

Dietary Intake of Lycopene Is Associated with Reduced Pancreatic Cancer Risk¹

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ABSTRACT Although fruits and vegetables have been implicated in the etiology of pancreatic cancer, the role of phytochemicals in these food groups has received little attention to date. In this study, we investigated the possible association between dietary carotenoids and pancreatic cancer risk. A case-control study of 462 histologically confirmed pancreatic cancer cases and 4721 population-based controls in 8 Canadian provinces took place between 1994 and 1997. Dietary intake was assessed by a self-administered FFQ. Unconditional logistic regression was used to assess associations between specific and total carotenoid intakes and the risk of pancreatic cancer. All tests of statistical significance were 2-sided. After adjustment for age, province, BMI, smoking, educational attainment, dietary folate, and total energy intake, lycopene, provided mainly by tomatoes, was associated with a 31% reduction in pancreatic cancer risk among men [odds ratio (OR) = 0.69; 95% CI: 0.46–0.96; $P = 0.026$ for trend] when comparing the highest and lowest quartiles of intake. Both β -carotene (OR = 0.57; 95% CI: 0.32–0.99; $P = 0.016$ for trend) and total carotenoids (OR = 0.58; 95% CI: 0.34–1.00; $P = 0.02$ for trend) were associated with a significantly reduced risk among those who never smoked. The results of this study suggest that a diet rich in tomatoes and tomato-based products with high lycopene content may help reduce pancreatic cancer risk. *J. Nutr.* 135: 592–597, 2005.

KEY WORDS: • *pancreatic cancer* • *diet* • *carotenoids* • *lycopene* • *cancer prevention*

Pancreatic cancer is the 4th leading cause of cancer-related deaths in both men and women in Canada (1). Survival is extremely low worldwide, with a 5-y survival rate of <5% (2), and a case fatality proportion of 99% within 12 mo of diagnosis (3). Several epidemiologic studies suggested that high consumption of fruits and vegetables, which are major sources of carotenoids, may play a role in the prevention of pancreatic cancer. Substantial evidence from experimental investigations showed that carotenoids precipitate cancer-preventing events, including antioxidant activity, enhancement of immune function, stimulation of gap junctional intercellular communication, induction of detoxifying enzymes, and inhibition of cellular proliferation (4,5). It was suggested that α -carotene

suppresses cytochrome P₄₅₀ 1A1, an activator of procarcinogens (6). β -Carotene may control growth-inhibitory and proapoptotic effects in cancer cells through the redox regulation of the nuclear transcription factor NF- κ B activity (7). Lycopene is the most efficient singlet oxygen quencher in vitro (8); lutein and zeaxanthin are scavengers of radical oxygen species (4), whereas β -cryptoxanthin may stimulate the expression of RB, an anti-oncogene and p73, a p53-related gene (9).

Despite the mechanistic hypotheses suggesting that intake of carotenoids may be related to reduced pancreatic cancer risk, no epidemiologic studies have addressed this issue to date. The present case-control study was undertaken to investigate the possible association between the intake of specific and total carotenoids and pancreatic cancer risk within the Canadian National Enhanced Cancer Surveillance System (NECSS).³ This study also examined the modifying effect of smoking on the association between dietary carotenoid intake and pancreatic cancer risk because free radicals in cigarette smoke can alter the concentrations of most carotenoids (10).

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³ Abbreviations used: NECSS, National Enhanced Cancer Surveillance System; OR, odds ratio; USDA-NCC, USDA-Nutrition Coordinating Center.

SUBJECTS AND METHODS

Study population. The NECSS is a multisite, population-based, case-control study involving 21,020 participants with 1 of 19 types of cancer identified through cancer registries in 8 of the 10 Canadian provinces, namely, Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan. The present investigation includes only pancreatic cancer cases, and is restricted to data obtained from direct interviews. The study population was described in detail elsewhere (11). Briefly, between April 1, 1994 and December 31, 1997, participating provincial registries identified pancreatic cancer cases as early as possible in the registration process to minimize the loss of subjects because pancreatic cancer is a rapidly fatal disease. All pancreatic cancer cases included in the NECSS were confirmed histologically, and defined according to the WHO's International Classification of Diseases, rubric 157 (12).

