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ORIGINAL PAPER

Fruit and vegetable consumption is inversely associated with having pancreatic cancer

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Abstract
Objective Studies on fruit, vegetable, fiber, and grain consumption and pancreatic cancer risk are inconclusive. We used a clinic-based case–control study specifically designed to address limitations of both cohort and case–control studies to examine the relationship.
Methods Participants were excluded who reported changing their diet within 5 years prior to study entry. And 384 rapidly ascertained cases and 983 controls (frequency matched on age (±5 years), race, sex, and residence) completed epidemiologic surveys and 144-item food frequency questionnaires. Odds ratios (OR) and 95% confidence intervals were calculated using logistic regression adjusted for age, sex, smoking, body mass index, energy intake, and alcohol consumption.
Results Comparing highest to lowest quintiles, we observed significant inverse associations (OR < 0.8) with significant trends ($p_{\text{trend}} < 0.05$) for citrus, melon, and berries, other fruits, dark green vegetables, deep yellow vegetables, tomato, other vegetables, dry bean and pea, insoluble fiber, soluble fiber, whole grains, and orange/grapefruit juice, and an increased association with non-whole grains. Results were similar after adjusting for diabetes or total sugar intake.
Conclusions We provide evidence that lower consumption of fruits, vegetables, whole grains, and fiber is associated with having pancreatic cancer. This may have a role in developing prevention strategies.

Keywords Diet · Risk · Questionnaire · Pancreatic cancer

Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Type 2 diabetes mellitus
FFQ	Food frequency questionnaire
NCI	National Cancer Institute
OR	Odds ratios
p_{trend}	p-value from test for trend
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

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Introduction

The most recent estimates from the International Agency for Research on Cancer (2002) [1] indicate that the mortality among those diagnosed with pancreatic cancer is high worldwide, with higher incidence occurring in more developed regions. Overall, the age-adjusted incidence rate for men is $8.1/10^5$ and women is $5.3/10^5$, with the age-adjusted mortality rate for men at $8.0/10^5$ and women at

5.4/10^5 [1]. In the United States, the American Cancer Society estimates that in 2010 there were 43,140 new cases of pancreatic cancer and 36,800 deaths [2, 3]. The high mortality-to-incidence ratio reflects the current status of pancreatic cancer diagnosis and treatment. Generally, the disease is diagnosed at a late stage, which contributes to low resection rates [4]. Prognosis is extremely poor, with a 1-year survival rate of 25% and a 5-year survival rate below 5% [5]. Attempts to identify early-stage pancreatic cancer are hindered by lack of understanding of its natural history [4], and although current imaging may be able to detect some precursor lesions [4, 5], the infrequency of disease within the population makes general population screening unfeasible. An important strategy at present is to focus on modifiable risk factor identification and prevention.

A number of risk factors have been reported to be associated with pancreatic cancer, most generally of modest effect. The risk factors consistently identified across studies of various designs include cigarette smoking, age, sex, family history, personal history of type 2 diabetes mellitus (DM) or pancreatitis, and obesity [6–8]. Dietary consumption results are somewhat variable [6, 8]. Based on an extensive literature review, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) reported that there is limited evidence to suggest that fruits protect against pancreatic cancer and there is inconsistent evidence of a risk relationship with vegetables [9]. Since 2006, four case–control studies have reported an inverse association between pancreatic cancer and fruits [10], vegetables [11], fibers [12, 13], or whole grains [13]. During the same period, five cohort studies have reported overall null associations between pancreatic cancer and fruits and vegetables [8, 14–17] except in high-risk group subanalyses [14, 16]. The European Prospective Investigation into Cancer and Nutrition study [8] recorded 555 pancreatic cancer cases out of 478,400 participants during an average follow-up of 8.9 years and reported non-significant results (adjusted trend p-value = 0.42, 0.93, 0.94) for total fruit and vegetable, total fruit, and total vegetable, respectively. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk study [14] recorded 300 pancreatic cancer cases out of 127,500 participants during an average follow-up of 10 years and reported several fruit and vegetable categories for which significant results (trend p-value = 0.01, 0.02) were observed for fruit juice among men only and fruits other than citrus, respectively. A prospective study using the Swedish Mammography Cohort and the Cohort of Swedish Men [15] recorded 135 pancreatic cancer cases out of 81,922 participants during an average follow-up of 6.8 years and reported non-significant results (adjusted trend p-value = 0.02, 0.66, 0.87) for total fruit and vegetable, total fruit, and total vegetable, respectively. The Multiethnic Cohort study [16] recorded 529 pancreatic cancer cases out of 183,522 participants during an average follow-up of 8.3 years and reported non-significant results (adjusted trend p-value = 0.134) for total vegetable, but in stratified analysis, total vegetables were significant (adjusted trend p-value = 0.02) among never smokers. Iowa Women's Health Study (IWHS) [17] recorded 256 pancreatic cancer cases out of 34,642 women participants during an average follow-up of 16.3 years and reported non-significant results (adjusted trend p-value = 0.38, 0.71, 0.14) for total fruit and vegetable, total fruit, and total vegetable, respectively.

A few possible explanations for the inconsistencies between case–control and cohort studies include information bias with respect to dietary ascertainment, homogeneous intake, and variability in histologically verified tumor types [8]. Selection in case–control studies could explain the observed inverse associations since most cohort studies reported null results, which are not affected by possible diet changes after cancer diagnosis.

Our objective was to evaluate fruit, vegetable, fiber, and grain consumption associations with pancreatic adenocarcinoma using a clinic-based case–control study specifically designed to address limitations of both cohort and case–control studies. Discriminating features of our case–control study include availability of demographic information to assess comparability of those who consented but did not complete the FFQ to those who did, the method of rapid ascertainment of cases, and questions on the food frequency questionnaire (FFQ) about dietary changes in the 5 years prior to enrollment. The rapid ascertainment protocol is advantageous, as the questionnaire was self-completed around time of recruitment, which was usually at the time of diagnosis of adenocarcinoma, reducing recall bias differences between cases and controls. The ability to identify recent diet change enabled us to better avoid reverse causation.

