Research Article

Cancer Epidemiology, Biomarkers & Prevention

Total Nut, Tree Nut, Peanut, and Peanut Butter Consumption and the Risk of Pancreatic Cancer in the Netherlands Cohort Study

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Abstract

Background: Nut intake has been associated with decreased cancer-related mortality, but few studies have examined the potential of nuts in the chemoprevention of pancreatic cancer. We prospectively investigated the association of total nut, tree nut, peanut, and peanut butter consumption with pancreatic cancer risk.

Methods: In the Netherlands Cohort Study, 120,852 men and women completed a baseline questionnaire, including a food frequency questionnaire, in 1986. After 20.3 years of follow-up, 583 incident pancreatic cancer cases, including 349 microscopically confirmed pancreatic cancer (MCPC) cases, were included in multivariable case–cohort analyses.

Results: Increased total nut consumption was associated with a nonsignificantly decreased MCPC risk in men [HR (95% confidence interval) for 10+ g/d vs. nonconsumers = 0.72 (0.47–1.11), $P_{trend} = 0.163$]. No clear association was found in women. For tree nut and peanut consumption, nonsignificant inverse associations were observed in men. In women, no or unclear associations were found for tree nut and peanut consumption. Peanut butter intake was related to a significantly reduced risk of MCPC in men [HR (95% confidence interval) for 5+ g/d vs. nonconsumers = 0.53 (0.28–1.00), $P_{trend} = 0.047$], but this relation was not clear in women. Evidence for a nonlinear dose–response relation with MCPC was found for tree nut intake only. The associations were weaker when looking at total pancreatic cancer.

Conclusions: Our results suggest that nuts and peanut butter might reduce pancreatic cancer risk in men. In women, no or unclear associations were found.

Impact: Nut consumption might reduce the risk of pancreatic cancer in men. *Cancer Epidemiol Biomarkers Prev; 27(3); 274–84. ©2018 AACR.*

Introduction

In 2012, pancreatic cancer was the 7th leading cause of cancer-related mortality worldwide, whereas its incidence ranked 12th of all cancers (1). Overall 5-year survival rates are estimated to be 8%, but only 2% for patients with metastasized disease (2). These low survival rates are due to the fact that the early disease stages usually are asymptomatic. Consequently, patients are often diagnosed when at an advanced stage of pancreatic cancer when curative surgical resection is not always possible (2–4). Moreover, no screening tests are available currently (4). Therefore, preventive strategies are urgently needed.

In literature, several modifiable lifestyle and dietary factors, such as smoking, obesity, and alcohol and red meat consumption, are suggested to increase pancreatic cancer risk, whereas a diet rich in vegetables, fruits, and whole grains might contribute to its prevention (5, 6). Nuts represent another food group that has been investigated for its potential cancer-chemopreventive activities, because recent meta-analyses have shown that increased nut consumption might decrease cancer risk and cancer-related mortality (7–10).

Nuts contain numerous bioactive compounds such as vitamin B6 and E, folate, selenium, fiber, mono- and polyunsaturated fatty acids, and many polyphenols (11, 12). Although the exact biological mechanism by which nuts might reduce pancreatic cancer risk has yet to be elucidated, possible mechanisms suggested in literature mainly relate to their anti-oxidant, anti-inflammatory, and immune-modulating activities (6, 13–15). Moreover, bioactive compounds in nuts might contribute to normal cell differentiation and DNA repair mechanisms, reduced tumor initiation and promotion, reduced angiogenesis, and induced apoptosis (6, 13–15). In addition, nut consumption might beneficially affect obesity, type 2 diabetes mellitus, and pancreatitis, which are well-known risk factors for pancreatic cancer (5, 6, 15).

