



## ORIGINAL CONTRIBUTIONS

### Prospective Study of Diet and Pancreatic Cancer in Male Smokers

Rachael Z. Stolzenberg-Solomon,<sup>1</sup> Pirjo Pietinen,<sup>2</sup> Philip R. Taylor,<sup>3</sup> Jarmo Virtamo,<sup>2</sup> and Demetrius Albanes<sup>1</sup>

There have been few prospective studies relating diet to pancreatic cancer, with most having fewer than 100 cases and only one examining dietary nutrients. The authors prospectively examined dietary factors hypothesized to be associated with exocrine pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort in Finland. Of the 27,111 male smokers aged 50–69 years with complete dietary information, as ascertained from a self-administered dietary history questionnaire given at baseline (1985–1988), 163 developed pancreatic cancer from 1985 through November 1997. Cox proportional hazards models were used to estimate smoking- and age-adjusted hazard ratios and 95% confidence intervals. Energy-adjusted butter consumption and saturated fat intake were positively associated with pancreatic cancer (highest quintile vs. lowest: hazard ratio (HR) = 1.40, 95% confidence interval (CI): 0.87, 2.25 ( $p$  trend = 0.04), and HR = 1.60, 95% CI: 0.96, 2.64 ( $p$  trend = 0.02), respectively). Energy intake and energy-adjusted carbohydrate intake were inversely associated with the disease (highest quintile vs. lowest: HR = 0.62, 95% CI: 0.36, 1.07 ( $p$  trend = 0.05), and HR = 0.62, 95% CI: 0.37, 1.03 ( $p$  trend = 0.02), respectively). These results support the hypothesis that a high intake of saturated fat may increase the risk of pancreatic cancer in smokers, while greater intakes of energy and carbohydrate may reduce the risk. *Am J Epidemiol* 2002;155:783–92.

carbohydrates; diet; dietary fats; energy intake; pancreatic neoplasms; prospective studies; smoking

**Editor's note:** An invited commentary on this article appears on page 793, and the authors' response appears on page 796.

Cancer of the exocrine pancreas ranks fourth for cancer mortality in US men and women and is among the most rapidly fatal cancers worldwide (1). There is no effective way to screen for this malignancy, and in most cases it is

diagnosed at an advanced stage, with a 5-year survival rate of less than 5 percent (1). Few consistent risk factors have been identified, with the exception of cigarette smoking, which has been estimated to account for approximately 25 percent of the incidence (2). Thirty percent to 50 percent of pancreatic cancers may be attributed to dietary factors (3), although the specific dietary components and mechanisms remain unclear, primarily because of limited and inconsistent study findings. The majority of studies examining the relation between diet and pancreatic cancer have used the case-control method, with retrospective ascertainment of diet; for this cancer site in particular, retrospective ascertainment is fraught with biases and can result in inaccurate risk estimates. Cohort studies, with collection of exposure data preceding diagnosis, are less prone to these biases. To our knowledge, there have only been four prospective studies of diet and pancreatic cancer (4–7), with most having fewer than 100 cases (4, 6, 7) and only one examining nutrients (7).

Previously, we reported a significant risk reduction and dose-response relation for exocrine pancreatic cancer associated with higher dietary folate status and intake in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

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Abbreviations: ATBC [Study], Alpha-Tocopherol, Beta-Carotene [Cancer Prevention Study]; SEARCH, Surveillance of Environmental Aspects Related to Cancers in Humans.

<sup>1</sup>Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

<sup>2</sup>National Public Health Institute, Helsinki, Finland.

<sup>3</sup>Cancer Prevention Studies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD.

Reprint requests to Dr. Rachael Stolzenberg-Solomon, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6006 Executive Blvd., MSC 7232, Bethesda, MD 20892-7232 (e-mail: rs221z@nih.gov).

(ATBC Study) cohort, a Finnish cohort of older male smokers (8, 9). In the present study, we examined other dietary factors thought to be associated with pancreatic cancer in this large prospective cohort of high-risk individuals.

## MATERIALS AND METHODS

The ATBC Study was a placebo-controlled, double-blinded primary prevention trial with a  $2 \times 2$  factorial design that tested the hypothesis of whether  $\alpha$ -tocopherol or  $\beta$ -carotene supplementation would reduce the incidence of lung cancer in male smokers (10). Between 1985 and 1988, 29,133 eligible men aged 50–69 years in southwestern Finland who smoked at least five cigarettes per day were randomized to receive supplements (50 mg/day of  $\alpha$ -tocopherol, 20 mg/day of  $\beta$ -carotene, or both) or placebo. Criteria for exclusion from the study included a history of malignancy other than nonmelanoma cancer of the skin or carcinoma in situ, severe angina upon exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, receipt of anticoagulant therapy, other medical problems which might limit long-term participation, and current use of supplements containing vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or  $\beta$ -carotene (>6 mg/day). The trial ended on April 30, 1993, and follow-up continued after randomization for the present study until death or through November 1997. This represents follow-up of up to 13 years (median, 10.2 years) and totals 260,006 person-years of observation. The study was approved by the institutional review boards of both the US National Cancer Institute and the Finnish National Public Health Institute, and all study participants provided written informed consent prior to the study's initiation. Details on the study's rationale, design, and methods have been published previously (10).

### Baseline characteristics, smoking, and dietary factors

At their baseline visit, the study participants completed questionnaires on general background characteristics, including medical and dietary history and smoking. For 10 subjects with incomplete data on years of smoking, we estimated years of smoking by subtracting the subjects' age at which they started smoking from their age at randomization.

Diet was assessed with a self-administered dietary history questionnaire, which determined the usual portion size and frequency of consumption during the previous year of over 200 food items, using a color picture booklet as a guide for food items and portion sizes (10). The questionnaire was linked to the food composition database of the National Public Health Institute in Finland. The dietary history questionnaire was designed for the ATBC Study, and its correlation coefficients for nutrients and foods ranged from 0.40 to 0.80 for validity (intermethod reliability) and from 0.56 to 0.88 for reliability (11).

