Meat and Fat Intake as Risk Factors for Pancreatic Cancer: The Multiethnic Cohort Study

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Background: **Meat intake has been associated with risk of exocrine pancreatic cancer, but previous findings have been inconsistent. This association has been attributed to both the fat and cholesterol content of meats and to food preparation methods. We analyzed data from the prospective Multiethnic Cohort Study to investigate associations between intake of meat, other animal products, fat, and cholesterol and pancreatic cancer risk.** ***Methods:*** **During 7 years of follow-up, 482 incident pancreatic cancers occurred in 190 545 cohort members. Dietary intake was assessed using a quantitative food frequency questionnaire. Associations for foods and nutrients relative to total energy intake were determined by Cox proportional hazards models stratified by gender and time on study and adjusted for age, smoking status, history of diabetes mellitus and familial pancreatic cancer, ethnicity, and energy intake. Statistical tests were two-sided.** ***Results:*** **The strongest association was with processed meat; those in the fifth quintile of daily intake (g/1000 kcal) had a 68% increased risk compared with those in the lowest quintile (relative risk = 1.68, 95% confidence interval = 1.35 to 2.07; P_{trend}<.01). The age-adjusted yearly incidence rates per 100 000 persons for the respective quintiles were 41.3 and 20.2. Intakes of pork and of total red meat were both associated with 50% increases in risk, comparing the highest with the lowest quintiles (both P_{trend}<.01). There were no associations of pancreatic cancer risk with intake of poultry, fish, dairy products, eggs, total fat, saturated fat, or cholesterol. Intake of total and saturated fat from meat was associated with statistically significant increases in pancreatic cancer risk but that from dairy products was not.** ***Conclusion:*** **Red and processed meat intakes were associated with an increased risk of pancreatic cancer. Fat and saturated fat are not likely to contribute to the underlying carcinogenic mechanism because the findings for fat from meat and dairy products differed. Carcinogenic substances related to meat preparation methods might be responsible for the positive association. [J Natl Cancer Inst 2005;97:1458–65]**

Pancreatic cancer is the most fatal cancer in adults; it is generally diagnosed at a late stage and is poorly responsive to therapeutic modalities. It ranks fourth among U.S. cancer deaths, and the 5-year survival rate is less than 5% *(1)*. Almost 32 000 new pancreatic cancer cases were estimated to have occurred in the United States in 2004 *(2)*.

Because of the poor prognosis and the minimal impact of conventional treatment methods *(3)*, it is important to focus on prevention of this disease. So far, only a few risk factors for pancreatic cancer have been identified, of which cigarette smoking is the most important *(4,5)*. Familial history of pancreatic cancer and a diagnosis of diabetes mellitus have also been associated with the disease *(3,5–11)*. Other risk factors include increasing age; sex, with higher incidence in men; and ethnicity, with higher incidence in Native Hawaiians and African-Americans *(12)*.

Various dietary factors have been investigated as potential risk factors for pancreatic cancer. Meat, dairy products, and eggs have been associated with elevated disease risks in some studies, although other studies reported null results *(13–16)*. Meat consumption has been analyzed as single items, such as pork, or as broader food groups, such as red meat. The risk increases have generally been attributed to the fat, saturated fat, or cholesterol content of meats and other animal products *(4,5,12,17)*. Alternatively, meat preparation methods, such as grilling and frying, have been proposed as a source of carcinogens *(3,12,17)*. Based on the available studies, however, firm conclusions about a role of meat or fat in the etiology of pancreatic cancer cannot be drawn.

The inconsistency of findings may be due in part to limitations of the studies undertaken so far. Most of these have been case–control investigations, and results from only a few prospective analyses have been published. In addition to possible recall bias in dietary reporting, case–control studies have necessarily relied largely on proxy interviews because of the high fatality rate of pancreatic cancer. Prospective studies assess diet before disease occurrence, avoiding both recall bias and the need for proxy interviews. However, because pancreatic cancer incidence is relatively low, most prospective studies have had too few cases and thus inadequate statistical power to detect the small relative risks expected with dietary exposures. The Multiethnic Cohort Study offers the opportunity for such an analysis, with a large number of incident pancreatic cancer cases.

This article presents the findings of 7-year prospective data from the Multiethnic Cohort Study on the relationship of meat, dairy product, and egg consumption and of fat, saturated fat, and cholesterol intake to pancreatic cancer risk.