To our knowledge, only two studies have investigated the association between nut consumption and pancreatic cancer risk in humans (16, 17). In a case–control study, no statistically significant relation was found between the consumption of "nuts and tasty snacks" and pancreatic cancer risk (16). Because nuts and tasty snacks were analyzed together as exposure variable, it is not possible to draw conclusions from this study for nut consumption alone. In a prospective cohort study, a significant inverse association was found between nut consumption frequency and pancreatic cancer risk (17). Nevertheless, this

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study was limited to women. Furthermore, little is known about whether the relation with pancreatic cancer risk differs between tree nuts, peanuts, and peanut butter.

In the present study, we investigated the association of total nut, tree nut, peanut, and peanut butter intake with the risk of pancreatic cancer in both men and women in the Netherlands Cohort Study on Diet and Cancer (NLCS).

Materials and Methods

Study design and population

The current study was performed within the NLCS, a prospective cohort study in the Netherlands initiated on September 17, 1986, to assess the relation between diet and cancer. Details of this study are reported elsewhere (18). In short, 120,852 males and females ages 55 to 69 years from 204 Dutch municipalities with computerized population registries were included. For efficiency reasons, a case-cohort design was used for data processing and analyses, by randomly sampling 5,000 participants from the total cohort at baseline to create a subcohort. Cancer cases were obtained from the total cohort, whereas person-years at risk were calculated in the subcohort as an estimation of the total person-years at risk in the entire cohort.

At baseline, participants completed a self-administered 11-page questionnaire, including a 150-item semiquantitative food frequency questionnaire (FFQ), on cancer risk factors. By filling in and returning the baseline questionnaire, participants agreed to participate in the NLCS. The entire cohort was followed up for cancer incidence during the subsequent 20.3 years (baseline until December 31, 2006) through annual record linkage to the Netherlands Cancer Registry and the Dutch National Database of Pathology Reports (PALGA; ref. 19). Cancer incidence follow-up is estimated to be at least 96% complete (20). Data on vital status of subcohort members were 100% complete after 20.3 years of follow-up. The institutional review boards of the Netherlands Organization for Applied Scientific Research TNO (Zeist) and Maastricht University (Maastricht) approved the NLCS. The NLCS was conducted in accordance with the Declaration of Helsinki.

The study population used in this analysis consisted of all subcohort members and incident pancreatic cancer cases (ICD-O-3 code C25), except for endocrine subtypes (ICD-O3 code C25.4), diagnosed during the follow-up period. Endocrine subtypes were excluded because of their different etiology and rarity. Cases were diagnosed by microscopic confirmation or physician diagnosis, which was made based on either clinical symptoms, physical examination, or imaging results.

Subcohort members and incident exocrine pancreatic cancer cases from the entire cohort were included if they had no prevalent cancer at baseline other than skin cancer. This resulted in 4,774 subcohort members and 763 pancreatic cancer cases, including 454 microscopically confirmed pancreatic cancer (MCPC) cases. Participants were then excluded if they had left more than 60 items or at least one item block of the FFQ blank, or if they had eaten less than 35 food items at least once per month. Subjects with missing data on confounding variables were excluded as well. Figure 1 presents a flow diagram of the number of subcohort members and cases on whom the analysis was based. In total, 3,759 subcohort members (78.7% of 4,774) and 583 pancreatic cancer cases (76.4% of 763), including 349 MCPC cases (76.9% of 454), were available for analysis.

Exposure measurement

The baseline questionnaire measured smoking habits, physical activity, anthropometry, disease history, dietary intake, and other cancer risk factors. The FFQ assessed information about habitual diet in the preceding year, including the consumption of "peanuts," "other nuts, mixed nuts" (tree nuts), and "peanut butter." The consumption frequency could range from "never or less than 1×/month" to "6–7×/week." In addition, participants could fill in the number of standard portion sizes they consumed per intake. For tree nuts and peanuts, a standard portion size was 28 grams. A standard portion size of peanut butter, a particularly popular spread in the Netherlands, was 15 grams per slice of bread. Consumption frequencies and portion sizes were multiplied to calculate mean daily intakes in grams. Total nut consumption was calculated as the sum of peanuts and tree nuts. To prevent observer bias, NLCS-personnel was blinded to the case/subcohort status of the participants during the entry, coding, and interpretation of the questionnaire data.