### Case ascertainment

Cases were ascertained from the Finnish Cancer Registry, which provides almost 100 percent case ascertainment in

Finland (12, 13). All relevant medical records for reported incident cases of pancreatic cancer were reviewed independently by two study physicians (10). Only cases confirmed by the study physicians as incident primary malignant neoplasm of the exocrine pancreas (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 157) (14) were used for the present analysis. Eighty percent of these confirmed cases had a histopathologic diagnosis assigned centrally by the study pathologists after examination of pathologic and cytologic specimens (10). Since their etiology may be different from that of the exocrine tumors, islet-cell carcinomas (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 157.4) (14) were excluded. There were 174 confirmed cases of exocrine pancreatic cancer; 163 of these subjects had completed the dietary questionnaires at baseline. The 163 case subjects with dietary data formed the basis for this report.

### Statistical analysis

Only subjects with complete dietary data ( $n = 27,111$ ) were included in the analyses. Nutrients and foods examined in previous studies (3, 15, 16) and/or hypothesized to be associated with pancreatic cancer (e.g., folate-containing foods) were included in this analysis. Factors were analyzed both as continuous variables (g/day) and as categorical variables, with quantiles for the latter being based on the distribution of each variable in the entire cohort. Trends across categories were tested using a calculated score variable based on the median values of the categories. For foods that were consumed by less than 20 percent of the cohort, categories were created using zero intake as the reference point. Cutpoints for the quantile categories of food and nutrients are listed in the Appendix. Food groups used in the analysis were based on all foods represented in the dietary history questionnaire and reflected Finnish cuisine.

Spearman correlations were calculated for assessment of correspondence between the study variables in the cohort. Because many of the dietary intake variables of interest were highly correlated with energy intake, data on all foods and nutrients (except coffee and tea, which were not correlated with energy) were energy-adjusted using the residual method described by Willett and Stampfer (17). In order to preserve the linear model assumption for the energy-adjustment regression, we individually transformed values for energy intake, foods, and nutrients to normalize the data, the most common transformation being the fourth power. The results of nutrient analyses presented in this paper are for dietary intake only, because only a small proportion of the cohort reported using supplements for the nutrients examined (range: from <1 percent for retinol to 12 percent for vitamin C).

Because many of the variables had skewed distributions, we used the nonparametric Wilcoxon rank sum test for continuous variables and the chi-squared test for categorical variables to compare the distribution among the cases with that among the noncases. Hazard ratios and 95 percent confidence intervals were determined using Cox proportional hazards models. All multivariable models were adjusted for

age at randomization and years of smoking, although none of the smoking variables (years of smoking, number of cigarettes smoked per day, pack-years of smoking) confounded the risk estimates. Other variables were added to individual models in a stepwise fashion; they were included in the individual models if they were associated with both the disease and the risk factor, had a chi-squared  $p$  value  $\leq 0.20$  in the full model, changed the risk estimate by at least 10 percent, or increased the precision of the risk estimate by narrowing the range of the confidence intervals. Additional variables examined in the analyses included ATBC trial interventions; dietary folate, saturated fat, and carbohydrate intakes; history of diabetes mellitus; occupational physical activity; and education. All statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, North Carolina), and statistical tests were two-tailed.

## RESULTS

Selected characteristics of the case and noncase subjects are shown in table 1. Food and nutrient intakes are shown in tables 2 and 3, respectively. Compared with noncases, cases were significantly older, had more years and pack-years of smoking, had greater energy-adjusted intakes of butter, fat, and saturated fat, and had less intake of energy and energy-adjusted sour milk products. Cases also tended to have a greater cream intake and a lower carbohydrate intake. The median interval between the baseline dietary questionnaire and pancreatic cancer diagnosis was 6.4 years (range: 0.06–12 years), and the median age at diagnosis for the cases was 64 years (range: 50–78 years).

Tables 4 and 5 present results from the multivariable proportional hazards models predicting pancreatic cancer hazard ratios for dietary food groups and nutrients, respectively. Because the trial interventions ( $\alpha$ -tocopherol and  $\beta$ -carotene supplementation), carbohydrate intake, education, diabetes mellitus, and physical activity did not confound the hazard ratios, results from models that adjusted for these factors are

not presented. Increasing energy-adjusted butter consumption and saturated fat intake showed significant trends for greater pancreatic cancer risk, while energy and carbohydrate intake showed significant inverse trends, although individual risk estimates within quintiles had confidence intervals that overlapped 1. Energy-adjusted cream consumption and fat intake showed borderline positive trends for cancer risk. Energy-adjusted butter intake was highly correlated with energy-adjusted saturated fat intake ( $r = 0.76$ ). Supplementation with any of the nutrients was not significantly related to pancreatic cancer (data not shown). The risk estimates for butter, cream, energy, carbohydrate, fat, and saturated fat were proportional over time.

## DISCUSSION

This analysis of the ATBC Study cohort showed significant positive trends for pancreatic cancer with energy-adjusted butter consumption and saturated fat intake, as well as significant inverse trends with energy and carbohydrate intake. Although they were not statistically significant, positive associations with cream and total fat intake were also observed.

The strength of this study was its large prospective nature. It had a greater number of cases than most other prospective studies examining diet and pancreatic cancer and thus provided greater power for detection of differences in risk factors. Our dietary data were of good quality and were collected before the development of disease (median, 6.4 years), which eliminated recall bias and made the data less likely to represent dietary changes due to latent disease. We were also able to examine detailed information on food consumption and nutrient intake and to adjust for energy intake and other potential confounders.

Energy-adjusted saturated fat intake accounted for most of the association between fat and pancreatic cancer; it was associated with a 60 percent excess risk (highest quintile vs. lowest), with a significant trend across quintiles. The observed

**TABLE 1. Baseline characteristics of pancreatic cancer case and noncase subjects, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985–1997**

Characteristic	Case subjects ( <i>n</i> = 163)		Noncase subjects ( <i>n</i> = 26,948)		<i>p</i> value*
	Median value or proportion	Interquartile range	Median value or proportion	Interquartile range	
Age (years)	58	55–62	57	53–61	0.0002
Height (cm)	174	170–179	174	169–178	0.26
Weight (kg)	79.4	70.5–87	78.3	70.6–86.9	0.77
Body mass index†	25.5	23.8–28.0	26.0	23.7–28.5	0.49
Cigarette smoking					
Years of smoking	40	34–43	36	31–42	0.003
Cigarettes per day	20	15–25	20	15–25	0.43
Pack-years of smoking	39	28–50	35	24–46	0.04
Elementary school education‡ (%)	76.1		78.3		0.49§

\* Wilcoxon rank sum test  $p$  value, except for elementary school education.