Like most other studies of pancreatic cancer that collected information directly from case subjects, the overall proportion of eligible cases that responded was low. Among men diagnosed with pancreatic cancer, 30% had died before an interview could be conducted, and consent was not granted by physicians for an additional 15%. For women, 28% had died before they could be contacted, and the attending physician refused consent to approach patients for an additional 16%. The vast majority of cases were ascertained within 1–3 mo of diagnosis; physician consent to send questionnaires to patients was generally obtained within 1 mo, and ~70% of questionnaires were returned within 2 mo of mailing. Response rates of eligible cases were 55% for men and 56% for women.

The NECSS used frequency matching in selecting the control population to achieve age and gender distributions similar to those of all cancer cases combined. Based on the projected number of incident cancer cases by province, the questionnaires were mailed to 8117 subjects during the 1996 calendar year using the same protocol as for cases. Questionnaires were not returned for 573 controls (7.4%) because of incorrect or changed addresses. Strategies for control selection varied by province, depending on data accessibility. In Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan, and British Columbia, provincial health insurance plans were tapped to obtain a random sample of the provincial population stratified by age and gender. In each of these provinces, >95% of residents are covered by public health care plans. Active military personnel and their families as well as indigenous peoples were excluded because they were covered by other plans. In Ontario, Ministry of Finance data were used to derive a stratified random sample, whereas Newfoundland and Alberta adopted a random digit-dialing method to enroll a population-based sample of controls. A total of 5039 controls were selected to serve as a common control group for all types of cancer. Response rates of 65 and 71% were achieved from the male and female control populations, respectively.

Questionnaires, with telephone follow-up for clarification when necessary, were mailed to study subjects to obtain information on residential and occupational histories and other risk factors for cancer. The NECSS questionnaire included questions on smoking history, height, weight, physical activity, and education attainment. This research was approved by the ethics committee of Health Canada and written, informed consent was obtained from each study subject.

Dietary assessment. Food consumption data were obtained via a semiquantitative FFQ derived from 2 instruments developed in the United States that have been widely validated previously, i.e., the short Block questionnaire (13) and the Willett questionnaire (14). Subtle changes were made to the questionnaire items to take into account differences in American and Canadian dietary practices. The FFQ includes questions on 69 different food and beverage items, including the frequency of consumption and the amounts consumed. Participants were asked how often they had consumed these foods per week in the time period 2 y before interview.

Food and beverage items were retrieved from the FFQ and used to estimate the daily intake of individual carotenoids, based on the USDA-Nutrition Coordinating Center (NCC) Carotenoid Database (15). This online database provides food composition values for 6 specific carotenoids contained in food and beverage items included in

the study questionnaire. Information on other nutrients, including total carotenoids, dietary folate, and total energy, was obtained through the 1997 Canadian Nutrient File.

Data were collected for 475 cases (264 men, 211 women) and 5039 controls (2547 men, 2492 women). We excluded controls < 30 y of age ($n = 237$) because pancreatic cancer cases are usually ≥ 30 y old. Furthermore, subjects with daily energy intake < 500 kcal (2.092 MJ) (10 cases and 54 controls) or > 5000 kcal (20.92 MJ) (3 cases and 27 controls) were excluded because such intakes are unrealistic and hence of questionable validity. Finally, a total of 462 cases (258 men, 204 women) and 4721 frequency-matched controls (2331 men, 2390 women) were eligible for analysis.

Statistical analysis. Food intake among cases and controls was analyzed according to carotenoid intake based on the USDA-NCC Carotenoid Database and the Canadian Nutrient File noted previously. Mean intakes were calculated separately for cases and controls. To compare the study population characteristics, we used the χ^2 test or Mantel extension test for categorical variables and the paired t test for continuous variables. To evaluate associations between carotenoids and pancreatic cancer risk, the study subjects were divided into 4 categories on the basis of quartiles of total and each specific energy-adjusted carotenoid intake in the control population. Odds ratios (ORs) and 95% CIs were calculated using unconditional logistic regression. Analyses were adjusted for matching variables (age group and province), lifetime cigarette consumption (0, >0–15, and >15 pack-y), BMI (<25, 25–29.9, and ≥ 30 kg/m²), educational attainment (y), dietary folate, and total energy intake.