Materials and methods

Study population description

This study was approved by the institutional review board. From May 2004 to December 2009, using a rapid ascertainment method described elsewhere [18], all 2,473 pancreatic adenocarcinoma cases were approached, of which 1,648 (66.6%) consented to participate in a prospective registry at time of their hospital visit. Over 99% of the cases were confirmed by histology (88%), medical record (10%), or death certificate (1%). During the same time period, a total of 2,708 potential controls (unrelated individuals without pancreatic adenocarcinoma) were approached at the

time of routine primary medical care and 1,514 (55.9%) consented. Controls were frequency matched to cases on age at time of recruitment (in 5-year increments), race, sex, and region of residence (Olmsted County; three-state (MN, WI, IA); or outside of area). Controls with prior diagnoses of cancer except non-melanoma skin cancer and personal history of pancreatitis were excluded. Written, informed consent was obtained from each individual for participation in the registry study. Both groups were asked to complete a questionnaire to collect information on demographic characteristics and potential risk factors. Missing self-reported demographic data on body mass index (BMI) and diabetes status were abstracted from medical records of cases and controls.

Dietary data from food frequency questionnaires

The FFQ used was a modified form of the New England Bladder Cancer FFQ developed by the NCI. Similar FFQs and their modified forms have been validated in US hospital-based populations [19, 20] with questionnaires developed by the National Cancer Institute (NCI) providing the most reproducible results [21]. Participants were asked to complete the scannable FFQ to obtain self-reported average consumption and frequency of intake of 144 food and beverage items (53 pertained to fruit, vegetable, grain, and fiber categories discussed here). As they completed the FFQ, cases and controls were asked to think about their usual dietary intake during the 5 years prior to study entry. The NCI software DietCalc [22] was used to create food groupings and estimate average nutrient intake. FFQs were returned by 816 (49.5%) cases and 1,290 (85.2%) controls among those consented. Participants were excluded from this analysis if they answered affirmatively or failed to answer the question, "Have you recently changed your diet?" and if the change occurred within the previous 5 years (420 cases and 286 controls). No individuals were found to have an extreme daily energy intake (<1,000 or >6,000 kcal/day; only 2 cases and 4 controls would be excluded if >4,000 kcal/day was the upper extreme). We excluded those who did not answer 17 or more items (12 cases; 21 controls). Therefore, 384 cases and 983 controls composed the final study sample.

Statistical analysis

To compare the study population characteristics, median, mean, and 95% confidence intervals (CI) for intake of food groupings were separately calculated for cases and controls. Sex-specific quintile cut-points for the dietary variables were based on the distribution of the control population. Dietary variables were created using the density method with energy-adjusted dietary items [23]. Logistic regression was used to calculate odds ratios (OR) and 95% CIs, adjusting for age, sex, smoking (current, former, never), BMI, energy intake (per 1,000 kcal), and number of drinks of alcohol per week. Tests for linear trends using the median within each quintile for the dietary groups included in the logistic regression were performed with the likelihood ratio test and with the Wald χ^2 value computed for the regression coefficient of each variable. The null hypothesis for this test was no linear trend in pancreatic adenocarcinoma risk across quintiles of intake. All tests of statistical significance were 2-sided, and p-values < 0.05 were considered significant. All analyses were generated using SAS® software (version [9.2]) [24].

Results

For our analyzed study group, cases compared to controls were more likely to be men, be slightly older, and have ever smoked (and if a past smoker, had tended to have quit more recently). Cases were more likely to have DM (especially new onset; Table 1 columns 1 and 2) compared to controls. Usual BMI was similar between cases and controls. When comparing male and female cases (not shown), men were slightly younger, had a higher usual BMI, were more likely to have ever smoked (difference seen mostly among ex-smokers rather than current smokers), and were more likely to have DM (especially if diagnosed greater than 3 years before pancreatic adenocarcinoma).

Comparing the demographic characteristics of our analyzed participants to those who completed a FFQ but who were excluded showed that the two groups were similar. The data available to us on all of our cases permitted us to assess the potential effect of not including data on the 1,549 patients who returned FFQs. A comparison of demographic characteristics for the 384 analyzed cases versus all 1,933 cases who completed a FFQ showed that our analyzed cases were more likely to be men, older, have DM (especially onset <3 years prior to study), and be a current smoker. The 983 analyzed controls and all 1,713 controls who completed a FFQ were very similar for most demographic characteristics, with the largest deviations occurring for DM and smoking (especially former smokers who quit <10 years prior to study), with the analyzed participants having lower values.

The median value and interquartile range are given for each food grouping (e.g., fruits, vegetables, fibers, and grains) by sex and case status in Table 2. We noted that the female controls have the highest intake value for most of the groupings and male cases have the lowest value. In general, female cases and male controls have similar values for each food grouping, with female cases having slightly higher median values. These patterns justified reporting of

Table 1 Characteristics of pancreatic adenocarcinoma cases and controls used in the analysis (no recent diet change), and all adenocarcinoma cases and controls who completed FFQs

