4	161	0.9	0.7–1.2
Night blindness	129	1.0	0.8–1.2	115	1.1	0.9–1.3
Height[b]						
Q1 (low)[c]	184	1.0	—	125	1.0	—
Q2	152	1.0	0.8–1.2	113	1.0	0.7–1.3
Q3	151	0.8	0.6–1.1	135	0.8	0.6–1.1
Q4	152	0.9	0.6–1.2	165	0.9	0.6–1.3
Trend test		$P = 0.40$			$P = 0.52$	
Weight[b]						
Q1 (low)[c]	181	1.0	—	112	1.0	—
Q2	155	0.9	0.7–1.1	153	1.2	0.9–1.5
Q3	154	0.8	0.7–1.1	139	1.0	0.7–1.3
Q4	149	0.7	0.5–0.9	134	0.8	0.6–1.1
Trend test		$P = 0.01$			$P = 0.07$	
BMI (weight/height^2)[b]						
Q1 (low)[c]	168	1.0	—	139	1.0	—
Q2	129	1.0	0.8–1.3	108	1.0	0.8–1.3
Q3	190	0.8	0.6–1.0	179	0.9	0.7–1.1
Q4	152	0.7	0.6–0.9	112	0.8	0.6–1.0
Trend test		$P < 0.01$			$P = 0.05$	

[a]Odds ratio obtained from separate models for each variable and adjusted for years of smoking and cancer history in first degree relatives and relative to those without the indicated medical condition or in the lowest measurement quartile.
[b]Assessed by physical examination.
[c]Cutpoints for quartiles of height were 154, 159, and 165 cm; for weight 50, 55, and 60 kg; and for BMI 20, 21, and 23.

cancer (trend test, $P < 0.10$), but not with stomach cancer. On the other hand, millet chaff, frequently eaten in the past but consumed by only a small per cent of the cohort by 1985, was linked to non-significantly increased risks for cancers of the oesophagus (OR = 1.5, 95% CI:0.9–2.3) and stomach (OR = 1.3, 95% CI:0.8–2.2). Fresh fruits, pickled vegetables, mouldy foods, and hot beverages were unrelated to the risks, with consumption levels in the mid 1980s being very low.

Table 4 examines associations between cancer risk and selected medical conditions reported during the baseline interview, and with height, weight, and body mass index (BMI) measured during the pre-trial physical examinations. Individuals with dysphagia had about a twofold elevated risk of developing oesophageal cancer in the subsequent 5 years, while the risk of stomach cancer was significantly increased among those reporting chronic gastritis (OR = 1.4, 95% CI:1.0–2.0). These findings likely reflect early or precursor stages of oesophageal and stomach cancers, respectively. No significant associations were observed with other reported medical conditions, including gastric ulcer, inflammations of the mouth and gums, and leukoplakia detected on physical examination.

Height, measured in 1985, was inversely related to the risk of both oesophageal and gastric cancers, although the trends were not significant. The risks, however, decreased significantly with increasing weight and BMI. When regression analyses incorporated both height and weight in the same model, the stronger protective effects appeared for weight.

For oesophageal cancer, a family (parents, sibs, children, spouse) history of any kind of cancer, which in Linxian primarily means cancers of the oesophagus and stomach, was associated with significantly elevated risk (OR = 1.4, 95% CI:1.1–1.8) (Table 5). The risks were

TABLE 5 *Odds ratios for cancers of the oesophagus and stomach associated with familial cancer history*

Indicators	Oesophagus			Stomach		
	Cases	OR[a]	95% CI	Cases	OR[a]	95% CI
Familial cancer history[b]						
No	360	1.0		332	1.0	—
Yes	279	1.4	1.1–1.8	206	1.0	0.8 1.3
Types of relatives with cancer[b]						
Father	119	1.6[c]	1.3–2.1	91	1.3[c]	1.0–1.7
Mother	148	1.8[c]	1.5–2.3	84	1.1[c]	0.8 1.4
Brother	45	1.4	0.9–2.2	41	1.4	0.8–2.2
Sister	28	1.6	0.8–3.1	21	0.9	0.4–1.7
Spouse	30	1.2[c]	0.8–1.8	27	1.0[c]	0.6–1.5
Number of first-degree relatives with cancer[d]						
0	377	1.0		350	1.0	—
1	190	1.5	1.1–1.9	142	1.1	0.8–1.5
>1	70	1.9	1.3–2.7	43	0.7	0.5–1.2
Trend test		$P < 0.01$			$P = 0.65$	

[a]Unless otherwise specified, odds ratios were adjusted for years of smoking and total number of siblings.
[b]Odds ratios relative to those without any familial cancer history.
[c]Adjusted for years of smoking only.
[d]Odds ratios relative to those without any cancer history in first degree relatives.

higher for a cancer history among parents or siblings than a spouse, and increased with the number of cancers diagnosed among first-degree relatives (parents, children or siblings). For stomach cancer, the risks were not elevated among individuals with a family history of cancer (OR = 1.0, 95% CI:0.8–1.3), although non-significant excess risks were found among those with a father or brother with cancer.

Factors that were significantly associated with cancer risk in the univariate analyses or that were of *a priori* interest (namely pickled vegetables, millet chaff, and alcohol intake) were selected for further multivariate analysis. Similar to the univariate analyses, years of smoking, low fresh vegetable and egg intake, low BMI, and cancer history in first-degree relatives, were each associated with elevated risks of oesophageal cancer, while for stomach cancer only low BMI was identified as a significant risk factor.

