ARTICLE

Dietary and Nutritional Factors and Pancreatic Cancer: a Case–Control Study Based on Direct Interviews

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Background: **The relationship between diet and pancreatic cancer remains unclear. In this study, we assessed the role of diet and nutrition as risk factors for pancreatic cancer, using data obtained from direct interviews only, rather than data from less reliable interviews with next of kin. We evaluated whether dietary factors could explain the higher incidence of pancreatic cancer experienced by black Americans compared with white Americans.** ***Methods:*** **We conducted a population-based case–control study of pancreatic cancer diagnosed in Atlanta (GA), Detroit (MI), and 10 New Jersey counties from August 1986 through April 1989. Reliable dietary histories were obtained for 436 patients and 2003 general-population control subjects aged 30–79 years.** ***Results:*** **Obesity was associated with a statistically significant 50%–60% increased risk of pancreatic cancer that was consistent by sex and race. Although the magnitude of risk associated with obesity was identical in blacks and whites, a higher percentage of blacks were obese than were whites (women: 38% versus 16%; men: 27% versus 22%). A statistically significant positive trend in risk was observed with increasing caloric intake, with subjects in the highest quartile of caloric intake experiencing a 70% higher risk than those in the lowest quartile. A statistically significant interaction between body mass index (weight in kg/height in m^2 for men and weight in kg/height in $m^{1.5}$ for women) and total caloric intake was observed that was consistent by sex and race. Subjects in the highest quartile of both body mass index and caloric intake had a statistically significant 180% higher risk than those in the lowest quartile.** ***Conclusions:*** **Obesity is a risk factor for pancreatic cancer and appears to contribute to the higher risk of this disease among blacks than among whites in the United States, particularly among women. Furthermore, the interaction between body mass index and caloric intake suggests the importance of energy balance in pancreatic carcinogenesis. [J Natl Cancer Inst 1998;90: 1710–9]**

In 1998, approximately 28 900 Americans will die from pancreatic cancer, the fifth leading cause of death from cancer in the United States *(1).* Despite the high mortality attributable to pancreatic cancer, little is known about its etiology. Cigarette smoking, the best established risk factor for pancreatic cancer, explains only about 25% of the incidence of the disease *(2).* Although about 15 epidemiologic studies of diet and pancreatic cancer have been conducted, the relationship remains unclear. Previous studies *(3,4)* have suggested that increased risks of this cancer are associated with high consumption of fat, carbohydrates, or animal protein and that decreased risks are associated with frequent consumption of fruits and vegetables, but these findings have not been observed consistently across studies or for both men and women in the same study. This lack of consistency may, in part, be due to misclassification of dietary information resulting from the predominance of next-of-kin interviews in previous case–control studies of pancreatic cancer *(5).* Because of the rapidly fatal course of this cancer, it has been difficult to conduct case–control studies based exclusively on direct interviews with the subjects in a population-based setting.

Our purpose was to conduct a large population-based, case–control study based only on direct interviews to assess the role that dietary and nutritional factors play in the etiology of pancreatic cancer. Because pancreatic cancer occurs 50% more frequently in blacks than in whites, an additional goal was to determine if dietary factors could explain the racial disparity in risk.

Subjects and Methods

A population-based, case–control study of cancers that occur substantially more frequently in blacks than in whites (i.e., cancers of the pancreas, prostate, and esophagus as well as multiple myeloma) was conducted in three areas of the United States. One general-population control group was the source of control subjects for all four types of cancer.

In this analysis, our case series included all cases of carcinoma of the pancreas (International Classification of Diseases for Oncology code = 157) newly di-

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See ''Notes'' following ''References.''

agnosed from August 1986 through April 1989 among 30- to 79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta, GA (DeKalb and Fulton counties), Detroit, MI (Macomb, Oakland, and Wayne counties), and 10 New Jersey counties. To ensure both the population-based nature of the case series and the completeness of case ascertainment, all cases of reported pancreatic cancer, regardless of the presence of tissue confirmation, were included initially. Because approximately 15% of the cases lacked tissue confirmation, an in-depth medical chart review was conducted to determine the accuracy of the diagnosis. On the basis of this review, 5.5% of identified patients with pancreatic cancer were excluded as being ''unlikely'' to have pancreatic cancer. Further details of the chart review were reported in an earlier publication *(6)*.

Because pancreatic cancer is a rapidly fatal disease, death was the major reason for nonresponse. Despite our emphasis on identifying and interviewing patients as quickly as possible (median time from diagnosis to interview = 7 weeks), 471 of the 1153 patients initially identified for study died before the interview could be conducted. Of the 682 surviving patients identified for study, 526 case patients were interviewed (percentage interviewed = 75% for whites and 81% for blacks).

To determine the comparability of those who died to those who lived long enough to be interviewed, we conducted interviews with next of kin of a sample of 325 deceased case patients. The next-of-kin interview was usually limited to broad categorical questions that next-of-kin respondents have been shown to answer reliably *(7)*. For most questions, the pattern of responses from next of kin of deceased case patients was similar to that from patients who were interviewed personally, including responses to questions on whether the subject ''ever smoked cigarettes,'' ''ever drank coffee regularly,'' and ''ever drank alcohol regularly.'' The overall percentage of case patients exposed to each factor, as reported by next-of-kin respondents, was similar to that reported by directly interviewed respondents for the following exposures: smoking (64% and 69%, respectively), coffee drinking (90% and 90%, respectively), and alcohol drinking (66% and 61%, respectively). For dietary habits, of the 60 individual foods from the main questionnaire, 19 were included in the next-of-kin questionnaire. For many of this subset of foods, next of kin and surviving patients reported similar mean food frequencies (e.g., collards/greens, carrots, cantaloupe, peaches, orange juice, and fried chicken). When differences between next of kin and surviving patients were observed, they appeared to be random with no consistent pattern of overreporting or underreporting by next-of-kin or direct interview status.

