Fruit and Vegetable Consumption in Relation to Pancreatic Cancer Risk: A Prospective Study

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Abstract

High consumption of fruits and vegetables has been associated with a lower risk of pancreatic cancer in many case-control studies. However, cohort studies on this relationship are limited and do not support an association. We examined the associations of overall consumption of fruits and vegetables and consumption of certain subgroups of fruits and vegetables with the incidence of pancreatic cancer among 81,922 women and men in the Swedish Mammography Cohort and the Cohort of Swedish Men. Hazard ratios (HR) with 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models. During an average follow-up of 6.8 years (1998-2004), 135 incident pancreatic cancer cases were diagnosed. After adjustment for age and other risk factors for pancreatic cancer, the HRs for the highest compared with the lowest category of intake were 1.13 (95% CI, 0.66-1.94) for total fruits and vegetables, 1.10 (95% CI, 0.64-1.88) for total fruits, and 1.08 (95% CI, 0.63-1.85) for total vegetables. Among specific subgroups of fruits and vegetables, a nonsignificant inverse association was observed with cruciferous vegetable consumption (≥3 servings/wk versus <1 serving/wk: HR, 0.70; 95% CI, 0.43-1.13). Cabbage consumption was associated with a statistically significant lower risk of pancreatic cancer (≥1 serving/wk versus never consumption: HR, 0.62; 95% CI, 0.39-0.99). Findings from this prospective study do not support a relationship of overall fruit and vegetable consumption with pancreatic cancer risk. The association between consumption of cruciferous vegetables and pancreatic cancer risk warrants further investigation. (Cancer Epidemiol Biomarkers Prev 2006;15(2):301–5)

Introduction

Whether diets high in fruits and vegetables lower the risk of pancreatic cancer remains unclear. Most case-control studies (1-15), although not all (16, 17), have reported an inverse association between consumption of fruits and/or vegetables and pancreatic cancer risk. In a meta-analysis of case-control studies, a 28% reduced risk of pancreatic cancer was observed for high versus low consumption of fruits and a 20% lower risk for high versus low consumption of vegetables (18). Among specific subgroups of vegetables, the most consistent association has been found for cruciferous vegetables (5, 10, 13, 19).

In contrast to case-control studies, prospective cohort studies on consumption of fruits and vegetables and pancreatic cancer risk are sparse, and the results have largely been null (20-25). Inconsistencies may be explained by differences in study design, case-control studies being more prone to systematic bias. On the other hand, many previous prospective studies on fruit and vegetable consumption and pancreatic cancer risk were small with few cases, ranging from 40 to 65 cases (22, 23, 25), or were conducted in special populations (20, 21, 25). Furthermore, for at least three studies, dietary information was based on a limited number of food items (20, 22, 24). To our knowledge, only one prospective study has examined the relationship between consumption of cruciferous vegetables and pancreatic cancer risk (21).

The purpose of the present study was to examine prospectively overall consumption of fruits and vegetables and consumption of certain subgroups of fruits and vegetables in relation to the incidence of pancreatic cancer among 81,922 women and men enrolled in the Swedish Mammography Cohort and the Cohort of Swedish Men.

Materials and Methods

Study Population. The Swedish Mammography Cohort and the Cohort of Swedish Men are two population-based prospective studies designed to investigate risk factors for chronic 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 central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire regarding diet, weight, height, and education. In the autumn of 1997, participants who were still alive and residing in the study area received a second questionnaire that included 350 items pertaining to diet, other lifestyle factors (e.g., smoking, physical activity, and dietary supplement use), and medical history. Similarly, the Cohort of Swedish Men was initiated in the autumn of 1997, when all men born between 1918 and 1952 and residing in central Sweden (Västmanland and Örebro counties) received a mailed questionnaire that was identical (with the exception of some sex-specific questions) to the Swedish Mammography Cohort questionnaire from 1997.

For the current analysis, we used information from respondents to the 1997 questionnaire, comprising 39,227 women and 48,850 men. We excluded participants with implausibly low or high total energy intake (i.e., 3 SDs from the mean value for $\log_e$-transformed energy in women and men separately), those with erroneous or missing national registration number, and those with a cancer diagnosis (except nonmelanoma skin cancer) before baseline. The total number of participants included in this analysis was 36,616 women and 45,306 men. This investigation was approved by the Regional Ethical Review Board in Stockholm.