To evaluate the combined effect of intake of individual carotenoids and selected lifestyle variables (smoking, BMI, age, and educational attainment), the P -value for a multiplicative interaction term added to a fully adjusted model was examined; when it was significant, the analysis was stratified on that variable. Tests for linear trend in the carotenoid variables included in logistic regression were performed by replacing the indicator variables in each multivariate model with a single variable representing the median frequency of consumption for a given intake category, and by using the Wald χ^2 value computed for the regression coefficient of this variable to test the null hypothesis of no linear trend in pancreatic cancer risk across quartiles of intake. This analysis focused on carotenoid intake from diet, rather from specific carotenoid supplements. At the time the study was conducted, questions about the consumption of such supplements were not included in the FFQ. Models were fit for men and women separately. All tests of statistical significance were 2-sided and P -values < 0.05 were considered significant. All analyses were conducted using SPSS statistical software (release 10.02, SPSS).

RESULTS

Selected characteristics of the study population are presented (Table 1). In both men and women, there were appreciable differences between cases and controls for age distributions with an excess of younger control subjects ($P < 0.05$); in addition, cases were more likely to use high amounts of tobacco ($P < 0.01$). Two years before the diagnosis of cancer, there was a higher pancreatic cancer risk with increased BMI in both genders ($P < 0.05$). Among men, cases were more likely to have greater total energy intake than controls ($P < 0.01$).

The main food sources of α -carotene in the diet were carrots and tomatoes. β -Carotene was derived primarily from potatoes, carrots, and spinach. β -Cryptoxanthin was supplied by oranges and fruit juices, whereas lycopene was mainly from tomatoes, tomato juice, and tomato sauce. Lutein + zeaxanthin were from broccoli and green-leaf vegetables, and total carotenoids were mainly from potatoes, carrots, and cantaloupes.

The ORs and corresponding 95% CIs for pancreatic cancer according to specific and total carotenoid intakes are summarized (Table 2). After adjustment for age, province, educational attainment, smoking, BMI, folate, and total energy

TABLE 1
Selected characteristics of the study population¹

	Men (n = 2589)		Women (n = 2594)	
	Cases (n = 258)	Controls (n = 2331)	Cases (n = 204)	Controls (n = 2390)
	n (%)			
Age, y				
30–34	2 (1)*	124 (5.5)	3 (1.5)†	62 (3)
35–39	6 (2)*	140 (6)	2 (1)†	124 (5)
40–44	6 (2)*	109 (4.5)	12 (6)†	224 (9)
45–49	15 (6)*	113 (5)	13 (6.5)†	335 (14)
50–54	27 (11)*	152 (7)	21 (10)†	274 (11)
55–59	33 (13)*	217 (9)	25 (12)†	269 (11)
60–64	52 (20)*	350 (15)	33 (16)†	351 (15)
65–69	62 (24)*	537 (23)	53 (26)†	377 (16)
70–74	55 (21)*	589 (25)	42 (21)†	374 (16)
Cigarette consumption, pack-y				
0	57 (22)†	571 (25)	87 (43)†	1196 (50)
>0–15	48 (19)†	706 (30)	45 (22)†	678 (28)
>15	150 (58)†	1026 (44)	69 (34)†	491 (21)
Missing	3 (1)	28 (1)	3 (1)	25 (1)
BMI 2 y before diagnosis, kg/m ²				
<25	86 (33)*	882 (38)	102 (50)†	1353 (57)
25–29.9	118 (46)*	1099 (47)	55 (27)†	717 (30)
≥30	54 (21)*	350 (15)	47 (23)†	320 (13)
Physical activity, ² h/mo				
<21	75 (29)	563 (24)	59 (29)	605 (25)
21–23	120 (47)	1207 (52)	108 (53)	1343 (56)
>23	62 (24)	561 (24)	37 (18)	442 (19)
Daily energy intake, kJ/d	8268 ± 3511†	7549 ± 2822	7265 ± 2541	6859 ± 2491

¹ Values are means ± SD or n (%). Symbols indicate different from controls: * $P < 0.05$; † $P < 0.01$.

² Defined as total number of hours per month of moderate and vigorous activities.

intake, a significant inverse association was observed between pancreatic cancer risk and lycopene intake in men (OR = 0.69; 95% CI: 0.46–0.96; $P = 0.026$ for trend), when comparing the highest quartile of intake with the lowest. Intakes of α -carotene, β -carotene, β -cryptoxanthin, lutein/zeaxanthin, and total carotenoids were not associated with pancreatic cancer risk.

