A Case Control Study on Risk Factors for Stomach Cancer in Urban Shanghai

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OBJECTIVE To examine the possible risk factors for stomach cancer among men and women in Shanghai, China.

METHODS In urban Shanghai, in-person interviews were completed for 311 cases newly diagnosed with stomach cancer of ages 30-74. Data were collected from April 1999 to October 1999 and compared to 1579 population-based controls (controls in three cancer studies used together). Information on demographic variables, smoking, diet consumption and others was collected from all subjects. Unconditional logistic regression was used to adjust the possible factors.

RESULTS Stomach cancer risk in men rose with smoking, eating hot and fried foods, chronic gastritis and a family history of gastric cancer among men; the risk among women was associated with the consumption of preserved,pickled and fried foods,heavy drinking, chronic gastritis, a history of ulcer disease and a family history of gastric cancer. A dose-response relationship was found (trends test,$P<0.01$) among men smokers. In contrast, the consumption of fresh vegetables and fruits, beans (especially soybeans) and soy products, plant oil, and eggs and egg products, was inversely associated with stomach cancer risk. After adjustment of the potential confounding variables, these associations remained significant.

CONCLUSIONS The present findings provide further evidence that smoking, eating salted foods (especially salted vegetables), oil-fried foods(including fried cereal, eggs, and peanuts), chronic gastritis, a family history of gastric cancer and so on increase the risk of stomach carcinoma in Shanghai. Fresh vegetables and fruits, beans and soybean products (even after adjusted for use of fresh vegetables and fruits), plant oil, and so on may have protective effects.

KEYWORDS: stomach cancer, etiology, case control study.

Stomah cancer is one of the most common cancers in China. It's the second most common malignancy, exceeded in frequency only by lung cancer in men in Shanghai, with an annual age-standardized incidence rate of 35.8/10,000 in 1999. Among women, it's the third most common malignancy, exceeded in frequency only by breast and lung cancer with an incidence rate of 17.5/10,000 [1]. To clarify risk factors for this common cancer, the National Cancer Prevention and Control Center and Information Center of China Ministry of Health organized the study on the detection methods of common malignancy incidence and the related risk factors. In urban Shanghai, as a part of the study, we conducted a large population-

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based case control study to explore the risk factors of stomach cancer.

MATERIALS AND METHODS

This study was part of a large population-based case-control study including cancers of the lung and breast. Between March 1, 1999 and October 31, 1999, permanent residents of 10 urban districts in Shanghai aged 30 to 74 years old who were newly diagnosed with stomach cancer were investigated. Of the 396 eligible patients, 85 (21.5%) were excluded because of death or other reasons. In the remaining 311 (78.5%; 198 men and 113 women) patients, 87.8% were confirmed by histology and 12.2% by other diagnostic methods including surgery, endoscopy, X-ray and ultrasound. Controls were selected among permanent residents of Shanghai, frequency matched to the expected distributions of cases by age (5-year category) and sex. A total of 1579 individuals were interviewed, including 651 men and 928 women.

After written informed consent was obtained, each subject was interviewed by a trained investigator. A structured questionnaire elicited information on demographic and socio-economic conditions, diet, cigarette smoking, alcohol drinking, history of selected diseases, family history of cancer and other factors. Questions on dietary factors included eating habits and usual food intake as long as 10 years before diagnosis. Specialists were responsible for the data quality control, such as monitoring the tape and checking the questionnaire. All data were coded and inputted two times.

Continuous variables such as food and BMI were divided into quartiles based on the distribution among controls, with approximately equal number of controls in each stratum. Other variables were divided according to professional information and the literature. Stomach cancer risk was estimated by odds ratios (ORs) and 95% confidence intervals (CI) using unconditional multiple logistic regression models. Further adjustment for other potential confounding variables was analyzed.

RESUITS

Because controls were selected based on the age distribution of three different cancers, the age distribution was different between cases and controls among men and women, as described in detail elsewhere(Tumour.2001,21:334-338:Risk of stomach cancer in relation to consumption of cigarettes and alcohol in Shanghai, in Chinese). So for the analysis, age was adjusted. The majority of cases included were in a 50-69 yrs age group (81.3% men and 73.5% women). The sex ratio between men and women was 1.75. The women control subjects were usually more highly educated than the patients.

