Short Communication

Fruit and Vegetable Consumption and Incidence of Gastric Cancer: A Prospective Study

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Abstract

Background: **Whether fruit and vegetable consumption may confer protection from gastric cancer remains controversial.**
Methods: **We prospectively investigated the association between consumption of fruits and vegetables and the incidence of gastric cancer among participants from two population-based cohort studies: 36,664 women in the Swedish Mammography Cohort and 45,338 men in the Cohort of Swedish Men. Participants completed a food-frequency questionnaire in 1997 and were followed up for cancer incidence through June 2005. Cox proportional hazards models were used to estimate multivariate hazard ratios (HR) and 95% confidence intervals (95% CI).**
Results: **During a mean follow-up of 7.2 years, we ascertained 139 incident cases of gastric cancer. Vegetable consumption was inversely associated with risk of gastric cancer, whereas no significant association was observed for fruit consumption. After controlling for age and other risk factors, women and men who consumed ≥2.5 servings/d of vegetables had a HR of 0.56 (95% CI, 0.34-0.93) for developing gastric cancer compared with those who consumed <1 serving/d. The respective HR for fruit consumption was 0.86 (95% CI, 0.52-1.43). Among specific subgroups of vegetables, consumption of green leafy vegetables and root vegetables was inversely associated with risk of gastric cancer; the multivariate HRs comparing ≥3 servings/wk with <0.5 serving/wk were 0.64 (95% CI, 0.42-0.99) for green leafy vegetables and 0.43 (95% CI, 0.27-0.69) for root vegetables.**
Conclusions: **Frequent consumption of vegetables may reduce the risk of gastric cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(10):1998–2001)

Introduction

Although gastric cancer incidence and mortality rates have been declining over the last half century, this malignancy remains the second leading cause of death from cancer worldwide (1). Dietary factors are supposed to play a major role in the etiology of gastric cancer (2). Fruits and vegetables, which are rich sources of carotenoids, vitamin C, folate, and phytochemicals, are among the most frequently investigated dietary factors in relation to risk of gastric cancer; yet, whether consumption of fruits and vegetables may confer protection from gastric cancer remains controversial. A recent report by the IARC (3) concluded that higher intake of fruits ''probably'' reduces the risk of gastric cancer and higher intake of vegetables ''possibly'' lowers the risk. However, the epidemiologic evidence is mainly based on case-control studies, which may be hampered by recall and selection bias. Prospective cohort studies on fruit and vegetable consumption and risk of gastric cancer have provided less convincing evidence of a possible protective effect (3).

The purpose of the present study was to examine prospectively the association between fruit and vegetable consumption and the incidence of gastric cancer in the Swedish Mammography Cohort and the Cohort of Swedish Men.

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Materials and Methods

Study Cohorts. The Swedish Mammography Cohort and the Cohort of Swedish Men are two population-based prospective studies designed to investigate risk factors for cancer and other diseases in middle-aged and elderly women and men in central Sweden. The Swedish Mammography Cohort was established between 1987 and 1990, when all women born between 1914 and 1948 and residing in Västmanland and Uppsala counties received a mailed questionnaire about diet, weight, height, and education (4). In the autumn of 1997, participants received a second questionnaire that was expanded to include ~350 items pertaining to diet and other lifestyle factors. Of the 56,030 women who were still alive and residing in the study area, 39,227 completed this questionnaire. The Cohort of Swedish Men was initiated in the autumn of 1997, when all men born between 1918 and 1952 and residing in Västmanland and Örebro counties received a mailed questionnaire that was identical (except for some sex-specific questions) to the Swedish Mammography Cohort questionnaire from 1997; 48,850 men answered the questionnaire.