There was evidence of an interaction between tobacco use and β -carotene ($P = 0.02$) as well as total carotenoids ($P = 0.013$). The risk of pancreatic cancer in relation to intake of carotenoids is presented by level of tobacco consumption (Table 3). Among those who never smoked, inverse dose-response relations were apparent between β -carotene (OR = 0.57; 95% CI: 0.32–0.99; $P = 0.016$ for trend) and total carotenoids (OR = 0.58; 95% CI: 0.34–1.00; $P = 0.02$ for trend) and pancreatic cancer, when comparing the highest with the lowest quartile of intakes. These results did not differ among subgroups defined by pack-years of cigarette smoking. Overall, there was no significant effect modification by BMI, age, physical activity, and educational attainment (data not shown).

DISCUSSION

This population-based case-control study demonstrated an inverse dose-response relation between lycopene and pancreatic cancer in men. Intakes of β -carotene and total carotenoids were significantly associated with reduced pancreatic cancer risk among those who never smoked. To the best of our knowledge, this is the first epidemiologic study to examine the role of specific dietary carotenoids in risk assessment of pancreatic cancer.

Previous observational investigations assessed the relation between lycopene serum concentrations and pancreatic cancer with consistent results. A case-control study found that plasma lycopene levels were significantly lower in pancreatic cancer cases than in matched controls (16). In the Washington County Cohort Study, in which subjects were followed for almost 15 y, significantly lower baseline serum lycopene levels were documented in subjects with pancreatic cancer than in matched cohort controls (17,18). Lower serum lycopene levels were observed in individuals with certain chronic diseases, including cancer, suggesting that lycopene intake reduces the occurrence, extent, or degree of these conditions, or that lycopene is depleted by oxidative stress and inflammatory processes (19). Interestingly, in vitro studies suggest that lycopene inhibits gap junction communication (20), activates phase II enzymes (21), suppresses eicosanoid metabolism by blocking cyclooxygenase-2 synthesis (22), and inhibits tumor cell growth by repressing insulin-like growth factor 1 receptor activation (23). However, these putative mechanisms remain speculative and require confirmation.

We observed a 42% reduction in pancreatic risk in relation to both β -carotene and total carotenoids among those who never smoked, but no clear evidence of an association between any individual or total carotenoid intakes and pancreatic cancer risk among past or current smokers. Exposure to tobacco smoke causes extensive β -carotene oxidation (24). It was reported that cigarette smoking is independently associated with lowered circulating concentrations of provitamin A carotenoids: in general, active smokers have >25% lower circulating concentrations of α -carotene, β -carotene, and β -cryptoxanthin than nonsmokers, even after adjusting for dietary

TABLE 2

Odds ratio (OR) and 95% CI for pancreatic cancer associated with dietary carotenoids^{1,2}