	Cases ($n = 384$)	Controls ($n = 983$)	All cases with FFQ ($n = 1,933$)	All controls with FFQ ($n = 1,713$)
Sex				
Female	163 (42.4%)	500 (50.9%)	989 (51.2%)	844 (49.3%)
Male	221 (57.6%)	483 (49.1%)	944 (48.8%)	869 (50.7%)
Age when approached				
Mean (SD)	67.0 (10.52)	65.8 (10.86)	64.2 (12.02)	65.3 (10.55)
Median	67.0	67.0	65.0	66.0
Q1, Q3	60.0, 75.0	59.0, 74.0	57.0, 73.0	59.0,74.0
Range	(31.0–92.0)	(24.0–94.0)	(19.0–92.0)	(24.0–94.0)
Diabetes mellitus type 2				
Yes	167 (43.5%)	68 (6.9%)	705 (36.5%)	184 (10.7%)
Onset ≥3 years ago	35 (9.1%)	43 (4.4%)	338 (17.5%)	119 (6.9%)
Onset <3 years ago	120 (31.3%)	21 (2.1%)	288 (14.9%)	33 (1.9%)
Missing	12 (3.3%)	4 (0.0%)	1,307 (67.6%)	1,561 (91.2 %)
No	214 (55.7%)	914 (93.0%)	1,228 (63.5%)	1,529 (89.3%)
Missing	3 (0.8%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Race				
American Indian/Alaskan Native	0 (0%)	4 (0.4%)	3 (0.2%)	5 (0.3%)
Asian/Asian American	3 (0.8%)	8 (0.8%)	16 (0.8%)	14 (0.8%)
Black/African American	4 (1%)	1 (0.1%)	22 (1.1%)	2 (0.1%)
White/Caucasian	373 (97.1%)	966 (98.3%)	1,870 (96.8%)	1,682 (98.3%)
Multiracial	4 (1%)	4 (0.4%)	19 (1%)	8 (0.5%)
Smoking				
Current	59 (15.4%)	37 (3.8%)	234 (12.1%)	62 (3.6%)
Former	163 (42.4%)	402 (40.9%)	836 (43.2%)	716 (41.8%)
Quit <10 years ago	20 (12.3%)	34 (8.5%)	135 (16.1%)	71 (9.9%)
Quit 10+ years ago	141 (86.5%)	361 (89.8%)	679 (81.2%)	631 (88.1%)
Missing	2 (1.2%)	7 (1.7%)	22 (2.6%)	14 (2.0%)
Never	160 (41.7%)	539 (54.8%)	855 (44.2%)	932 (54.4%)
Missing	2 (0.5%)	5 (0.5%)	8 (0.4 %)	3 (0.2 %)
Usual BMI[a]				
Mean (SD)	27.6 (5.31)	26.7 (4.24)	27.8 (5.40)	27.1 (4.92)
Median	26.8	26.3	27.1	26.5
Q1, Q3	24.0, 30.3	23.7, 29.0	24.2, 30.5	23.9, 29.5
Range	(15.3–53.0)	(14.0–49.0)	(0.2–58.2)	(2.4–63.8)
Alcohol (drinks/week)				
Mean (SD)	0.8 (1.46)	0.8 (1.20)	0.8 (1.70)	0.8 (1.19)
Median	0.3	0.3	0.2	0.3
Q1, Q3	0.1, 1.0	0.1, 1.0	0.0, 0.9	0.1, 1.0
Range	(0.0–11.3)	(0.0–11.3)	(0.0–25.0)	(0.0–11.3)

SD Standard deviation, *Q1* Quintile 1, *Q3* Quintile 3

[a] *Analyzed* cases = 379(98.7%) and controls = 954(97.1%); *all FFQ* cases = 1,872, and controls = 1,652

median sex-specific dietary intake and constructing quintiles separately by sex for our sample.

Many of the food groupings in our study are moderately (Pearson's r^2 60–80) or highly correlated (Pearson's $r^2 \geq 0.80$). The "total fruit" grouping is highly correlated with "citrus, melon, and berries" (0.85) and "other fruit" (0.80) groupings. The "total vegetable" grouping is highly correlated with "other vegetable" (0.81) grouping and moderately correlated with "dark green vegetable" (0.62) grouping. "Total dietary fiber" is highly correlated with

Table 2 Food groupings analyzed among pancreatic adenocarcinoma cases and controls

	Quintile					
	1	2	3	4	5	Trend p-value[a]
Citrus, melon, and berries (svg/1,000 kcal)						
Cases (M/F)	99 (57/42)	87 (57/30)	67 (38/29)	62 (30/32)	69 (39/30)	0.032
Odds ratio (95% CI)	1.00 (ref)	0.93 (0.64–1.34)	0.77 (0.52–1.13)	0.71 (0.48–1.06)	0.70 (0.47–1.04)	
Males: Median (Range)	0.15 (0.00–0.24)	0.33 (0.24–0.43)	0.56 (0.43–0.67)	0.79 (0.67–0.93)	1.15 (0.93–3.33)	
Female: Median (Range)	0.23 (0.01–0.35)	0.45 (0.35–0.57)	0.69 (0.57–0.83)	0.95 (0.83–1.17)	1.45 (1.17–4.02)	
Other fruits (svg/1,000 kcal)						
Cases (M/F)	94 (59/35)	101 (61/40)	77 (39/38)	53 (26/27)	59 (36/23)	0.008
Odds ratio (95% CI)	1.00 (ref)	1.12 (0.78–1.61)	0.89 (0.61–1.30)	0.61 (0.40–0.92)	0.73 (0.49–1.10)	
Males: Median (Range)	0.20 (0.01–0.32)	0.45 (0.32–0.57)	0.71 (0.57–0.84)	1.00 (0.84–1.21)	1.60 (1.21–3.15)	
Female: Median (Range)	0.31 (0.02–0.49)	0.65 (0.49–0.79)	0.94 (0.79–1.08)	1.24 (1.08–1.47)	1.81 (1.47–3.63)	
Total fruit (svg/1,000 kcal)						
Cases (M/F)	102 (67/35)	92 (48/44)	78 (40/38)	59 (35/24)	53 (31/22)	0.0009
Odds ratio (95% CI)	1.00 (ref)	1.00 (0.70–1.44)	0.82 (0.56–1.20)	0.64 (0.42–0.96)	0.57 (0.37–0.86)	
Males: Median (Range)	0.46 (0.01–0.72)	0.91 (0.72–1.14)	1.36 (1.14–1.54)	1.78 (1.54–2.07)	2.48 (2.07–4.98)	
Female: Median (Range)	0.68 (0.03–1.00)	1.25 (1.00–1.47)	1.71 (1.47–1.93)	2.18 (1.93–2.54)	3.02 (2.54–5.66)	
Dark green vegetables (svg/1,000 kcal)						
Cases (M/F)	122 (73/49)	83 (51/32)	67 (39/28)	70 (37/33)	42 (21/21)	0.0002
Odds ratio (95% CI)	1.00 (ref)	0.69 (0.49–0.99)	0.59 (0.41–0.86)	0.64 (0.44–0.93)	0.43 (0.28–0.65)	
Males: Median (Range)	0.02 (0.00–0.03)	0.05 (0.03–0.07)	0.09 (0.07–0.12)	0.17 (0.12–0.27)	0.38 (0.27–2.82)	
Female: Median (Range)	0.04 (0.00–0.06)	0.08 (0.06–0.10)	0.12 (0.10–0.16)	0.21 (0.16–0.32)	0.50 (0.32–2.64)	
Deep yellow vegetables (svg/1,000 kcal)						
Cases (M/F)	105 (59/46)	94 (56/38)	80 (47/33)	52 (28/24)	53 (31/22)	0.0007
Odds ratio (95% CI)	1.00 (ref)	0.88 (0.62–1.26)	0.79 (0.55–1.14)	0.56 (0.37–0.84)	0.58 (0.39–0.86)	
Males: Median (Range)	0.03 (0.00–0.05)	0.06 (0.05–0.07)	0.09 (0.07–0.10)	0.12 (0.10–0.15)	0.20 (0.15–1.26)	
Female: Median (Range)	0.05 (0.01–0.06)	0.08 (0.06–0.09)	0.12 (0.09–0.14)	0.17 (0.14–0.20)	0.27 (0.20–1.35)	
Tomato (svg/1,000 kcal)						
Cases (M/F)	95 (50/45)	87 (47/40)	80 (57/23)	68 (38/30)	54 (29/25)	0.0033
Odds ratio (95% CI)	1.00 (ref)	1.04 (0.72–1.50)	0.86 (0.59–1.25)	0.82 (0.56–1.20)	0.57 (0.38–0.86)	
Males: Median (Range)	0.11 (0.02–0.14)	0.17 (0.14–0.19)	0.23 (0.19–0.27)	0.30 (0.27–0.36)	0.51 (0.36–3.37)	
Female: Median (Range)	0.13 (0.03–0.16)	0.19 (0.16–0.22)	0.24 (0.22–0.27)	0.31 (0.27–0.37)	0.49 (0.37–2.04)	