Patients and Methods

Study Design

The Multiethnic Cohort Study in Hawaii and Los Angeles was established to investigate lifestyle exposures, especially diet, in relation to disease outcomes, especially cancer. The respective

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DOI: 10.1093/jnci/dji292

institutional review boards (University of Hawaii and University of Southern California) approved the study proposal. Recruitment procedures, study design, and baseline characteristics have been reported elsewhere *(18)*. In brief, the cohort comprised more than 215 000 men and women aged 45–75 years at cohort creation who were enrolled in the study between 1993 and 1996. All study participants initially completed a self-administered comprehensive questionnaire that included a detailed dietary assessment, as well as sections on demographic factors; body weight and height; lifestyle factors other than diet, including smoking history; history of prior medical conditions, including diabetes mellitus; and familial history of cancer. Follow-up of the cohort for cancer incidence and mortality entails active contact with the subjects, as well as passive computerized linkages to cancer registries and death certificate files in Hawaii and California and to the National Death Index.

Study Population

Multiethnic Cohort Study participants who did not belong to one of the five targeted ethnic groups (African-American, Latino, Japanese-American, Native Hawaiian, and Caucasian) were excluded from this analysis (n = 13 994). In addition, we excluded individuals with extreme diets (i.e., extreme energy and macronutrient intakes) (n = 8265). To do so, we first excluded individuals in the top and bottom 10% tails of the log energy distribution. We then computed a robust standard deviation (RSD), assuming a truncated normal distribution. Finally, we excluded all individuals with energy values out of the range of mean ± 3 RSD. We used a similar procedure to exclude individuals with extreme fat, protein, or carbohydrate intakes (i.e., outside the range of mean ± 3.5 RSD). Subjects with a pancreatic cancer diagnosis before baseline that was either self-reported in the questionnaire or identified by registry linkages (n = 59) and subjects with missing information on smoking status or a diagnosis of diabetes mellitus at baseline (n = 2968) were also excluded. As a result, data on 190 545 participants were available for this analysis.

Dietary Assessment

Dietary intake was assessed at baseline using a comprehensive questionnaire especially designed and validated for use in this multiethnic population. The development of the self-administered quantitative food frequency questionnaire (QFFQ) has been described elsewhere *(18,19)*. In brief, the collection of 3-day measured dietary records from about 60 men and women of each ethnic group served as the basis for the selection of food items for the QFFQ. The minimum set of food items contributing at least 85% of the intake of a specific list of nutrients for each ethnic group was selected and supplemented by the inclusion of food items that were common in the diet of a particular ethnic group, irrespective of their nutrient contribution. The QFFQ inquires about the usual frequency, based on eight or nine categories, and amount, based on three portion sizes per food item, of food consumption. The reference portion sizes were also derived from the 3-day measured dietary records.

For processing dietary intake data, we used a food composition table that has been developed and maintained at the Cancer Research Center of Hawaii (CRCH). The CRCH food composition table includes a large recipe database and many unique foods consumed by the multiethnic population *(18)*. For questionnaire items covering more than one food, nutrient profiles of the items were calculated using a weighted average of the specific foods based on the frequency of use in the 24-hour recalls obtained as part of a calibration study *(19)*. Food intake measured by the QFFQ was linked to the CRCH food composition table, to convert daily grams to daily nutrients consumed from that food. Before food group intake was calculated, the food mixtures from the QFFQ were disaggregated to the ingredient level using a customized recipe database. For example, the salami on a pizza was counted toward the processed meat group, and the tomatoes on that pizza were counted toward the vegetable group. Food group intake was calculated as grams per day of the basic food commodities. Food groups used in the current analyses were beef, pork, poultry, red meat (beef, pork, and lamb), processed meat (processed red meat and processed poultry), fish, dairy products, and eggs. Several nutrients were examined, including total fat, saturated fat, and cholesterol, both in total and separated by food sources (red and processed meat, and dairy products).

For validation and calibration purposes, a substudy was incorporated into the initial dietary assessment. Details about this calibration study have been published previously *(19)*. In total, 1606 study participants who were randomly chosen out of subgroups defined by sex and ethnicity completed three unannounced 24-hour dietary recalls via telephone during a period of approximately 3 months and an additional QFFQ 3 months afterwards. Average correlation coefficients for nutrient intake between the recall measurement and the QFFQ ranged from 0.26 in African-American women to 0.57 in Caucasian men. Average correlation coefficients for nutrient densities (i.e., nutrient per 100 or 1000 kcal) were about twice as high, with a range of 0.57 to 0.74 across sex- and ethnicity-specific strata.

