RESEARCH COMMUNICATION

Allium Vegetables and Stomach Cancer Risk in China

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Abstract

Although the incidence of stomach cancer has been declining, it remains the second leading cause of cancer death worldwide. Potential protective effects of allium vegetables against cancer have been reported by a few epidemiologic studies in Chinese populations, but the sample sizes of these studies were relatively small. We examined the associations between allium vegetable consumption and stomach cancer in a large population-based case-control study in Shanghai (750 cases and 750 age- and gender-matched controls) and Qingdao (128 cases and 128 age- and gender-matched controls). Epidemiological data were collected by a standard questionnaire, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression in SAS. After adjusting for matching variables, education, body mass index, pack-years of smoking, alcohol drinking, salt intake, and fruit and vegetable intake, inverse relationships with dose response pattern were observed between frequency of onion intake and stomach cancer in Qingdao (*P* for trend=0.02) and Shanghai (*P* for trend=0.04) populations. In Shanghai, negative dose-response relationships were observed between monthly intake of onions (*P*=0.03), monthly intake of garlic stalks (*P*=0.04) and distal cancer (but not with cardia cancer). Negative association was also noted between intake of garlic stalks (often vs. never) and risk of stomach cancer in Qingdao (OR=0.30; 95% CI: 0.12-0.77). Our results confirm the protective effect of allium vegetables (especially garlic and onions) against stomach cancer.

Key Words: allium vegetable - garlic - onion - stomach cancer - risk factor - epidemiology - China

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Introduction

Allium vegetables, which include garlic, onions, shallots, leeks, scallions and chives, contain high levels of flavanols and organosulfur compounds. From animal and in vitro studies, allium vegetables have been shown to have an anticarcinogenic potential of bioactive compounds, e.g. allyl sulfides (Nakagawa et al., 2001; Wargowich et al., 1996), and an antibacterial effect against Helicobacter pylori (H. pylori), which is known to be important in stomach carcinogenesis (Jonkers et al., 1999). The antibacterial effect, which is attributed to garlic's thiosulfinate concentration, has recently been quantified. Studies have reported that garlic extract could inhibit H. pylori growth in vitro (Canizares et al., 2004; Garcia-Arata et al., 1999; Sivan et al., 1997). More general anticarcinogenic effects may derive from the organosulfur compounds in garlic that are responsible for its odor and flavor (Lawson et al., 1991). Previous animal studies have also shown that a compound extracted from garlic and onions, diallyl sulfide, has strong cancer inhibitory properties (Nakagawa et al., 2001; Reddy et al., 1993; Belman 1983; Wargowich 1987; Wargowich et al., 1988).

Because allium vegetables, especially garlic and onions, have been shown to have anticarcinogenic potential and an antibacterial effect against H. pylori, we hypothesized that allium vegetable intake is protective against stomach cancer

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development. Epidemiological studies of stomach cancer in relation to dietary habits suggest that consumption of allium vegetables, especially garlic and onions, may reduce the risk of stomach cancer (Table 1). Review and meta-analysis of garlic and stomach cancer studies have been published (Fleischauer et al., 2000; Fleischauer and Arab, 2001). In our study, we examined the relationship between allium vegetable intake and stomach cancer using a large matched case-control study conducted in Shanghai and Qingdao, China.

Materials and Methods

Study Population. Shanghai is a municipality under the direct jurisdiction of the Chinese central government. It is the largest economic and trade center in the country and a comprehensive industrial base. Age-adjusted (world standard) incidence rate of stomach cancer was 38.2/100,000 during 1993-1994, which is the second highest cancer incidence in Shanghai after lung cancer (Jin et al., 1994). Qingdao (Tsingtao) city is located in the southeastern Shandong province in East China on the Yellow Sea. Qingdao is a major fishing and trade port of China and is the leading industrial city of Shandong. Description of the case-control study population (eligibility of study participants and response rates) and the collection of epidemiological data have been published elsewhere (Yu et al., 1995). Briefly, a population-based case-control study was conducted in Shanghai and Qingdao in 1991. Data included interview questionnaires and medical record reviews. Eligible cases were individuals with incident primary stomach cancer who were under 80 years of age, and who were diagnosed between October 1991 and December 1993 among residents of Shanghai and Qingdao. Case-finding was organized by the Health Station for Disease Control in each of the study areas. Community controls were