The control series consisted of a random sample of the general population stratified on age (5-year intervals), race, sex, and study area so that the control group would be frequency matched to the expected distribution of these factors among patients with all four types of cancer in our larger study, combined. Control subjects aged 30–64 years were chosen by random-digit dialing *(8)*. Eighty-six percent of all households contacted provided a household census that served as the sampling frame for selection of control subjects under age 65 years. Of the 1568 control subjects selected from these households, we interviewed 1227 (percentage interviewed = 78% for whites and 78% for blacks). Control subjects aged 65–79 years consisted of a stratified random sample drawn from Health Care Financing Administration rosters of the population aged 65 years or older in each study area. Of the 1232 older control subjects selected, we interviewed 926 (percentage interviewed = 78% for whites and 73% for blacks).

Interviews were typically conducted in the subject's home by a trained interviewer. Before the interview, written informed consent to participate in the study was obtained from each subject. The study was also reviewed and approved by the institutional review board of the National Cancer Institute. The questionnaire was designed to elicit detailed information on dietary and nutritional factors, alcohol intake, smoking habits, medical conditions, family history of cancer, usual occupation, and socioeconomic status. The effects of cigarette smoking and alcohol consumption on the risk of pancreatic cancer in this study have been reported in earlier publications *(2,9)*.

The methods used for the dietary assessment are described in detail elsewhere *(10)*. Briefly, subjects were asked to recall their usual adult frequency of consumption of 60 specific food items or groups of similar food items (e.g., collards, mustard or turnip greens, and kale). Subjects were instructed to provide information on their usual eating habits during most of their adult life, excluding any recent changes in diet (i.e., those that occurred in the past 5 years before the interview) that may have occurred for any reason, such as illness or a change in lifestyle. Subjects also were queried about the number of meals they usually ate during a typical weekday, their regular use of vitamin supplements (i.e., at least once per week), and their usual adult height and weight, which were used to compute body mass index (BMI) (weight in kg/height in m^2 for men and weight in kg/height in $m^{1.5}$ for women) *(11)*. For both men and women, these sex-specific algorithms for computation of the BMI have been shown to be highly correlated with weight, are independent of stature, and accurately reflect body composition *(11)*. Subjects in the highest quartile of BMI (i.e., $\geqslant$27.2 for men; $\geqslant$34.4 for women) were considered to be ''obese'' *(12)*.

To evaluate dietary factors in relation to risk of pancreatic cancer, both food-group and nutrient-based analyses were conducted. Individual foods were categorized into food groups; the composition of each food group is given in the ''Appendix'' section. Intake of selected nutrients was computed on the basis of the subject's frequency of consumption of each food item and the nutrient content of an average serving. The nutrient content of an average serving was based on sex-specific portion sizes and food composition data obtained from the National Health and Nutrition Examination Survey (NHANES II) nutrient database *(13,14)*. For each food group and macronutrient, consumption categories were created by dividing the frequency distribution of consumption for the control group into approximate quartiles. To examine the effect of energy-related nutrient intake on pancreatic cancer risk while holding total energy intake constant, we used the nutrient density method, incorporating both the percentage of total calories from a specified nutrient and total food calories into the model *(15)*.

The effects of dietary factors on the risk of pancreatic cancer were quantified as an odds ratio (OR). ORs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis *(16,17)*. Statistical models included terms for exposure (i.e., dietary factors of interest such as food groups, vitamins, minerals, macronutrients, or coffee consumption), matching factors (i.e., age at diagnosis/interview, race, sex, and study area), as well as potential confounders (i.e., cigarette smoking, alcohol consumption, diabetes mellitus [diagnosed at least 5 years before the diagnosis of cancer], cholecystectomy [occurring at least 2 years before the diagnosis of cancer], BMI, income [men], and marital status [women]). To test for linear trend, we computed the Wald statistic. The exposure variable was treated as continuous in the model by entering the median value for each level of the categorical variable among the controls. To test for interaction, we included a cross-product term in the model. As in all dietary analyses, multiple comparisons were made, increasing the number of statistically significant findings. To address this problem, we focused on results that were consistent for both men and women, rather than on statistically significant findings.

Some of the subjects whom we interviewed were excluded from analysis for the following reasons: the presence of pancreatic cancer judged unlikely (16 cases), presence of islet cell carcinoma (10 cases), no medical record available for review (six cases), unsatisfactory interview (one case patient and seven control subjects), missing data (12 case patients and 11 control subjects), and unreliable dietary histories (i.e., subjects with extremely low or high amount of food consumed, 45 case patients and 132 control subjects). Thus, the dietary analysis was based on first-person interviews with 436 ''likely'' case patients with a diagnosis of carcinoma of the exocrine pancreas and 2003 population control subjects.