Statistical analysis

The relation between nut and peanut butter consumption and pancreatic cancer risk was investigated with Cox proportional hazards models to estimate age- and sex-adjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI). Person-years at risk were calculated in the subcohort from the date of entry in the cohort (September 17, 1986) until pancreatic cancer diagnosis or censoring. Participants were censored in the case of loss to follow-up, death, migration, or end of follow-up (December 31, 2006), whichever occurred first.

To compare energy-adjustment methods, multivariable-adjusted models including daily total energy intake were compared to nutrient density models. Because the results of these models were similar, we present only those obtained from the first method.

Confounders were selected on the basis of literature and earlier pancreatic cancer analyses in the NLCS (21–29), and were defined as those variables that were related to both the exposure and outcome. Predefined confounders, which were included in the final model irrespective of their effect on the estimates, were: age (years; continuous); sex (men/women; in the analyses for the total population); cigarette smoking [status (never/former/current), frequency (n/d; continuous, centered), and duration (years; continuous, centered)]; body mass index (BMI; kg/m^2; continuous); family history of pancreatic cancer (no/yes); history of diabetes (no/yes); educational level [primary school or lower vocational education (low)/secondary school or medium vocational education (medium)/university or higher vocational education (high)]; total energy intake (kcal/d; continuous) and alcohol consumption (g/d; continuous). Potential confounders considered were height; nonoccupational physical activity; history of gallstones, cholecystectomy, gastric ulcers, hypertension, and hepatitis; intake of fruit, vegetables, red meat, and coffee; and nutritional supplement use. A variable was regarded as a confounder if it changed the HR with at least 10% when using a backward stepwise selection procedure. On the basis of this procedure, only the predefined confounders were included in the final multivariable-adjusted model.

All analyses were performed for males and females separately and for the total population, for total pancreatic cancer (non-MCPC and MCPC combined) and for MCPC alone. The restriction to MCPC cases was performed to obtain a higher degree of