Table 1. Epidemiological Studies of Allium Vegetables and Stomach Cancer

Author, year	Country and Subjects	Vegetables	Consumption	OR (95% CI) or RR (95% CI)	Confounder Adjustment
Case-control					
Tajima, 1985	Japan	Onion	<1	Referent	Age and sex
	93 cases, 186 controls	1-3	1.15 (NA)		
			≥4	2.13 (NA)	
You, 1989	China	Garlic	0 kg/year	Referent	Age, sex income and other
	564 cases,		0.1-1.5 kg/year	0.8 (0.5-1.2)	allium vegetables
	1131 controls		>0.5 kg/year	0.7 (0.4-1.0)	
		Garlic Stalks	0 kg/year	Referent	
			0.1-0.5 kg/year	1.0 (0.7-1.4)	
			>0.5 kg/year	0.7 (0.5-1.1)	
		Onions	0 kg/year	Referent	
			0.1-0.5 kg/year	0.8 (0.6-1.0)	
			>0.5 kg/year	1.0 (0.8-1.4)	
		Scallions	≤9.0 kg/year	Referent	
			9.1-18.0 kg/year	1.0 (0.8-1.3)	
			>18.0 kg/year	0.8 (0.5-1.0)	
		Chinese Chives	<1.5 kg/year	Referent	
			1.6-3.7kg/year	0.7 (0.6-1.0)	
			>3.7kg/year	0.6 (0.4-0.8)	
Buiatti, 1989	Italy	Cooked garlic	Tertile low	Referent	Age, sex, study are, SES,
	640 males, 376 females,		Medium	0.6 (NA)	residence migration from
	1159 controls		High	0.4 (NA)	South, family history of
		Raw onions	Tertile low	Referent	stomach cancer, and Quetelet
			Medium	0.8 (NA)	index
			High	0.8 (NA)	
		Onion/garlic	Tertile low	Referent	
		condiments	Medium	1.0 (NA)	
			High	0.8 (NA)	
Hansson, 1993	Sweden	Garlic	0 serv/mo	Referent	Age, sex and province
	218 males, 120 females,	> 0	0.89 (0.64-1.24)		
	669 controls	Onion	0	Referent	
			3 times/month	0.84 (0.54-1.29)	
			7 times/month	0.83 (0.56-1.22)	
			11 times/month	0.84 (0.56-1.24)	
		Leek	0	Referent	
			0.9 times/month	0.76 (0.56-1.04)	
			3 times/month	0.63 (0.44-0.92)	

Table 1. Epidemiological Studies of Allium Vegetables and Stomach Cancer (continued)

Author, year	Country and Subjects	Vegetables	Consumption	OR (95% CI) or RR (95% CI)	Confounder Adjustment
Ji, 1998	China	Allium vegetables	Male		
	770 males, 354 females,		Q1 (low)	Referent	Age, income, education, and
	1451 controls		Q2	1.3 (0.9-1.7)	smoking and alcohol drinking
			Q3	1.1 (0.8-1.5)	(males only)
			Q4 (high)	0.8 (0.6-1.1)	
			Female		
			Q1 (low)	Referent	
			Q2	0.9 (0.6-1.3)	
			Q3	0.8 (0.6-1.2)	
			Q4 (high)	0.8 (0.5-1.2)	
Gao, 1999	China	Garlic Raw	<1 serv/mo	Referent	Age, sex, income, alcohol,
	110 males, 43 females,		≥4 serv/mo	0.31 (0.2-0.4)	smoking, tea intake, leftover
	234 controls	Onion	<1 serv/mo	Referent	gruel, pickled vegetables,
			≥4 serv/mo	0.17 (0.08-0.36)	meat, fruit, tomatoes, eggs,
		Welsh onion	<1 serv/mo	Referent	snap bean
			≥4 serv/mo	0.22 (0.15-0.31)	
		Chinese chives	<1 serv/mo	Referent	
			≥ 4 serv/mo	0.40 (0.17-0.94)	
De Stefani, 2001	160 cases	Allium vegetables		0.56 (0.34–0.92)	Age, gender, residence,
	320 controls				total enery intake, fruit intake
Cohort					
Dorant, 1996	Netherlands	No supplements		Referent	Age, sex, alcohol, smoking,
	106 males,	Garlic supplements only		1.27 (0.6-2.6)	vit c, β-carotene, family history
	33 females,	Other supplements		Referent	of stomach cancer and stomach
	3123 subcohort	Garlic and other		1.28 (0.5-3.7)	disorders, other allium vegetables
	members	supplements Onion	0 /day	Referent	
			≥0.5 /day	0.5 (0.26-0.95)	

selected from the same street or community where the respective cases resided and were matched to the cases by age (within 3 years) and gender. Among the eligible persons, the one living in the nearest residence to that of the case was selected as control. The Shanghai study included 750 stomach cancer cases (128 cardia and 622 distal), and 750 controls, and the Qingdao study included 201 stomach cancer cases and 201 controls.