Table 2 contined

	Quintile					
	1	2	3	4	5	Trend p-value[a]
Dry beans and peas (svg/1,000 kcal)						
Cases (M/F)	83 (49/34)	106 (66/40)	67 (33/34)	61 (36/25)	67 (37/30)	0.033
Odds ratio (95% CI)	1.00 (ref)	1.30 (0.91–1.87)	0.80 (0.54–1.18)	0.76 (0.51–1.14)	0.81 (0.55–1.20)	
Males: Median (Range)	0.01 (0.00–0.02)	0.03 (0.02–0.04)	0.05 (0.04–0.06)	0.07 (0.06–0.09)	0.14 (0.09–0.85)	
Female: Median (Range)	0.01 (0.00–0.02)	0.03 (0.02–0.03)	0.04 (0.03–0.06)	0.07 (0.06–0.08)	0.13 (0.08–0.81)	
White potato (svg/1,000 kcal)						
Cases (M/F)	78 (43/35)	63 (33/30)	67 (33/34)	79 (50/29)	97 (62/35)	0.3339
Odds ratio (95% CI)	1.00 (ref)	0.79 (0.53–1.18)	0.86 (0.58–1.28)	0.93 (0.63–1.38)	1.14 (0.78–1.66)	
Males: Median (Range)	0.13 (0.02–0.19)	0.24 (0.19–0.28)	0.33 (0.28–0.39)	0.47 (0.39–0.55)	0.71 (0.55–1.51)	
Female: Median (Range)	0.12 (0.01–0.18)	0.22 (0.18–0.26)	0.33 (0.26–0.41)	0.50 (0.41–0.63)	0.79 (0.63–2.24)	
Other starches (svg/1,000 kcal)						
Cases (M/F)	81 (38/43)	87 (57/30)	84 (51/33)	57 (30/27)	75 (45/30)	0.2184
Odds ratio (95% CI)	1.00 (ref)	1.04 (0.71–1.52)	1.05 (0.72–1.53)	0.71 (0.47–1.07)	0.92 (0.62–1.35)	
Males: Median (Range)	0.06 (0.00–0.08)	0.11 (0.08–0.13)	0.16 (0.13–0.18)	0.21 (0.18–0.25)	0.34 (0.25–0.87)	
Female: Median (Range)	0.08 (0.01–0.11)	0.13 (0.11–0.15)	0.18 (0.15–0.21)	0.26 (0.21–0.30)	0.38 (0.30–1.55)	
Other vegetables (svg/1,000 kcal)						
Cases (M/F)	103 (58/45)	97 (52/45)	82 (50/32)	57 (35/22)	45 (26/19)	<.0001
Odds ratio (95% CI)	1.00 (ref)	1.06 (0.74–1.52)	0.87 (0.60–1.25)	0.57 (0.38–0.85)	0.49 (0.32–0.75)	
Males: Median (Range)	0.23 (0.03–0.31)	0.37 (0.31–0.43)	0.49 (0.43–0.56)	0.63 (0.56–0.73)	0.88 (0.73–2.04)	
Female: Median (Range)	0.32 (0.11–0.41)	0.48 (0.41–0.56)	0.61 (0.56–0.68)	0.76 (0.68–0.88)	1.09 (0.88–3.11)	
Total vegetables (svg/1,000 kcal)						
Cases (M/F)	99 (60/39)	98 (56/42)	65 (32/33)	70 (42/28)	52 (31/21)	0.0005
Odds ratio (95% CI)	1.00 (ref)	1.12 (0.78–1.61)	0.73 (0.50–1.08)	0.73 (0.50–1.07)	0.56 (0.37–0.84)	
Males: Median (Range)	0.95 (0.23–1.18)	1.36 (1.18–1.53)	1.63 (1.53–1.78)	1.97 (1.78–2.22)	2.56 (2.22–5.59)	
Female: Median (Range)	1.15 (0.55–1.37)	1.55 (1.37–1.72)	1.84 (1.72–2.04)	2.30 (2.04–2.62)	3.06 (2.62–5.98)	
Insoluble dietary fiber (g/1,000 kcal)						
Cases (M/F)	134 (79/55)	89 (48/41)	58 (30/28)	46 (29/17)	57 (35/22)	<.0001
Odds ratio (95% CI)	1.00 (ref)	0.70 (0.50–1.00)	0.50 (0.34–0.73)	0.38 (0.25–0.57)	0.48 (0.33–0.71)	
Males: Median (Range)	4.42 (0.87–5.14)	5.73 (5.14–6.31)	6.71 (6.31–7.19)	7.71 (7.19–8.44)	9.97 (8.44–19.70)	
Female: Median (Range)	5.07 (1.78–5.97)	6.55 (5.97–7.07)	7.53 (7.07–8.09)	8.65 (8.09–9.32)	10.54 (9.32–20.33)	