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Table 1. Age-standardized baseline characteristics of 36,616 women and 45,306 men according to total fruit and vegetable consumption

Characteristics	Total fruit and vegetable consumption (servings/d)			
	<2.5	2.5-3.9	4.0-5.4	≥5.5
Women				
Age (y)	64.6	62.6	61.3	60.5
Postsecondary education (%)	9.5	14.6	19.9	24.2
Current smoker (%)	30.7	22.1	17.8	14.5
Body mass index (kg/m^2)	25.2	25.1	24.9	25.0
Exercise (h/wk)	1.9	2.1	2.3	2.5
History of diabetes (%)	3.7	3.4	3.7	3.9
Regular multivitamin use (%)	14.4	16.2	19.2	25.4
Alcohol consumption (g/d)	2.7	3.5	4.0	4.2
Men				
Age (y)	61.4	59.8	59.7	60.1
Postsecondary education (%)	9.4	15.3	19.7	23.9
Current smoker (%)	26.3	17.3	14.2	11.7
Body mass index (kg/m^2)	26.1	25.7	25.6	25.6
Exercise (h/wk)	2.1	2.4	2.6	2.8
History of diabetes (%)	5.8	6.0	6.1	6.3
Regular multivitamin use (%)	6.4	8.6	11.9	15.5
Alcohol consumption (g/d)	8.9	10.2	11.0	11.3

NOTE: Fruits include apples, pears, bananas, oranges, grapefruit, orange/grapefruit juice, berries, and other fruits. Vegetables include spinach, iceberg lettuce, leafy salad, tomato, tomato juice, carrots, beets, cabbage, broccoli, Brussels sprouts, cauliflower, kale, pepper, green peas, onion, leek, garlic, and mixed vegetables.

Dietary Assessment. Dietary intake was assessed with a 96-item food-frequency questionnaire. Participants were asked 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 per day. The frequency responses were converted into average consumption of each fruit and vegetable item (servings per day or week). The average daily intake of individual fruit and vegetable items (not including potatoes, beans, and lentils) was then combined to obtain total fruit and/or vegetable consumption (see footnote to Table 1). We also combined specific fruits and vegetables into the following groups: citrus fruits, consisting of oranges, grapefruits, orange/grapefruit juice, and other citrus fruits; green leafy vegetables, consisting of spinach, iceberg salad, and leaf lettuce; and cruciferous vegetables, consisting of all types of cabbages, cauliflower, broccoli, and Brussels sprouts. In our validation study of the food-frequency questionnaire, the Spearman correlation coefficients between the mean of four 1-week diet records and the dietary questionnaire ranged from 0.5 to 0.7 for fruit items and from 0.4 to 0.6 for vegetable items.[4]

Follow-up and Case Ascertainment. Incident cases of pancreatic cancer were ascertained through computerized record linkage of the study population with the national and regional Swedish Cancer registers. The Swedish Cancer Register has been estimated to be close to 100% complete (26). Cases of pancreatic cancer were defined as primary malignant neoplasm of the exocrine pancreas (International Classification of Diseases, Ninth Revision code 157). Islet-cell carcinomas (International Classification of Diseases, Ninth Revision code 157.4) were excluded because the etiology of these tumors may be different from that of the exocrine pancreas. Ascertainment of dates of death for deceased participants and dates of migration was accomplished by linkage to the Swedish Death and Population registers.

Statistical Analysis. Each participant accumulated follow-up time beginning at baseline and ending at the date of diagnosis of pancreatic cancer, death, migration, or December 31, 2004, whichever came first. Consumption of fruit and vegetables was categorized into approximate quartiles. We used Cox proportional hazards models (27) to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Tests based on the likelihood ratio test showed no evidence that the proportional hazards assumption was violated. Separate analyses for women and men showed similar associations. Therefore, we present results for both sexes combined, adjusting for sex as a stratum variable in the Cox model to allow for different baseline hazard rates. All Cox models were additionally stratified by age in months. In multivariate analyses, in addition to age and sex, we controlled for education, body mass index (calculated as the weight in kilograms divided by the square of height in meters), physical activity, history of diabetes, cigarette smoking status and pack-years of smoking (the average number of packs smoked per day multiplied by the number of years of smoking), multivitamin supplement use, and intakes of total energy and alcohol.