† Weight (kg)/height (m)<sup>2</sup>.

‡ Sixth to eighth grade or less.

§ Chi-squared test.

**TABLE 2. Baseline energy-adjusted food intakes of pancreatic cancer case and noncase subjects, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985-1997**

Food intake* (g/day)	Case subjects (n = 163)		Noncase subjects (n = 26,948)		p value†
	Median value	Interquartile range	Median value	Interquartile range	
Dairy products	737	580-947	747	528-963	0.95
Milk (whole and low-fat)	545	346-817	533	291-769	0.27
Sour milk products	51.4	2.3-185.0	76.1	7.9-225.0	0.05
Cheese	14.7	7.9-31.9	16.7	8.4-31.8	0.15
Cream	6.7	3.9-20.6	6.4	3.7-12.7	0.06
Butter	45.7	23.2-61.0	38.3	15.4-55.1	0.003
Vegetable oils	0.4	0-1.2	0.5	0-1.4	0.17
Red meat	130.0	103.2-165.9	128.7	100.0-165.1	0.77
Beef	22.2	12.5-36.0	21.2	12.5-33.0	0.64
Poultry	11.0	0-20.8	8.5	0-17.4	0.29
Fish	32.9	20.4-45.6	32.8	20.3-50.4	0.63
Pork	36.6	27.2-48.0	36.9	27.3-49.1	0.71
Fried meat‡	116	72-168	121	85-165	0.74
Processed meats	62.2	36.0-93.8	61.2	39.7-91.2	0.75
Processed fish	3.8	1.1-8.2	3.5	0.9-7.9	0.68
Organ meats	3.5	0-6.5	3.7	0.5-7.6	0.19
Eggs	45.4	30.6-63.7	44.4	29.9-65.1	0.82
Rye products	80.1	42.3-128.2	83.2	49.0-123.2	0.62
Wheat products	98.0	65.7-135.2	97.4	64.1-134.8	0.60
Vegetables§	94.7	55.9-134.8	94.4	59.9-140.1	0.37
Fresh vegetables	31.2	16.0-68.0	35.2	17.1-64.7	0.39
Cooked vegetables	18.1	7.8-32.5	17.0	6.7-32.7	0.67
Cruciferous vegetables	9.1	2.3-17.9	9.7	3.2-19.6	0.40
Root vegetables	18.5	9.3-31.5	19.9	10.3-34.2	0.47
Potatoes	165	129-225	168	129-217	0.92
Legumes	3.9	2.1-6.3	3.9	1.9-6.9	0.88
All fruits and berries	98.8	49.2-172.2	105.2	57.2-165.7	0.60
Citrus fruits	27.1	8.2-74.6	31.8	9.3-79.6	0.25
Berries	25.5	9.3-45.8	26.5	12.4-47.8	0.25
Vegetables and legumes¶	98.2	60.4-137.3	99.2	63.7-145.7	0.36
Vegetables, legumes, and fruits¶	210.7	130.1-300.4	212.9	140.7-305.2	0.30
Coffee	600	420-660	550	420-770	0.73
Tea#	0	0-31.4	0	0-62.9	0.06

\* All food intakes were adjusted for energy intake by the residual method (except coffee and tea).

† Wilcoxon rank sum test.

‡ Intake was measured in frequency of intake per year.

§ Excludes potatoes and legumes.

¶ Excludes potatoes.

# The proportion of tea drinkers was 17% among cases and 36% among noncases (chi-squared test:  $p = 0.06$ ).

positive associations with foods containing high amounts of saturated fat (i.e., butter and cream) reinforce the nutrient findings. To our knowledge, no other prospective cohort study has examined the relation between fat intake and pancreatic cancer, and results from case-control studies that have examined this relation are inconsistent. A large collaborative population-based case-control report on pancreatic cancer comprising 802 cases from five studies conducted in Australia, Canada, Poland, and the Netherlands (Surveillance of Environmental Aspects Related to Cancers in Humans (SEARCH)) found an overall nonsignificant inverse association with energy-adjusted total fat intake (18, 19). At three sites, significant inverse associations were reported (19), and at the other two sites a nonsignificant inverse association and a significant positive association were reported (19-21). For

energy-adjusted saturated fat, the large pooled report showed a nonsignificant inverse association (18, 19); two sites showed significant inverse associations, one site showed no association, and two sites showed nonsignificant positive associations (19, 21). Compared with those reported in the pooled analysis (19), the results from the individual SEARCH site reports (20, 22-24) for fat and saturated fat differed somewhat, but the data were analyzed differently (use of continuous nutrient variables and/or the nutrient variables' not being adjusted for as many factors). Of the other five case-control studies that have examined diet and pancreatic cancer, two have found significant inverse associations with either energy-adjusted total fat or energy-adjusted saturated fat in men (16, 25), one found a significant positive association with total fat (19, 26), and two showed no association with

**TABLE 3. Baseline energy-adjusted dietary nutrient intakes of pancreatic cancer case and noncase subjects, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985-1997**