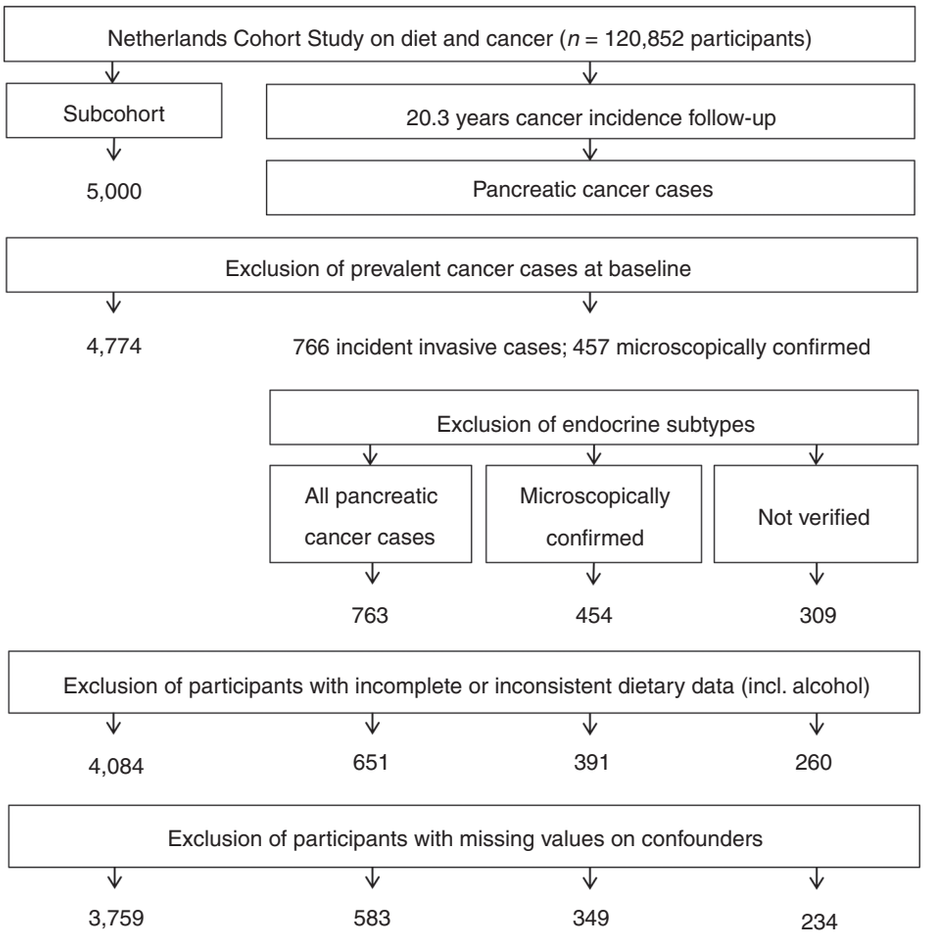

Figure 1.
Flow diagram of the number of subcohort members and cases on whom the analyses were based.

diagnostic certainty, because cases without histological confirmation may reflect other types or nonpancreatic cancers (29).

Total nut, tree nut, peanut, and peanut butter intakes were analyzed separately on a categorical and continuous scale. For the categorical analyses, nut and peanut butter consumption were categorized as follows: 0, 0.1–<5, 5–<10, 10+ g/d for total nuts and peanuts and 0, 0.1–<5, 5+ g/d for tree nuts and peanut butter, because of the smaller numbers of cases in the higher intake categories. The lowest intake category was regarded as the reference group. Linear trends between nut and peanut butter consumption categories and pancreatic cancer risk were evaluated with Wald tests, after fitting median values of nut consumption per intake category as continuous terms in the regression models. Median values were based on the distribution of the variables in the subcohort. For continuous analyses, an increment of five grams per day was chosen.

Standard errors were calculated using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the cohort (30). The validity of the proportional hazard assumption was checked for each covariate based on scaled Schoenfeld residuals (31), by visual inspection of log-minus-log survival plots, and by including time-covariate interactions into the models. The statistical significance of these interaction terms was evaluated with the Wald test. No violations were found for the exposure variables. In cases where the proportional hazards assumption was violated for confounders, time-varying covariates were kept in the model.

To further investigate the dose–response relations between nut consumption and pancreatic cancer risk, restricted cubic splines with three fixed knots (0, 5, and 10 g/d) were used to graphically present the dose-response curves without making a priori assumptions about their shapes. Wald tests were performed to evaluate the linearity of these relations.

Possible interactions with other pancreatic cancer risk factors were evaluated by analyzing total nut consumption and pancreatic cancer risk in strata of the following factors: baseline BMI (18.5–<25/≥25 kg/m^2), smoking status (never/former/current), alcohol consumption (0/0.1–<15/≥15 g/d), and educational level (low/medium/high). Interactions with these factors were tested by including cross-product terms in the Cox regression models and performing Wald tests.

All *P*-values were two-sided and were considered statistically significant if smaller than 5%. Analyses were performed using Stata software (Version 14.0; StataCorp).

Sensitivity analyses

As additional analyses, associations of tree nut, peanut, and peanut butter consumption with pancreatic cancer risk were mutually adjusted. The analyses were also repeated with non-consumers of both nuts and peanut butter as the reference

category. To check for potential reversed causation, median nut consumption of cases diagnosed in the first 2 years of follow-up was compared with the median nut intake of cases diagnosed later in time. Subsequently, Kruskall-Wallis tests were performed to test whether these were significantly different. In addition, a subgroup analysis was performed in which pancreatic cancer cases diagnosed in the first 2 years of follow-up were excluded. In another subgroup analysis, respondents with diabetes were excluded. Moreover, analyses of peanut butter consumption were repeated, restricted to respondents who had stated having had a constant peanut butter intake during the 5 years before baseline. Unfortunately, these data were unavailable for total nut, tree nut, and peanut consumption.