Identification of Pancreatic Cancer Cases

Incident exocrine pancreatic cancer cases were identified by record linkages to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry. All three registries are members of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. Case ascertainment was complete through December 31, 2001. Diagnoses of ICD-O-2 codes C25.0–C25.3 and C25.7–C25.9 were defined as exocrine pancreatic cancer. Endocrine pancreatic cancers were not included as cases, but follow-up was censored for subjects with these tumors at the date of diagnosis.

Statistical Analysis

We applied Cox proportional hazards models using age as the time metric to calculate relative risks. Person-times were calculated beginning at the date of cohort entry, defined as questionnaire completion or, for the few individuals (n = 1113) who were younger than 45 when they completed the baseline questionnaire, as the date the participant turned 45. Person-times ended at the earliest of the following dates: date of pancreatic cancer diagnosis, date of death, or December 31, 2001, the closure date of the study. Tests based on Schoenfeld residuals showed no evidence that proportional hazards assumptions were violated for any analysis. Separate models for men and women showed similar patterns. Therefore, we present models including both sexes, adjusting for sex as a stratum variable to allow for different baseline

hazard rates. All Cox models were additionally stratified by follow-up time, categorized as 2 years or less, more than 2 to 5 years, and more than 5 years. Food group and nutrient exposures were investigated in disease models in terms of quintiles. Four dummy variables were created to represent the quintiles, which were based on the distribution of each exposure across the entire cohort (men and women). Median values for sex- and ethnic-specific quintiles were used in the respective models to test for trend. Age at cohort entry, ethnicity, history of diabetes mellitus, history of familial pancreatic cancer, smoking status (never, former, or current smoker), and energy intake (logarithmically transformed) were used as adjustment factors in all multivariable models. Energy was included so that the associations with foods and nutrients could be analyzed independently of their relationship to overall energy intake. In additional analyses, we adjusted for pack-years of smoking as a more detailed measure of smoking. However, the risk estimates did not change, and therefore we chose to use only the smoking status variable because the data for this variable were more complete than those for pack-years of smoking. In addition, models were adjusted for body mass index, educational attainment, fruit and vegetable intake, and alcohol consumption. However, risk estimates changed only marginally (data not shown) and therefore these adjustments were not included in the final models.

To reduce measurement error in the dietary assessments, we analyzed daily food and nutrient intakes in terms of densities, i.e., as intake per 100 or 1000 kcal. As noted above, in the validation study we found that energy-adjusted intake produced substantially higher correlation coefficients with the reference instrument than did crude intake *(19)*. This phenomenon has also been reported in other studies *(20)*. Densities measure the contribution of the food or nutrient to the overall diet and are therefore interpreted differently from absolute measures. By contrast, the use of absolute values assumes that a specific amount of a food or nutrient will have the same effect on risk, regardless of the energy content of the remaining diet. However, we also fitted all models using absolute measurements of intake (grams per day), and the results (data not shown) led to the same conclusions. For nutrients, intake was further adjusted by applying sex- and ethnicity-specific calibration functions derived from regression models of 24-hour recall intakes on intakes in the QFFQ based on the calibration substudy. Two sets of calibrated nutrients were computed. The first set included additional covariates in the model, such as age and body mass index, as described *(19)*, whereas the second set did not. Individuals with extreme diets were excluded from the calibration models as described above. The calibrated nutrients were then used in a Cox regression model to test the trend in risk with increasing intake. The results from the two sets of calibrated nutrients were identical; therefore, we present those not adjusted for other covariates because fewer individuals were excluded due to missing values. Calibration-adjusted intakes were not computed for foods because the day-to-day variability in food consumption is too high except for very broad groupings, such as all meat as a single item.

The likelihood ratio test was used to determine the statistical significance of the interaction between smoking status and dietary variables with respect to pancreatic cancer. The test compares a main effects, no-interaction model with a fully parameterized model containing all possible interaction terms for the variables of interest. All analyses were performed using SAS Statistical Software, version 8 (SAS Institute, Inc., Cary, NC), and all statistical tests were two-sided.