RESULTS

BMI, Energy Intake, and Meals per Day

Table 1 shows the independent effects of BMI, total calories from food, and number of meals per day on the risk for pancreatic cancer. For both men and women, the highest quartile of the BMI was associated with a 50% increase in risk. For men, the trend in risk with increasing BMI was significant (P = .019), although, in the second and third quartiles, there was little or no increased risk. For women, the trend was not significant, but those in the upper three quartiles experienced a 40%–50% higher risk than those in the lowest quartile. For men and women combined, ORs for the lowest to the highest quartile were 1.0, 1.1 (95% CI = 0.8–1.5), 1.3 (95% CI = 1.0–1.8), and 1.6 (95% CI = 1.1–2.1), respectively, and this trend was significant (P = .003). Blacks and whites experienced similar BMI-related risks; the OR for the highest BMI quartile was 1.5 for both blacks (95% CI = 0.8–2.5) and whites (95% CI = 1.0–2.3). Blacks, especially black women, tended to be more obese than whites.

Table 1. Numbers of case patients, control subjects, and odds ratios (ORs) for pancreatic cancer, according to dietary factors, by sex*

Factor	Men			Women		
	No. of case patients	No. of control subjects	OR† (95% CI)	No. of case patients	No. of control subjects	OR† (95% CI)
BMI‡,§,‖						
1	51	308	1.0 (referent)	40	188	1.0 (referent)
2	39	310	0.8 (0.5–1.3)	54	187	1.4 (0.9–2.3)
3	55	311	1.1 (0.7–1.7)	57	180	1.5 (0.9–2.4)
4	73	302	1.5 (1.0–2.3)	62	192	1.5 (0.9–2.5)
			P = .019**			P = .129**
Total calories from food¶,#						
1	43	309	1.0 (referent)	41	187	1.0 (referent)
2	49	308	1.0 (0.6–1.6)	54	185	1.4 (0.8–2.2)
3	60	307	1.2 (0.8–1.9)	50	188	1.4 (0.9–2.3)
4	66	307	1.4 (0.9–2.1)	68	187	2.0 (1.2–3.2)
			P = .112**			P = .004**
No. of meals per day‖,#						
⩾3	141	707	1.0 (referent)	145	427	1.0 (referent)
2	70	457	0.9 (0.6–1.3)	62	281	0.6 (0.4–0.9)
1	7	67	0.6 (0.3–1.4)	6	39	0.4 (0.2–1.1)
			P = .244**			P = .002**

*BMI = body mass index; 95% CI = 95% confidence interval.

†ORs were adjusted for age at diagnosis/interview, race, study area, diabetes mellitus, cholecystectomy, cigarette smoking, alcohol consumption, income (men), and marital status (women).

‡BMI = weight in kg/height in m^2 for men; BMI = weight in kg/height in $m^{1.5}$ for women.

§Quartile outpoints for BMI—men: 17.35–23.13, 23.17–25.07, 25.09–27.18, and ⩾27.2 (kg/m^2); women: 20.49–27.54, 27.56–30.25, 30.30–34.21, and ⩾34.43 ($kg/m^{1.5}$).

‖ORs were also adjusted for calories from food.

¶Quartile cutpoints for calories from food (kcal)—men: 305–1361, 1363–1756, 1757–2167, ⩾2168; and women: 236–989, 991–1296, 1297–1621, and ⩾1628.

#ORs were also adjusted for BMI (women).

**Two-sided P value for test of linear trend. P values are considered statistically significant for $P<.05$.

Among female control subjects, 38% of blacks were in the highest BMI quartile compared with 16% of whites, whereas among male control subjects, 27% of blacks were in the highest quartile compared with 22% of whites.

Among women, we observed a significant gradient in risk with increasing caloric intake (P = .004); women in the highest quartile of caloric intake experienced twice the risk of those in the lowest quartile. A significant trend in risk also was associated with number of meals consumed per day among women (P = .002). Women who consumed only one meal per day had a 60% reduction in risk compared with those who consumed three or more meals per day. Among men, similar patterns were seen. Men in the highest quartile of caloric intake had a nonsignificant 40% increased risk compared with those in the lowest quartile, whereas men who consumed one meal per day had a nonsignificant 40% reduction in risk. For men and women combined, ORs for the lowest to the highest caloric intake quartile were 1.0, 1.2 (95% CI = 0.9–1.7), 1.4 (95% CI = 1.0–1.9), and 1.7 (95% CI = 1.2–2.3) (P for trend = .001); ORs for subjects who ate three or more meals per day, two meals per day, and one meal per day were 1.0, 0.8 (95% CI = 0.6–0.98), and 0.5 (95% CI = 0.3–0.96), respectively (P for trend = .006). Blacks and whites experienced similar patterns of risk associated with total caloric intake and number of meals consumed per day.

Pancreatic cancer risk is cross-classified by both BMI and total caloric intake in Table 2. Men and women above the median for both BMI and caloric intake experienced a significant 70% increased risk compared with those below the median for both BMI and caloric intake. In contrast, men and women above the median for either BMI or caloric intake and below the median for the other factor had no increased risk. For both men and women, a significant interaction was found between BMI and caloric intake (P = .028 for men; P = .037 for women). Similar interactions were apparent for blacks and whites, with a significant 70% increase in risk for blacks and a significant 60% increase in risk for whites above the median for both BMI and caloric intake (P for interaction = .044 for blacks and .013 for whites). For the total study group combined, we estimated risk by quartiles of both BMI and caloric intake. ORs for subjects in the highest two quartiles of BMI and caloric intake were significantly elevated relative to those in the lowest quartile of both BMI and caloric intake (quartile 3 of BMI/quartiles 3 and 4 of caloric intake: 2.1 [95% CI = 1.1–4.1] and 2.2 [95% CI = 1.2–4.2], respectively; quartile 4 of BMI/quartiles 3 and 4 of caloric intake: 2.2 [95% CI = 1.1–4.1] and 2.8 [95% CI = 1.5–5.2], respectively). No significantly elevated ORs were observed for other levels of BMI/caloric intake.