For the present analyses, we used information from respondents to the 1997 questionnaire. We excluded participants with implausible values for total energy intake (i.e., 3 SDs from the mean value for $\log_e$-transformed energy in women and men separately), those with incorrect or missing national registration number, and those with a cancer diagnosis (except nonmelanoma skin cancer) before January 1, 1998. After these exclusions, the study population consisted of 82,002 participants (36,664 women and 45,338 men), ages 45 to 83 years at start of follow-up. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Dietary Assessment. Dietary intake was measured using a 96-item food-frequency questionnaire. Participants were asked

Table 1. Baseline characteristics of women in the Swedish Mammography Cohort and men in the Cohort of Swedish Men according to fruit and vegetable consumption in 1997

	Fruit and vegetable consumption (servings/d)							
	Women (Swedish Mammography Cohort)				Men (Cohort of Swedish Men)			
	<2.0	2.0-3.4	3.5-4.9	≥5.0	<2.0	2.0-3.4	3.5-4.9	≥5.0
No. participants	3,169	7,478	9,217	16,800	8,499	13,647	11,085	12,107
Age (y)*	65.2	63.1	61.6	60.7	61.8	60.3	59.5	59.9
Postsecondary education (%)	9.0	12.9	17.7	23.4	8.5	13.5	18.0	22.9
History of diabetes (%)	3.7	3.5	3.5	3.9	5.8	6.0	5.8	6.9
Current smoker (%)	37.4	27.5	23.3	19.3	36.5	25.7	21.8	18.8
Pack-years*,†	18.5	16.3	14.9	13.7	24.4	21.2	19.6	18.9
Dietary intake								
Total energy (kcal/d)*	1,382	1,561	1,683	1,915	2,329	2,561	2,700	2,976
Alcohol (g/d)*	2.8	3.6	4.2	4.5	8.7	10.1	10.9	11.3
Processed meat (servings/wk)*	2.3	2.8	3.0	3.2	3.4	3.9	4.1	4.4

NOTE: Fruits and vegetables include apples/pears, bananas, citrus fruit, orange/grapefruit juice, berries, and other fruits, including spinach, lettuce, green salad, white cabbage, red cabbage, Chinese cabbage, cauliflower, broccoli, Brussels sprouts, carrots, beetroots, tomatoes/tomato juice, sweet pepper, onion, leek, garlic, green peas, and mixed vegetables.
Values, except for the number of participants and age, are standardized according to the age distribution of the study population at baseline.
*Mean values.
†Pack-years were calculated among past and current smokers only.

to indicate how often, on average, over the past year they had consumed each food item. Eight categories for frequency of consumption were provided, ranging from never to three or more times daily. The frequency responses were converted into average consumption of each fruit and vegetable item (servings daily or weekly). For this analysis, the main food groups of interest were fruit and vegetables combined, fruit, and vegetables. Vegetables did not include potatoes. Total fruit included orange/grapefruit juice because results were similar when fruit juice was excluded. We also combined specific vegetables into the following five subgroups: green leafy vegetables (including spinach, lettuce, and green salad), cabbages (white cabbage, red cabbage, Chinese cabbage, cauliflower, broccoli, and Brussels sprouts), root vegetables (carrots and beetroots), fruiting vegetables (tomatoes/tomato juice and sweet pepper), and onion, leek, and garlic. The remaining two vegetable items on the food-frequency questionnaire (green peas and mixed vegetables) were examined separately. In our validation study of the food-frequency questionnaire, the Spearman correlation coefficients between the average of four 1-week diet records and the food-frequency questionnaire ranged from 0.5 to 0.7 for fruit items and from 0.4 to 0.6 for vegetable items.[3]

Assessment of Nondietary Factors. The questionnaire collected information on education, weight, height, smoking history, physical activity, use of dietary supplements, some medications, and history of diabetes. We calculated body mass index as weight in kilograms divided by the square of height in meters. Pack-years of smoking were calculated by multiplying an average lifetime number of packs smoked daily (1 pack = 20 cigarettes) with number of years of smoking.

Case Ascertainment and Follow-up. Follow-up for cancer incidence, death, and migrations entails passive computerized record linkages of study participants (using the national registration number assigned to each Swedish resident) with the national and regional Swedish Cancer registers, the Swedish Death Registry, and the Swedish Population Registry. The Swedish Cancer Registry provides ~100% case ascertainment in Sweden (5, 6). Gastric cancer included cancers coded as 151 according to the Ninth Revision of the International Classification of Diseases.

