

Short Communication

A Prospective Study of Diet and Stomach Cancer Mortality in United States Men and Women

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Abstract

Frequent consumption of fruits, vegetables, and whole grains has been associated with a reduced risk of stomach cancer in the majority of case-control studies of these factors; however, prospective studies have been less consistent. We examined the association between selected major food groups (citrus fruits, vegetables, whole grains, and processed meats) and risk of fatal stomach cancer in the Cancer Prevention Study (CPS) II cohort of 1.2 million United States men and women. During 14 years of follow-up, we documented 439 stomach cancer deaths in women and 910 in men after exclusion of individuals with prevalent cancers, inadequate diet information, and recent weight loss at baseline in 1982. After controlling for other risk factors, none of the food groups examined were associated with risk of stomach cancer except for an unexpected increased risk with vegetable consumption in women [relative risk (RR) = 1.25; 95% confidence interval (CI), 0.99–1.58; highest versus lowest tertile, $P = 0.06$ for trend]. A high overall plant food intake (a sum of vegetables, citrus fruit, and whole grains) was associated with reduced risk in men (RR = 0.79; 95% CI, 0.67–0.93; highest versus lowest tertile, $P = 0.003$ for trend), but not in women (RR = 1.18; 95% CI, 0.93–1.50; $P = 0.16$ for trend). Of individual foods examined, liver consumption greater than twice/week was associated with an increased risk of fatal stomach cancer in women (RR = 1.96; 95% CI, 1.09–3.53) and men (RR = 1.63; 95% CI, 1.02–2.62) compared with nonconsumers. This study supports a modest role for plant foods in reducing the risk of fatal stomach cancer in men, but not in women.

Introduction

Dietary factors are thought to contribute to the large international variation in stomach cancer rates (1) and to the global decline in stomach cancer incidence over the last half-century

(2–4), although certain aspects of this relationship remain unclear. Citrus fruit, vegetables, and whole grains, high in antioxidant vitamins and polyphenols (5), may lower stomach cancer risk by protecting the gastric epithelium from inflammatory responses caused by *Helicobacter pylori* and by reducing endogenous carcinogenic nitrosamine formation (2, 6). The majority of the >30 published case control studies report an inverse association between one or more of these food groups and stomach cancer (1), whereas prospective studies have been fewer and less consistent (7–16). Consumption of processed meats, which contain nitrosamine precursors, has been inconsistently associated with stomach cancer in both case-control and prospective studies (1).

Although there have been a considerable number of epidemiological studies of diet and stomach cancer, most have been case-control studies that are susceptible to recall bias (2). Previous prospective studies of diet and stomach cancer have generally been small (9–11, 13, 14), thus limiting statistical power to examine risk separately by gender or other potential risk modifiers. In addition, past studies have not simultaneously controlled for important confounders such as socioeconomic status, cigarette smoking, and aspirin use (7, 13–16). The purpose of this study was to evaluate the association of dietary factors, especially citrus fruit, vegetables, whole grains, and processed meats, with risk of fatal stomach cancer in a large prospective cohort of United States men and women.

Materials and Methods

Study Cohort and Follow-up. In 1982, 508,351 men and 676,306 women completed a mailed questionnaire for the ACS's² CPS II. The questionnaire obtained information on medical history, demographic characteristics, diet and life-style habits, and medication use. Participants were recruited and enrolled by ACS volunteers in all 50 of the United States, the District of Columbia, and Puerto Rico and were followed-up for vital status through December 31, 1996, as described previously (17). Death certificates or codes for cause of death were obtained for 98.8% of all known deaths. Stomach cancer deaths were defined as International Classification of Diseases-9 codes 150.0–150.9 (18).

We excluded participants from this analysis if they reported prevalent cancer at baseline (except nonmelanoma skin cancer; $n = 82,349$), if they lost >20 pounds over the previous year ($n = 20,797$), or if diet information was incomplete ($n = 111,466$). The final analytic cohort consisted of 533,391 women and 436,654 men in whom 439 and 910 deaths from stomach cancer occurred, respectively.