Results

Approximately 45% of the study participants were men. The ethnic distribution was as follows: 29% Japanese-American, 25% Caucasian, 22% Latino, 17% African-American, and 7% Native Hawaiian. Mean energy intake reported by men ranged from 2195 kcal/day in African-Americans to 2780 kcal/day in Native Hawaiians; that reported by women ranged from 1808 kcal/day in Caucasians to 2371 kcal/day in Native Hawaiians. Further characteristics of study participants are shown in Table 1. Among the 190 545 participants included in the analysis, 482 developed incident exocrine pancreatic cancer during the 7 years of follow up. Pancreatic cancer patients were, on average, 5 years older than nonpatients at cohort entry and included a higher percentage of men than nonpatients. Current smoking, a prior diagnosis of diabetes mellitus, and a familial history of pancreatic cancer were statistically significantly more common among cancer patients than among nonpatients. There also were statistically significant differences in the ethnic distributions among pancreatic cancer patients and nonpatients; higher percentages of patients than

Table 1. Characteristics of pancreatic cancer patients (cases) and subjects without pancreatic cancer (non-cases) in the Multiethnic Cohort Study

Characteristic	Cases (n = 482)	Non-cases (n = 190 063)	P value*
Age at cohort entry, mean (SD)	65 (7)	60 (9)	<.001
Follow-up years, mean (SD)	4.33 (2.28)	7.38 (1.39)	<.001
Body mass index, mean (SD)	25.8 (4.6)	26.0 (5.1)	.41
Men, %	51.2	45.3	.01
Smoking status			< .001
Never smoker, %	37.1	44.0	
Ex-smoker, %	41.3	40.0	
Current smoker, %	21.6	16.0	
Diagnosis of diabetes mellitus, %	19.1	11.8	<.001
Familial history of pancreatic cancer, %	4.8	1.7	<.001
Ethnicity			<.001
African-American, %	21.8	17.2	
Japanese-American, %	33.8	28.5	
Latino, %	15.2	22.3	
Caucasian, %	21.2	24.8	
Native Hawaiian, %	8.1	7.2	

*P value from t tests for continuous measures and chi-square tests for categorical measures.

Table 2. Relative risks (with 95% confidence intervals) of exocrine pancreatic cancer across quintiles of daily intake of meat, dairy products, and eggs in the Multiethnic Cohort Study, $n = 190\,545$*

Food group	Quintile of intake					P_{trend}
	1	2	3	4	5	
Beef						
Median intake	3.1	7.7	11.8	16.7	25.9	
No. of cases	93	103	103	89	94	
Unadjusted RR	1	1.05 (0.87 to 1.26)	1.13 (0.94 to 1.37)	1.06 (0.87 to 1.28)	1.22 (1.01 to 1.48)	.06
Multivariable RR	1	1.01 (0.84 to 1.22)	1.08 (0.89 to 1.30)	1.02 (0.84 to 1.24)	1.21 (0.99 to 1.47)	.03
Pork						
Median intake	0.4	1.8	3.5	5.7	9.7	
No. of cases	75	87	95	112	113	
Unadjusted RR	1	1.18 (0.96 to 1.44)	1.21 (0.98 to 1.48)	1.60 (1.32 to 1.95)	1.77 (1.46 to 2.15)	<.01
Multivariable RR	1	1.14 (0.93 to 1.40)	1.12 (0.91 to 1.39)	1.44 (1.18 to 1.76)	1.53 (1.25 to 1.87)	<.01
Poultry						
Median intake	6.2	12.1	17.7	25.3	43.4	
No. of cases	97	105	101	103	76	
Unadjusted RR	1	1.18 (0.97 to 1.42)	1.21 (1.00 to 1.46)	1.29 (1.07 to 1.55)	1.00 (0.81 to 1.22)	.40
Multivariable RR	1	1.17 (0.97 to 1.41)	1.21 (1.00 to 1.46)	1.30 (1.07 to 1.57)	1.01 (0.82 to 1.25)	.45
Red meat (beef, pork, and lamb)						
Median intake	4.5	11.0	16.8	23.4	35.0	
No. of cases	86	95	113	83	105	
Unadjusted RR	1	1.10 (0.90 to 1.33)	1.34 (1.11 to 1.62)	1.10 (0.90 to 1.35)	1.54 (1.27 to 1.86)	<.01
Multivariable RR	1	1.06 (0.87 to 1.29)	1.27 (1.05 to 1.54)	1.03 (0.84 to 1.26)	1.45 (1.19 to 1.76)	<.01
Processed meat						
Median intake	1.7	4.5	7.3	10.8	18.1	
No. of cases	59	101	116	96	110	
Unadjusted RR	1	1.63 (1.32 to 2.02)	1.91 (1.55 to 2.35)	1.63 (1.31 to 2.02)	1.95 (1.58 to 2.40)	<.01
Multivariable RR	1	1.59 (1.28 to 1.97)	1.80 (1.46 to 2.21)	1.47 (1.18 to 1.82)	1.68 (1.35 to 2.07)	<.01
Fish						
Median intake	1.1	3.8	6.4	9.8	17.3	
No. of cases	96	87	92	99	108	
Unadjusted RR	1	0.90 (0.74 to 1.09)	0.93 (0.77 to 1.12)	1.03 (0.85 to 1.24)	1.06 (0.88 to 1.27)	.26
Multivariable RR	1	0.85 (0.70 to 1.03)	0.84 (0.69 to 1.03)	0.90 (0.74 to 1.10)	0.91 (0.75 to 1.11)	.49
Dairy products						
Median intake	19.4	47.8	81.6	126.9	218.8	
No. of cases	93	89	90	117	93	
Unadjusted RR	1	0.99 (0.82 to 1.21)	0.95 (0.78 to 1.15)	1.14 (0.95 to 1.37)	0.91 (0.75 to 1.10)	.90
Multivariable RR	1	1.04 (0.86 to 1.27)	1.04 (0.86 to 1.27)	1.30 (1.07 to 1.57)	1.05 (0.86 to 1.29)	.06
Eggs						
Median intake	1.6	3.4	5.2	7.8	15.0	
No. of cases	103	80	111	86	102	
Unadjusted RR	1	0.77 (0.63 to 0.94)	1.16 (0.97 to 1.39)	0.86 (0.71 to 1.04)	1.00 (0.83 to 1.20)	.50
Multivariable RR	1	0.75 (0.62 to 0.92)	1.11 (0.93 to 1.33)	0.82 (0.68 to 1.00)	0.94 (0.78 to 1.13)	.99