Food Groups

Table 3 presents pancreatic cancer risk by the major food groups and their subcategories. The only food group showing a significant trend in risk with increasing consumption in both men and women was cruciferous vegetables (men: P = .004; women: P = .002). Men and women in the highest (most frequent) quartile of cruciferous vegetable consumption (i.e., more than four times per week) experienced a significant 50%–60% decrease in risk compared with subjects in the lowest quartile (i.e., less than 1.5 servings per week). For men and women

Table 2. Odds ratios (ORs) for pancreatic cancer according to body mass index and total caloric intake from food, by sex and race*

	Total caloric intake from food							
	Men†		Women†		White‡		Black‡	
BMI	Low	High	Low	High	Low	High	Low	High
Low								
OR	1.0§	0.9	1.0§	1.0	1.0§	0.9	1.0§	0.9
95% CI	(referent)	0.6–1.4	(referent)	0.6–1.6	(referent)	0.6–1.3	(referent)	0.5–1.6
No. of case patients/ No. of control subjects	46/308	44/310	51/190	43/185	65/284	62/305	32/215	25/191
High								
OR	1.0	1.7	0.9	1.7	0.9	1.6	0.9	1.7
95% CI	0.6–1.6	1.1–2.6	0.5–1.4	1.1–2.7	0.6–1.4	1.1–2.4	0.5–1.5	1.01–2.7
No. of case patients/ No. of control subjects	46/309	82/304	44/182	75/190	56/250	94/250	34/241	63/245
	$P = .028$‖		$P = .037$‖		$P = .013$‖		$P = .044$‖	

*BMI = body mass index, calculated as weight in kg/height in m^2 (men) or weight in kg/height in $m^{1.5}$ (women); OR = odds ratio; 95% CI = 95% confidence interval.

†ORs were also adjusted for race.

‡ORs were also adjusted for sex.

§Baseline category is low BMI (below median—men = <25.2 kg/m^2; women = <30.3 kg/$m^{1.5}$), low caloric intake from food (below median—men = <1757; women = <1297). ORs were adjusted for age at diagnosis/interview, study area, diabetes mellitus, cholecystectomy, cigarette smoking, alcohol consumption, income (men), and marital status (women).

‖Two-sided *P* value for test of interaction between BMI and total caloric intake; *P* values are considered statistically significant for $P<.05$.

Table 3. Odds ratios (ORs*) for pancreatic cancer, according to consumption level in major food groups and their subcategories, by sex

	Men					Women				
	Quartiles of consumption					Quartiles of consumption				
Food group	Low 1	2	3	High 4	*P*†	Low 1	2	3	High 4	*P*†
Dairy products	1.0	1.0	1.0	0.8		1.0	0.9	0.9	0.9	
Bread, grains, and cereal	1.0	1.1	2.1‡	2.2‡	.001	1.0	1.3	1.3	0.9	
Breaded and fried foods	1.0	1.2	1.2	1.2		1.0	1.1	0.9	1.0	
Meat, poultry, and fish	1.0	0.8	0.9	0.9		1.0	0.9	0.7	0.6	.040
Poultry and fish	1.0	1.6	1.8‡	1.5		1.0	0.8	0.6	0.5‡	.002
Red meat	1.0	0.9	0.9	0.7		1.0	1.2	1.1	1.0	
Processed meats	1.0	0.8	0.9	0.8		1.0	0.7	1.0	0.7	
Fruits	1.0	1.2	1.1	0.9		1.0	1.1	1.3	1.1	
Citrus	1.0	1.1	1.2	0.9		1.0	1.2	1.4	1.2	
Noncitrus	1.0	0.8	0.9	0.7		1.0	0.6	0.7	0.8	
Raw	1.0	0.9	0.9	0.8	.012	1.0	0.9	1.0	0.9	
Fruits rich in vitamin A	1.0	1.0	1.4	1.0		1.0	0.9	1.0	1.1	
Vegetables	1.0	0.7	0.7‡	0.6‡	.035	1.0	0.9	0.8	0.9	
Cruciferous	1.0	0.7‡	0.5‡	0.5‡	.004	1.0	0.7	0.6‡	0.4‡	.002
Dark green	1.0	0.7	0.7	0.8		1.0	0.9	0.6‡	0.6‡	.017
Dark yellow	1.0	0.8	0.8	0.6‡		1.0	1.0	1.1	1.0	
Legumes	1.0	1.0	1.0	0.8		1.0	1.3	0.9	0.8	
Raw	1.0	1.0	0.9	0.8		1.0	0.5‡	0.6‡	0.4‡	.003
Desserts	1.0	1.1	1.1	1.0		1.0	1.3	1.3	1.8‡	.035

*ORs were adjusted for age at diagnosis/interview, race, study area, calories from food, diabetes mellitus, cholecystectomy, body mass index, cigarette smoking, alcohol consumption, income (men), and marital status (women).

†Two-sided *P* value for test of linear trend. Only significant *P* values (i.e., $P<.05$) are given.