Epidemiological data collection. Interviews with the study participant were conducted by trained interviewers at the participant's home using a structured, pilot-tested questionnaire. Information collected included: (1) demographic characteristics, (2) medical history of subjects and family members, (3) tobacco use, (4) alcohol consumption, and (5) dietary information including tea drinking, vegetable and fruit intake, salt consumption, and allium vegetable consumption. The participants were asked questions about dietary factors in the 80s (i.e. approximately 10 years before diagnosis for cases). Allium vegetable data included frequency of allium vegetable intake and family monthly consumption of each vegetable in kilograms. Allium vegetables included were onion leaves, scallions, garlic stalks, garlic, onions and Chinese chives.

Statistical analysis. Minimum detectable ORs were calculated for various exposure proportions in controls, using a two-sided test, 0.05 α level and 80% power for univariate analysis. Our Shanghai study (with 750 cases and 750 controls) was adequate to detect ORs ranging from 0.52 to 0.72, and when frequency of exposure was 5-55% in controls. Because the etiology of the proximal part of stomach cancer (cardia and gastroesophageal junction) is different from that in other parts of the stomach (distal), and because there may be subsite-specific differences in stomach cancer risk associated with allium vegetable consumption (Dorant et al., 1996), we evaluated whether the role of allium vegetable consumption varies in cardia and distal cancer in the Shanghai study. Our Shanghai study (128 cardia cases and 622 distal cases) was adequate to detect ORs ranging from 0.24 to 0.44 for cardia cancer, and ORs ranging from 0.49 to 0.69 for distal cancer, and when frequency of exposure was 5-55% in controls. Two types of analyses were conducted, first for all stomach cancer, then stratified by tumor location (cardia and distal). In Qingdao, because the stomach cancer cases were not distinguished by tumor location, only all case analyses were performed. Based on the power calculation for univariate analysis, our sample size (201 cases and 201 controls) was adequate to detect OR ranging from 0.31 to 0.52, and when the frequency of exposure was between 5-55% in controls. Pack-years of smoking were computed by multiplying the number of packs of cigarettes smoked per day by the total years of smoking. Body mass index (BMI in kg/m2) was calculated by dividing the body weight by the height squared. Intake of vegetables and fruit were categorized into "never", "occasional" d(few times/year), "less often" (few times/month), and "often" (few times/week). For each type of allium vegetable (onion leaves, scallions, garlic stalks, garlic, onions and Chinese chives), frequencies of intake were collected, using the same categories as noted above. Because of the limited numbers in these categories, "occasional", and "less often" categories were collapsed. The categorization of monthly intake (in kg) was based on the distributions in the controls. Median distribution of the controls was used as the cutoff point. Monthly intake was categorized into "never", "low" and "high". The "never" category was used as a referent. Conditional logistic regression maintaining the matched-pairs was used to estimate the effect of allium vegetable intake on stomach cancer risk while adjusting for education, BMI, pack-years of smoking, alcohol drinking, salt intake, and vegetable and fruit intake. Trend test was computed by treating the categorical variable as a continuous predictor in the conditional logistic regression models. All analyses were conducted in SAS version 8.12.

Results

Table 2 shows the means and distribution of demographic and potential confounding variables by case-control status in Shanghai and Qingdao. As expected in an age- and gender-matched case-control study, similar means of age and gender distribution were observed in cases and controls (62.9 years and 62.4 years in Shanghai and 61.0 years and 60.8 years in Qingdao). There were more men (64-71%) than women (29-36%) in both places. In Shanghai, cardia cases were generally older (mean age=66 years) and more often men (69%) than distal cases (mean age=62 years; 63% men). Most people had education ≤ high school (>93% in both cases and controls). The mean of BMI was similar in cases and controls, with slightly higher BMI in Qingdao than in Shanghai. More smokers were found in the stomach cancer group (48-64%) than in the controls (43-54%), with a slightly higher proportion of smokers in distal (49%) than in cardia cancer (45%) in Shanghai. Mean of pack-years was higher in stomach cancer cases than in controls. The majority of study participants were non-drinkers (>62% in cases and in controls). Similar means of salt intake were observed in cases and controls. Most people were frequent vegetable eaters, with a higher proportion of frequent eaters in controls than in cases. Controls tended to eat fruits more frequently than stomach cancer cases, and slightly more cardia cancer cases (58%) ate fruits more frequently than distal cases (54%). The proportion of people who ate fruits more frequently was lower in Qingdao than in Shanghai (35% versus 65% among controls). Based on prior knowledge of stomach cancer risk factors and our confounding assessment, education, BMI, pack-years of smoking, alcohol drinking, salt intake, and fruit and vegetable intake were adjusted for when estimating the

Table 2. Means and Distribution of Demographic and Other Selected Variables among Stomach Cancer Cases and Controls in Shanghai and Qingdao