Table 2 contined

	Quintile					
	1	2	3	4	5	Trend p-value[a]
Soluble dietary fiber (g/1,000 kcal)						
Cases (M/F)	124 (72/52)	90 (50/40)	68 (37/31)	42 (30/12)	60 (32/28)	<.0001
Odds ratio (95% CI)	1.00 (ref)	0.85 (0.60–1.22)	0.63 (0.43–0.91)	0.37 (0.25–0.57)	0.58 (0.39–0.86)	
Males: Median (Range)	2.27 (0.56–2.60)	2.81 (2.60–2.98)	3.19 (2.98–3.32)	3.56 (3.32–3.79)	4.27 (3.79–6.50)	
Female: Median (Range)	2.57 (0.82–2.88)	3.13 (2.88–3.32)	3.50 (3.32–3.69)	3.91 (3.69–4.15)	4.79 (4.15–7.58)	
Total dietary fiber (g/1,000 kcal)						
Cases (M/F)	134 (81/53)	89 (48/41)	55 (26/29)	50 (33/17)	56 (33/23)	<.0001
Odds ratio (95% CI)	1.00 (ref)	0.71 (0.50–1.01)	0.45 (0.31–0.66)	0.42 (0.28–0.63)	0.47 (0.32–0.70)	
Males: Median (Range)	6.63 (1.45–7.69)	8.51 (7.69–9.18)	9.88 (9.18–10.47)	11.30 (10.47–12.22)	14.48 (12.22–26.88)	
Female: Median (Range)	7.64 (2.73–8.80)	9.78 (8.80–10.46)	11.07 (10.46–11.80)	12.53 (11.80–13.68)	15.38 (13.68–28.69)	
Non-whole grains (svg/1,000 kcal)						
Cases (M/F)	56 (40/16)	73 (41/32)	87 (47/40)	77 (38/39)	91 (55/36)	0.0006
Odds ratio (95% CI)	1.00 (ref)	1.46 (0.96–2.23)	2.03 (1.34–3.07)	1.70 (1.11–2.61)	2.10 (1.38–3.20)	
Males: Median (Range)	1.07 (0.36–1.33)	1.48 (1.33–1.65)	1.79 (1.65–1.93)	2.10 (1.93–2.28)	2.64 (2.28–4.47)	
Female: Median (Range)	1.02 (0.35–1.24)	1.40 (1.24–1.57)	1.70 (1.57–1.85)	2.05 (1.85–2.25)	2.61 (2.25–3.86)	
Whole grains (svg/1,000 kcal)						
Cases (M/F)	104 (65/39)	89 (50/39)	70 (38/32)	58 (37/21)	63 (31/32)	0.0149
Odds ratio (95% CI)	1.00 (ref)	0.91 (0.63–1.30)	0.77 (0.52–1.12)	0.62 (0.42–0.93)	0.70 (0.47–1.03)	
Males: Median (Range)	0.28 (0.01–0.43)	0.54 (0.43–0.64)	0.74 (0.64–0.86)	0.98 (0.86–1.17)	1.43 (1.17–3.83)	
Female: Median (Range)	0.31 (0.04–0.44)	0.56 (0.44–0.67)	0.78 (0.67–0.88)	1.00 (0.88–1.13)	1.38 (1.13–4.11)	
Total grains (svg/1,000 kcal)						
Cases (M/F)	73 (47/26)	77 (43/34)	91 (57/34)	63 (30/33)	80 (44/36)	0.2234
Odds ratio (95% CI)	1.00 (ref)	1.30 (0.87–1.94)	1.59 (1.07–2.36)	1.12 (0.74–1.70)	1.43 (0.96–2.13)	
Males: Median (Range)	1.65 (0.52–1.94)	2.21 (1.94–2.41)	2.61 (2.41–2.85)	3.03 (2.85–3.30)	3.66 (3.30–6.35)	
Female: Median (Range)	1.64 (0.39–1.94)	2.15 (1.94–2.35)	2.53 (2.35–2.74)	2.99 (2.74–3.22)	3.60 (3.22–6.90)	
Orange/grapefruit juice (g/1,000 kcal)						
Cases (M/F)	96 (48/48)	88 (45/43)	67 (45/22)	81 (49/32)	52 (34/18)	0.0012
Odds ratio (95% CI)	1.00 (ref)	1.05 (0.73–1.53)	0.71 (0.49–1.05)	0.86 (0.59–1.25)	0.52 (0.35–0.79)	
Males: Median (Range)	0.08 (0.00–1.11)	2.33 (1.11–3.44)	5.07 (3.44–8.75)	15.52 (8.75–43.97)	105.78 (43.97–655.57)	
Female: Median (Range)	0.03 (0.00–0.98)	2.27 (0.98–4.07)	7.33 (4.07–12.43)	20.90 (12.43–64.43)	131.81 (64.43–761.09)	

Table 2 contined

	Quintile					Trend p-value[a]
	1	2	3	4	5	
Tomato/vegetable juice (g/1,000 kcal)						
Cases (M/F)	115 (69/46)	45 (30/15)	93 (43/50)	55 (34/21)	76 (45/31)	0.0848
Odds ratio (95% CI)	1.00 (ref)	0.91 (0.60–1.40)	1.27 (0.90–1.79)	0.61 (0.42–0.90)	0.83 (0.58–1.20)	
Males: Median (Range)	0	0.58 (0.00–1.44)	3.10 (1.44–4.13)	5.82 (4.13–9.09)	17.56 (9.09–610.83)	
Female: Median (Range)	0	0.25 (0.00–0.72)	2.62 (0.72–3.94)	5.28 (3.94–7.96)	17.73 (7.96–346.41)	

Number of cases, median intake (range) for each sex, and odds ratios with 95% confidence interval for associations between dietary consumption and pancreatic cancer (generated by constructing quintiles of intakes based on controls within each sex)

g grams, *svg* servings, *kcal* kilocalories, *mg* milligrams, *mcg* micrograms

[a] Using a logistic model adjusted for energy, smoking, BMI, age, sex, and drinks of alcohol per week

"soluble dietary fiber" (0.88) and "insoluble dietary fiber" (0.98) groupings. "Total grain" is highly correlated with "non-whole grains" (0.83), and moderately correlated with "whole grains" (0.69).