To calculate the P value for trend across categories, participants were assigned the median value for their category of consumption and this variable was entered as a continuous term in the Cox model. The likelihood ratio test was used to assess statistical interaction. All P values are based on two-sided tests. All statistical analyses were carried out using SAS software, release 9.1 (SAS Institute, Inc., Cary, NC).

Results

The median consumption of total fruit and vegetables was 4.7 servings/d for women and 3.6 servings/d for men. Women and men with high fruit and vegetable consumption were younger, smoked less, exercised more, consumed more alcohol, and were more likely to have a postsecondary education and to use multivitamin supplements than were women and men with low consumption of fruits and vegetables (Table 1).

Over an average follow-up of 6.8 years (553,530 person-years) from 1998 through 2004, 135 participants (61 women and 74 men) were diagnosed with pancreatic cancer. We observed no significant associations between consumption of total fruits and vegetables, total fruits, or total vegetables and risk of pancreatic cancer (Table 2). The multivariate HRs for the top compared with the bottom category of consumption were 1.13 (95% CI, 0.66-1.94) for total fruits and vegetables,

[4]A. Wolk, unpublished data.

1.10 (95% CI, 0.64-1.88) for total fruits, and 1.08 (95% CI, 0.63-1.85) for total vegetables. We categorized participants into deciles of total fruit and vegetable consumption to examine more extreme levels of consumption; the multivariate HR for women and men in the highest decile (≥7.9 servings/d; including 19 cases) compared with those in the lowest decile (<1.7 servings/d; including 17 cases) was 1.14 (95% CI, 0.54-2.40). The results for fruit and vegetable consumption presented in Table 2 were essentially unchanged after we excluded the 26 cases diagnosed during the first 2 years of follow-up (data not shown).

A nonsignificant inverse association between consumption of cruciferous vegetables and risk of pancreatic cancer was observed (Table 2). In this study population, cabbage was the most frequently consumed cruciferous vegetable, and in analyses of the individual cruciferous vegetables (cabbage, broccoli or Brussels sprouts, and cauliflower) only cabbage consumption was statistically significantly inversely associated with pancreatic cancer risk. The multivariate HR for one or more servings of cabbage per week compared with never consumption was 0.62 (95% CI, 0.39-0.99). The corresponding HR was 0.82 (95% CI, 0.48-1.41) for consumption of broccoli or Brussels sprouts; for cauliflower consumption, the HR was 0.71 (95% CI, 0.40-1.24). There was no association between citrus fruit or green leafy vegetable consumption and pancreatic cancer risk (Table 2). However, participants who consumed one or more servings of spinach per week had a statistically nonsignificant lower risk of pancreatic cancer (multivariate HR, 0.59; 95% CI, 0.30-1.16) compared with those who never consumed spinach.

We examined whether the relation between cruciferous vegetable consumption and risk of pancreatic cancer varied according to cigarette smoking status. The multivariate HRs for three or more servings of cruciferous vegetables per week compared with less than one serving per week were 0.53 (95% CI, 0.23-1.22; P_{trend} = 0.14) among never smokers (including 48 cases) and 0.84 (95% CI, 0.46-1.53; P_{trend} = 0.53) among ever smokers (including 87 cases). A test for interaction between cruciferous vegetable consumption and smoking status was not statistically significant (P = 0.43).

Discussion

In this large population-based prospective study of Swedish women and men, overall fruit and vegetable consumption was not associated with pancreatic cancer risk. However, we observed an inverse association between consumption of cruciferous vegetables, especially of cabbage, and risk of pancreatic cancer.