Variables	SHANGHAI All Stomach cancer	SHANGHAI Cardia Cancer	SHANGHAI Distal Cancer	SHANGHAI Control	QINGDAO All Stomach cancer	QINGDAO Control
Mean ± SD						
Age (years)	62.9 ± 11.5	66.2 ± 9.4	62.2 ± 11.8	62.4 ± 11.5	61.0 ± 13.0	60.8 ± 13.2
BMI (kg/m^2)	21.8 ± 2.8	22.3 ± 2.7	21.7 ± 2.8	22.2 ± 2.8	23.1 ± 2.9	23.6 ± 3.0
Pack-years of smoking	15.7 ± 21.5	15.2 ± 22.4	15.8 ± 21.4	13.6 ± 20.4	21.8 ± 22.8	17.7 ± 23.0
Salt intake (kg/year)	3.4 ± 1.6	3.0 ± 1.3	3.5 ± 1.6	3.5 ± 1.7	4.6 ± 1.3	4.6 ± 1.3
N (%)						
Gender						
Male	478 (63.7)	88 (68.8)	390 (62.7)	478 (63.7)	143 (71.1)	143 (71.1)
Female	272 (36.3)	40 (31.3)	232 (37.3)	272 (36.3)	58 (28.9)	58 (28.9)
Education						
≤ High School	715 (95.3)	120 (93.8)	595 (95.7)	714 (95.2)	186 (92.5)	195 (97.0)
> High School	35 (4.7)	8 (6.3)	27 (4.3)	36 (4.8)	15 (7.5)	6 (3.0)
Smoking						
No	387 (51.7)	70 (54.7)	317 (51.1)	430 (57.4)	72 (35.8)	93 (46.3)
Yes	362 (48.3)	58 (45.3)	304 (48.9)	319 (42.6)	129 (64.2)	108 (53.7)
Alcohol drinking						
No	509 (67.9)	88 (68.8)	421 (67.7)	516 (68.8)	124 (61.7)	124 (61.7)
Yes	241 (32.1)	40 (31.3)	201 (32.3)	234 (31.2)	77 (38.3)	77 (38.3)
Vegetable intake*						
Less frequent	16 (2.1)	3 (2.4)	13 (2.1)	4 (0.5)	20 (10.0)	13 (6.5)
Frequent	731 (97.9)	124 (97.6)	607 (97.9)	739 (99.5)	181 (90.0)	188 (93.5)
Fruit intake*						
Less frequent	338 (45.4)	53 (41.7)	285 (46.1)	264 (35.5)	143 (71.1)	130 (64.7)
Frequent	407 (54.6)	74 (58.3)	333 (53.9)	479 (64.5)	58 (28.9)	71 (35.3)

*Less frequent (never and occasional), frequent (less often and often).

effects of allium vegetables on stomach cancer risk.

The multivariate ORs and 95% CIs for individual allium vegetables and stomach cancer risk in Shanghai are presented in Table 3. All of the highest frequency categories of "often" for each allium vegetable showed protective ORs, except for scallions. A negative dose-response relationship was only observed between onion intake and stomach cancer risk (P for trend=0.04). The trend remains significant (P for trend=0.0461) after adjusting for the other allium vegetables in the same model (data not shown). We did not observe a clear relationship between frequency intake of allium vegetables and cardia cancer risk, which may be due partly to small number in some of the categories. For distal cancer, each allium vegetable "often" category had an OR below 1, except for scallions. A negative dose-response pattern was observed between increasing intake of onions with decreasing distal cancer risk (P for trend=0.04).

Table 4 shows corresponding ORs and 95% CIs for cardia cancer and distal cancer according to quartile ranking of monthly allium vegetable consumption in Shanghai. No clear dose-response pattern was observed between monthly allium vegetable consumption and cardia cancer. However, we observed negative dose-response patterns between increasing intake of scallions (P=0.09) and garlic stalks (P=0.04) with decreasing distal cancer risk. The trend for garlic stalks remains significant (P=0.04) even after adjusting for the other allium vegetables in the model (data not shown). The ORs of the "high" intake category when compared to the "never" category were 0.60 (95% CI: 0.37-0.99) for scallions and 0.72 (95% CI: 0.52-0.99) for garlic stalks.