‡95% confidence interval does not include 1.0.

combined, ORs for the lowest to the highest quartiles of cruciferous vegetable intake were 1.0, 0.7 (95% CI = 0.5–0.9), 0.5 (95% CI = 0.4–0.8), and 0.5 (95% CI = 0.4–0.8) (*P* for trend = .0004). The risk reduction was greater for whites (OR = 0.5; 95% CI = 0.3–0.8) than for blacks (OR = 0.7; 95% CI = 0.4–1.3). However, the percentage of black control subjects who were frequent consumers of cruciferous vegetables was higher than the percentage of white control subjects (32% versus 19%, respectively), indicating that a racial difference in cruciferous vegetable consumption does not explain the higher risk of pancreatic cancer among blacks than among whites. Protective effects were apparent for each food included in the cruciferous vegetable category (data not shown). No risk reductions were consistently observed for both male and female frequent con-

sumers of other types of vegetables. A significant trend in risk was associated with frequent consumption of total vegetables among men but not among women.

Protective effects were not readily apparent for fruit intake. Frequent consumption of raw fruit was associated with a nonsignificant 20% decreased risk among men but with little or no risk reduction among women. Frequent consumption of noncitrus fruit was associated with a nonsignificant 30% reduced risk in men and a nonsignificant 20% reduced risk in women, and the trends were neither significant nor consistent.

The associations for other food groups were not consistent among both men and women. Men showed a significant gradient in risk rising to a twofold increase in the highest quartile of intake of bread, grains, and cereals ($P = .001$), but no clear trend was seen among women. Consumption of poultry and fish was associated with a significant inverse trend in risk with increasing intake among women ($P = .002$) but not among men. A significant risk gradient with increasing consumption of desserts also was apparent among women ($P = .035$) but not among men.

Vitamins, Minerals, and Related Dietary Constituents

The risk of pancreatic cancer for dietary consumption of specific vitamins and minerals is given in Table 4. Increasing intake of vitamin C from vegetables was associated with a significant inverse trend in risk in men ($P = .008$) and a nonsignificant inverse trend in women. Subjects who consumed the most vitamin C from vegetables (i.e., highest intake quartile = 60 mg or more per day) experienced a significant 40%–50% decrease in risk compared with those in the lowest consumption quartile (i.e., less than 30 mg per day). When cruciferous vegetables were removed from this nutrient index, a protective effect of vitamin C from vegetables was no longer apparent. ORs for the lowest to the highest intake quartile were 1.0, 1.0 (95% CI = 0.7–1.4), 0.9 (95% CI = 0.6–1.2), and 0.9 (95% CI = 0.7–1.3) for men and women combined.

A protective effect was seen for phosphorus consumption in both men and women, but neither the reductions in risk nor the inverse trends were statistically significant. Several other dietary constituents (e.g., iron, potassium, riboflavin, xanthin, cryptoxanthin, and retinol) were associated with increased or decreased risk in one sex but not in the other and typically with no consistent or significant dose–response relationship.

Macronutrients and Related Dietary Constituents

Table 5 shows pancreatic cancer risk according to level of macronutrient intake. Frequent consumption of carbohydrates

Table 4. Odds ratios (ORs*) for pancreatic cancer, according to consumption of specific micronutrients, by sex

	Men					Women				
	Quartiles of consumption					Quartiles of consumption				
Micronutrient	Low 1	2	3	High 4	P†	Low 1	2	3	High 4	P†
Vitamin C	1.0	1.4	1.1	0.9		1.0	0.8	0.9	1.1	
From fruit	1.0	1.5	1.0	1.2		1.0	0.9	1.0	1.2	
From vegetable	1.0	0.8	0.7	0.5‡	.008	1.0	0.6‡	0.6‡	0.6	
Vitamin A	1.0	0.9	1.0	0.7		1.0	1.3	1.1	1.2	
From fruit	1.0	0.1	1.2	1.1		1.0	0.8	1.3	1.2	
From vegetable	1.0	0.9	0.8	0.7		1.0	0.9	1.0	0.9	
From animal	1.0	1.0	1.0	1.1		1.0	0.9	1.3	1.4	
Lutein	1.0	0.8	0.6‡	1.0		1.0	0.7	0.5‡	0.6	
Xanthin	1.0	1.1	0.8	1.2		1.0	0.7	0.5‡	0.7	
α-Carotene	1.0	0.9	0.8	0.8		1.0	1.0	1.3	0.9	
β-Carotene	1.0	1.1	0.7	1.1		1.0	0.9	0.8	0.9	
Cryptoxanthin	1.0	1.7‡	1.5	1.5		1.0	0.9	0.9	1.3	
Lycopene	1.0	0.7	0.8	0.7		1.0	0.8	0.9	1.3	
Provitamin A	1.0	1.2	0.9	0.7		1.0	0.9	0.1	0.8	
Retinol	1.0	0.7	1.0	0.9		1.0	1.4	1.5	1.8	
B vitamins										
Folate	1.0	1.0	0.9	1.0		1.0	0.8	0.8	0.9	
Thiamine	1.0	2.0	1.6	1.3		1.0	1.2	1.7	1.1	
Riboflavin	1.0	0.9	0.9	0.7		1.0	1.4	1.6	1.8	
Niacin	1.0	1.3	1.1	1.3		1.0	1.0	1.2	1.1	
Calcium	1.0	1.3	0.8	0.8		1.0	0.8	0.8	0.9	
Phosphorus	1.0	0.8	0.8	0.5		1.0	0.6	0.6	0.8	
Iron	1.0	1.7	1.0	1.1		1.0	1.9‡	2.3‡	1.8	
Sodium	1.0	0.9	0.8	0.9		1.0	1.3	1.2	0.6	
Potassium	1.0	0.7	0.7	0.6		1.0	0.9	0.9	1.0	

*ORs were adjusted for age at diagnosis/interview, race, study area, calories from food, diabetes mellitus, cholecystectomy, body mass index, cigarette smoking, alcohol consumption, income (men), and marital status (women).