DISCUSSION

This nested case-control study, using data collected before cancer diagnosis and thus not subject to recall bias due to changes following cancer onset, evaluated several risk factors for oesophageal and stomach cancers in Linxian, a rural county in China with an exceptionally high incidence of these tumours. Prior studies involving interviews with cancer patients or their relatives and controls in Linxian and the retrospective assessment of diet and other factors failed to uncover any dominant risk factors that would account for the area's high rates.[3,7]

We first evaluated risk factors associated with these cancers in other locations. In western countries, tobacco smoking has been clearly linked to a substantially increased risk of oesophageal cancer and, in some studies, to a modest excess of stomach cancer.[8] Earlier studies in Linxian, however, had observed at most a small excess risk for cancers of the oesophagus and gastric cardia among smokers.[3,7] In the current study we found the risk for oesophageal cancer increased significantly with duration of tobacco use, with long-term smokers having about twice the risk of non-smokers. There was no dose-response relation with daily number of cigarettes, possibly because of the combination of cigarettes and hand-rolled tobacco leaves used by individuals, and their uncertainty as to actual amounts consumed, as well as to the relatively low amounts smoked and consequent limited range of exposure. It may also be that sustained exposure is more important than intensity of smoking in this population whose very high rates of oesophageal cancer cannot be explained by tobacco intake. Alcohol drinking, a major risk factor for oesophageal but not stomach cancer in western countries,[9] was not implicated in our study, but consumption levels were quite low.

Low intake of fresh fruits and vegetables and poor nutrition have been found to be major risk factors for oesophageal and stomach cancers in a number of epidemiological investigations[10,11] including several in

China.[12–17] We also found, as did one[7] of two earlier observational studies in Linxian,[3,7] that high consumption of fresh vegetables was associated with a reduced risk of oesophageal cancer. The findings are encouraging, since availability of these foods is increasing in Linxian. Prior surveys in Linxian have shown low serum levels of certain dietary nutrients.[1,18–20] We did not collect complete dietary information in this follow-up of trial participants and could not estimate usual adult intake levels of beta-carotene, vitamin C or other specific nutrients. However, as we have reported separately, after 5¼ years of intervention, cancer mortality was significantly reduced among intervention trial participants receiving daily supplementation with beta-carotene, vitamin E, and selenium.[5]

We failed to find significantly increased cancer risks associated with intake of mouldy foods or pickled vegetables, consistent with recent epidemiological studies in Linxian.[3,7] These foods have long been suspected as major risk factors for oesophageal and gastric cardia cancers in Linxian, and mass education campaigns to avoid their intake have taken place since the late 1970s. By 1985, less than 10% of residents consumed these foods, usually at low levels. Pickled vegetables were reported to be determinants of oesophageal cancer in other areas of China[21] and in Hong Kong,[22] but in Linxian do not appear to be a substantial contributor to the area's high cancer rates.

Consumption of eggs, a main animal protein source in Linxian, was related to a significantly reduced risk of oesophageal cancer. This finding could reflect socioeconomic or nutritional status (e.g. diet quality, calories), but may be a direct effect since eggs are high in several micronutrients such as retinol and riboflavin.[23] It is noteworthy that riboflavin and niacin supplementation was linked to lower incidence of oesophageal (but not stomach) cancer in this trial.[5]

Millet chaff, a locally consumed food, was associated with an increased risk of both oesophageal and stomach cancers, although the increases were not statistically significant. Millet gruel was reported to increase risk of oesophageal cancer in one study in Shanxi, China,[17] and silica fragments in millet bran have been postulated to play a role in Linxian.[24] Millet intake, however, was associated with reduced rates of oesophageal cancer in a correlation study in Shanxi.[21] In Linxian, only a few residents consumed this food by the mid1980s, precluding detailed assessment of risk and dose-response trends.

Body mass index was inversely associated with risk of both oesophageal and stomach cancers, with risks reduced by 20 30% among those in the upper BMI quartile. This index may partly reflect general nutrient status of the study participants. None of the subjects suffered from debilitating diseases at the start of the trial, so the increased risk with lower BMI may reflect long-standing undernutrition. Risk was higher among those of short stature, a characteristic determined in childhood, although low weight seemed a stronger correlate of risk. In the baseline examination we also obtained information on several medical conditions, such as night blindness or inflammation at the corners of the mouth, which may in part be nutritionally determined, but these were unrelated to subsequent development of cancer. Leukoplakia also was not a risk factor, but dysphagia for oesophageal cancer, and chronic gastritis for stomach cancer, were markers of risk.

We found that a history of cancer, which in Linxian is primarily of the oesophagus/gastric cardia, among parents and siblings was associated with increased risk of oesophageal cancer. This finding suggests, as reported elsewhere,[3,7,25–26] that genetic factors may play a role in the development of these cancers, although shared environmental exposures in early life may also be important. Further supporting an early life or genetic involvement is that, for oesophageal cancer, the OR were consistently higher for cancer in a parent or sib than in a spouse. We did not have information on the relatives with cancer, however, that might help distinguish genetic from environmental determinants of the familial occurrence.

In summary, as part of a randomized trial, this prospective study indicates that specific and general measures of nutrition, as well as tobacco smoking and familial cancer history, influence the risk of cancer in the Linxian population. The associations tended to be stronger for oesophageal than stomach cancer. Together with observations of protective effects of vitamin/mineral supplementation among the trial participants[5] from whom the cases and controls arose, the nutritional deficits observed in this analysis suggest that a strategy of dietary modification and supplements may help lower the exceptional rates of oesophageal and gastric cancers in endemic areas such as Linxian.

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