Carotenoid	Gender	Quartiles of energy-adjusted carotenoid intakes				P for trend
		1	2	3	4	
α -Carotene	Male	358 \pm 212	694 \pm 284	1051 \pm 214	2060 \pm 1044	0.90
Dietary intake, $\mu\text{g}/\text{d}$		68/696	77/549	58/516	45/501	
Cases/Controls, n		1.00	0.68 (0.46–0.98)	0.80 (0.54–1.19)	1.01 (0.67–1.53)	
Multivariate OR (95% CI)						
	Female	341 \pm 182	651 \pm 270	1013 \pm 200	2059 \pm 1147	0.13
Dietary intake, $\mu\text{g}/\text{d}$		45/443	42/590	58/623	51/638	
Cases/Controls, n		1.00	1.65 (1.04–2.61)	1.31 (0.84–2.04)	1.56 (0.98–2.42)	
Multivariate OR (95% CI)						
β -Carotene	Male	6215 \pm 3832	10,621 \pm 3522	15,788 \pm 3173	25,763 \pm 14,196	0.58
Dietary intake, $\mu\text{g}/\text{d}$		69/634	64/532	69/565	46/531	
Cases/Controls, n		1.00	0.93 (0.63–1.38)	0.89 (0.61–1.30)	1.22 (0.80–1.87)	
Multivariate OR (95% CI)						
	Female	5953 \pm 3387	9803 \pm 2882	14,935 \pm 3269	22,059 \pm 10,683	0.40
Dietary intake, $\mu\text{g}/\text{d}$		40/505	39/607	61/574	56/608	
Cases/Controls, n		1.00	1.30 (0.80–2.12)	0.83 (0.53–1.30)	0.96 (0.60–1.51)	
Multivariate OR (95% CI)						
P-Cryptoxanthin	Male	77 \pm 66	162 \pm 83	267 \pm 80	598 \pm 314	0.46
Dietary intake, $\mu\text{g}/\text{d}$		75/676	77/565	51/524	45/497	
Cases/Controls, n		1.00	0.73 (0.51–1.05)	1.02 (0.68–1.53)	1.09 (0.72–1.62)	
Multivariate OR (95% CI)						
	Female	837 \pm 716	1139 \pm 753	1951 \pm 820	7234 \pm 6510	0.27
Dietary intake, $\mu\text{g}/\text{d}$		52/462	37/575	52/615	55/642	
Cases/Controls, n		1.00	1.50 (0.95–2.38)	1.26 (0.82–1.94)	1.23 (0.80–1.87)	
Multivariate OR (95% CI)						
Lycopene	Male	898 \pm 772	1215 \pm 859	2106 \pm 917	7585 \pm 6505	0.026
Dietary intake, $\mu\text{g}/\text{d}$		56/651	58/536	63/518	71/557	
Cases/Controls, n		1.00	0.78 (0.51–1.19)	0.76 (0.49–1.16)	0.69 (0.46–0.96)	
Multivariate OR (95% CI)						
	Female	837 \pm 716	1139 \pm 753	1951 \pm 820	7234 \pm 6510	0.27
Dietary intake, $\mu\text{g}/\text{d}$		42/487	41/604	48/621	65/582	
Cases/Controls, n		1.00	1.38 (0.84–2.56)	1.05 (0.65–1.70)	0.91 (0.56–1.43)	
Multivariate OR (95% CI)						
Lutein + Zeaxanthin	Male	767 \pm 380	1105 \pm 382	1702 \pm 499	3574 \pm 1585	0.63
Dietary intake, $\mu\text{g}/\text{d}$		85/704	53/594	61/516	49/448	
Cases/Controls, n		1.00	1.19 (0.81–1.74)	0.99 (0.68–1.44)	1.13 (0.76–1.68)	
Multivariate OR (95% CI)						
	Female	752 \pm 368	1057 \pm 348	1576 \pm 418	3690 \pm 1694	0.23
Dietary intake, $\mu\text{g}/\text{d}$		42/435	41/546	57/622	56/691	
Cases/Controls, n		1.00	1.09 (0.68–1.75)	1.12 (0.70–1.78)	1.25 (0.79–1.98)	
Multivariate OR (95% CI)						
Total carotenoids	Male	1514 \pm 955	2578 \pm 851	3813 \pm 729	6365 \pm 3359	0.68
Dietary intake, ³ RE/d		71/645	66/532	62/542	49/543	
Cases/Controls, n		1.00	0.92 (0.62–1.36)	0.84 (0.58–1.23)	1.22 (0.80–1.86)	
Multivariate OR (95% CI)						
	Female	1448 \pm 848	2444 \pm 696	3629 \pm 759	5551 \pm 2642	0.50
Dietary intake, RE/d		42/494	0/608	56/596	58/596	
Cases/Controls, n		1.00	1.11 (0.69–1.78)	0.92 (0.58–1.44)	0.91 (0.58–1.44)	
Multivariate OR (95% CI)						

¹ Values are means \pm SD or OR (95% CI).² OR and 95% CI from the logistic regression model adjusted for age, province, smoking, educational attainment, BMI, folate, and total energy intake.³ Defined as retinol equivalent.

intake and other demographic factors (10,25). Moreover, depressed plasma β -carotene concentrations were reported in response to enhanced metabolic turnover resulting from smoking-induced oxidative stress (26). If this putative oxidative mechanism can be shown to affect the relation between β -carotene and smoking, it would help explain why β -carotene and total carotenoids, which come from similar sources, were associated with a reduced pancreatic cancer risk in this study only among those who never smoked.

The major strengths of our study include its uniqueness, the large number of pancreatic cancer cases, histological diagnosis

of pancreatic cancer cases, and general population sampling. Ours is the first study to examine the role of dietary carotenoid intakes in risk assessment of pancreatic cancer. The large sample size permitted subgroup analyses by sex and smoking status. Histological confirmation of diagnosis reduced the possibility of disease misclassification, whereas the population-based approach to subject selection facilitated extrapolation of our results to the general population.