*All intakes are given as grams per 1000 kcal/day. In unadjusted analyses, Cox models were stratified for sex and time on study. In multivariable analyses, Cox models were stratified for sex and time on study and adjusted for age at cohort entry, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, and energy intake. RR = relative risk.

nonpatients were African-Americans, Japanese-Americans, and Native Hawaiians.

The associations between consumption of meat, dairy products, and eggs with pancreatic cancer are shown in Table 2. In the study population, median daily meat consumption, in terms of densities, ranged from 3.5 grams of pork per 1000 kcal to 17.7 grams of poultry per 1000 kcal. In general, high intakes of red meat and of processed meat were associated with an increased risk for pancreatic cancer, whereas consumption of poultry, fish, dairy products, and eggs showed no such association. The strongest risk factor was processed meat consumption; those in the fifth quintile of processed meat intake had an almost 70% higher risk than those in the first quintile. Median daily intake of processed meat was approximately 2 g/1000 kcal in the lowest quintile and 18 g/1000 kcal in the highest quintile; a statistically significant, albeit not monotonic, trend of increasing risk across quintiles was observed in both the sex- and time-stratified (i.e., unadjusted) models and the multivariable models. Consumption of pork and of total red meat (i.e., pork, beef, and lamb) were both associated with risk increases of approximately 50%, comparing the highest quintile of consumption with the lowest. Statistically significant positive trends were observed for both variables, although the trend for total red meat was not monotonic. The overall findings for red meat and processed meat were consistent in most ethnic groups considered separately (data not shown), but the numbers of cases were too small for meaningful analyses. The incidence rates, age adjusted to the age distribution of person-years in the cohort, were 28.1 and 42.7 per 100 000 persons per year in the lowest and the highest quintile of red meat intake and 20.2 and 41.3 in the respective quintiles for processed meat intake.

Median intake of total fat and percentage of energy intake from total fat were 63 g/day and 30%, respectively. Fat intake from red meat and processed meat was slightly higher than fat intake from dairy products (data not shown). Total fat showed no association with pancreatic cancer risk (data not shown). Table 3 shows the associations between percentage of energy as fat and risk of pancreatic cancer. None of the tests for trend showed

Table 3. Relative risks (with 95% confidence intervals) of exocrine pancreatic cancer across quintiles of total fat, saturated fat, and cholesterol intake in the Multiethnic Cohort Study, $n = 190\,545$*