Smoking

In this study, "smoking" indicates a quantity of usage of at least 1 cigarette per day for at least 6 months duration. Table 1 shows that among men, smoking was associated with an age-adjusted OR of 1.84 (95% CI1.20-2.81) for stomach cancer. Nevertheless, elevated risks were observed for individuals who smoked at a younger age and those who were heavy smokers. The age-adjusted OR for those with the smoking amount of 50 pack-years or over was 3.36 (95% CI =1.80-6.29). The risk of stomach cancer significantly increased if their smoking had started at less than an age of 18yrs. As there were only 11 women smokers, there was no statistical relation between smoking and stomach cancer among women.

Alcohol drinking

Here drinking is defined as a quantity of liquor consumption for at least 1 time per week over a period of 6 months, including spirituous liquor, beer, yellow rice wine and wine. According to the alcohol intake evaluated by Chinese Food Composition Tables [2], as is showed in Table 1, the age-adjusted OR was 1.29 for male stomach cancer, approaching to statistical significance; a increased risk (OR:1.89, 95%CI:1.17-3.07) was found among heavy drinkers (weekly liquor consumption >585g); but after adjusting for other confounding factors, such as smoking, etc., the OR decreased to 1.48(95%CI =0.90-2.45)(Table 1). For men no obvious relationship was observed among age of initial drinking, number of times and drinking years for stomach cancer (Not shown in the Tables). Among women, heavy drinking (weekly liquor consumption > 281g)enhanced the risk of stomach cancer, and there was a dose-response relationship between intake of liquor and stomach cancer.

Tea drinking

Tea drinking is defined here as a quantity of tea consumption for at least twice a week, with a 3-month duration. Risks of stomach cancer associated with tea drinking were reduced slightly, but not significantly, with age-adjusted OR of 0.88 (0.63-1.24) for male

and 0.70 (0.45–1.10) for female. However, it has not been found in further analysis that there was dose–effect relationship between tea drinking and protection of gastric cancer. In urban Shanghai, most of the residents drink green tea, with a proportion of 94.1% for men and 91.4% for women. Few people there drink black tea and oolong.

Ginseng

Ginseng intake in this study means that one takes ginseng at least once a week over a duration of 2 months. Studies of the relationship between ginseng and stomach cancer are limited. As shown in Table 1, among men, ginseng intake was inversely related to risk of stomach cancer, with an age–adjusted OR of 0.91 (95%CI=0.83–0.98). The dose–response relation was close to reaching a significant level for all ginseng consumption, with a P value of 0.06. Among women, the corresponding OR was 0.73 (95%CI=0.45–1.18) showing no significant trend.

Diet

Several eating habits were associated with an excess risk, including preference for high saltiness and hot soup/porridge. The age–adjusted ORs were 3.58(95% CI: 1.25–10.29) and 1.75 (95%CI: 1.16–2.66) in men and 1.05(95%CI: 0.49–2.24) and 2.41(95%CI: 1.38–4.20) among women, respectively. A risk which rose with frequent irregular meals was only seen with women, age–adjusted OR =3.06 (95%CI: 1.62–5.80). (Not listed in the Tables)

Table 2 presents the relationship of age–adjusted ORs based on consumption of various kinds of food and stomach cancer. Intake of preserved foods and fried foods was associated with an elevated risk, especially among women. On the other hand, fresh fruits, fresh vegetables, beans and soy products, and eggs and egg products tended to inversely relate to risk, especially in the highest quartile of intake. Consumption of preserved foods, particularly preserved vegetables, was one of the main risk factors, with age–adjusted OR of 2.26 in the highest quartile (trend test $P<0.01$). In both men and women, fried food consumption associated with excess risk.

Reduced risks were associated with intake of vegetable oil, bean products, eggs and egg products, fresh fruits and fresh vegetables, especially fresh beans, and so on. Of all food groups, the reduced risk was most pronounced for fresh fruits and fresh beans. The ORs of fresh fruits were 0.54 in the highest quartile of intake among men($P<0.01$), and 0.39 in the corresponding quartile among women ($P<0.01$). Similarly, the ORs of fresh beans were 0.47 (95%CI= 0.29–0.75) in the highest quartile of intake among men ($P<0.01$), and 0.35 (95% CI =0.19 –0.65) in the corresponding quartile among women($P<0.01$). Table 2.