Inverse associations between fruit and/or vegetable consumption and pancreatic cancer risk have been found almost consistently in case-control studies (1-15). It is possible, however, that the relationships observed in case-control

Table 2. HR and 95% CI values for pancreatic cancer according to fruit and vegetable consumption

	Categories of consumption				
	1	2	3	4	P_{trend}
All fruits and vegetables					
Servings/d	<2.5	2.5-3.9	4.0-5.4	≥5.5	
No. cases	31	33	32	39	
Person-years of follow-up	119,722	148,792	125,398	159,618	
Age- and sex-adjusted HR (95% CI)	1.0	0.99 (0.60-1.62)	1.12 (0.68-1.85)	1.13 (0.69-1.84)	0.54
Multivariate HR (95% CI)*	1.0	1.04 (0.63-1.73)	1.16 (0.69-1.97)	1.13 (0.66-1.94)	0.62
All fruits					
Servings/d	<1.0	1.0-1.4	1.5-2.4	≥2.5	
No. cases	46	21	38	30	
Person-years of follow-up	187,119	106,592	145,746	114,073	
Age- and sex-adjusted HR (95% CI)	1.0	0.75 (0.45-1.26)	1.04 (0.67-1.61)	1.03 (0.64-1.65)	0.72
Multivariate HR (95% CI)*	1.0	0.83 (0.48-1.41)	1.12 (0.70-1.80)	1.10 (0.64-1.88)	0.66
All vegetables					
Servings/d	<1.5	1.5-2.4	2.5-3.4	≥3.5	
No. cases	35	39	21	40	
Person-years of follow-up	127,189	152,174	121,403	152,764	
Age- and sex-adjusted HR (95% CI)	1.0	1.04 (0.66-1.65)	0.75 (0.44-1.30)	1.21 (0.76-1.94)	0.52
Multivariate HR (95% CI)*	1.0	1.03 (0.64-1.67)	0.72 (0.40-1.30)	1.08 (0.63-1.85)	0.87
Citrus fruits					
Servings/wk	<1.0	1.0-2.9	3.0-6.9	≥7.0	
No. cases	52	20	35	28	
Person-years of follow-up	218,446	98,380	127,714	108,990	
Age- and sex-adjusted HR (95% CI)	1.0	0.86 (0.51-1.45)	1.22 (0.80-1.90)	1.09 (0.68-1.73)	0.57
Multivariate HR (95% CI)*	1.0	0.88 (0.52-1.50)	1.26 (0.81-2.00)	1.12 (0.68-1.83)	0.53
Green leafy vegetables					
Servings/wk	<1.0	1.0-2.9	3.0-6.9	≥7.0	
No. cases	48	28	44	15	
Person-years of follow-up	166,304	140,242	170,082	76,902	
Age- and sex-adjusted HR (95% CI)	1.0	0.84 (0.52-1.34)	1.10 (0.72-1.66)	0.82 (0.45-1.47)	0.80
Multivariate HR (95% CI)*	1.0	0.93 (0.57-1.53)	1.21 (0.76-1.92)	0.88 (0.47-1.67)	0.99
Cruciferous vegetables					
Servings/wk	<1.0	1.0-1.4	1.5-2.9	≥3.0	
No. cases	57	23	22	33	
Person-years of follow-up	177,414	104,238	115,999	155,879	
Age- and sex-adjusted HR (95% CI)	1.0	0.85 (0.52-1.39)	0.68 (0.41-1.11)	0.81 (0.52-1.25)	0.30
Multivariate HR (95% CI)*	1.0	0.81 (0.49-1.33)	0.63 (0.37-1.06)	0.70 (0.43-1.13)	0.14

*Multivariate HRs were adjusted for age (in months), sex, education (less than high school, high school graduate, or more than high school), body mass index (<23.0, 23.0-24.9, 25.0-29.9, or ≥30 kg/m^2), physical activity (hours/wk; four categories), cigarette smoking status and pack-years of smoking (never, past <20 pack-years, past ≥20 pack-years, current <20 pack-years, current 20 to 39 pack-years, or current ≥40 pack-years), history of diabetes (yes or no), multivitamin supplement use (no use, occasional use, or regular use), and intakes of total energy (continuous) and alcohol (quartiles). Fruits and vegetables were included simultaneously in the multivariate model. Citrus fruits, green leafy vegetables, and cruciferous vegetables were included simultaneously in the multivariate model.

studies have been overstated because dietary intake is assessed after the diagnosis of pancreatic cancer, which might lead to recall bias. In addition, selection bias is a problem in situations of low participation rates among controls because those who participate are likely to be more health conscious and, therefore, are likely to consume more fruits and vegetables than nonrespondents. Selection bias may also be introduced if the case series was restricted to those cases that were still alive at the time of interview. Case-control studies of pancreatic cancer are especially susceptible to bias due to the high and rapid fatality rates.