Statistical Analysis. Each participant accrued follow-up time from January 1, 1998 to the date of diagnosis of gastric cancer, death, migration, or June 30, 2005, whichever came first. Participants were grouped into categories of consumption of combined fruits and vegetables (<2.0, 2.0-3.4, 3.5-4.9, and ≥5 servings/d), fruit or vegetables (<1.0, 1.0-1.4, 1.5-2.4, and ≥2.5 servings/d), and subgroups of vegetables (<0.5, 0.5-2.9, and ≥3 servings/wk). Cox proportional hazards models (7) were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for each category of fruit and vegetable intake compared with the lowest category. Age in months and sex were adjusted for as stratum variables in the Cox model. All multivariate models were further controlled for education, self-reported diabetes, smoking, and intakes of total energy, alcohol, and processed meat. In addition, models were adjusted for body mass index, physical activity, aspirin use, multivitamin supplement use, and consumption of red meat, poultry, fish, tea, and coffee. However, risk estimates changed only marginally, and therefore, these adjustments were not included in the final models. Tests based on the likelihood ratio test showed no evidence that the proportional hazards assumption was violated for any of the analyses.

In additional analyses, we excluded the first 3 years of follow-up to remove early cases in whom the relation between fruit and vegetable consumption and gastric cancer risk may have been biased because of changes in diet due to preclinical symptoms. We also conducted analyses stratified by smoking status. The likelihood ratio test was used to assess statistical interaction. We did tests for trend using the median value for each category to form a continuous variable. All analyses were done with Statistical Analysis System statistical software version 9.1 (SAS Institute, Inc., Cary, NC), and all statistical tests were two sided.

Results

Baseline characteristics of participants according to combined fruit and vegetable consumption are shown in Table 1. In general, relative to women and men with a low consumption of fruits and vegetables, those with higher consumption were younger, smoked less, and were more likely to have a postsecondary education. They also consumed more alcohol and processed meat. Men in the highest category of fruit and vegetable consumption were also more likely to have diabetes than men with lower fruit and vegetable consumption.

[3] A. Wolk, unpublished data.

The mean duration of follow-up was 7.2 years (total of 591,556 person-years) between 1998 and June 30, 2005. During follow-up, 139 participants (55 women and 84 men) were diagnosed with gastric cancer. Compared with women and men in the lowest category of combined fruit and vegetable consumption (<2 servings/d), those with a higher level of consumption had a lower risk of gastric cancer, although there was no clear dose-response relationship (Table 2). The results were similar for women and men; the multivariate HRs for ≥5 servings/d versus <2 servings/d of fruit and vegetables were 0.53 (95% CI, 0.21-1.31) in women and 0.50 (95% CI, 0.25-0.97) in men. The inverse association between fruit and vegetable consumption and gastric cancer risk was more pronounced when the first 3 years of follow-up were excluded (Table 2).

The association between fruit and vegetable consumption and risk of gastric cancer was somewhat stronger among never smokers than among ever smokers; the multivariate HRs for ≥5 servings/d versus <2 servings/d of fruit and vegetables were 0.38 (95% CI, 0.17-0.88) among never smokers (including 60 cases) and 0.66 (95% CI, 0.33-1.32) among ever smokers (including 79 cases). A test for interaction between fruit and vegetable consumption and smoking status in relation to gastric cancer risk was not statistically significant (P = 0.89).

When we examined fruit and vegetables separately, consumption of vegetables, but not fruit, was statistically significantly inversely associated with risk of gastric cancer (Table 2). Women and men who consumed ≥2.5 servings/d of vegetables had a multivariate HR of 0.56 (95% CI, 0.34-0.93) compared with those who consumed <1.0 serving/d. The corresponding HRs were 0.56 (95% CI, 0.22-1.40) in women and 0.54 (95% CI, 0.29-0.98) in men. Excluding the first 3 years of follow-up strengthened the inverse association with vegetable consumption (Table 2).

Among specific subgroups of vegetables, consumption of green leafy vegetables and root vegetables was associated with a statistically significant reduced risk of gastric cancer (Table 3). The multivariate HRs comparing ≥3 servings/wk with <0.5 serving/wk were 0.64 (95% CI, 0.42-0.99) for green leafy vegetables and 0.43 (95% CI, 0.27-0.69) for root vegetables. There were no statistically significant associations with other vegetable subgroups (Table 3) or with consumption of green peas or mixed vegetables (data not shown). None of the individual fruit items (apples/pears, bananas, citrus fruits, and orange/grapefruit juice) was significantly related to gastric cancer risk (data not shown). There was a nonsignificant inverse association between consumption of berries and risk of gastric cancer; the multivariate HR for women and men who consumed ≥3 servings/wk of berries compared with those who consumed <0.5 serving/wk was 0.69 (95% CI, 0.39-1.23).