Other factors

In this study, the mental state of patients before diagnosis was considered to be in three levels, including better condition, normal and worse condition (also depression). Compared with controls, patients tended to have less education and worse mental state. The age–adjusted OR was 2.66(95%CI=1.04–6.79) in educationally disadvantaged women. Increased risk was seen in those under depression, with ORs of 1.76 (95%CI=1.15–2.68) among men and 2.12 (95%CI= 1.34–3.33) among women. Not shown in the Tables.

History of chronic gastritis, especially atrophy gastritis (CAG), conferred about a 2–fold increased risk for all stomach cancer, with age–adjusted ORs of 1.57 and 2.41 among men and 1.98 and 2.37 among women, respectively. There was a high proportion of history of stomach and duodenal ulcer among women patients (OR:2.76, 95%CI:1.53–4.97). Information on surgery for stomach and duodenal ulcer was not associated with stomach cancer. The excess risk pertained to those who had stomach polypi among women (OR:7.27), but not among men. The elevated risk was also observed among those with a family history of gastric cancer, both in men and women, with ORs of 2.85 (95%CI=1.69–4.80) and 2.60 (95%CI= 1.43–4.73) respectively. Not shown in the Tables.

Multivariate analysis

With an unconditional logistic regression model, we analyzed the risk factors for men and women. Table 3 shows that stomach cancer risk in men increased with cigarette smoking, eating hot and fried foods, chronic gastritis, emotional depression, a lower ability for controlling their behavior and a family history of gastric cancer; the risk among women was associated with less education, the consumption of preserved, salted and fried foods, heavy drinking, emotional depression, chronic gastritis, history of ulcer disease and a family history of gastric cancer. In contrast, the consumption of the fresh vegetables and fruits, beans (especially soybeans) and soy products, plant oil, and eggs and egg products, was inversely associated with stomach cancer risk.

Table 1. Odds ratio (OR) and 95% CI of stomach cancer in relation to life habits

	Men				Women		
	Case/control	OR[a]	*P* for trend		Case/control	OR[a]	*P* for trend
Smoking status							
non-smoking	45/231	1.00			102/866	1.00	
ever-smoking	153/420	1.84(1.20-2.81)			11/62	1.03(0.42-2.51)	
Pack-year of smoking				Pack-year of smoking			
<20	52/154	1.40(0.73-2.71)		<20	6/47	0.66(0.20-2.21)	
20-34	49/118	1.56(0.90-2.69)		≥20	5/15	2.39(0.63-9.12)	
35-49	22/83	1.81(1.10-2.99)					
≥50	30/65	3.36(1.80-6.29)	*P*<0.00				*P*=0.56
Age of starting smoking				Age of starting smoking			
>25 year old	33/123	1.59(0.92-2.77)		>18 year old	7/23	2.14(0.88-5.19)	
19-25 year old	67/185	1.74(1.06-2.83)		≤18 year old	4/39	0.75(0.26-2.15)	
≤18 year old	53/112	2.34(1.37-4.00)	*P*<0.00				*P*=0.69
Drinking status							
non-drinking	96/358	1.00			103/875	1.00	
ever-drinking	102/293	1.29(0.89-1.85)			10/53	1.67(0.82-3.39)	
Liquid consumption				Liquid consumption			
<106 g/week	14/56	0.87(0.42-1.82)		<106 g/week	2/29	0.76(0.18-3.29)	
106-280 g/week	21/72	1.18(0.64-2.15)		106- g/week	4/16	2.42(0.78-7.49)	
281-585 g/week	26/82	1.03(0.58-1.82)		>281 g/week	4/8	3.46(0.89-13.42)	*P*<0.01
>585 g/week	41/83	1.89(1.17-3.07)	*P*<0.05				
Regular tea drinking							
no	65/204	1.00			84/607	1.00	
yes	133/447	0.88(0.63-1.24)			29/321	0.70(0.45-1.10)	
Tea consumption(10g/year)				Tea consumption(10g/year)			
no	66/207*	1.00		no	84/614**	1.00	
≤63.5-	30/111	0.77(0.47-1.27)		≤12.5	6/80	0.59(0.25-1.39)	
63.5-	35/111	0.92(0.57-1.49)		12.6-	7/80	0.70(0.31-1.58)	
136.4-	37/109	1.01(0.63-1.61)		36.1-	8/77	0.85(0.39-1.83)	
>245	30/113	0.82(0.50-1.35)	*P*=0.99	>85	8/77	0.78(0.36-1.67)	*P*=0.32
Regular ginseng intake							
no	145/420	1.00			89/700	1.00	
yes	53/231	0.91(0.83-0.98)			24/228	0.73(0.45-1.18)	
Ginseng consumption(10g/year)				Ginseng consumption(10g/year)			
no	150/436***	1.00		no	90/722****	1.00	
≤3.4	6/45	0.41(0.17-0.99)		≤2	5/41	0.80(0.31-2.11)	
3.5-	19/58	0.97(0.56-1.68)		2.1-	5/53	0.70(0.27-1.80)	
10.1-	12/56	0.64(0.33-1.23)		8.1-	8/57	1.06(0.49-2.30)	
>30	11/56	0.60(0.30-1.17)	*P*=0.06	>30	5/55	0.61(0.24-1.57)	*P*=0.36