†Two-sided *P* value for test of linear trend. Only significant *P* values (i.e., $P<.05$) are given.

‡95% confidence interval does not include 1.0.

Table 5. Odds ratios (ORs*) for pancreatic cancer, according to level of macronutrient consumption using the density method, by sex

Macronutrient	Men					Women				
	Percentage of total food calories by quartile					Percentage of total food calories by quartile				
	Low 1	2	3	High 4	*P*†	Low 1	2	3	High 4	*P*†
Total carbohydrates	1.0	1.2	1.0	1.2		1.0	1.3	1.4	1.6	
Complex carbohydrates	1.0	0.9	1.2	1.5	.038	1.0	0.8	0.9	0.8	
Starch	1.0	1.0	1.0	1.7‡	.013	1.0	1.6‡	1.4	1.1	
Simple sugar	1.0	0.9	0.5‡	0.8		1.0	1.3	1.5	1.4	
Fiber	1.0	0.9	0.9	0.6‡	.040	1.0	0.9	0.8	0.9	
From fruit	1.0	1.1	1.1	0.8		1.0	0.6	0.9	0.8	
From vegetable	1.0	0.8	0.9	0.4‡		1.0	1.0	1.1	0.8	
From grain	1.0	1.2	1.6	1.4		1.0	1.3	1.1	1.1	
Total fat	1.0	1.1	1.1	0.7		1.0	0.9	0.9	0.6	
From animal	1.0	1.4	1.4	0.9		1.0	0.9	0.7	0.9	
From vegetable	1.0	1.1	1.1	1.3		1.0	0.9	0.7	0.7	
Saturated fat	1.0	1.3	1.1	0.6	.028	1.0	0.9	0.7	0.9	
Oleic acid	1.0	1.2	1.3	1.0		1.0	0.8	0.9	0.7	
Linoleic acid	1.0	1.3	1.1	1.2		1.0	1.0	0.7	0.7	
Cholesterol	1.0	0.9	1.2	1.4		1.0	1.0	1.1	0.8	
Total protein	1.0	0.7	0.8	0.8		1.0	0.9	0.8	0.7	
From animal	1.0	1.0	0.9	1.1		1.0	0.8	0.8	0.6	
From vegetable	1.0	1.1	1.3	1.3		1.0	0.8	0.8	0.8	

*ORs were adjusted for age at diagnosis/interview, race, study area, calories from food, diabetes mellitus, cholecystectomy, cigarette smoking, alcohol consumption, body mass index, income (men), and marital status (women).

†Two-sided *P* value for test of linear trend. Only significant *P* values (i.e., $P<.05$) are given.

‡95% confidence interval does not include 1.0.

was related to increased risk in both men and women. Among men, a significant positive trend in risk with increasing starch consumption was apparent ($P = .013$). Men who frequently consumed a diet rich in starch had an OR of 1.7 (95% CI = 1.1–2.5) when compared with those who frequently consumed a diet low in starch. Among women, increased risk was associated with consumption of simple sugar rather than of starch, although the trend in risk was neither significant nor consistent.

A nonsignificant 60% decrease in risk also was observed among men in the highest quartile for fiber from vegetables, but only a nonsignificant 20% risk reduction was observed among women.

Vitamin Supplements

Use of vitamin supplements (i.e., multivitamins, B vitamins, vitamins A and C, and cod-liver oil) was examined in relation to pancreatic cancer risk (data not shown). The proportion of control subjects reporting vitamin use was 49% in women, 37% in men, 43% in whites, and 39% in blacks. Vitamin C was the only supplement whose use appeared related to risk but not consistently by sex or race. Women who ever used vitamin C had an OR of 0.5 (95% CI = 0.3–0.9), whereas male users experienced no reduction in risk. Blacks who used vitamin C also had a reduced risk (OR = 0.4; 95% CI = 0.2–0.9), but whites showed no risk reduction.

Coffee Drinking

Table 6 presents the relationship between pancreatic cancer risk and coffee-drinking habits. Men who were regular coffee drinkers at some time in their lives (i.e., those who drank at least one cup per week for a year or longer) experienced no overall increased risk, whereas women who were regular drinkers had a nonsignificant 40% increased risk. Among coffee drinkers, no gradient in risk with increasing amount consumed was observed for either men or women.

When the effects of coffee drinking were examined by race, some differences were noted. Whites experienced no overall excess risk associated with regular coffee drinking (OR = 0.7; 95% CI = 0.4–1.2) and no dose–response relationship. However, blacks who were regular coffee drinkers had an overall OR of 1.7 (95% CI = 1.0–2.7), with a nonsignificant positive trend in risk with increasing amount consumed. When the analysis among blacks was limited to nonsmokers, the OR was 1.0 (95% CI = 0.4–2.6), and no trend with increasing coffee intake was evident (ORs for nonsmokers were 1.0 for 1 cup, 1.7 for 2 cups, and 1.2 for 3 or more cups per day).