Daily nutrient intake*	Case subjects (n = 163)		Noncase subjects (n = 26,948)		p value†
	Median value	Interquartile range	Median value	Interquartile range	
Energy (kcal)	2,616	2,204-3,054	2,721	2,254-3,263	0.04
Carbohydrate (g)	290	262-316	296	268-323	0.08
Starch	146	125-160	143	122-164	0.76
Fiber (g)	24	19-30	24	20-30	0.35
Insoluble fiber	10.4	8.3-13.0	10.7	8.5-13.2	0.41
Soluble fiber	5.3	4.5-6.4	5.4	4.5-6.4	0.23
Protein (g)	100	92-109	100	92-109	0.59
Animal protein	68.1	59.6-76.3	69.1	60.1-78.8	0.42
Milk protein	29.7	23.9-36.7	30.8	23.4-38.5	0.43
Vegetable protein	30.6	26.8-34.8	30.6	26.3-35.2	0.72
Fat	121	111-133	119	109-129	0.03
Saturated fat (g)	61.8	53.2-70.4	58.5	49.2-70.0	0.004
Monounsaturated fat (g)	35.6	32.2-39.5	35.2	31.9-38.6	0.17
Polyunsaturated fat (g)	9.4	7.4-12.4	10.1	7.4-14.8	0.29
$\omega$ -3 fish oils (g)	0.41	0.29-0.56	0.40	0.28-0.57	0.66
Linoleic acid (mg)	6,728	5,060-9,256	6,910	5,262-11,557	0.25
$\alpha$ -Linolenic acid (mg)	1,470	1,146-1,949	1,543	1,141-2,054	0.25
Cholesterol (mg)	551	469-652	537	453-641	0.24
Folate ( $\mu$ g)	315	280-356	326	291-363	0.05
Vitamin A ( $\mu$ g)	1,565	1,200-2,185	1,564	1,132-2,262	0.58
Carotenoids ( $\mu$ g)	3,790	2,650-4,984	3,863	2,821-5,337	0.49
$\beta$ -Carotene ( $\mu$ g)	1,652	1,097-2,368	1,713	1,092-2,702	0.55
Lycopene ( $\mu$ g)	597	257-999	593	292-1,022	0.57
Vitamin C (mg)	82.8	63.0-112.5	87	66-115	0.20
Vitamin E (mg)	10.0	8.3-12.5	10.3	8.5-13.9	0.16
$\alpha$ -Tocopherol (mg)	8.5	7.1-10.8	9.2	7.0-12.4	0.22
Vitamin D ( $\mu$ g)	4.9	3.5-6.4	4.9	3.4-6.7	0.91
Calcium (mg)	1,311	1,110-1,561	1,348	1,099-1,606	0.37
Selenium ( $\mu$ g)	86.4	76.4-97.1	86.5	77.6-96.2	0.89
Nitrite (mg)	1.8	1.4-2.5	1.9	1.4-2.5	0.43
Nitrate (mg)	52	36-71	54	39-73	0.41
Sodium (mg)	4,689	4,350-5,225	4,789	4,324-5,299	0.41

\* All nutrient intakes were adjusted for energy intake by the residual method.

† Wilcoxon rank sum test.

energy-adjusted total or saturated fat (27, 28). The lack of consistency in these studies probably reflects the difficulties and biases associated with collecting dietary data from persons with this rapidly fatal gastrointestinal cancer (including selection bias, use of surrogate responses, and recall bias), as well as differences in analytical approach. In particular, the inverse fat associations in a large proportion of the case-control studies may have been observed because cases changed their diets in response to symptoms of the disease. This could occur among subjects with pancreatic cancer, particularly with regard to fat intake, since fat malabsorption and diarrhea could result from a diseased pancreas. Although attempts are made in case-control studies to collect information on diet prior to the appearance of disease symptoms, recent intake exerts a powerful influence on the accuracy of dietary recall (29, 30).

Energy intake and energy-adjusted carbohydrate intake were associated with decreased pancreatic cancer risk in a dose-response manner in our study. Three case-control stud-

ies (25-27) have shown inverse associations with energy intake (one being statistically significant (26)), although the majority of studies have shown positive associations (16, 18-24, 31), with odds ratios in the range of 1.5-2.0 for the highest quartile versus the lowest. The pooled SEARCH study observed positive associations between energy and pancreatic cancer in both men and women that were accounted for primarily by carbohydrate intake (continuous odds ratio = 1.67, 95 percent confidence interval: 1.25, 2.24) (18). Other case-control studies have shown no consistent association between carbohydrate intake and pancreatic cancer (16, 25, 28), and one showed a significant inverse association (26). Silverman et al. (16), in a large case-control study that attempted to collect data on usual dietary intake and weight prior to symptoms of illness, observed a statistically significant interaction between body mass index (weight (kg)/height (m)<sup>2</sup>) and total caloric intake, such that persons in the highest body mass index and caloric-intake quartiles tended to have a 70 percent greater risk than those in the lowest quartiles.

**TABLE 4. Adjusted hazard ratios and 95% confidence intervals for pancreatic cancer according to energy-adjusted baseline food intakes, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985-1997\***