a:adjusted for age; *4, **7, ***21, ****23 not applicable.

DISCUSSION

In this population-based,case control study of stomach cancer conducted among residents in urban Shanghai, we found cigarette smoking to be a key risk factor. It was consistent with the previous study of stomach cancer in Shanghai in 1989, which showed that about 30% of stomach cancer patients were attributed to smoking, (OR =1.5)[3]. An increased risk of stomach cancer among cigarette smokers has been observed in

numerous case-control and cohort studies [3-11]. Among studies that reported a positive association, most found the excess risk to be moderate, with ORs ranging approximately from 1.5 to 2.5 overall and increasing among heavy, young-age and long-term smokers. Tobacco smoke contains a variety of carcinogenic agents, including N-nitroso compounds and nitrogen oxides that may promote endogenous formation of N-nitroso adducts, which have been linked to gastric carcinogenesis. An association with alcohol drinking has not been consistently demonstrated in previous epidemiological studies of stomach cancer. No increased risk was found in the previous study in Shanghai in 1989 [3], but there have been some reports of elevated risk for stomach cancer[5]. In this study, we found that heavy drinking was associated with the risk of stomach cancer among women. Considering the lower proportion of females drinking alcohol (PARP< 5%), the drinking is not an important risk factor among women in the country.

Green tea contains Vitamin C, E and in addition, the cancer-inhibiting effects of polyphenls and other compounds[6]. The reason that we didn't find a reduced risk with tea drinking may be due to the small sample size. With the high proportion of green tea drinking among residents, it is reasonable to further study the relationship between green tea and stomach cancer in Shanghai.

There are few reports concerning ginseng and stomach cancer [7,8]. In our study, only men but not women, showed a significant reduced risk of stomach cancer among those intaking ginseng, but no dose-response relation was apparent. It's necessary to further study the relationship between ginseng use and stomach cancer, to focus on the biologic effects of ginseng and to collect more epidemiological data.

Dietary factors are generally considered to play a major role in gastric carcinogenesis. Most studies have demonstrated a reduced risk associated with consumption of fresh fruits and vegetables [9-11]. Our study also suggested that there is a protective effects of ingesting fresh vegetables and fruits which contain high concentrations of antioxidant vitamins, such as vitamin C and E. These agents may block the intragastric formation of carcinogenic N-nitroso compounds. Similarly, the inverse association with an intake of soy products may be related to the various proteinase inhibitors, unsaturated fatty acids and other antioxidant agents. Moreover, much more attention has been paid to the healthful effect of soy isoflavones and glucosides with the flavonoids as its aglycones (mainly including soy glycoside and genistin), as well as soy saponin.