Nutrient	Quintile of intake					P_{trend}†
	1	2	3	4	5	
% energy from fat						
Median	20.5	26.2	30.1	33.9	39.0	
No. of cases	111	89	105	87	90	
Unadjusted RR	1	0.82 (0.68 to 0.99)	1.10 (0.92 to 1.31)	0.93 (0.77 to 1.13)	1.01 (0.84 to 1.22)	.47
Multivariable RR	1	0.81 (0.67 to 0.98)	1.09 (0.91 to 1.30)	0.91 (0.76 to 1.11)	0.95 (0.78 to 1.15)	.90 (.56)
% energy from fat from dairy products						
Median	1.1	2.3	3.5	4.9	7.5	
No. of cases	116	92	96	91	87	
Unadjusted RR	1	0.88 (0.73 to 1.05)	0.93 (0.77 to 1.11)	0.95 (0.79 to 1.14)	0.89 (0.74 to 1.07)	.45
Multivariable RR	1	0.90 (0.75 to 1.09)	0.99 (0.82 to 1.20)	1.07 (0.88 to 1.30)	1.03 (0.84 to 1.27)	.24 (.20)
% energy from fat from red meat and processed meat						
Median	1.3	2.9	4.3	6.0	8.8	
No. of cases	76	114	83	104	105	
Unadjusted RR	1	1.46 (1.21 to 1.77)	1.04 (0.84 to 1.28)	1.52 (1.25 to 1.85)	1.63 (1.34 to 1.99)	<.01
Multivariable RR	1	1.41 (1.16 to 1.71)	0.98 (0.79 to 1.21)	1.39 (1.14 to 1.69)	1.44 (1.18 to 1.76)	<.01 (<.01)
% energy from saturated fat						
Median	5.5	7.3	8.8	10.2	12.2	
No. of cases	110	92	100	89	91	
Unadjusted RR	1	0.94 (0.78 to 1.13)	1.06 (0.88 to 1.27)	1.00 (0.83 to 1.21)	1.04 (0.86 to 1.25)	.58
Multivariable RR	1	0.93 (0.77 to 1.12)	1.06 (0.88 to 1.28)	1.02 (0.84 to 1.24)	1.04 (0.85 to 1.28)	.49 (.37)
% energy from saturated fat from dairy products						
Median	0.7	1.4	2.2	3.1	4.7	
No. of cases	117	91	97	89	88	
Unadjusted RR	1	0.85 (0.71 to 1.02)	0.93 (0.77 to 1.11)	0.92 (0.77 to 1.11)	0.89 (0.74 to 1.07)	.43
Multivariable RR	1	0.88 (0.73 to 1.06)	0.99 (0.82 to 1.20)	1.04 (0.85 to 1.26)	1.03 (0.84 to 1.27)	.26 (.20)
% energy from saturated fat from red meat and processed meat						
Median	0.5	1.1	1.7	2.3	3.3	
No. of cases	76	117	81	101	107	
Unadjusted RR	1	1.49 (1.23 to 1.80)	1.01 (0.82 to 1.25)	1.48 (1.21 to 1.80)	1.67 (1.37 to 2.03)	<.01
Multivariable RR	1	1.43 (1.18 to 1.74)	0.96 (0.77 to 1.18)	1.36 (1.11 to 1.65)	1.48 (1.21 to 1.81)	<.01 (<.01)
Cholesterol density (mg/1000 kcal/day)						
Median intake	56.8	81.6	100.4	120.8	156.8	
No. of cases	97	102	97	88	98	
Unadjusted RR	1	1.04 (0.86 to 1.25)	1.13 (0.94 to 1.36)	1.10 (0.91 to 1.34)	1.17 (0.97 to 1.41)	0.33
Multivariable RR	1	1.03 (0.85 to 1.24)	1.10 (0.91 to 1.33)	1.06 (0.87 to 1.29)	1.09 (0.89 to 1.32)	.96 (.08)

*In unadjusted analyses, Cox models were stratified for sex and time on study. In multivariable analyses, Cox models were stratified for sex and time on study and adjusted for age at cohort entry, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, and energy intake. RR = relative risk.

†P_{trend} values using calibration-corrected nutrient intakes are given in parentheses. The calibration equations were sex and ethnicity specific and did not include additional covariates.

statistically significant associations, whether or not they were based on the calibration-adjusted nutrient intakes. In the separate analysis of fat from red and processed meat and fat from dairy products, however, we found that fat from meat but not fat from dairy products was associated with increased risks for pancreatic cancer. The risk in the fifth quintile was approximately 40% higher than that in the first quintile, with a statistically significant positive trend across quintiles.

Median saturated fat intake and percentage of energy intake from saturated fat in the study population were 18 g/day and almost 9%, respectively. The associations with saturated fat intake were similar to those with total fat. Overall, percentage of energy from saturated fat showed no association with pancreatic cancer risk. Separate analyses for saturated fat from meat and from dairy sources showed positive associations between the risk for pancreatic cancer and fat from red meat and processed meat and essentially no association with fat from dairy products. Saturated fat from meat, measured in terms of energy percentage, was associated with a 50% increase in pancreatic cancer risk, comparing the highest quintile of intake with the lowest. Median cholesterol intake in the cohort was 193 mg/day. Neither absolute nor relative cholesterol intake was statistically significantly related to pancreatic cancer risk, and no statistically significant trend was seen across quintiles. The same associations for trends were seen in analyses using calibration-corrected nutrient intakes as in analyses using uncorrected measurements (Table 3).