Table 2 also shows the number of cases along with an OR and 95% CI, and trend test of OR across quintiles, which were constructed using the control population values for each sex. Associations between food groupings and pancreatic adenocarcinoma were determined by using a multivariable logistic regression model adjusting for age, sex, energy (per 1,000 kcal), BMI, smoking (current, former, never), and drinks of alcohol per week and compared the four highest quintiles to the reference (lowest consumption). Significant results (test for trend p-value (p_{trend}) < 0.05) for an inverse association between pancreatic adenocarcinoma and food groupings (OR [95% CI]) were citrus, melon, and berries (OR = 0.70[0.47–1.04]), other fruit (OR = 0.73[0.49–1.10]), total fruit (OR = 0.57[0.37–0.86]), dark green vegetable (OR = 0.43 [0.28–0.65]), deep yellow vegetable (OR = 0.58[0.39–0.86]), tomato (OR = 0.57[0.38–0.86]), other vegetable (OR = 0.49[0.32–0.75]), dry bean and pea (OR = 0.81[0.55–1.20]), total vegetables (OR = 0.56[0.37–0.84]), insoluble fiber (OR = 0.48[0.33–0.71]), soluble fiber (OR = 0.58[0.39–0.86]), total dietary fiber (OR = 0.47[0.32–0.70]), whole grains (OR = 0.70[0.47–1.03]) and orange/grapefruit juice (OR = 0.52[0.35–0.79]). There was an increased association between having pancreatic adenocarcinoma and non-whole grains (OR = 2.10[1.38–3.20]). It is important to note that the correlation between whole and non-whole grains was low ($r^2 = 0.17$); therefore, the discordant associations for these categories are not likely due to simple dietary replacement of one grain for the other.

Because DM is a known risk factor for pancreatic adenocarcinoma and because diabetics may be advised to modify their diet, we investigated whether adding DM (categorized as no DM, DM diagnosis less than 3 years prior to completing questionnaire, or DM diagnosis 3 years or more prior to questionnaire) to our logistic model would significantly change our results (not shown). There were two food groupings where higher consumption was inversely associated with having pancreatic adenocarcinoma, and that changed in statistical significance after adding DM to the analyses ("citrus, melon, and berries": p_{trend} changed from 0.03 to 0.07 and fifth (highest intake) quintile compared to first (lowest intake) quintile OR (95% CI) changed from 0.70 (0.47–1.04) to 0.75 (0.49–1.17); and "other starches": p_{trend} changed from 0.21 to 0.05 and fifth quintile compared to first quintile OR (95% CI) changed from 0.92 (0.62–1.35) to 0.76 (0.49–1.19). We also examined the presented model in only non-diabetics. There were two significant differences between the presented model and the non-DM model analysis that were not

significantly different when DM adjustment was used (for "dry bean and pea" p_{trend} changed from 0.03 to 0.32) and fifth quintile compared to first quintile OR (95% CI) changed from 0.81 (0.55–1.20) to 0.84 (0.50–1.39), and for "tomatoes," p_{trend} changed from 0.003 to 0.24 and fifth quintile compared to first quintile OR (95% CI) changed from 0.57 (0.38–0.86) to 0.68 (0.41–1.12), indicating a possible interaction effect which is beyond the scope of this study to address further.

In addition, total sugar intake was considered as a possible confounder for our fruit and vegetable food groupings and was adjusted for in an alternative version of the presented model. Higher consumption of one food grouping was inversely associated with having pancreatic adenocarcinoma, which became statistically non-significant when adjusted for sugar intake in the analyses ("dry bean and pea" p_{trend} changed from 0.03 to 0.08).

A sensitivity analysis was conducted (data not shown) to determine the impact of failure to exclude those who reported a diet change within the last 5 years. There was one food grouping (associated with an increased risk of pancreatic adenocarcinoma) that increased in statistical significance when those reporting a recent diet change were included in the analyses ("other starches," p_{trend} changed from 0.22 to 0.03). Among males who reported a recent diet change, the median values for both fruit groupings and both fiber groupings decreased. Among women, the median values increased for both fruit groupings and decreased for both the fiber and grain groupings. These observed changes affirm the importance of our strategy to use the recent diet change data to exclude subjects when determining our final sample, increasing confidence that our associations may be related to causation.

To investigate possible residual confounding by smoking, we conducted a sensitivity analysis restricting our data to only never smokers (Table 3). The categories of citrus, melon, and berries (OR = 0.70[95% CI 0.47–1.04]), other fruit (OR = 0.73[95% CI 0.49–1.10]), dry bean and pea (OR = 0.81[95% CI 0.55–1.20]), and whole grains (OR = 0.70[95% CI 0.47–1.03]) were no longer significant in the subanalysis. However, only the OR for the highest quintile of the citrus, melon, and berries category changed by over 10%, suggesting that the significant changes were related to a reduced sample size. As a finer stratification of smoking exposure, we used a pack-years categorical adjustment in our logistic regression model and found no significant difference from the presented model results (Table 2) for associations between any food groupings and pancreatic adenocarcinoma.