Prospective cohort studies are best suited to evaluate the potential protective role of fruits and vegetables against pancreatic cancer because dietary intake is assessed before the outcome and reporting is not biased by changes in dietary intake after the diagnosis. Our results for total fruit and total vegetable consumption are in agreement with findings from previous prospective cohort studies, in which no significant association was observed (20-25).

Few epidemiologic studies have examined the relationship between cruciferous vegetable consumption and pancreatic cancer risk. In a large population-based case-control study where only direct interviews were used (13), men and women in the highest quartile of cruciferous vegetable consumption (i.e., more than four times per week) had a statistically significant 50% decreased risk of pancreatic cancer compared with those in the lowest quartile (i.e., less than 1.5 servings/wk). In another large population-based case-control study based on direct interviews only (10), the odds ratio for the highest versus the lowest quartile of cruciferous vegetable consumption was 0.76 (95% CI, 0.56-1.0). Two smaller case-control studies (5, 7) also showed strong inverse associations between consumption of cruciferous vegetable and risk of pancreatic cancer. The only previous prospective study on cruciferous vegetables and risk of pancreatic cancer, the Alpha-Tocopherol Cancer Prevention Study (21), found no significant association (HR, 0.82; 95% CI, 0.50-1.32, for highest versus lowest quintile). However, this study was conducted among Finnish male smokers (21), and results from our study suggested a stronger inverse association between cruciferous vegetable consumption and pancreatic cancer risk among never smokers compared with ever smokers, although a test for interaction was not statistically significant.

A protective effect of cruciferous vegetables against cancer may be plausible due to their high content of glucosinolates, which are degraded into isothiocyanates by enzymatic action of plant-specific myrosinase or intestinal microflora (28, 29). The anticarcinogenic properties of isothiocyanates may be related to the inhibition of the metabolic activation of carcinogens by phase I enzymes of the cytochrome P450 family, along with induction of phase II detoxifying and cellular defensive enzymes (29). A study in rats showed that a mixture of glucosinolate breakdown products strongly induced pancreatic phase II enzymes (30). Isothiocyanates have been shown to block the initiation phase of pancreatic carcinogenesis in animal models (31) and to inhibit growth of human pancreatic cancer cell lines (32).

Among the individual cruciferous vegetables we examined, only cabbage consumption was statistically significantly associated with a lower risk of pancreatic cancer, although the results for other cruciferous vegetables were suggestive of inverse associations. This difference may be because cabbage is often eaten raw, whereas cauliflower, broccoli, and Brussels sprouts are usually consumed after being cooked. The plant enzyme myrosinase is inactivated by cooking. One study found that the bioavailability of isothiocyanates was about three greater in raw than in cooked broccoli (33). In another study, volunteers who consumed uncooked watercress excreted isothiocyanates in the range of 17.2% to 77.7% of the total isothiocyanates consumed, but when the myrosinase activity was inactivated by cooking, excretion was decreased to 1.2% to 7.3% of the total (34).

Our study has several important strengths. First, the prospective study design avoids recall and selection bias. Second, the practically complete follow-up of the study population through linkages to various population-based registers minimizes the concern that our results have been affected by differential follow-up. Furthermore, we had detailed data on potential confounding variables, which we controlled for in the analyses. A limitation to this study is the use of a self-administered food-frequency questionnaire to assess diet intake. Random misclassification of fruit and vegetable consumption could attenuate the risk estimates. Nevertheless, results from our validation study suggest that consumption of fruits and vegetables was reported reasonably well. Also, it is unlikely that misclassification explained the lack of association over extreme levels of overall fruit and vegetable consumption because it is improbable that participants were misclassified from one extreme category to the other (deciles). Finally, the duration of follow-up in our cohorts was relatively short. Hence, we cannot rule out the possibility that an inverse association for overall fruit and vegetable consumption was missed because the dietary information collected at baseline did not reflect long-term fruit and vegetable consumption and the etiologically relevant point in time between exposure and outcome.

In summary, the results from this prospective cohort study do not support a strong role for fruit and vegetable consumption in the prevention of pancreatic cancer. Our findings, however, do not rule out the possibility of a protective role for specific fruit or vegetable subgroups, such as cruciferous vegetables, or for specific nutrients or phytochemicals.

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