Discussion

Our findings indicate that BMI, caloric intake, and number of meals consumed per day may be related to the risk of pancreatic cancer. Obesity was associated with a significant 60% excess risk that was consistent by both race and sex. A significant positive trend in risk with increasing caloric intake also was observed, with subjects in the highest quartile of caloric intake experiencing a 70% higher risk than those in the lowest quartile. In addition, a gradient in risk with increasing meals per day was apparent in both races and sexes. Subjects who consumed one meal per day had a 50% reduction in risk compared with those who consumed three or more meals per day.

The effects of BMI and energy intake on pancreatic cancer risk have been examined in at least 12 previous studies *(18–29)*, with inconsistent findings. BMI was associated with modest in-

Table 6. Numbers of case patients, control subjects, and odds ratios for pancreatic cancer, according to coffee-drinking habits, by sex and race*

Coffee-drinking status	Men†			Women†		
	No. of case patients	No. of control subjects	OR‡ (95% CI)	No. of case patients	No. of control subjects	OR‡ (95% CI)
Nondrinker	26	172	1.0 (referent)	23	123	1.0 (referent)
Ever drinker	192	1059	0.9 (0.5–1.4)	190	624	1.4 (0.9–2.4)
Cups drank per day						
⩽1	53	345	1.0 (referent)	65	217	1.0 (referent)
2	57	297	1.1 (0.7–1.7)	52	168	1.0 (0.7–1.6)
3	31	155	1.0 (0.6–1.7)	26	113	0.7 (0.4–1.1)
4–5	23	136	0.8 (0.4–1.4)	32	90	1.0 (0.6–1.7)
⩾6	28	125	0.9 (0.5–1.7)	15	35	1.0 (0.5–2.2)
	White§			Black§		
Nondrinker	26	93	1.0 (referent)	23	202	1.0 (referent)
Ever drinker	251	996	0.7 (0.4–1.2)	131	690	1.7 (1.0–2.7)
Cups drank per day						
⩽1	55	202	1.0 (referent)	63	360	1.0 (referent)
2	75	282	1.0 (0.7–1.5)	34	183	1.1 (0.7–1.8)
3	46	194	0.7 (0.5–1.2)	11	74	0.8 (0.4–1.7)
4–5	39	179	0.6 (0.4–1.0)	16	48	1.5 (0.7–2.9)
⩾6	36	138	0.8 (0.4–1.3)	7	24	1.5 (0.6–3.9)

*OR = odds ratio; 95% CI = 95% confidence interval.

†ORs were also adjusted for race.

‡ORs were adjusted for age at diagnosis/interview, study area, cigarette smoking, alcohol consumption, diabetes mellitus, cholecystectomy, body mass index, calories from food, income (men), and marital status (women).

§ORs were also adjusted for sex.

creased risks, with ORs ranging from 1.2 to 1.7, in some studies from the United States *(20,29)* and China *(23)*, and in a cohort study of obese individuals in Denmark *(27)*. In contrast, a multinational case–control study of pancreatic cancer *(18,21,22)* and some case–control studies in the United States *(25,26,28)* and Greece *(24)* revealed no clear relationship to BMI. Caloric intake emerged as a risk factor in one U.S. study *(28)* and in the multinational study *(22)*, with a doubling of risk for subjects in the upper two quintiles of caloric intake compared with those in the lowest quintile. Energy intake, however, was not related to increased risk in two other studies *(19,23)* where it was assessed. To our knowledge, the present study is the first to examine the relationship between number of meals consumed per day and pancreatic cancer risk.

The hypothesis that energy intake and number of meals consumed per day are risk factors for pancreatic cancer is supported by data from animal studies. First, frequent food consumption may increase the amount of intraduodenal chyme, thus stimulating the duodenum to release the gastrointestinal hormone cholecystokinin (CCK). CCK, a major regulator of pancreatic growth and enzyme secretion *(30,31)*, has been shown to act as a promoter of pancreatic carcinogenesis in rodents *(32,33)*. Second, energy restriction in rats has been found to inhibit pancreatic carcinogenesis *(34,35)*, perhaps by decreasing levels of carcinogen-activating enzymes in the pancreas or by decreasing tropic stimuli to the pancreas *(36)*, although energy restriction does not appear to act as an inhibitor in hamsters *(37)*. A limitation of our study is that we could not fully assess the effects of frequency and quantity of food consumption because information was not collected on snacking between meals.

Our study revealed for the first time a significant interaction between BMI and total caloric intake in relation to pancreatic cancer risk. This finding was noted in both sexes and races. Subjects above the median for both BMI and caloric intake experienced a 70% higher risk than those below the median for both factors, rising to 180% for those in the highest quartile of BMI and caloric intake. In contrast, no increased risk was found for subjects above the median for either BMI or caloric intake and below the median for the other factor, suggesting that energy balance may play a key role in pancreatic carcinogenesis. It may be that caloric intake in excess of that required to maintain energy balance (i.e., intake that leads to obesity) increases risk. In further studies evaluating the role of energy balance, it will be important to include data on physical activity, which were not obtained in our study.