The demographic characteristic comparisons of participants who did and did not complete the questionnaire after recruitment showed that the two groups were similar. The data available to us on all of our cases permitted us to assess the potential effect of not capturing data on the 832 patients who did not return FFQs. The demographic characteristics of the 816 patients who completed the FFQ and the 832 patients who did not were respectively ~9 months versus ~6 months for median days from approach to death. The median age for patients not completing the FFQ was 65.9 years, compared to 66.3 for those who did. When grouped by stage, 31.3% of early-stage (I and II) patients completed the FFQ, compared to 44.7% of late stage (III and IV). There were also modest differences among those who completed the FFQ compared to those who did not by usual BMI (median, 27.5 vs. 28.4), DM (38.1% vs. 49%), and current smoker (23.6 vs. 15.6%) and former smoker status (36.9 vs. 43.4%). We excluded participants who reported a recent change in diet (420 of the 816 cases), and we predict that a similar or higher proportion of the 832 patients who did not complete the FFQ would have been excluded if we had their data. Moreover, the impact of smoking and BMI would have been adjusted in the model, and we anticipate that DM would not have a large effect on results based on our analyzed dataset.

Discussion

In this study, we found that higher consumption of fruits, vegetables (except potatoes and starchy vegetables), fiber, and whole grains were inversely associated with having pancreatic adenocarcinoma, and higher consumption of non-whole grains was associated with having pancreatic adenocarcinoma. Previous reports on an association between intake of these dietary groups and pancreatic cancer have been largely inconsistent. Variable study designs and ascertainment bias may partially explain the inconsistencies. Case–control studies that are subject to selection bias have typically shown association while cohort studies avoid this issue and generally report null results. This clinic-based case–control study contributes to the existing body of work that shows that people with pancreatic adenocarcinoma report lower average fruit and vegetable intake.

There were several features of our case–control study design that strengthen reliability of the reported results. Over 99% of the adenocarcinoma cases were confirmed by pathology or through medical record, allowing for a well-defined case population. The recruitment protocol enabled rapid ascertainment of cases, increasing the probability of self-completion and enrollment of available cases at all stages of disease. The importance of this is manifested in reports of misclassification by proxies between 51.7 and 78.6% across food groups [25]. Cohorts are able to avoid this problem, but generally are hindered by small sample sizes of incident cases collected during follow-up and lack

of clinical detail, as well as ability to account for important dietary and health changes over time. We tried to minimize bias due to disease status influence on dietary intake by excluding those individuals who reported a diet change in the 5 years prior to study entry. We were also able to utilize available clinical detail on demographic characteristics to confirm that individuals who did not complete the FFQ after recruitment were similar to participants who did. This analysis showed that our study population is likely representative of the population who did not complete the questionnaire.

There are limitations that affect retrospective designs requiring participant recall of past events and behavior. Differential misclassification and recall of dietary patterns between cases and controls could contribute to biased risk estimates. This is more likely to be true with well-known disease-associated risk factors (e.g., high fat diet and heart disease) or when there is a stigma associated with a specific risk factor (e.g., consumption of fatty foods is widely believed to be unhealthy, therefore may be underreported in controls). In these situations, cases may differentially recall past behaviors and consumption patterns compared to controls. However, within this study, cases were rapidly enrolled and completed the FFQ in close proximity to or at the time of diagnosis, thus potentially reducing the effect of such bias. In retrospective population-based studies of rapidly fatal disease, bias can occur due to demise of eligible cases (with a higher proportion of later-stage disease), reducing enrollment numbers and/or number of self-completed questionnaires. The rapid case-ascertainment strategy used here helps mitigate this bias, as we were usually able to obtain self-completed questionnaires, but were still challenged with the demise of eligible late-stage cases, possibly resulting in non-random non-response. There were individuals who did not answer portions of the FFQ, which could have biased reported results if missing values differed by case status. However, we found that the absolute difference in percent of missing responses between cases and controls averaged less than 1%. Smoking is a strong risk factor for pancreatic cancer and is inversely associated with fruit and vegetable intake. Since smoking was only crudely controlled for in our study, residual confounding is a possibility, although our sensitivity analysis in Table 3 provides evidence against it.

Table 3 Food groupings associated with pancreatic adenocarcinoma among never smokers

	Quintile					Trend p-value[a]
	1	2	3	4	5	
Citrus, melon, and berries (svg/1,000 kcal)						
Cases (M/F)	36 (18/18)	36 (19/17)	30 (10/20)	23 (11/12)	35 (15/20)	0.1509
Odds ratio (95% CI)	1.00 (ref)	0.92 (0.53–1.58)	0.79 (0.45–1.39)	0.56 (0.31–1.03)	0.80 (0.46–1.40)	
Males: Median (Range)	0.17 (0.00–0.27)	0.35 (0.27–0.46)	0.57 (0.46–0.69)	0.81 (0.69–0.95)	1.22 (0.95–3.33)	
Female: Median (Range)	0.27 (0.05–0.39)	0.51 (0.39–0.60)	0.74 (0.60–0.87)	0.98 (0.87–1.17)	1.45 (1.17–4.02)	
Other fruits (svg/1,000 kcal)						
Cases (M/F)	37 (19/18)	38 (17/21)	33 (11/22)	26 (15/11)	26 (11/15)	0.064
Odds ratio (95% CI)	1.00 (ref)	1.04 (0.61–1.78)	0.87 (0.50–1.51)	0.68 (0.38–1.22)	0.67 (0.37–1.20)	
Males: Median (Range)	0.21 (0.01–0.33)	0.47 (0.33–0.60)	0.74 (0.60–0.84)	1.03 (0.84–1.31)	1.69 (1.31–3.15)	
Female: Median (Range)	0.39 (0.06–0.57)	0.73 (0.57–0.87)	1.02 (0.87–1.16)	1.29 (1.16–1.54)	1.85 (1.54–3.63)	
Dry beans and peas (svg/1,000 kcal)						
Cases (M/F)	33 (16/17)	47 (23/24)	26 (10/16)	28 (16/12)	26 (8/18)	0.2041
Odds ratio (95% CI)	1.00 (ref)	1.56 (0.92–2.65)	0.79 (0.44–1.43)	0.88 (0.50–1.58)	0.87 (0.49–1.57)	
Males: Median (Range)	0.01 (0.00–0.02)	0.03 (0.02–0.04)	0.05 (0.04–0.06)	0.07 (0.06–0.09)	0.14 (0.09–0.85)	
Female: Median (Range)	0.01 (0.00–0.02)	0.02 (0.02–0.03)	0.04 (0.03–0.05)	0.06 (0.05–0.08)	0.12 (0.08–0.81)	
Whole grains (svg/1,000 kcal)						
Cases (M/F)	40 (21/19)	38 (16/22)	27 (15/12)	23 (12/11)	32 (9/23)	0.1169
Odds ratio (95% CI)	1.00 (ref)	0.94 (0.56–1.59)	0.67 (0.38–1.18)	0.58 (0.32–1.03)	0.78 (0.45–1.34)	
Males: Median (Range)	0.29 (0.05–0.45)	0.55 (0.45–0.63)	0.71 (0.63–0.86)	1.00 (0.86–1.18)	1.51 (1.18–2.37)	
Female: Median (Range)	0.36 (0.04–0.50)	0.62 (0.50–0.73)	0.81 (0.73–0.92)	1.02 (0.92–1.16)	1.43 (1.16–4.11)	