Food	Quantile of intake									
	1†	2		3		4		5		p for trend
		HR‡	95% CI‡	HR	95% CI	HR	95% CI	HR	95% CI	
Milk products	1.00	1.27	0.77, 2.10	1.46	0.90, 2.38	1.08	0.64, 1.81	1.08	0.64, 1.81	0.89
Milk (whole and low-fat)	1.00	1.24	0.74, 2.10	1.49	0.90, 2.47	1.12	0.66, 1.92	1.47	0.89, 2.44	0.21
Sour milk products	1.00	1.06	0.68, 1.66	0.87	0.54, 1.40	0.72	0.44, 1.18	0.76	0.47, 1.25	0.11
Cheese	1.00	0.96	0.61, 1.51	0.77	0.47, 1.24	0.89	0.56, 1.42	0.73	0.45, 1.20	0.21
Cream	1.00	1.01	0.59, 1.72	1.27	0.76, 2.11	1.25	0.75, 2.08	1.50	0.93, 2.43	0.06
Butter	1.00	0.73	0.41, 1.28	0.98	0.58, 1.65	1.40	0.87, 2.27	1.40	0.87, 2.25	0.04
Vegetable oils§	1.00	1.16	0.78, 1.73	0.82	0.52, 1.27	0.92	0.60, 1.42			0.81
Red meat	1.00	0.88	0.54, 1.44	0.84	0.51, 1.39	1.28	0.81, 2.01	0.95	0.58, 1.56	0.71
Beef	1.00	1.09	0.66, 1.81	1.11	0.67, 1.83	1.19	0.73, 1.96	1.30	0.79, 2.12	0.28
Poultry§	1.00	0.81	0.52, 1.29	1.15	0.76, 1.74	1.25	0.84, 1.88			0.53
Fish	1.00	1.22	0.75, 1.97	1.14	0.70, 1.86	1.07	0.65, 1.76	0.91	0.54, 1.52	0.59
Pork	1.00	1.00	0.61, 1.61	0.99	0.61, 1.60	0.94	0.57, 1.53	1.01	0.62, 1.64	0.96
Fried meat¶	1.00	0.76	0.46, 1.24	0.89	0.56, 1.43	0.81	0.50, 1.31	0.98	0.61, 1.55	0.96
Processed meats	1.00	0.76	0.47, 1.23	0.65	0.39, 1.08	0.97	0.61, 1.54	1.04	0.66, 1.65	0.63
Processed fish	1.00	1.20	0.73, 1.97	1.13	0.68, 1.88	1.24	0.75, 2.03	1.22	0.74, 2.01	0.38
Organ meats§	1.00	0.82	0.53, 1.27	1.03	0.68, 1.55	0.71	0.45, 1.12			0.31
Eggs	1.00	1.05	0.65, 1.70	0.93	0.57, 1.53	1.27	0.80, 2.02	0.86	0.52, 1.44	0.84
Rye products	1.00	0.85	0.53, 1.37	0.71	0.43, 1.16	0.92	0.58, 1.46	0.86	0.54, 1.37	0.56
Wheat products	1.00	1.20	0.71, 2.01	1.57	0.96, 2.56	1.11	0.66, 1.88	1.23	0.73, 2.05	0.54
Vegetables#	1.00	0.92	0.58, 1.48	0.97	0.61, 1.55	0.89	0.55, 1.44	0.77	0.47, 1.27	0.32
Fresh vegetables	1.00	1.09	0.69, 1.72	1.02	0.64, 1.64	0.68	0.40, 1.15	0.96	0.59, 1.55	0.41
Cooked vegetables	1.00	1.18	0.72, 1.94	1.14	0.69, 1.87	1.18	0.72, 1.93	1.13	0.69, 1.87	0.53
Cruciferous vegetables§	1.00	0.81	0.50, 1.31	0.84	0.52, 1.35	0.94	0.59, 1.49	0.82	0.50, 1.32	0.44
Root vegetables	1.00	0.82	0.50, 1.33	0.90	0.56, 1.45	1.03	0.66, 1.63	0.69	0.42, 1.14	0.34
Potatoes	1.00	0.82	0.50, 1.36	1.18	0.75, 1.86	0.80	0.48, 1.32	1.02	0.63, 1.64	0.98
Legumes	1.00	1.23	0.75, 2.03	1.13	0.68, 1.88	1.54	0.96, 2.48	0.89	0.52, 1.53	0.89
All fruits and berries	1.00	0.81	0.50, 1.30	0.72	0.44, 1.17	0.85	0.53, 1.36	0.85	0.53, 1.35	0.52
Citrus fruits	1.00	1.15	0.73, 1.82	0.74	0.44, 1.23	1.14	0.72, 1.81	0.79	0.47, 1.31	0.53
Berries	1.00	0.62	0.39, 1.01	0.74	0.47, 1.17	0.57	0.35, 0.94	0.72	0.46, 1.14	0.12
Vegetables and legumes**	1.00	0.84	0.52, 1.36	0.97	0.61, 1.54	0.90	0.56, 1.44	0.72	0.43, 1.19	0.29
Vegetables, fruits, and legumes**	1.00	0.82	0.52, 1.30	0.67	0.41, 1.09	0.82	0.51, 1.30	0.74	0.46, 1.20	0.24
Coffee	1.00	1.48	0.89, 2.46	1.12	0.61, 2.03	1.72	1.01, 2.86	0.95	0.54, 1.68	0.62
Tea§	1.00	0.73	0.47, 1.13	0.69	0.44, 1.09					0.10

\* All food intakes were adjusted for energy intake by the residual method (except coffee and tea) and adjusted for age and years of smoking.

† Reference category.

‡ HR, hazard ratio; CI, confidence interval.

§ Reference category was an intake of zero.

¶ Intake was measured in frequency of consumption per year.

# Excludes potatoes and legumes.

\*\* Excludes potatoes.

However, the majority of retrospective case-control studies, including those showing positive associations with energy intake (3, 18, 21, 31-34), have shown no association with body mass index. Interestingly, of studies that have examined the relation between energy intake and colon cancer, another gastrointestinal cancer, many prospective investigations have similarly found inverse associations with greater energy intake, while case-control studies have observed positive associations (35). The inverse association observed in some of these prospective studies may be explained by the greater energy intake associated with energy expenditure from greater physical activity (36), which is protective against colon cancer (36). Although physical activity did not confound our risk estimates, it was crudely measured in our study, and energy may be a marker for greater activity. These facts, coupled with our findings, may indicate that excess energy intake in case-control studies may be related to a higher metabolic rate due to the disease or systematic overreporting of energy intake by cases (3).

The associations we observed with fat and saturated fat were independent of energy and carbohydrate intake. The mechanisms that may explain our findings regarding fat are speculative. Interestingly, animal studies have found that polyunsaturated fat ( $\omega$ -6 fatty acids) enhances pancreatic cancer risk more than saturated fat, while many epidemiologic studies have found the reverse (37). Rodents fed high-fat diets have a greater incidence of pancreatic tumorigenesis than rodents fed low-fat diets with a similar caloric content, which suggests that the effects of fat may involve more than the effect of caloric density (37, 38). Saturated fats, in particular, are more readily stored than carbohydrate and protein, are less efficiently oxidized for energy, are inadequately mobilized by lipolytic stimuli, and increase the expression of genes associated with adipocyte proliferation (39). These unique aspects of energy obtained from fat may account for its cancer-promoting effects (40). In rats, moderate caloric restriction protects against promotion of carcinogenesis in azaserine-induced pancreatic tumors (41, 42). The fact that

**TABLE 5. Adjusted hazard ratios and 95% confidence intervals for pancreatic cancer according to energy-adjusted baseline nutrient intakes, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, 1985-1997\***