Additional adjustment was performed for adherence to the Mediterranean diet as measured with the alternate Mediterranean diet (aMed; ref. 32) score. Because nuts comprise one of the components of the aMed score and because alcohol consumption is positively associated with pancreatic cancer risk, an adapted version was used (excluding nuts and alcohol), which ranged from 0 (no adherence) to 7 (maximal adherence; ref. 33).

To determine the sensitivity of the nonparametric response curves to assumptions regarding the number and placement of knots, detailed cubic spline regression analyses were performed. In these, the performance of three additional models [(i) three fixed knots: 0, 1, and 5 g/d, (ii) percentiles: 10^{th}, 50^{th}, and 90^{th} percentiles, and (iii) four fixed knots: 0, 1, 5, and 10 g/d] were compared with the model with three fixed knots (0, 5, and 10 g/d) using the Akaike Information Criterium (AIC; ref. 34).

An array approach sensitivity analysis (35) was performed to determine how strong and imbalanced unmeasured confounders would have to be to alter the association between total nut consumption and pancreatic cancer risk.

Results

Mean total nut consumption (SD) in the subcohort was 8.0 (14.1) g/d in men and 4.3 (8.4) g/d in women. For tree nut, peanut, and peanut butter, these values were 1.0 (3.4), 7.0 (13.3), and 1.4 (4.2) in men and 1.1 (3.9), 3.3 (6.9), and 1.2 (3.6) in women, respectively. The percentages of men in the subcohort, among all pancreatic cancer cases, and among MCPC cases were 49.2%, 51.1%, and 53.9%, respectively. Table 1 presents baseline characteristics, stratified by gender. Participants with a higher nut intake were younger, higher educated, less frequently hypertensive, had a higher total energy intake, consumed more alcohol and fruit, and used nutritional supplements more often. Females who consumed more nuts were leaner and more often ever smokers, consumed more vegetables and red meat, less often reported a history of gallstones or cholecystectomy, and those in the highest consumption category were less likely to be diabetic. Males with a higher nut intake were less likely to report a history of gastric ulcers or a positive family history of pancreatic cancer.

Table 2 shows the age- and sex-adjusted and multivariable-adjusted HRs for total pancreatic cancer according to total nut, tree nut, peanut, and peanut butter consumption in men and women separately and in the total population. In multivariable-adjusted analyses, increasing total nut intake was associated with a nonstatistically significant decreasing risk of total pancreatic cancer in men [HR (95% CI) for 10+ g/d vs. nonconsumers = 0.71 (0.50–1.03), $P_{trend} = 0.097$]. No association was found in women and a nonstatistically significant inverse association in the total population. For tree nuts and peanuts, also nonstatistically

Table 1. Baseline characteristics [mean (SD) or percent] according to total nut intake in male and female subcohort members