Table 5 shows the ORs and 95% CIs for individual allium vegetables and stomach cancer risk in Qingdao. In this population, more people were frequent consumers of allium vegetables than in Shanghai. In Qingdao controls, 57% of people categorized themselves as "often" onion eaters as opposed to only 31% in Shanghai controls. In addition, 54% of Qingdao controls categorized themselves as "often" garlic consumers as opposed to only 4% of Shanghai controls. We observed a dose-response pattern between onions and stomach cancer risk in Qingdao (P for trend=0.02), although the trend became borderline significant (P=0.07) after adjusting for other allium vegetables in the model. The OR of the "occasional" category when compared to the "never" was 0.21 (95% CI: 0.06-0.79). The OR of the "often" category when compared to the "never" was 0.14 (95% CI: 0.03-0.71). Slight dose-response relationships were also observed for garlic (P for trend=0.06) and garlic stalks (P for trend=0.07). Table 5 also shows the ORs and 95% CIs

Table 3. Frequency of Allium Vegetable Intake and Stomach Cancer Risk in Shanghai

	All Stomach Cancer			Cardia			Distal		
Vegetable	Cases	Controls	OR*&95% CI	Cases	Controls	OR*&95% CI	Cases	Controls	OR*&95% CI
Onion Leaves									
Never	387 (51.6)	408 (54.4)	1.00	51 (39.8)	52 (40.6)	1.00	336 (54.0)	356 (57.2)	1.00
Occasional	344 (45.9)	321 (42.8)	1.22 (0.94-1.57)	72 (56.3)	71 (55.5)	0.91 (0.45-1.83)	272 (43.7)	250 (40.2)	1.25 (0.95-1.66)
Often	19 (2.5)	21 (2.8)	0.88 (0.43-1.82)	5 (3.91)	5 (3.91)	0.94 (0.20-4.39)	14 (2.3)	16 (2.6)	0.80 (0.35-1.84)
P for trend			0.3015			0.8306			0.2947
Scallions									
Never	532 (70.9)	526 (70.1)	1.00	68 (53.1)	71 (55.5)	1.00	464 (74.6)	455 (73.2)	1.00
Occasional	197 (26.3)	209 (27.9)	0.87 (0.64-1.19)	55 (43.0)	53 (41.4)	0.93 (0.45-1.90)	142 (22.8)	156 (25.1)	0.81 (0.57-1.15)
Often	21 (2.8)	15 (2.0)	1.48 (0.69-3.19)	5 (3.9)	4 (3.1)	1.13 (0.24-5.36)	16 (2.6)	11 (1.8)	1.49 (0.60-3.74)
P for trend			0.9279			0.9615			0.6438
Garlic Stalks									
Never	269 (35.9)	261 (34.8)	1.00	39 (30.5)	52 (40.6)	1.00	230 (37.0)	209 (33.6)	1.00
Occasional	452 (60.3)	457 (60.9)	0.94 (0.74-1.21)	85 (66.4)	69 (53.9)	1.56 (0.77-3.18)	367 (59.0)	388 (62.4)	0.84 (0.64-1.10)
Often	29 (3.9)	32 (4.3)	0.77 (0.43-1.40)	4 (3.1)	7 (5.5)	0.81 (0.16-3.96)	25 (4.0)	25 (4.0)	0.77 (0.40-1.47)
P for trend			0.4413			0.4912			0.1806
Garlic									
Never	398 (53.1)	411 (54.8)	1.00	59 (46.1)	73 (57.0)	1.00	339 (54.5)	338 (54.3)	1.00
Occasional	331 (44.1)	309 (41.2)	1.11 (0.87-1.41)	68 (53.1)	50 (39.1)	1.85 (0.96-3.58)	263 (42.3)	259 (41.6)	0.99 (0.76-1.29)
Often	21 (2.8)	30 (4.0)	0.68 (0.37-1.26)	1 (0.8)	5 (3.9)	0.27 (0.03-2.76)	20 (3.2)	25 (4.0)	0.72 (0.38-1.38)
P for trend			0.9682			0.3216			0.5636
Onions									
Never	262 (35.5)	266 (36.0)	1.00	45 (35.2)	47 (36.7)	1.00	217 (34.9)	219 (35.2)	1.00
Occasional	305 (40.7)	252 (33.6)	1.20 (0.42-1.73)	61 (47.7)	55 (43.0)	0.94 (0.38-2.35)	244 (39.2)	197 (31.7)	1.27 (0.86-1.90)
Often	183 (24.8)	232 (31.4)	0.66 (0.42-1.02)	22 (17.2)	26 (20.3)	0.70 (0.22-2.23)	161 (25.9)	206 (33.1)	0.62 (0.38-1.01)
P for trend			0.0403			0.5175			0.0367
Chinese Chives									
Never	110 (14.7)	116 (15.5)	1.00	17 (13.3)	17 (13.3)	1.00	93 (15.0)	99 (15.9)	1.00
Occasional	553 (73.7)	514 (68.5)	1.12 (0.81-1.56)	90 (70.3)	83 (64.8)	0.72 (0.23-2.29)	463 (74.4)	431 (69.3)	1.15 (0.81-1.62)
Often	87 (11.6)	120 (16.0)	0.61 (0.38-0.99)	21 (16.4)	28 (21.9)	0.28 (0.07-1.19)	66 (10.6)	92 (14.8)	0.66 (0.39-1.11)
P for trend			0.1020			0.0641			0.2525