Nutrient	Quantile of intake									
	1†	2		3		4		5‡		p for trend
	HR‡	95% CI‡		HR	95% CI		HR	95% CI		
Energy	1.00	1.02	0.64, 1.62	1.19	0.76, 1.85	0.80	0.49, 1.31	0.62	0.36, 1.07	0.05
Carbohydrate	1.00	1.02	0.65, 1.60	0.89	0.56, 1.41	0.68	0.42, 1.12	0.62	0.37, 1.03	0.02
Starch¶	1.00	0.84	0.49, 1.44	1.45	0.89, 2.34	1.74	1.09, 2.79	0.82	0.46, 1.46	0.42
Fiber§	1.00	0.94	0.59, 1.51	0.79	0.47, 1.31	0.87	0.52, 1.46	1.01	0.59, 1.74	0.90
Insoluble fiber§	1.00	0.76	0.47, 1.23	0.84	0.52, 1.37	0.90	0.55, 1.47	0.95	0.57, 1.60	0.99
Soluble fiber§	1.00	1.09	0.68, 1.74	0.95	0.57, 1.59	0.95	0.56, 1.63	1.02	0.56, 1.63	0.91
Protein	1.00	1.34	0.83, 2.14	1.19	0.73, 1.93	0.99	0.59, 1.65	1.02	0.61, 1.70	0.70
Animal protein	1.00	1.12	0.70, 1.79	1.08	0.67, 1.74	0.82	0.49, 1.38	1.02	0.63, 1.67	0.73
Milk protein	1.00	1.56	0.96, 2.52	1.23	0.74, 2.04	1.08	0.64, 1.82	1.06	0.63, 1.79	0.74
Vegetable protein§,¶	1.00	1.01	0.61, 1.67	1.41	0.86, 2.28	1.31	0.78, 2.21	1.10	0.61, 1.98	0.45
Fat	1.00	1.16	0.68, 1.98	1.31	0.78, 2.20	1.18	0.69, 1.99	1.62	0.99, 2.65	0.07
Saturated fat	1.00	0.90	0.51, 1.61	1.53	0.92, 2.55	1.47	0.88, 2.45	1.60	0.96, 2.64	0.02
Monounsaturated fat¶	1.00	0.88	0.52, 1.49	1.05	0.63, 1.76	0.77	0.44, 1.35	1.19	0.71, 2.01	0.56
Polyunsaturated fat¶	1.00	0.76	0.47, 1.24	1.24	0.79, 1.94	0.98	0.59, 1.65	1.18	0.66, 2.10	0.45
ω-3 fish oils	1.00	0.97	0.60, 1.60	1.04	0.64, 1.69	1.16	0.72, 1.86	0.96	0.58, 1.58	0.90
Linoleic acid¶	1.00	0.90	0.55, 1.47	1.35	0.85, 2.15	1.15	0.68, 1.93	1.19	0.65, 2.17	0.49
α-Linolenic acid¶	1.00	1.09	0.69, 1.73	1.10	0.68, 1.79	1.04	0.61, 1.77	1.11	0.65, 1.91	0.77
Cholesterol¶	1.00	0.93	0.54, 1.57	0.94	0.55, 1.61	1.17	0.70, 1.97	0.92	0.53, 1.59	0.96
Vitamin A§	1.00	1.03	0.62, 1.72	1.28	0.78, 2.10	1.37	0.84, 2.24	1.21	0.71, 2.03	0.29
Carotenoids§	1.00	0.70	0.41, 1.17	1.25	0.79, 1.98	1.02	0.62, 1.69	0.88	0.50, 1.55	0.94
β-Carotene§	1.00	0.81	0.48, 1.35	1.32	0.83, 2.09	1.18	0.72, 1.93	0.97	0.56, 1.68	0.66
Lycopene§	1.00	0.92	0.57, 1.48	0.93	0.57, 1.51	1.01	0.62, 1.65	1.06	0.64, 1.77	0.79
Vitamin C§	1.00	1.04	0.66, 1.65	0.78	0.47, 1.29	0.95	0.57, 1.57	0.91	0.52, 1.59	0.65
Vitamin E§,¶	1.00	1.40	0.87, 2.26	1.48	0.89, 2.45	1.17	0.66, 2.08	1.38	0.74, 2.56	0.53
α-Tocopherol¶	1.00	0.88	0.54, 1.41	1.17	0.74, 1.85	0.85	0.49, 1.46	1.10	0.62, 1.98	0.79
Vitamin D¶	1.00	1.14	0.70, 1.86	1.26	0.78, 2.05	1.16	0.70, 1.92	1.17	0.69, 1.97	0.56
Calcium¶	1.00	1.27	0.80, 2.02	1.01	0.62, 1.65	0.78	0.46, 1.31	0.83	0.49, 1.38	0.17
Selenium	1.00	0.84	0.51, 1.37	0.96	0.60, 1.54	0.97	0.60, 1.56	1.00	0.62, 1.61	0.85
Nitrite	1.00	0.91	0.57, 1.45	0.75	0.46, 1.23	0.79	0.48, 1.29	1.06	0.67, 1.67	0.98
Nitrate	1.00	0.90	0.56, 1.43	0.82	0.51, 1.33	0.92	0.58, 1.47	0.79	0.49, 1.29	0.41
Sodium	1.00	1.34	0.83, 2.16	1.26	0.78, 2.05	0.83	0.49, 1.42	1.02	0.62, 1.70	0.53

\* All nutrient intakes were adjusted for energy intake by the residual method and for age and years of smoking.

† Reference category.

‡ HR, hazard ratio; CI, confidence interval.

§ Additionally adjusted for energy-adjusted folate intake.

¶ Additionally adjusted for energy-adjusted saturated fat intake.

our energy-adjusted fat associations were independent of energy intake may argue against this, however. In addition, fats and fatty acids in chyme entering the duodenum stimulate the release of cholecystokinin, and chronic cholecystokininemia in rodents stimulates pancreatic enzyme secretion, hypertrophy, and hyperplasia and increases the susceptibility of the pancreas to carcinogens (43, 44). Fat and saturated fat could also potentially increase insulin resistance (39, 45-48), which may play a role in pancreatic cancer development, as suggested by the association with diabetes mellitus (15). Increasing the saturated fatty acid content or decreasing the polyunsaturated fatty acid content within cell membranes through diet adversely alters insulin binding and responsiveness (46). Finally, our associations with pancreatic cancer were observed with high-fat dairy products, and fat-soluble organochlorine compounds are potential contaminants of food (especially foods with a high fat content, such as butter and cream) that persist in the environment, are stored long-term in adipose tissue, and have been associated with pancreatic cancer in some studies (49-52). Use of organochlorine compounds has been limited in Finland; the pesticide *p,p'*-dichlorodiphenyltrichloroethane (DDT) was

banned in the early 1970s, and use of polychlorinated biphenyls was almost nonexistent during the mid-1980s (53). Given the older age of the ATBC population, however, it is possible that the butter and cream intakes quantified by our dietary questionnaire also reflected earlier intake from a time when organochlorine compounds were present at higher concentrations in these foods.