	Men				Women			
	Total nut intake (g/d; median)				Total nut intake (g/d; median)			
	0 (0.0)	0.1–<5 (2.5)	5–<10 (8.5)	10+ (21.4)	0 (0.0)	0.1–<5 (2.1)	5–<10 (7.8)	10+ (15.7)
n[a]	584	596	236	434	773	692	214	230
Age (y)	61.8 (4.4)	61.2 (4.1)	60.8 (4.3)	60.5 (4.0)	62.2 (4.3)	61.1 (4.2)	60.1 (4.0)	60.7 (3.9)
BMI (kg/m^2)	25.0 (2.7)	24.8 (2.4)	24.9 (2.6)	25.0 (2.5)	25.3 (3.8)	25.1 (3.4)	24.3 (3.2)	24.5 (3.3)
Height (cm)	175.7 (6.6)	176.9 (6.4)	177.5 (6.5)	176.8 (6.8)	165.0 (6.4)	165.5 (5.8)	165.6 (6.0)	165.9 (6.2)
Ever cigarette smokers (%)	86.8	84.7	85.2	88.5	37.8	39.5	48.1	49.1
University or higher vocational education (%)	15.8	19.1	24.6	25.1	6.1	10.8	14.0	12.6
Nonoccupational physical activity (min/d)	83.0 (72.2)	82.1 (66.6)	71.1 (56.8)	82.3 (66.8)	63.4 (54.1)	67.2 (48.6)	72.5 (55.6)	61.0 (37.1)
Family history of pancreatic cancer (%)	1.5	0.3	0.9	0.7	1.0	1.0	0.5	1.3
History of diabetes (%)	4.5	2.4	3.8	2.8	3.5	3.8	3.3	0.9
History of gallstones (%)	5.5	4.9	5.1	4.8	15.8	14.2	12.2	9.1
History of cholecystectomy (%)	4.3	4.4	4.7	4.4	15.4	12.6	9.8	10.0
History of gastric ulcer (%)	13.9	11.2	11.0	11.1	5.8	4.2	1.4	3.5
History of hypertension (%)	25.3	24.5	24.2	22.8	32.3	27.0	23.8	25.2
History of hepatitis (%)	9.3	12.3	13.1	11.3	12.9	16.2	17.3	13.5
Food intake								
Energy (kcal/d)	2,100 (528)	2,080 (462)	2,212 (469)	2,353 (466)	1,594 (375)	1,672 (370)	1,785 (411)	1,922 (360)
Alcohol (g/d)	13.0 (16.7)	13.4 (16.4)	16.7 (18.5)	19.1 (16.8)	4.9 (9.4)	5.9 (8.8)	7.1 (9.4)	8.8 (11.1)
Fruit (g/d)	148.4 (114.2)	155.0 (102.5)	166.3 (134.3)	163.0 (120.5)	184.4 (120.6)	197.3 (112.5)	206.7 (119.3)	210.5 (123.8)
Vegetables (g/d)	187.1 (81.5)	187.3 (70.4)	188.0 (75.6)	186.0 (73.5)	182.9 (74.5)	195.1 (76.3)	200.5 (73.8)	204.6 (72.7)
Red meat (g/d)	94.1 (45.8)	91.9 (39.0)	92.9 (35.9)	95.4 (41.7)	79.8 (39.5)	80.6 (35.4)	81.0 (37.8)	83.5 (38.8)
Coffee (g/d)	572.1 (333.4)	563.8 (263.5)	549.5 (256.7)	586.6 (252.5)	494.1 (254.9)	506.1 (238.7)	502.2 (246.1)	500.4 (213.5)
Nutritional supplement user (%)	21.9	22.5	27.1	25.4	34.2	36.9	38.8	44.8

[a]Number of subcohort members excluding participants with incomplete or inconsistent dietary data (including alcohol consumption) or missing values on predefined confounder variables.

Table 2. Age- and sex-adjusted and multivariable-adjusted HRs (and 95% CIs) for total pancreatic cancer according to nut consumption; NLCS, 1986–2006