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² The abbreviations used are: ACS, American Cancer Society; CPS II, Cancer Prevention Study II; BMI, body mass index; CI, confidence interval; RR, relative risk.

Table 1 Baseline characteristics and risk factors according to food group intake in 436,654 men and 533,391 women from the CPS II, 1982–1996^a

	Mean age (yr)		BMI 30+ (%)		Regular aspirin use (%)		Current smokers (%)		White (%)		College education (%)		Regular vitamin C users (%)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Citrus fruit/juices ^b														
1 (low)	57	55	11	12	7	7	28	26	93	92	26	18	9	10
2	56	54	10	11	8	9	19	18	94	93	40	27	10	13
3 (high)	58	57	9	10	10	10	16	17	96	96	46	31	14	16
Vegetables ^c														
1 (low)	57	56	11	12	7	8	26	23	93	91	26	18	8	10
2	57	55	10	10	9	9	20	19	95	95	39	27	11	14
3 (high)	57	56	9	10	9	9	16	18	96	95	46	33	13	17
Whole grains ^d														
1 (low)	56	56	11	12	8	8	27	26	93	92	29	20	7	9
2	56	55	11	11	8	9	22	20	94	93	38	25	10	12
3 (high)	59	57	8	8	10	10	14	14	96	95	45	32	15	18
Processed meat ^e														
1 (low)	59	57	8	10	9	8	14	19	94	94	43	28	13	15
2	57	55	10	10	9	9	21	21	95	95	38	25	11	13
3 (high)	57	55	11	12	9	9	26	21	92	91	30	23	9	11

^a Standardized to the age distribution of all men and women in the CPS II.

^b Tertiles of times/wk: men (<2, 2–6, and 7); women (<3, 3–6, and 7).

^c Vegetables: sum of days/week consuming the following items: green leafy vegetables, tomatoes, cabbage/broccoli/brussels sprouts, carrots, and squash/corn. Tertiles: men (<8, 8–13, and 13+); women (<9, 9 to <14, and 14+).

^d Sum of days/week consuming brown rice/whole wheat/barley, bran/corn muffins, oatmeal/shredded wheat/bran cereals. Tertiles: men (<1, 1 to <4, and 4+); women (<1, 1 to <4.5, and 4.5+).

^e Sum of days/week consuming smoked meats, frankfurters/sausage, fried bacon, and ham. Tertiles: men (<1, 1 to <4.5, and 4.5+); women (<1.5, 1.5 to <3, and 3+).

Dietary Assessment. Our dietary questionnaire has been described previously (19). Briefly, it asked about consumption of 32 foods using the following wording: “On average, how many days per week do you eat the following foods?” Main exposures included gender-specific tertiles of the following: “vegetables” (a sum of reported frequencies for green leafy vegetables, tomatoes, cabbage/broccoli/Brussels sprouts, carrots, and squash/corn); “citrus fruit” (citrus fruits/juices); “whole grains” (brown rice/whole wheat/barley, bran/corn muffins, oatmeal/shredded wheat/bran cereals); and “processed meats” (smoked meats, frankfurters/sausage, fried bacon, and ham). We also created a score representing higher intakes of potentially beneficial plant foods (“plant food”) by summing the frequencies of reported vegetables, citrus fruit, and whole grains. Individual foods, and a separate question on intake of “raw vegetables” were also examined.

Statistical Analyses. We used Cox proportional hazards models (20) to examine the association between dietary factors and stomach cancer mortality while adjusting for other potential risk factors. The time-axis used was follow-up time since enrollment in 1982. Age-adjustment was accomplished by stratifying on exact year of age at enrollment within each Cox model (21). Covariates were modeled using dummy variables. Multivariate models included terms for educational attainment, race, cigarette smoking history, aspirin use, vitamin C use, multivitamin use, family history of stomach cancer, and BMI in kg/m². Variables examined but not included, because they did not confound the association between diet and disease, were history of stomach problems (defined as a history of gastric or duodenal ulcers, chronic indigestion, regular use of antacids or regular use of Tagamet), exercise level, use of snuff or chewing tobacco, alcohol use, menopausal status, and history of estrogen use.