Limitations of our study include the lack of generalizability to other populations, measurement error, and the range of dietary intakes. Because the subjects in this study were older male smokers (e.g., a group at high risk of pancreatic cancer), our results may not be generalizable to nonsmoking populations. Smokers tend to be less well nourished for many nutrients as a result of poorer-quality diets and the direct antinutrient effects of cigarette smoke (54). Energy and carbohydrate intake in our study may be markers for greater nutrient intake and better nutritional status, since energy and carbohydrate are correlated with many nutrients, and their combined effect may additionally explain the protective association that we observed. Dietary data do not necessarily reflect absorbed or biologically active dose and may contain measurement error from nutritional assessment

techniques and nutrient databases, and in our study, subjects could potentially have changed their diets since baseline—all of which could attenuate risk estimates. However, the dietary history instrument used in this study is of high quality (11), and heavy smokers (>15 cigarettes/day) with low levels of education are less likely to make healthy dietary changes (55–58). Saturated fat may be correlated with carcinogens (i.e., heterocyclic amines and polyaromatic hydrocarbons) in foods not quantified in our dietary data. However, this seems unlikely, because foods that are very high in saturated fat (cream and butter) were related to pancreatic cancer, while meats that may contain mutagens as well as saturated fat were not. Finally, the range of intakes for some nutrients (i.e., sodium, polyunsaturated fat) may have been too narrow in our population or may have been above or below a threshold needed to observe an association if one existed.

In conclusion, we observed positive associations for pancreatic cancer with intakes of butter, fat, and saturated fat, as well as modest inverse associations with energy and carbohydrate intake, in a cohort of smokers. Given the high-quality prospective nature of our dietary data, this study is among the strongest to have examined the diet-pancreatic cancer relation thus far. With the exception of energy intake, our findings are consistent with present guidelines for a healthy diet. Diet is a potentially modifiable factor in the prevention of pancreatic cancer, and modification of diet may particularly benefit smokers, who are at higher risk of the disease. More studies examining dietary factors in cohorts with good-quality dietary measures are needed for better elucidation of the role of diet in the etiology of pancreatic cancer.

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## APPENDIX

Cutpoints for the quantile categories of foods and nutrients evaluated in this study are as follows.

### Foods (g/day, except for fried meats)

- Dairy products:  $\leq 469$ ,  $>469$  and  $\leq 665$ ,  $>665$  and  $\leq 825$ ,  $>825$  and  $\leq 1,019$ ,  $>1,019$
- Milk (whole and low-fat):  $\leq 235$ ,  $>235$  and  $\leq 444$ ,  $>444$  and  $\leq 620$ ,  $>620$  and  $\leq 827$ ,  $>827$
- Sour milk products:  $\leq 1.4$ ,  $>1.4$  and  $\leq 42.3$ ,  $>42.3$  and  $\leq 130.0$ ,  $>130.0$  and  $\leq 287.6$ ,  $>287.6$
- Cheese:  $\leq 6.9$ ,  $>6.9$  and  $\leq 13.0$ ,  $>13.0$  and  $\leq 21.2$ ,  $>21.2$  and  $\leq 36.9$ ,  $>36.9$
- Cream:  $\leq 3.3$ ,  $>3.3$  and  $\leq 5.3$ ,  $>5.3$  and  $\leq 8.0$ ,  $>8.0$  and  $\leq 18.1$ ,  $>18.1$
- Butter:  $\leq 10.3$ ,  $>10.3$  and  $\leq 31.1$ ,  $>31.1$  and  $\leq 44.6$ ,  $>44.6$  and  $\leq 59.2$ ,  $>59.2$
- Vegetable oils: 0,  $>0$  and  $\leq 0.3$ ,  $>0.3$  and  $\leq 0.8$ ,  $>0.8$  and  $\leq 1.8$ ,  $>1.8$
- Red meat:  $\leq 93.0$ ,  $>93.0$  and  $\leq 117.3$ ,  $>117.3$  and  $\leq 141.6$ ,  $>141.6$  and  $\leq 175.6$ ,  $>175.6$
- Beef:  $\leq 10.8$ ,  $>10.8$  and  $\leq 17.5$ ,  $>17.5$  and  $\leq 25.1$ ,  $>25.1$  and  $\leq 36.8$ ,  $>36.8$
- Poultry: 0,  $>0$  and  $\leq 11.1$ ,  $>11.1$  and  $\leq 19.1$ ,  $>19.1$
- Fish:  $\leq 17.9$ ,  $>17.9$  and  $\leq 27.7$ ,  $>27.7$  and  $\leq 38.6$ ,  $>38.6$  and  $\leq 55.8$ ,  $>55.8$
- Pork:  $\leq 25.2$ ,  $>25.2$  and  $\leq 33.1$ ,  $>33.1$  and  $\leq 41.2$ ,  $>41.2$  and  $\leq 52.5$ ,  $>52.5$
- Fried meat (frequency per year):  $\leq 77.3$ ,  $>77.3$  and  $\leq 106.3$ ,  $>106.3$  and  $\leq 135.6$ ,  $>135.6$  and  $\leq 177.8$ ,  $>177.8$
- Processed meats:  $\leq 35.2$ ,  $>35.2$  and  $\leq 52.2$ ,  $>52.2$  and  $\leq 71.5$ ,  $>71.5$  and  $\leq 100.6$ ,  $>100.6$
- Processed fish:  $\leq 0.40$ ,  $>0.40$  and  $\leq 2.40$ ,  $>2.40$  and  $\leq 4.84$ ,  $>4.84$