The increased risks we observed with high intake of preserved foods, particularly preserved vegetables among women, fried foods and highly pickled foods are consistent with previous observations. Ji et al. had reported that intake of preserved foods in both sexes showed a dose-response relation [9] with stomach cancer in Shanghai. Preserved and fried foods are the possible sources of N-nitroso compounds and PAH (polycyclic aromatic hydrocarbon). Our study also suggested that eating habits may be linked to excess stomach cancer, such as a preference for intake of

Table 2. Odds ratio (OR) and 95% CI of stomach cancer in relation to quartiles of food group consumption

	Men					Women				
Food groups	Q1(low)	Q2	Q3	Q4(high)	*P* for trend	Q1(low)	Q2	Q3	Q4(high)	*P* for trend
Fresh vegetables	1.00	0.60*	0.64*		*P=0.01*	1.00	0.87	0.32*		*P<0.01*
Fresh fruits	1.00	0.71	0.52*	0.54*	*P<0.01*	1.00	0.54*	0.67	0.39*	*P<0.01*
Vegetable oil	1.00	0.84	0.68	0.58*	*P*<0.05	1.00	0.78	1.01	0.87	*P=0.94*
Soybean products	1.00	0.90	0.60*	0.41*	*P<0.01*	1.00	0.87	0.85	0.85	*P=0.56*
Fresh beans	1.00	0.63*	0.85	0.47*	*P=0.01*	1.00	0.79	0.54*	0.35*	*P<0.01*
Dry beans	1.00	0.90	1.05	0.77	*P=0.42*	1.00	0.90	0.63	0.48*	*P=0.01*
Eggs and products	1.00	1.02	0.82		*P=0.27*	1.00	1.12	0.44*		*P=0.01*
Preserved foods	1.00	1.16	1.29	0.96	*P=0.60*	1.00	1.50	1.60	2.20	*P<0.01*
Preserved vegetables	1.00	0.97	1.30	1.09	*P=0.46*	1.00	1.61	2.67*	2.26*	*P<0.01*
Oil fried foods	1.00	0.82	1.11	1.27	*P=0.21*	1.00	1.35	1.36	2.46	*P<0.01*
Fried flour-products	1.00	0.98	1.71*		*P<0.01*	1.00	1.17	1.70*		*P<0.05*

*OR significant Q1: first quartile Q2: second quartile Q3: third quartile Q4: highest quartile

Table 3. Multivariate analysis of main risk factors of stomach cancer in urban Shanghai

Model	Variables	β	SE(β)	*P* value	OR	95%CI	
						lower	upper
I(Men)	Age (year)	−0.0914	0.0466	0.0496	0.913	0.833	1.000
	Smoke consumption(pack-year)						
	<20	0.2892	0.3090	0.3493	1.335	0.729	2.447
	20–34	0.3485	0.2623	0.1840	1.417	0.847	2.369
	5–49	0.4217	0.2451	0.0853	1.524	0.943	2.464
	≥50	0.8675	0.3166	0.0061	2.381	1.280	4.428
	Hot soup or porridge*	0.3495	0.1551	0.0242	1.418	1.047	1.922
	Fresh fruits*	−0.4837	0.2514	0.0544	0.617	0.377	1.009
	Fresh beans*	−0.7153	0.2669	0.0074	0.489	0.290	0.825
	Soybean products(g/month)						
	330.1–	−0.0971	0.2258	0.6672	0.907	0.583	1.413
	631.1–	−0.5194	0.2497	0.0375	0.595	0.365	0.970
	>1033	−0.9005	0.2725	0.0010	0.406	0.238	0.693
	Vegetable oil*	−0.5544	0.2490	0.0260	0.574	0.353	0.936
	Fried flour-products*	0.6043	0.2234	0.0068	1.830	1.181	2.835
	Ability of mental-control	0.3765	0.1626	0.0206	1.457	1.059	2.004
	Mental condition before diagnosis	0.5551	0.2171	0.0106	1.742	1.138	2.666
	History of chronic gastritis	0.4478	0.2252	0.0468	1.565	1.006	2.433
	Family history of lineal relative	1.0497	0.2903	0.0003	2.857	1.617	5.046
II(Women)	Age (year)	0.1040	0.0614	0.0901	1.110	0.984	1.251
	Education	−0.2120	0.1171	0.0702	0.809	0.643	1.018
	Fresh vegetables*	−0.9271	0.3766	0.0138	0.396	0.189	0.828
	Fresh fruits*	−0.8488	0.3423	0.0132	0.428	0.219	0.837
	Fresh beans(g/month)						
	695.1–	−0.1155	0.2734	0.6727	0.891	0.521	1.522
	1500.1–	−0.6274	0.3129	0.0450	0.534	0.289	0.986
	>3150	−1.0743	0.3479	0.0020	0.342	0.173	0.675
	Eggs and egg-products*	−0.8604	0.3320	0.0095	0.423	0.221	0.811
	Preserved vegetables(g/month)						
	60.1–	0.5327	0.3643	0.1436	1.704	0.834	3.479
	180.1–	0.9836	0.3384	0.0037	2.674	1.378	5.190
	>450	0.8257	0.3480	0.0177	2.284	1.155	4.517
	Fried foods*	1.1867	0.3285	0.0003	3.276	1.721	6.237
	Liquid consumption*	1.8080	0.7415	0.0148	6.098	1.426	26.084
	mental condition before diagnosis	0.6882	0.2378	0.0038	1.990	1.249	3.171
	History of ulcer disease	0.6748	0.3114	0.0302	1.964	1.067	3.615
	History of chronic gastritis	0.8596	0.2651	0.0012	2.362	1.405	3.971
	Family history of lineal relative	1.0728	0.3348	0.0014	2.924	1.517	5.635