We examined whether the relationship between diet and fatal stomach cancer varied by level of education, history of stomach problems, vitamin supplement use, smoking, attained

age, BMI, family history of stomach cancer, regular aspirin use, and major change in diet over the previous 10 years. The likelihood ratio test was used to test for interaction (22). In addition, we conducted lag analyses excluding the first 4 years of follow-up to remove early cases in whom the relationship between diet and cancer may have been biased from changes in diet attributable to undiagnosed stomach cancer. Trend tests were conducted by assigning a numeric value from 1 to 5 to each quintile and modeling trend as a continuous variable.

Results

Baseline characteristics of CPS II men and women, according to food group tertiles, are provided in Table 1. Men and women who reported more frequent consumption of citrus fruit, vegetables, and whole grains and lower consumption of processed meat were, on average, slightly older, more educated, less likely to smoke, more likely to be vitamin C users, and less likely to be obese. For frequency of foods consumed per week, women reported more citrus fruit (4.3 ± 2.8) and vegetables (11.6 ± 6.0) compared with men (fruit, 3.8 ± 2.8 ; vegetables, 10.6 ± 5.8) and less processed meat (women, 2.1 ± 2.1 ; men, 2.8 ± 3.8); whole grain intake was similar (women, 3.5 ± 3.8 ; men, 3.4 ± 3.8).

In men, more frequent consumption of citrus fruit, vegetables and whole grains was associated with a decreased risk of stomach cancer, and intake of processed meats was associated with increased risk, in analyses adjusted only for age (Table 2). After controlling for important risk factors, the associations with food groups no longer remained. However, compared with men in the lowest tertile, men in the top two tertiles of the plant food score had a reduced risk of fatal stomach cancer (RR = 0.76; 95% CI, 0.65–0.90, and RR = 0.79; 95% CI, 0.67–0.93; $P = 0.003$ for trend). Of individual foods examined in men (data not shown), cabbage (RR = 0.82; 95% CI, 0.62–1.04; $P = 0.03$ for trend) and carrots (RR = 0.86; 95% CI, 0.69–

Table 2 Risk of fatal stomach cancer by major food groups—CPS II men and women, 1982–1996

Food group	(Reference)	Tertile		P
		2	3	
Citrus fruit/juice				
Men, cases (n)	334	270	306	
Age-adjusted	1.00	0.84 (0.71–0.98)	0.75 (0.64–0.87)	<0.001
Multivariate-adjusted ^a	1.00	0.94 (0.80–1.11)	0.88 (0.75–1.03)	0.11
Women, cases (n)	156	95	188	
Age-adjusted	1.00	0.95 (0.73–1.22)	0.85 (0.68–1.05)	0.12
Multivariate-adjusted	1.00	1.07 (0.83–1.39)	0.97 (0.78–1.21)	0.79
Vegetables				
Men, cases (n)	336	283	291	
Age-adjusted	1.00	0.83 (0.71–0.97)	0.76 (0.65–0.89)	<0.001
Multivariate-adjusted	1.00	0.92 (0.78–1.08)	0.89 (0.76–1.05)	0.17
Women, cases (n)	161	133	145	
Age-adjusted	1.00	1.04 (0.83–1.31)	1.08 (0.86–1.35)	0.51
Multivariate-adjusted	1.00	1.17 (0.93–1.48)	1.25 (0.99–1.58)	0.06
Whole grains				
Men, cases (n)	319	254	337	
Age-adjusted	1.00	0.87 (0.74–1.03)	0.77 (0.66–0.90)	<0.001
Multivariate-adjusted	1.00	0.94 (0.79–1.11)	0.90 (0.77–1.06)	0.20
Women, cases (n)	143	153	143	
Age-adjusted	1.00	1.05 (0.84–1.32)	0.83 (0.66–1.05)	0.11
Multivariate-adjusted	1.00	1.14 (0.90–1.43)	0.97 (0.77–1.24)	0.83
Plant foods ^b				
Men, cases (n)	360	260	290	
Age-adjusted	1.00	0.68 (0.58–0.80)	0.65 (0.56–0.76)	<0.001
Multivariate-adjusted	1.00	0.76 (0.65–0.90)	0.79 (0.67–0.93)	0.003
Women, cases (n)	152	131	156	
Age-adjusted	1.00	0.92 (0.73–1.17)	0.96 (0.77–1.21)	0.75
Multivariate-adjusted	1.00	1.06 (0.83–1.34)	1.18 (0.93–1.50)	0.16
Processed meat				
Men, cases (n)	157	553	200	
Age-adjusted	1.00	1.06 (0.88–1.26)	1.20 (0.97–1.47)	0.09
Multivariate-adjusted	1.00	1.03 (0.86–1.23)	1.08 (0.87–1.33)	0.47
Women, cases (n)	185	130	124	
Age-adjusted	1.00	0.96 (0.77–1.20)	1.12 (0.89–1.41)	0.39
Multivariate-adjusted	1.00	0.99 (0.79–1.24)	1.11 (0.88–1.39)	0.43