*Adjusted for matching variables (age, gender), education, BMI, pack-years of smoking, alcohol drinking, salt intake, and vegetable and fruit intake

Table 4. Monthly Allium Vegetable Intake and Stomach Cancer Risk in Shanghai

Vegetable	Cardia Cases	Controls	OR* & 95% CI	Distal Cases	Controls	OR* & 95% CI
Onion Leaves						
Never	51 (39.8)	54 (42.2)	1.00	336 (54.0)	349 (56.1)	1.00
Low	38 (29.7)	35 (27.3)	1.08 (0.49-2.41)	187 (30.1)	157 (25.2)	1.28 (0.95-1.73)
High	39 (30.5)	39 (30.5)	0.97 (0.42-2.20)	99 (15.9)	116 (18.7)	0.92 (0.63-1.34)
P for trend			0.9235			0.9225
Scallions						
Never	68 (54.4)	71 (55.5)	1.00	464 (74.6)	455 (73.2)	1.00
Low	19 (14.8)	26 (20.3)	0.52 (0.21-1.32)	99 (15.9)	89 (14.3)	1.00 (0.68-1.48)
High	41 (32.0)	31 (24.2)	1.32 (0.59-2.93)	59 (9.5)	78 (12.5)	0.60 (0.37-0.99)
P for trend			0.4489			0.0859
Garlic Stalks						
Never	39 (30.5)	52 (40.6)	1.00	230 (37.0)	209 (33.6)	1.00
Low	39 (30.5)	41 (32.0)	1.13 (0.51-2.48)	226 (36.3)	208 (33.4)	0.94 (0.69-1.27)
High	50 (39.1)	35 (27.3)	2.00 (0.89-4.52)	166 (26.7)	205 (33.0)	0.72 (0.52-0.99)
P for trend			0.0874			0.0409
Garlic						
Never	59 (46.1)	73 (57.0)	1.00	339 (54.5)	338 (54.3)	1.00
Low	37 (28.9)	29 (22.7)	1.66 (0.79-3.46)	173 (27.8)	154 (24.8)	1.06 (0.79-1.42)
High	32 (25.0)	26 (20.3)	1.71 (0.77-3.80)	110 (17.7)	130 (20.9)	0.85 (0.61-1.17)
P for trend			0.1486			0.3974
Onions						
Never	45 (35.2)	47 (36.7)	1.00	217 (34.9)	219 (35.2)	1.00
Low	46 (35.9)	42 (32.8)	0.97 (0.38-2.47)	211 (33.9)	198 (31.8)	1.12 (0.75-1.67)
High	37 (28.9)	39 (30.5)	0.74 (0.25-2.18)	194 (31.2)	205 (33.0)	0.95 (0.61-1.49)
P for trend			0.5336			0.7123
Chinese Chives						
Never	17 (13.3)	17 (13.3)	1.00	93 (15.0)	99 (15.9)	1.00
Low	48 (37.5)	45 (42.2)	0.51 (0.16-1.64)	276 (44.4)	263 (42.3)	1.13 (0.78-1.62)
High	63 (49.2)	57 (44.5)	0.76 (0.23-2.44)	253 (40.7)	260 (41.8)	1.02 (0.70-1.50)
P for trend			0.8579			0.9395

*Adjusted for matching variables (age, gender), education, BMI, pack-years of smoking, alcohol drinking, salt intake, and vegetable and fruit intake

of monthly allium vegetable intake in Qingdao. We observed an association between garlic stalk and onion intake with stomach cancer risk. The "never" category was used as a referent. The category of "low" intake of garlic stalks yielded an OR of 0.19 (95% CI: 0.08-0.45) and the "high" intake of garlic stalks yielded an OR of 0.30 (95% CI: 0.13-0.73). For onions, a negative dose-response pattern was observed (P for trend=0.004) and remains strongly significant after adjusting for the other allium vegetables (P=0.007). The ORs were 0.29 (95% CI: 0.09-0.94) for the "low" intake category and 0.07 (95% CI: 0.01-0.52) for the "high" intake category.