We also conducted an analysis based on estimated intake of nitrosamine, the major contributor to which was processed meat. Although there was a statistically significant association between nitrosamine intake and pancreatic cancer risk (relative risk = 1.26, 95% confidence interval = 1.01 to 1.56, for the fifth versus the first quintile), the trend was not statistically significant ($P = .29$). Finally, we found no evidence for an interaction between the meat food groups and smoking on the risk of pancreatic cancer (data not shown).

Discussion

This analysis of incident exocrine pancreatic cancer cases in a multiethnic population showed red meat and processed meat

consumption to be strong risk factors for the disease, associated with 50% and 70% increases in risk across quintiles, respectively. The effect seemed to be independent of energy intake. Because the analysis of total fat and saturated fat intakes showed a statistically significant increase in risk only for meat sources, rather than overall and for dairy sources, fat is more likely to be an indicator of meat consumption than to be directly involved in the underlying carcinogenic mechanism. Cholesterol intake was not related to pancreatic cancer risk.

To date, seven prospective studies have investigated associations between consumption of various meats and pancreatic cancer *(13–16,21–23)*. Two found statistically significant positive associations with disease risk *(22,23)*, whereas four reported no associations *(13–16)* and one found a decreased risk with pork and sausage consumption *(21)*. All of these studies except one *(13)* included fewer than 200 pancreatic cancer patients or used limited dietary assessment methods covering only a few food items *(13,15,21–23)*. Two cohort studies, the Nurses' Health Study (NHS) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort (ATBC study), that used comprehensive dietary assessments and reported null findings for meat intake also analyzed intake of fats as an exposure variable. Findings from the NHS *(14)* were null for fat or fatty acid intakes and disease risk, whereas results from the ATBC study showed increases in risk with saturated fat intake and butter consumption *(16)*. Dairy product and egg consumption also were studied prospectively in two studies *(14,15)*, but no association with pancreatic cancer was found. Because these studies were undertaken in selected study populations, i.e., nurses and male smokers, the findings might not be completely generalizable. It is also possible that the different results of our study and the NHS and ATBC study reflect different patterns of meat consumption in the three cohorts. For example, Caucasian men and women in our study ate less red meat, especially pork, and more poultry than those in the NHS and ATBC study.

Case–control studies of meat consumption and pancreatic cancer have also yielded inconsistent findings. Seven case–control studies reported a positive association between intake of different kinds of meat and pancreatic cancer *(24–31)*, whereas four case–control studies did not *(32–35)*. The positive associations were found for different meat items or groups: all meat *(26,28,30,31)*, red meat *(24)*, beef *(26,27,29)*, pork *(25,29)*, pork products *(25,30)*, and chicken *(26)*. Studies investigating the association of the intake of various dairy products with pancreatic cancer risk generally found no convincing associations *(26,29,34,35)*. One study reported an increased risk of pancreatic cancer among men only *(25)*, and another reported a decrease in risk with the consumption of fermented milk products *(32)*. Associations with fat intake have also been investigated in five case–control studies, all of which found no association *(26,35–38)*. For cholesterol, three of seven case–control studies showed statistically significantly increased risks with increasing intake *(36,38,39)*, whereas four studies reported null findings *(26,32,35,37)*. An increased risk with cholesterol intake in one study was assumed to be due to higher consumption of eggs among case patients than among control subjects *(39)*.

In addition to total and saturated fat intake, exposure to mutagenic compounds produced during the cooking or preservation process has been considered as a possible explanation for the link between consumption of red meat and processed meat and pancreatic cancer risk. Heterocyclic amines are formed when meats are cooked at high temperatures, and polycyclic aromatic hydrocarbons are formed when meats are charcoal broiled or grilled *(40,41)*. Both classes of compounds have been shown to be carcinogenic in animals *(42)* and could account for the red meat association. N-nitroso compounds, which are found in nitrite-preserved meats or produced endogenously in the stomach when such meats are consumed, might underlie the positive association between processed meat consumption and pancreatic cancer risk *(4,31)*. Research into associations between meat preparation methods and cancer has been carried out mainly in the setting of colorectal cancer *(43)*, but a few case–control studies of pancreatic cancer are also available. Anderson et al. *(24)* found an increased risk of pancreatic cancer related to consumption of grilled or barbecued red meat but no statistically significant associations with meats prepared in other ways. Other studies have reported increased pancreatic cancer risks with the consumption of fried, grilled, cured, or smoked meats or foods *(28,31,33)*. Intake of meat that was not fried, grilled, cured, or smoked was not associated with cancer risk *(28,33)*, suggesting the possible role of polycyclic aromatic hydrocarbons, heterocyclic amines, or nitrosamines formed during these cooking or preserving processes. Because fat, saturated fat, and cholesterol do not seem to be responsible for the increased risk of pancreatic cancer we observed with increasing intake of red meat or processed meat, our results also support the hypothesis that preparation methods such as grilling, frying, or curing play a role in the etiology of the disease. The findings for nitrosamines in our study to some extent affirm this theory; because detailed information about preferences for doneness and preparation methods of meat have been obtained in a more recent follow-up questionnaire on the Multiethnic Cohort Study subjects, further pursuit of this hypothesis will be undertaken in the future.