Discussion

In this prospective study of Swedish women and men, consumption of vegetables was inversely associated with risk of gastric cancer after controlling for potential confounders. Risk was 44% lower in the highest compared with the lowest category of vegetable consumption. The most protection seemed to come from consumption of green leafy vegetables and root vegetables. No significant association was observed between fruit consumption and gastric cancer risk.

The prospective nature of the study design ruled out the problem of recall and selection bias, and the practically complete follow-up of the study population reduced the concern that our results have been affected by differential follow-up rates. The observation that our findings persisted, and were even stronger, after exclusion of incident cases that occurred during the first 3 years of follow-up suggests that the observed association between vegetable consumption and gastric cancer risk was not the result of dietary changes related to preclinical disease. Our study is limited by an inability to examine gastric cancer risk according to anatomic and histologic subtype. Another limitation is the use of a self-administered food-frequency questionnaire to assess dietary intake, which will inevitably lead to some misclassification of fruit and vegetable consumption. However, random non-differential misclassification of consumption of fruits and vegetables would most likely weaken rather than exaggerate any true relationship. Finally, we cannot exclude that our findings are attributable to residual or uncontrolled confounding. Nevertheless, we adjusted for a wide range of potential risk factors for gastric cancer in multivariate analysis, and these adjustments had minimal effect on the risk estimates.

Although the majority of ~40 case-control studies have reported an inverse association between consumption of fruit and/or vegetables and risk of gastric cancer, prospective cohort studies have been less convincing (3). A comprehensive

Table 2. HRs and 95% CIs of gastric cancer according to consumption of fruits and vegetables among 82,002 Swedish women and men, 1998-2005

Servings/d	Cases	Person-years of follow-up	Age- and sex-adjusted HR (95% CI)	Multivariate HR (95% CI)*	Multivariate HR (95% CI)*,†
Fruit and vegetables					
<2.0	33	82,030	1.00	1.00	1.00
2.0-3.4	34	151,913	0.64 (0.39-1.03)	0.63 (0.38-1.02)	0.60 (0.33-1.13)
3.5-4.9	33	147,193	0.68 (0.42-1.11)	0.66 (0.39-1.10)	0.58 (0.31-1.12)
≥5.0	39	210,420	0.58 (0.36-0.94)	0.54 (0.32-0.91)	0.37 (0.19-0.74)
P_{trend}			0.08	0.06	0.01
Fruit					
<1.0	52	199,743	1.00	1.00	1.00
1.0-1.4	28	113,869	0.93 (0.59-1.48)	0.93 (0.58-1.49)	0.64 (0.34-1.21)
1.5-2.4	33	155,879	0.85 (0.55-1.32)	0.86 (0.55-1.36)	0.74 (0.42-1.28)
≥2.5	26	122,065	0.85 (0.53-1.38)	0.86 (0.52-1.43)	0.66 (0.35-1.24)
P_{trend}			0.47	0.53	0.23
Vegetables					
<1.0	29	68,255	1.00	1.00	1.00
1.0-1.4	17	67,399	0.68 (0.37-1.24)	0.66 (0.36-1.21)	0.67 (0.31-1.45)
1.5-2.4	38	162,602	0.69 (0.42-1.13)	0.67 (0.41-1.11)	0.72 (0.38-1.36)
≥2.5	55	293,300	0.60 (0.38-0.96)	0.56 (0.34-0.93)	0.44 (0.23-0.84)
P_{trend}			0.08	0.05	0.01

*Multivariate hazard ratios were adjusted for age (in months), sex, education (less than high school, high school graduate, or more than high school), smoking status and pack-years of smoking (never smoker, past smoker and <20 pack-years, past smoker and ≥20 pack-years, current smoker and <20 pack-years, or current smoker and ≥20 pack-years), diabetes (yes/no), and intakes of total energy (continuous), alcohol (quartiles), and processed meat (<1.5, 1.5-4.9, or ≥5 servings/wk).
†Excluding the first 3 years of follow-up.