Discussion

We found onion consumption to be inversely associated with stomach cancer risk in Shanghai and Qingdao. The highest category of onion intake was associated with reduced stomach cancer risk [Shanghai's OR=0.66 (95% CI: 0.42-1.02) and Qingdao's OR=0.14 (95% CI: 0.03-0.71)]. In addition, after adjusting for potential confounders and the other allium vegetables, a negative dose-response relationship was observed between onion consumption and stomach cancer risk in both populations. A decreased risk of distal stomach cancer was observed with increasing onion consumption. In Shanghai, based on monthly consumption in kg, we found that intake of garlic stalks was associated with a decreased risk of distal stomach cancer, and with a clear dose-response relationship. In Qingdao, we consistently observed an inverse association between intake of garlic stalks, garlic, and onions and stomach cancer. A strong dose-response relationship was observed between monthly intake of onions and stomach cancer.

Most epidemiological studies, including a cohort study, have suggested a decreased risk of stomach cancer with increasing consumption of garlic, onions, or related allium vegetables. One study conducted in a high-risk area of China found that onions were protective against stomach cancer; the OR of the highest frequency intake category was 0.17 (95% CI: 0.08-0.36), which is very similar to our observation in Qingdao (Gao et al., 1999). The only cohort study of allium vegetables (the Netherland Cohort Study) to date showed a strong inverse association between onion consumption and stomach cancer incidence (Dorant et al., 1996). The observation was restricted to distal cancer only. Our results were consistent with that study, as we observed a negative dose-response relationship between onions and distal stomach cancer only. One study in Japan found a positive association between high onion intake and stomach cancer, which may be explained by the selection of hospital patients with severe gastric diseases as controls (Tajima et

Table 5. Frequency and Monthly Allium Vegetable Intake and Stomach Cancer Risk in Qingdao

Frequency	Cases	Controls	OR* & 95% CI	Monthly Amount	Cases	Controls	OR* & 95% CI
Onion Leaves				Onion leaves			
Never	36 (17.9)	39 (19.4)	1.00	Never	36 (17.9)	39 (19.4)	1.00
Occasional	154 (76.6)	146 (72.6)	1.20 (0.67-2.15)	Low	115 (57.2)	105 (52.2)	1.29 (0.70-2.37)
Often	11 (5.5)	16 (8.0)	0.78 (0.30-2.05)	High	50 (24.9)	57 (28.4)	0.96 (0.50-1.86)
P for trend			0.9087	P for trend			0.7539
Scallions				Scallions			
Never	47 (23.4)	34 (16.9)	1.00	Never	47 (23.4)	34 (16.9)	1.00
Occasional	75 (37.3)	89 (44.3)	0.49 (0.25-0.93)	Low	69 (34.3)	83 (41.3)	0.49 (0.26-0.94)
Often	79 (39.3)	78 (38.8)	0.68 (0.33-1.42)	High	85 (42.3)	84 (41.8)	0.68 (0.33-1.40)
P for trend			0.4086				0.4204
Garlic Stalks				Garlic Stalks			
Never	39 (19.4)	14 (7.0)	1.00	Never	39 (19.4)	14 (7.0)	1.00
Occasional	115 (57.2)	140 (69.7)	0.21 (0.09-0.50)	Low	75 (37.3)	101 (50.3)	0.19 (0.08-0.45)
Often	47 (23.4)	47 (23.4)	0.30 (0.12-0.77)	High	87 (43.3)	86 (42.8)	0.30 (0.13-0.73)
P for trend			0.0660	P for trend			0.1462
Garlic				Garlic			
Never	16 (8.0)	11 (5.5)	1.00	Never	16 (8.0)	11 (5.5)	1.00
Occasional	96 (47.8)	81 (40.3)	0.71 (0.27-1.88)	Low	100 (49.8)	96 (47.8)	0.66 (0.25-1.76)
Often	89 (44.3)	109 (54.2)	0.45 (0.15-1.30)	High	85 (42.3)	94 (46.8)	0.58 (0.20-1.70)
P for trend			0.0606	P for trend			0.3812
Onions				Onions			
Never	19 (9.5)	8 (4.0)	1.00	Never	19 (9.5)	8 (4.0)	1.00
Occasional	72 (35.8)	78 (38.8)	0.21 (0.06-0.79)	Low	83 (41.3)	87 (43.5)	0.29 (0.09-0.94)
Often	110 (54.7)	115 (57.2)	0.14 (0.03-0.71)	High	99 (49.3)	105 (52.5)	0.07 (0.01-0.52)
P for trend			0.0204	P for trend			0.0042
Chinese Chives				Chinese Chives			
Never	23 (11.4)	13 (6.5)	1.00	Never	23 (11.4)	13 (6.5)	1.00
Occasional	147 (73.1)	150 (74.6)	0.51 (0.27-1.11)	Low	93 (46.3)	95 (47.3)	0.48 (0.21-1.09)
Often	31 (15.4)	38 (18.9)	0.44 (0.18-1.08)	High	85 (42.3)	93 (46.3)	0.49 (0.22-1.10)
P for trend			0.1060	P for trend			0.2139

*Adjusted for matching variables (age, gender), education, BMI, pack-year of smoking, alcohol drinking, salt intake, and vegetable and fruit intake

al., 1985).