Another limitation of our study is that usual adult weight was not included in the next-of-kin interview because it seemed unlikely that next of kin could accurately recall the subject's usual adult weight. If patients who survived long enough to be interviewed had higher usual adult weights than those who died before the interview could be conducted, the point estimates for BMI might be biased. It seems unlikely, however, that nonresponse bias affected the results pertaining to BMI because, in two case–control studies nested within cohorts where weight was obtained several years before the development of pancreatic cancer, subjects who developed pancreatic cancer weighed more at 12.7 and 7.5 years, respectively, before diagnosis than those who did not develop pancreatic cancer *(20,38)*.

We also found that frequent consumers of cruciferous vegetables (i.e., more than four servings per week) had a 50% reduction in risk. A protective effect associated with consumption of vegetables has been reported in at least 10 previous studies of pancreatic cancer *(25,29,39–46)*, with cruciferous vegetables being responsible for 20%–50% of the reductions

in risk in studies conducted by Olsen et al. *(45)*, Bueno de Mesquita et al. *(39)*, and Ji et al. *(40)*. These findings are consistent with animal studies *(47–50)* indicating that constituents of cruciferous vegetables—including isothiocyanates, thiocyanates, and glucobrassicin, which when hydrolyzed produces indoles—have cancer-inhibiting effects. In particular, high doses of the antioxidant Oltipraz, a synthetic dithiolthione structurally similar to anticarcinogenic dithiolthiones found in oils derived from cruciferous vegetables, have been shown to inhibit pancreatic carcinogenesis in Syrian golden hamsters *(51)*.

A protective effect also appeared to be associated with frequent consumption of vitamin C from vegetable sources. Although it has been suggested that high intake of vitamin C may reduce pancreatic cancer risk *(4)*, it is noteworthy that no risk reduction was associated with consumption of fruits high in vitamin C (i.e., citrus fruits) or with the use of vitamin C supplements. Indeed, the decreased risk associated with vitamin C from vegetables seemed mainly due to the protective effect of cruciferous vegetables rather than to vitamin C per se.

Numerous studies of pancreatic cancer *(3)* have examined the relationship between coffee drinking and pancreatic cancer risk. Although results of most studies do not support an association, positive findings from a small number of studies *(26,44,52–58)* have raised the possibility of a weak association for heavy coffee drinking. However, there is general consensus that any weak effect is likely to be a result of residual confounding by smoking or other sources of confounding or bias *(3,59)*. Our results are consistent with this view.

In our study, obesity was the only factor that contributed to the higher incidence of pancreatic cancer among blacks than among whites, particularly in women. Although the magnitude of risk associated with obesity was identical in blacks and whites (OR = 1.5), a higher proportion of blacks were obese compared with whites (women = 38% versus 16%; men = 27% versus 22% respectively). We found no clear evidence that caloric intake, cruciferous vegetables consumption, or other dietary factors contributed to the high rates of pancreatic cancer among blacks in the United States. Previous results from our case–control study suggested that heavy consumption of alcohol could explain part, but not all, of the higher incidence among blacks *(9)*.

In conclusion, our study benefited from the use of direct interviews, which reduced the potential for misclassification of dietary information that has plagued earlier studies based predominantly on next-of-kin interviews. In both sexes and races, we found significant interactions between BMI and caloric intake, suggesting that energy balance may play an important role in pancreatic carcinogenesis. In addition, protective effects were associated with a decreased frequency of meals and high intake of cruciferous vegetables, providing further leads to the next generation of studies into the origins of pancreatic cancer.

APPENDIX

The following are individual foods included in each food group:

Dairy products: cheese; milk; ice cream.

Bread, grains, and cereal: bread, rolls, or biscuits; cold cereal; hot cereal; rice; spaghetti, macaroni, or noodles.

Meat, poultry, and fish: bacon or sausage; chicken; beef; fish; liver, liverwurst, or chopped liver; lunch meats; mixed dish with meat (e.g., chili, pork and beans, spaghetti and meat balls); other pork or ham; stew.

Poultry and fish: chicken; fish.

Red meat: excludes chicken and fish from ''Meat, poultry, and fish'' list.

Processed meats: bacon or sausage; lunch meat; hot dogs; other pork or ham.

Fruits: apples or pears; apricots; bananas; cantaloupe; grapefruit; oranges or tangerines; orange or grapefruit juice; fresh peaches or nectarines; canned peaches; watermelon.

Citrus fruits: grapefruit; oranges or tangerines.

Noncitrus fruits: excludes grapefruit; oranges or tangerines; and orange or grapefruit juice from ''Fruits'' list.

Raw fruits: excludes apricots (more likely to be consumed as canned or dried); canned peaches; and orange or grapefruit juice from ''Fruits'' list.

Fruits rich in vitamin A: apricots; cantaloupe; watermelon.

Vegetables: green string beans or lima beans; red beets; broccoli; cooked cabbage; coleslaw; carrots; cauliflower; southern greens (collards, mustard greens, or kale); okra; green peas; black-eyed peas or cow peas; white potatoes; sweet potatoes or yams; raw tomatoes; cooked tomatoes; tomato or V-8 juice; tossed salad; spinach; vegetable soup; mixed vegetables; zucchini or yellow squash.

Cruciferous vegetables: broccoli; cooked cabbage; coleslaw; cauliflower; southern greens.

Dark green vegetables: broccoli; southern greens; spinach.

Dark yellow vegetables: carrots; mixed vegetables with carrots; sweet potatoes or yams.

Legumes: green peas; black-eyed peas or cow peas; green string beans or lima beans.

Raw vegetables: From question on questionnaire, ''How often did you usually have any raw vegetables?''

Desserts: ice cream; cakes, pies, and cookies; doughnuts.

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