Table 3. HRs and 95% CIs of gastric cancer according to consumption of subgroups of vegetables among 82,002 Swedish women and men, 1998-2005

	Vegetable consumption (servings/wk)			P_{trend}
	<0.5	0.5-2.9	≥3.0	
Green leafy vegetables				
Cases	45	44	50	
Person-years of follow-up	114,440	212,910	264,206	
Age- and sex-adjusted HR (95% CI)	1.00	0.65 (0.42-0.99)	0.65 (0.43-0.98)	0.16
Multivariate HR (95% CI)*	1.00	0.64 (0.42-0.99)	0.64 (0.42-0.99)	0.17
Cabbages				
Cases	38	69	32	
Person-years of follow-up	111,612	313,198	166,746	
Age- and sex-adjusted HR (95% CI)	1.00	0.79 (0.53-1.17)	0.73 (0.45-1.17)	0.27
Multivariate HR (95% CI)*	1.00	0.78 (0.52-1.17)	0.70 (0.43-1.15)	0.30
Root vegetables				
Cases	27	52	60	
Person-years of follow-up	66,880	257,388	267,288	
Age- and sex-adjusted HR (95% CI)	1.00	0.49 (0.31-0.79)	0.44 (0.28-0.71)	0.02
Multivariate HR (95% CI)*	1.00	0.49 (0.30-0.79)	0.43 (0.27-0.69)	0.02
Fruiting vegetables				
Cases	25	34	80	
Person-years of follow-up	84,666	126,419	380,471	
Age- and sex-adjusted HR (95% CI)	1.00	1.18 (0.70-2.00)	1.02 (0.64-1.62)	0.72
Multivariate HR (95% CI)*	1.00	1.20 (0.71-2.04)	1.04 (0.64-1.67)	0.76
Onion, leek, and garlic				
Cases	38	47	54	
Person-years of follow-up	107,790	198,365	285,401	
Age- and sex-adjusted HR (95% CI)	1.00	0.89 (0.58-1.38)	0.91 (0.59-1.41)	0.81
Multivariate HR (95% CI)*	1.00	0.89 (0.57-1.39)	0.90 (0.58-1.41)	0.78

NOTE: Green leafy vegetables include spinach, lettuce, and green salad; cabbages include white cabbage, red cabbage, Chinese cabbage, cauliflower, broccoli, and Brussels sprouts; root vegetables include carrots and beetroots; fruiting vegetables include tomatoes/tomato juice and sweet pepper.

*Multivariate hazard ratios were adjusted for age (in months), sex, education (less than high school, high school graduate, or more than high school), smoking status and pack-years of smoking (never smoker, past smoker and <20 pack-years, past smoker and ≥20 pack-years, current smoker and <20 pack-years, or current smoker and ≥20 pack-years), diabetes (yes/no), and intakes of total energy (continuous), alcohol (quartiles), and processed meat (<1.5, 1.5-4.9, or ≥5 servings/wk).

review by the IARC identified 12 prospective studies that investigated the relationship between fruit and/or vegetable consumption and risk of gastric cancer (3). Although most prospective studies found inverse associations, with relative risks typically between 0.6 and 0.9, only 5 of those 12 studies observed a statistically significant inverse relationship for consumption of total fruits (8-10), total vegetables (8, 11), or fruit and vegetables combined (12). Recent findings from a prospective study of Finnish male smokers (13) showed a statistically significant inverse association of fruit consumption with risk of gastric noncardia cancer but no association with gastric cardia cancer. In contrast, another prospective study in China (14) recently observed an inverse association between fruit consumption and risk of gastric cardia cancer but not gastric noncardia cancer. In the European Prospective Investigation into Cancer and Nutrition cohort (15), there was no overall association between consumption of fruits or vegetables and risk of gastric cardia or gastric noncardia cancer; however, an increment of 100 g/d of vegetables was associated with a nonsignificant 34% lower risk of gastric cancer of the intestinal type.

In the present study, the strongest inverse associations were observed with consumption of green leafy vegetables and root vegetables, which are important sources of several carotenoids, particularly β-carotene. To our knowledge, only three previous prospective studies have examined consumption of green leafy vegetables (15-17) and root vegetables (15, 16) in relation to risk of gastric cancer, and these studies found no significant associations.

In summary, the findings from this prospective study suggest that frequent consumption of vegetables may reduce the risk of gastric cancer. These findings add further support to current dietary recommendations to increase vegetable consumption.

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