Model I and II rational test (Ho: β =0): $P<0.0001$

*Fresh vegetables, fried-flour products, eggs and egg products refer to highest trichotomy compared to first; others is highest quartile to first.

boiling hot soup/porridge, which may cause lesions in the gastric mucosa. Since these variables may be especially prone to recall bias, further studies are needed, especially in other populations.

Socioeconomic status (SES) is usually determined by education and family income. A recent cohort study

conducted in Holand showed that after adjustment for age, a lower overall stomach cancer risk was found among men with the highest attained level of education [12]. In our study, we also found that education was related to stomach cancer for women, but not for men, perhaps due to overall lower education in women. From the point of a biologic mechanism for stomach caner, less education and lower income are not independent risk factors, but confounded by other risk factors. The association with mental depression and poor emotional control may influence immunity and hormonal status.

Chronic gastritis, especially CAG (chronic atrophic gastritis), has been consistently linked to stomach cancer[13]. The pathogenesis of gastric cancer (GC), is thought to involve a multistep and multifactorial process. Research in a population in Linqu County, China, discovered that over 90% of adults had chronic atrophic gastritis, 50% had developed to superficial intestinal metaplasia(IM), and 20% had mild dysplasia (DYS).

Although environment factors may be the major cause of stomach cancer, heredity also plays an important role. The contribution of environmental and genetic factors has been explored in several high-incidence areas. A great deal of data have shown that stomach cancer has a familial susceptibility and familial aggregation, with a 2-3 fold risk for stomach caner. Recently, a study in Japan observed that a positive history of stomach cancer in one or more first-degree relatives was associated with a significantly increased risk of death from the disease in both men (RR 1.60; 95% CI 1.11-2.31) and women (RR 2.47; 95% CI 1.50-4.06) [11]. A multicenter, population-based case control study in the United States found that a familial tendency, particularly for non-cardia gastric tumors, was largely explained by an association with a family history of stomach cancer (OR = 2.52, 95% CI 1.50-4.23) [15]. Our data support the hypothesis that heredity is related to stomach cancer, even if adjusted by other contributing factors, and that the family history of stomach cancer in a lineal relative is an independent risk factor.

Although our findings are consistent with most previous studies of stomach cancer, several potential limitations of our study should be noted. The main reason for non-participation among cases was death, thus raising the possibility of survival bias. Efforts were made to minimize potential recall bias in various ways, including extensive training of interviewers, use of a standardized questionnaire and ascertainment of the usual diet 10 years prior to the interview. Certain variables relevant for gastric cancer etiology were not collected in our study, including carriage of *Helicobacter pylori*, histological type and occupational exposure, so that confounding or modifying effects would be difficult to detect.

It's necessary to expand the number of cases and to further study the risk factors of stomach cancer and to understand the function of green tea and ginseng and so on based on different histological types.

In conclusion, our population-based case control study of stomach cancer in Shanghai confirmed previous reports of protective effects associated with high consumption of fresh vegetables, fruits, beans, soy products and so on, and elevated risks associated with a high intake of preserved and pickled foods, hot and fried foods, irregular meals and so on. It is advised to have a healthful diet. One should intake more fresh food, consume less preserved and fried food; do not start smoking or stop if you are a smoker; give up heavy drinking; remain optimistic; treat chronic gastric disease in a timely manner; and frequently screen those who have a family history of stomach cancer. Following this advice may reduce the incidence of gastric cancer.

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