^a Adjusted for age, education, smoking, BMI, multivitamin and vitamin C use, aspirin use, race, and family history.

^b Plant foods, sum of citrus fruit, vegetables, and whole grain intake. Tertiles: men (<13.5, 13.5 to <21.5, and 21.5+); women (<15.5, 15.5 to <23.5, and 23.5+).

1.06; $P = 0.05$ for trend) consumed at least three times/week were associated with a reduced risk of fatal stomach cancer, compared with nonconsumption. Cold cereal eaten more than five times/week was also related to lower risk (RR = 0.83; 95% CI, 0.68–1.00; $P = 0.03$ for trend). Liver consumption more than two times/week was associated with an increased risk compared with nonconsumption, although the trend across intake categories was not significant (RR = 1.63; 95% CI, 1.02–2.62; $P = 0.91$).

In women, we observed no association between any food group or plant food score and stomach cancer risk in age-adjusted or multivariate models, except for an unexpected increased risk in the highest tertile of vegetable consumption (RR = 1.25; 95% CI, 0.99–1.58; $P = 0.06$ for trend) and raw vegetable consumption (RR = 1.33; 95% CI, 1.04–1.70; $P = 0.02$ for trend; not shown). Women consuming brown rice, whole wheat, or barley six to seven times/week were also at greater risk of fatal stomach cancer compared with those with no intake (RR = 1.41; 95% CI, 1.04–1.91; $P = 0.05$ for trend). Consumption of liver at least twice per week (RR = 1.96; 95% CI, 1.09–3.53; $P = 0.003$ for trend) or ham at least twice per week (RR = 1.52; 95% CI, 1.07–2.16; $P = 0.02$ for trend) was associated with increased risk of death from stomach cancer compared with nonconsumers.

Because frequent consumption of liver was associated with an increased risk of fatal stomach cancer in both men and women, we adjusted further for factors associated with liver consumption (*e.g.*, being foreign-born or having migrant parents) in addition to related factors already in the models (nonwhite race, less education, and older age). This did not alter our findings.

Inclusion of all four food groups in the multivariate models did not change our results for each food group. Analyses excluding the first 4 years of follow-up were similar to the overall analyses for both genders. The relationship between dietary factors and stomach cancer mortality was not modified by education level, attained age, BMI, vitamin use, or aspirin use in men or women. For men with a positive family history of stomach cancer, consuming whole-grain products >4 days/week *versus* <1 was associated with lower risk (RR = 0.31; 95% CI, 0.15–0.64) compared with those with no family history of stomach cancer (RR = 0.96; 95% CI, 0.81–1.12; $P = 0.004$ for interaction). In both men and women, the relation between diet and stomach cancer risk was modified by a history of stomach problems at baseline. In men, a stronger decrease in risk with higher plant food intake was observed among those who had a history of stomach problems at baseline (RR = 0.56; 95% CI, 0.40–0.78) compared with those without

stomach problems (RR = 0.87; 95% CI 0.73–1.05; $P = 0.003$ for interaction). Conversely, risk of fatal stomach cancer with higher plant food intake was higher among women with stomach problems (RR = 2.11; 95% CI 1.12–3.97) compared with those without stomach problems (RR = 1.08; 95% CI 0.84–1.38; $P = 0.13$ for interaction).