Our study is also subject to certain limitations. Because the assessment of dietary exposure was retrospective, recall bias cannot be completely excluded. A prospective cohort ap-

TABLE 3

Odds ratio (OR) and 95% CI for pancreatic cancer associated with dietary carotenoids and tobacco use^{1,2}

Tobacco use	Carotenoid	Quartiles of energy-adjusted carotenoid intakes				P for trend
		1	2	3	4	
Never smoked	β -Carotene	1.00	1.09 (0.60–1.99)	0.72 (0.41–1.28)	0.57 (0.32–0.99)	0.016
	Cases/Controls, n	27/467	27/470	39/432	48/441	
	Total carotenoids	1.00	1.10 (0.61–2.00)	0.79 (0.45–1.38)	0.58 (0.34–1.00)	0.020
Past smokers	β -carotene	1.00	1.24 (0.78–1.97)	0.98 (0.64–1.51)	1.38 (0.86–2.22)	0.44
	Cases/Controls, n	50/425	40/451	59/502	40/486	
	Total carotenoids	1.00	1.07 (0.68–1.70)	0.94 (0.61–1.47)	1.22 (0.76–1.97)	0.62
Current smokers	β -Carotene	1.00	0.83 (0.47–1.46)	0.82 (0.47–1.44)	1.61 (0.85–3.04)	0.24
	Cases/Controls, n	32/285	36/260	39/248	25/254	
	Total carotenoids	1.00	0.76 (0.44–1.34)	0.85 (0.49–1.49)	1.70 (0.90–3.23)	0.15
	Cases/Controls, n	33/291	37/262	37/246	24/250	

¹ Values are OR (95% CI).

² OR and 95% CI from the logistic regression model adjusted for age, sex, province, educational attainment, BMI, folate, and total energy intake.

proach has several advantages when studying associations between nutritional factors and cancer risk. However, because of the relatively low incidence of pancreatic cancer, the largest cohort to date examining diet and pancreatic cancer risk included only 178 pancreatic cancer cases throughout 18 y of follow-up (27). We could not adjust OR estimates for the potentially confounding effect of diabetes mellitus and family history of pancreatic cancer because this information was not collected at baseline. Nevertheless, we expect that diabetes did not confound the association between dietary carotenoids and pancreatic cancer risk because diet is likely to be an initial risk factor for both chronic diseases, rather than lying on their causal pathways. In addition, it was suggested that the importance of diabetes is much reduced if pancreatic cancer cases of recent onset are excluded (28). In addition, it is unlikely that the confounding effect of family aggregation of pancreatic cancer may explain the associations we found because genetic/familial predisposition is relatively rare (29). Moreover, confirmation of a hereditary component is particularly challenging because pancreatic cancer may occur only infrequently in some of the hereditary cancer syndromes, in accordance with reduced frequency of the deleterious, predisposing mutations (30).

Although the USDA-NCC Carotenoid Database used in the present analysis represents the most current and comprehensive data available to date, data were not available for all of the Canadian food items we investigated. In addition, the carotenoid content of foods is highly variable depending on a number of factors, including geographical area and growing conditions, cultivar or variety, processing techniques, method of food preparation, and length and conditions of storage (4). As a consequence, the likelihood of nondifferential misclassification cannot be completely excluded, raising the possibility that some associations were obscured.

Another limitation is the consequence of early and high case fatality associated with the disease. As in other epidemiologic studies of pancreatic cancer, cases who died before the questionnaire could be administered were not included in the analysis. Bias may have been introduced in the present investigation if rapidly fatal cases had a different etiology from cases with longer survival, or if the dietary carotenoids under study influenced survival. However, because there was no discrimination in the selection of study subjects based on their demographic characteristics and lifestyle factors, such as age, dietary

patterns, smoking, or educational attainment, survivors are still representative of the study population. Consequently, selection bias is unlikely to be substantial.

In conclusion, we found a significantly reduced pancreatic cancer risk with dietary intake of lycopene among men. A significant inverse association was also observed between pancreatic cancer risk and both dietary β -carotene and total carotenoid intakes among those who never smoked. As a whole, our data supported the association of a diet rich in vegetables with a reduction in risk of pancreatic cancer. More studies assessing associations between dietary carotenoids and the risk of pancreatic cancer are warranted to better elucidate the role of diet in the etiology of pancreatic cancer.

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