Only groups that significantly changed for never smokers are shown. Number of pancreatic adenocarcinoma cases, median intake (range) for each sex, and odds ratios with 95% confidence interval for associations between dietary consumption and pancreatic cancer (generated by constructing quintiles of intakes based on controls within each sex)

g grams, *svg* servings, *kcal* kilocalories, *mg* milligrams, *mcg* micrograms

[a] Using a logistic model adjusted for energy, smoking, BMI, age, sex, and drinks of alcohol per week

Currently, there are two main hypotheses as to how an individual's dietary intake could influence pancreatic cancer development and progression: (1) dietary components affect insulin insensitivity or insulin resistance pathways; or (2) dietary components reduce DNA damage/mutation by reducing oxidative stress and inflammation [26]. Intertwined within these two hypothesized modes of pancreatic cancer development are other modifiable pancreatic cancer risk factors: diabetes [27], obesity [28, 29], and cigarette smoking [30, 31].

Several plausible biologic mechanisms have been hypothesized to explain the potential protective relationship between fiber [32, 33] and whole grains [34, 35] with pancreatic cancer [12, 13] through insulin resistance, triglyceride levels, and high density lipoprotein levels. Additionally, in some studies, investigators reported associations for individual non-whole grain products [36–39] or null associations for grains [40] and fiber [41]. Our results support an inverse association of higher whole grains and fiber intake (soluble and insoluble dietary fiber) with pancreatic cancer and an increased associated with higher non-whole grain consumption.

It has been proposed that whole grains can affect cholesterol or inflammatory pathways and have an inverse relation with levels of insulin, markers of glycemic control, cholesterol, homocysteine, C-peptide, and leptin [42]. Overall, whole grains are richer in antioxidants and fiber, producing the presumed beneficial effect of reducing risk of pancreatic cancer [43]. Wheat-germ extract has been shown in vitro to reduce glucose uptake and decrease nucleic acid ribose synthesis, resulting in anti-proliferation of pancreatic adenocarcinoma cells [44]. However, a dietary pattern with low glycemic load often contains high fiber and whole grains, making it difficult to determine the specific basis for an association [43, 45].

The second hypothesized mode of action is based on dietary components that are thought to have the ability to reduce oxidative stress and/or inflammation, thereby protecting against pancreatic cancer development. In one large case–control study [46], a "fruit and vegetable dietary pattern" was associated with a lower proportion of pancreatic cancer patients, and other case–control studies have reported a similar association with intake of fruit [10, 47, 48], non-citrus fruits [49], cruciferous vegetables [50], or both fruits and vegetables [36–39, 51–53]. In contrast, some case–control studies have found pancreatic cancer associated with higher intake of both fruits and vegetables [32, 54] or potatoes [49]. Moreover, the results of prospective studies have largely been null for fruit [15, 40, 55, 56], cruciferous vegetables [41], or fruit and vegetable intake combined [8, 14–16, 40, 41, 55, 57], with one study showing an increased risk associated with fruit intake [58], and decreased risk associated with fruit and vegetable intake combined [56], or in men only [14].

Within our study sample, evidence was observed to support that higher fruit and vegetable consumption, including citrus, melon, and berries, other fruit, dark green vegetables, deep yellow vegetables, other vegetables, tomatoes, and dry beans and peas, were all significantly inversely associated with pancreatic adenocarcinoma. Cruciferous vegetables may provide protection against cancer when the plant enzyme, myrosinase, or intestinal microflora degrades glucosinolates into isothiocyanates [59, 60]. Isothiocyanates inhibit the metabolic activation of carcinogens by phase I cytochrome P450 family enzymes or by phase II detoxifying and cellular defensive enzymes [59]. In the laboratory, glucosinolate mixtures have been shown to induce pancreatic phase II enzymes [61], and isothiocyanates prevent the initiation phase of pancreatic carcinogenesis [62] to inhibit growth of human pancreatic cancer cell lines [63].

It has been demonstrated that some raw vegetables are more strongly inversely associated with pancreatic cancer than their cooked counterparts [64]. Myrosinase is inactivated by cooking, with studies reporting three times greater bioavailability of its enzymatic product, isothiocyanates, in raw broccoli [65] and a large reduction in excretion seen after consumption of cooked watercress compared to uncooked [66]. However, because our FFQ did not ask about vegetable preparation, we were unable to address the question of cooked versus raw vegetable consumption associations with pancreatic cancer.

In conclusion, our study demonstrates that eating a diet higher in fruits, vegetables, fiber, and whole grains is inversely associated with pancreatic cancer and that this association follows a dose-dependent pattern. However, these results need to be confirmed in other well-designed case–control and prospective studies. It is usually of interest to identify specific micronutrients found in foods, which may be responsible for such a reduction in cancer risk. While such an analysis can provide potential targeted intervention and pathways to investigate, it is important to note that single dietary items are generally not consumed in isolation. Although the exact mechanism is uncertain and prospective study results have largely been null, both experimental evidence and some observational studies (mostly case–control) would suggest eating fruits and vegetables appears to reduce the risk of developing pancreatic adenocarcinoma. The results here support promoting a diet rich in fruits, vegetables, fiber, and whole grains as a pancreatic cancer prevention strategy.

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