Discussion

In this large prospective cohort of United States men and women, none of the food groups we examined were independently related to stomach cancer risk. However, in men, a diet pattern high in potentially beneficial plant foods (citrus fruit, vegetables, and whole grains combined) was associated with a lower risk of fatal stomach cancer. In women, plant foods were not associated with a reduced risk of fatal stomach cancer.

Our results with respect to plant foods are more modest than those from previous case-control studies (1). Several explanations may account for these findings. Case-control studies are subject to recall bias (2), and this may be particularly true in studies of diet and stomach cancer. Second, many studies have not controlled for important risk factors. Our risk estimates for all food groups were attenuated after adjustment for confounders, especially education. Finally, most studies of diet and stomach cancer have been conducted in countries with high rates of stomach cancer or in people originally from high-risk areas (1). Our cohort may not be comparable with high-risk populations with greater rates of childhood *H. Pylori* infection, different foods, and different methods of food preparation and storage. Previous prospective studies of fruits and vegetables that reported significant inverse relationships with stomach cancer were primarily from high-risk populations (9, 10, 15, 16).

The reasons why plant foods were not associated with reduced risk of fatal stomach cancer in women are unclear. Stomach cancer is twice as common in men as in women (2) for reasons that are largely unknown but may involve reproductive factors (23) or differences in nutritional status (24). Few previous studies reported findings by gender, either because of small numbers of cases in women, or because results were similar in both genders, limiting our ability to compare our findings with those of others.

Among men with a history of stomach problems at baseline, the relationship between plant foods and stomach cancer was more strongly protective than among those without stomach problems. These findings are similar to a recent prospective cohort study including 208 male and 57 female cases (8). Conversely, there was a suggestion of increased risk of stomach cancer with higher plant food intake among women with a history of stomach problems in our study. We have no clear explanation of why we observed divergent findings by gender. In our study, a history of stomach problems was associated with increased stomach cancer risk in men but not in women. It is possible that men and women report such problems differently (e.g., men may ignore problems until a later stage) and that, in men, a history of stomach problems is a marker for precancerous lesions that may regress with higher intake of protective plant constituents. Future studies should stratify on stomach problems or precursor lesions to further examine this issue.

Men and women who consumed liver at least twice per week were at greater risk of stomach cancer compared with nonconsumers, a finding which has previously been reported (25). Differences in age, race, country of origin, and parental birthplace could not explain this association. Either a component of liver or another behavioral correlate may be responsible.

Liver contains at least three times the amount of iron as other red meat sources (26). Iron is known to catalyze oxidative reactions leading to tissue injury, and thus may act as a coinitiator or promoter of already initiated cancer (27).

The strengths of our study include its size, the ability to control for multiple risk factors, and the ability to stratify by gender and several potential risk modifiers. Our limitations included an inability to examine risk by anatomical or histological subtype, or by *H. Pylori* infection status (6). Our measure of diet in 1982 relied on a single brief questionnaire, and we were unable to examine the relationship of noncitrus fruits, salt intake, and allium vegetables with the risk of fatal stomach cancer. Such misclassification would tend to attenuate associations between diet and disease.

In summary, a diet pattern high in vegetables, citrus fruit, and whole grains was related to a modestly lower risk of stomach cancer only among men in our study. The lack of findings in women and the increased risk with liver consumption deserve additional investigation. Future studies should examine stomach cancer risk by gender, history of stomach problems and precursor lesions, anatomical subsite, and, if possible, *H. Pylori* status.

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