>4.84 and ≤9.38, >9.38  
 Organ meats: 0, >0 and ≤3.6, >3.6 and ≤7.5, >7.5  
 Eggs: ≤27.0, >27.0 and ≤38.4, >38.4 and ≤51.4, >51.4 and ≤71.2, >71.2  
 Rye products: ≤40.2, >40.2 and ≤70.0, >70.0 and ≤97.6, >97.6 and ≤134.6, >134.6  
 Wheat products: ≤56.4, >56.4 and ≤84.3, >84.3 and ≤110.8, >110.8 and ≤145.2, >145.2  
 Vegetables: ≤52.9, >52.9 and ≤79.9, >79.9 and ≤110.1, >110.1 and ≤153.7, >153.7  
 Fresh vegetables: ≤13.7, >13.7 and ≤27.3, >27.3 and ≤44.8, >44.8 and ≤74.3, >74.3  
 Cooked vegetables: ≤4.7, >4.7 and ≤12.5, >12.5 and ≤22.2, >22.2 and ≤37.4, >37.4  
 Cruciferous vegetables: ≤1.8, >1.8 and ≤7.0, >7.0 and ≤13.1, >13.1 and ≤22.7, >22.7  
 Root vegetables: ≤8.5, >8.5 and ≤15.6, >15.6 and ≤24.6, >24.6 and ≤38.8, >38.8  
 Potatoes: ≤120.0, >120.0 and ≤152.5, >152.5 and ≤185.6, >185.6 and ≤230.6, >230.6  
 Legumes: ≤1.7, >1.7 and ≤3.1, >3.1 and ≤4.8, >4.8 and ≤7.9, >7.9  
 All fruits and berries: ≤25.9, >25.9 and ≤54.3, >54.3 and ≤87.6, >87.6 and ≤133.9, >133.9  
 Citrus fruits: ≤5.3, >5.3 and ≤22.6, >22.6 and ≤46.2, >46.2 and ≤90.9, >90.9  
 Berries: ≤9.7, >9.7 and ≤20.4, >20.4 and ≤33.5, >33.5 and ≤54.6, >54.6  
 Vegetables and legumes: ≤56.8, >56.8 and ≤84.3, >84.3 and ≤115.4, >115.4 and ≤160.3, >160.3  
 Vegetables, fruits, and legumes: ≤125.0, >125.0 and ≤183.3, >183.3 and ≤244.5, >244.5 and ≤330.2, >330.2  
 Coffee: ≤321.4, >321.4 and ≤450.0, >450.0 and ≤624.9, >624.9 and ≤878.6, >878.6  
 Tea: 0, >0 and ≤157.1, >157.1

#### Nutrients (daily intake)

Energy (kcal): ≤2,155, >2,155 and ≤2,541, >2,541 and ≤2,917, >2,917 and ≤3,410, >3,410  
 Carbohydrate (g): ≤260.7, >260.7 and ≤285.2, >285.2 and ≤306.1, >306.1 and ≤330.2, >330.2  
 Starch (g): ≤116.5, >116.5 and ≤134.8, >134.8 and ≤150.5, >150.5 and ≤169.2, >169.2  
 Fiber (g): ≤18.8, >18.8 and ≤22.6, >22.6 and ≤26.3, >26.3 and ≤31.0, >31.0  
 Insoluble fiber (g): ≤8.0, >8.0 and ≤9.8, >9.8 and ≤11.6, >11.6 and ≤13.9, >13.9  
 Soluble fiber (g): ≤4.3, >4.3 and ≤5.1, >5.1 and ≤5.8, >5.8 and ≤6.7, >6.7

Protein (g): ≤90.2, >90.2 and ≤97.4, >97.4 and ≤103.6, >103.6 and ≤111.2, >111.2  
 Animal protein (g): ≤57.8, >57.8 and ≤65.7, >65.7 and ≤72.6, >72.6 and ≤81.4, >81.4  
 Milk protein (g): ≤21.5, >21.5 and ≤28.1, >28.1 and ≤33.7, >33.7 and ≤40.6, >40.6  
 Vegetable protein (g): ≤25.3, >25.3 and ≤65.7, >65.7 and ≤72.6, >72.6 and ≤81.4, >81.4  
 Fat (g): ≤106, >106 and ≤115, >115 and ≤123, >123 and ≤132, >132  
 Saturated fat (g): ≤47.2, >47.2 and ≤54.9, >54.9 and ≤62.1, >62.1 and ≤70.3, >70.3  
 Monounsaturated fat (g): ≤31.0, >31.0 and ≤34.0, >34.0 and ≤36.5, >36.5 and ≤39.4, >39.4  
 Polyunsaturated fat (g): ≤7.2, >7.2 and ≤8.6, >8.6 and ≤10.8, >10.8 and ≤16.3, >16.3  
 ω-3 fish oils (g): ≤0.26, >0.26 and ≤0.35, >0.35 and ≤0.46, >0.46 and ≤0.62, >0.62  
 Linoleic acid (mg): ≤4,981, >4,981 and ≤6,148, >6,148 and ≤7,946, >7,946 and ≤13,419, >13,419  
 α-Linolenic acid (mg): ≤1,071, >1,071 and ≤1,363, >1,363 and ≤1,738, >1,738 and ≤2,166, >2,166  
 Cholesterol (mg): ≤435, >435 and ≤503, >503 and ≤571, >571 and ≤672, >672  
 Vitamin A (μg): ≤1,059, >1,059 and ≤1,369, >1,369 and ≤1,794, >1,794 and ≤2,461, >2,461  
 Carotenoids (μg): ≤2,630, >2,630 and ≤3,428, >3,428 and ≤4,353, >4,353 and ≤5,777, >5,777  
 β-Carotene (μg): ≤992, >992 and ≤1,422, >1,422 and ≤1,998, >1,998 and ≤2,922, >2,922  
 Lycopene (μg): ≤236, >236 and ≤466, >466 and ≤736, >736 and ≤1,161, >1,161  
 Vitamin C (mg): ≤62, >62 and ≤79, >79 and ≤97, >97 and ≤123, >123  
 Vitamin E (mg): ≤8.1, >8.1 and ≤9.5, >9.5 and ≤11.3, >11.3 and ≤15.2, >15.2  
 α-Tocopherol (mg): ≤7.0, >7.0 and ≤8.1, >8.1 and ≤9.7, >9.7 and ≤13.0, >13.0  
 Vitamin D (μg): ≤3.1, >3.1 and ≤4.2, >4.2 and ≤5.5, >5.5 and ≤7.3, >7.3  
 Calcium (mg): ≤1,036, >1,036 and ≤1,256, >1,256 and ≤1,442, >1,442 and ≤1,676, >1,676  
 Selenium (μg): ≤75.3, >75.3 and ≤83.1, >83.1 and ≤90.0, >90.0 and ≤98.8, >98.8  
 Nitrite (mg): ≤1.3, >1.3 and ≤1.7, >1.7 and ≤2.1, >2.1 and ≤2.7, >2.7  
 Nitrate (mg): ≤35.5, >35.5 and ≤47.5, >47.5 and ≤60.4, >60.4 and ≤79.2, >79.2  
 Sodium (mg): ≤4,210, >4,210 and ≤4,609, >4,609 and ≤4,978, >4,978 and ≤5,433, >5,433