There are some potential limitations to this analysis. The study population is from Hawaii and California only. However, the cohort was population based in design to maximize the generalizability of findings to the U.S. population *(10)*. Also, the use of frequency questionnaires as assessment instruments can cause diet to be measured with error *(44)*, and measurement error is certainly present in our data. We attempted to minimize this limitation by rigorous design of the questionnaire; by emphasizing nutrient densities in the analyses, which resulted in better correlations between the food frequency questionnaire and more accurate comparison measurements of dietary intake *(19,20)*; and by incorporating calibration-adjusted nutrient variables into the analyses. The use of densities results in another possible limitation to the study, in that associations based on absolute intakes could differ. However, when we analyzed the data using absolute amounts, the findings were similar. Another potential limitation relates to the fact that our efforts to correct for nutrient measurement errors were probably incomplete because the 24-hour dietary recall method used as a standard was no doubt imperfect *(20)*. Nevertheless, this adjustment should result in relative risks closer to the true value. We found that the effect of calibration was negligible. Another possible limitation pertains to the findings of statistically significant associations with foods but not nutrients. Although measurement error could be greater for nutrients than foods, it should be noted that our foods incorporated broad categories composed of many different items, each of which might have been measured with some error. Also, a statistically significant association was found for fat from meat

but not fat from dairy products, and there is no reason to suspect that the measurement error for these two fat sources would be substantially different. Another limitation could result from the fact that we adjusted our analyses for diabetes mellitus as a confounding factor. Both red meat and processed meat intake have been positively associated with diabetes mellitus *(45–47)*, which itself is considered as a risk factor for pancreatic cancer *(8)*; therefore, diabetes mellitus could be an intermediate rather than a confounding factor. If so, adjusting for it could have distorted the observed associations. However, after exclusion of all participants with self-reported diabetes mellitus from the analysis, red meat and processed meat were still statistically significantly positively associated with pancreatic cancer in our study (data not shown).

Our study also has several strengths. One is the large sample size, which resulted in the largest number of incident pancreatic cancer patients yet analyzed in a prospective study and therefore considerable statistical power. With 482 cancer patients, this study had an 80% power to detect as statistically significant a monotonic trend in risk across quintiles, with a relative risk in the highest quintile of 1.44, using a critical value of 0.05. Second, the prospective design ruled out the problem of recall bias, which can influence the findings from case–control studies. Third, due to the multiethnic background of the participants, the cohort included considerable dietary heterogeneity, facilitating the identification of meaningful associations. Indeed, keeping in mind the fact that comparisons between studies have to be made cautiously owing to the different dietary assessment protocols, the ranges across quintiles were large when compared with the corresponding ranges for the NHS *(14)* and the ATBC study *(16)*, although the absolute intake of meat and fat was relatively low in our population. Fourth, unlike many earlier studies, the food frequency questionnaire used was quantitative and comprehensive and therefore permitted adjustment for energy intake.

In conclusion, our findings suggest that intakes of red meat and processed meat are positively associated with pancreatic cancer risk and thus are potential target factors for disease prevention. The results raise the possibility that individuals might reduce their risk of pancreatic cancer by reducing consumption of red and processed meat. The age-adjusted incidence rates were 20.2 versus 41.3 and 28.1 versus 42.7 per 100 000 persons per year for the lowest versus the highest quintile of processed meat and red meat intakes, respectively. However, because the fat components of the meats did not seem to account for the findings, other compounds in these foods that are responsible for the association need to be identified. Future analyses of meat and pancreatic cancer risk should focus on meat preparation methods and related carcinogens.

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NOTES

This work was supported in part by grant R37 CA054281 from the National Cancer Institute, U.S. Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the agency.

Manuscript received March 4, 2005; revised July 22, 2005; accepted August 8, 2005.