We did not observe a clear association between allium vegetable consumption and cardia cancer risk. None of the previous studies, aside from the cohort study, separated stomach cancer into subsites (cardia and distal). It is important to take into account tumor site, because it has been suggested that the etiology of cancer in the proximal part of the stomach (cardia and gastroesophageal junction) is different from that in the other part of the stomach (distal). Thus there may be subsite-specific differences in stomach cancer risk associated with allium vegetable consumption (Dorant et al., 1996). In addition, there is a possibility that cardia cancer has an etiology that is more similar to esophageal adenocarcinoma than to distal cancer (Wang et al., 1986). A large case-control study of esophageal cancer also conducted in Shanghai found no association between allium vegetable consumption and risk of esophageal cancer in men or women (Gao et al., 1994). However, a case-control study in a high-risk area in China found that allium vegetables (garlic, onions, Welsh onions and Chinese chives) were inversely associated with esophageal cancer risk (Gao et al., 1999). Whether the anticarcinogenic compounds in allium vegetables have a different effect on different areas of the stomach requires further investigation.

Several experimental studies have shown that extracts from garlic and onions have anticancer properties (for recent reviews, see Herman-Antosiewicz and Singh, 2004; Milner, 2001). Belman was the first to find that tumor promotion was inhibited by onion and garlic oil in a dose-response manner in the skin (Belman, 1983). Interestingly, Sparnins et al. found that organosulfur compounds from garlic and onions have inhibitory effects on benzo(a)pyrene-induced cancer of the mouse forestomach (Sparnins et al., 1988). They also found that these compounds can induce glutathione S-transferase activity in the forestomach. In vitro assays also showed that allium vegetables or their bioactive constituents could inhibit proliferation and cause cycle arrest and/or apoptosis in several cancer cells (Nakagawa et al., 2001; Xiao et al., 2004; Kwon et al., 2002; Sakamoto et al., 1997; Sundaram and Milner, 1996). In vitro, sulfur compounds in garlic and onions have been shown to depress nitrosamine formation and bioactivation (Dion et al., 1997). Studies have shown that they induce the antitumorigenic NSAID-activated gene by a p-53-dependant mechanism (Bottone et al., 2002), activate Bcl-2, Bax and p-53 genes (Hong et al., 2000), and protect against induced mammary epithelial cell DNA adduct formation (Schaffer et al., 1997).Sivan et al. have demonstrated in vitro that *H. pylori* is susceptible to garlic extract at a fairly moderate concentration. Even some antibiotic-resistant *H. pylori* strains are susceptible to garlic (Sivan et al., 1997).The results of experimental studies support epidemiological findings that higher intake of allium vegetables is associated with a reduction in the risks of some cancers.

Although our findings are consistent with most previous studies of stomach cancer, several potential limitations of our study should be discussed. Disease and exposure misclassification may exist in our study. In our study, most of the stomach cancer cases were pathologically, surgically or endoscopically diagnosed (85%) (Yu et al., 1995); therefore, disease misclassification is likely minimal. Misclassification of exposure, however, is more likely to have occurred. Differential recall of dietary intake due to awareness of disease status may be possible. In addition, recall of dietary intake can be influenced by current dietary habits, which may be different from those in the relevant reference period due to symptoms of disease. Our questionnaire asked about dietary habits in the 80's, prior to the disease diagnoses, which may have minimized potential misclassification bias for allium vegetable intake. Data of allium vegetable consumption collected included intake frequency and monthly consumption in kg for each type of vegetable. Because it is very difficult to remember precisely how often each vegetable was consumed, misclassification of exposure is likely to have occurred. All allium vegetable consumption was categorized into three groups because of the low numbers of consumers in some of the categories. This crude categorization of consumption may have limited the ability to detect a relationship between higher levels of vegetable intake and stomach cancer risk. In this study, *H. pylori* infection status was not available. While *H. pylori* infection is an established risk factor for stomach cancer, garlic extract has been shown to have antibacterial activity against *H. Pylori*; thus *H. pylori* infection may act more as an intermediate than as a confounder. Statistical adjustment for *H. pylori* infection in the analyses may not be appropriate.

In conclusion, our large population based case-control studies of stomach cancer confirmed previous reports of protective effects associated with allium vegetable consumption. Future epidemiological studies of allium vegetables and stomach cancer should separate stomach cancer into cardia and non-cardia cancer. Prospective studies are needed to confirm the protectiveness of garlic or onions against stomach cancer because of their great potential as low-cost remedies to reduce stomach cancer incidence among high-risk populations.

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