	Median intake[a]		Men				Women				Total population	
Food item	Men	Women	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted HR[c] (95% CI)
Total nuts (g/d)												
0	0.0	0.0	8,888	108	1.00 (reference)	1.00 (reference)	13,527	115	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	2.5	2.1	9,675	94	0.80 (0.59–1.09)	0.85 (0.62–1.17)	12,389	108	1.10 (0.83–1.45)	1.11 (0.83–1.49)	0.94 (0.77–1.16)	0.98 (0.79–1.22)
5–<10	8.5	7.8	3,951	37	0.78 (0.52–1.17)	0.78 (0.50–1.19)	3,883	26	0.91 (0.57–1.44)	0.89 (0.54–1.44)	0.84 (0.62–1.15)	0.85 (0.62–1.16)
10+	21.4	15.7	7,124	59	0.71 (0.50–1.00)	0.71 (0.50–1.03)	4,280	36	1.09 (0.72–1.63)	0.98 (0.63–1.50)	0.85 (0.65–1.11)	0.84 (0.63–1.11)
P_{trend}					0.097	0.097			0.912	0.679	0.223	0.165
Continuous, per 5 g/d increment					0.96 (0.91–1.01)	0.95 (0.90–1.01)			1.00 (0.93–1.07)	0.97 (0.90–1.06)	0.97 (0.93–1.01)	0.96 (0.92–1.01)
Tree nuts (g/d)												
0	0.0	0.0	21,393	239	1.00 (reference)	1.00 (reference)	23,847	204	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	1.6	1.6	6,704	48	0.64 (0.46–0.89)	0.68 (0.48–0.95)	8,365	71	1.03 (0.77–1.38)	1.02 (0.74–1.39)	0.83 (0.66–1.03)	0.86 (0.69–1.08)
5+	8.6	8.9	1,541	11	0.64 (0.34–1.21)	0.66 (0.34–1.26)	1,866	10	0.67 (0.34–1.29)	0.63 (0.32–1.24)	0.65 (0.41–1.03)	0.65 (0.41–1.04)
P_{trend}					0.077	0.106			0.262	0.206	0.038	0.051
Continuous, per 5 g/d increment					0.85 (0.62–1.17)	0.86 (0.63–1.18)			0.98 (0.77–1.24)	0.96 (0.75–1.24)	0.92 (0.75–1.13)	0.93 (0.75–1.14)
Peanuts (g/d)												
0	0.0	0.0	9,995	114	1.00 (reference)	1.00 (reference)	15,936	136	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	2.5	2.1	10,542	104	0.88 (0.66–1.18)	0.92 (0.68–1.24)	12,635	102	1.03 (0.78–1.35)	1.05 (0.79–1.40)	0.96 (0.78–1.17)	0.99 (0.80–1.22)
5–<10	8.5	8.5	3,285	29	0.81 (0.52–1.25)	0.77 (0.49–1.21)	2,556	24	1.26 (0.78–2.04)	1.11 (0.67–1.84)	0.99 (0.71–1.37)	0.94 (0.67–1.31)
10+	21.4	17.1	5,816	51	0.81 (0.56–1.16)	0.82 (0.56–1.19)	2,951	23	1.01 (0.62–1.63)	0.94 (0.57–1.55)	0.89 (0.67–1.19)	0.88 (0.65–1.19)
P_{trend}					0.303	0.293			0.742	0.885	0.491	0.372
Continuous, per 5 g/d increment					0.96 (0.91–1.02)	0.96 (0.91–1.02)			1.00 (0.92–1.08)	0.97 (0.88–1.06)	0.97 (0.93–1.02)	0.96 (0.92–1.01)
Peanut butter (g/d)												
0	0.0	0.0	21,202	216	1.00 (reference)	1.00 (reference)	24,879	209	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	1.2	1.2	5,164	61	1.21 (0.89–1.66)	1.24 (0.89–1.72)	5,967	54	1.13 (0.82–1.56)	1.11 (0.79–1.55)	1.17 (0.94–1.47)	1.19 (0.95–1.51)
5+	9.6	6.9	3,272	21	0.66 (0.41–1.06)	0.66 (0.41–1.08)	3,232	22	0.85 (0.53–1.37)	0.86 (0.53–1.39)	0.74 (0.53–1.04)	0.75 (0.53–1.05)
P_{trend}					0.079	0.095			0.553	0.566	0.083	0.095
Continuous, per 5 g/d increment					0.93 (0.77–1.11)	0.93 (0.77–1.13)			0.91 (0.74–1.12)	0.90 (0.73–1.11)	0.92 (0.80–1.06)	0.92 (0.80–1.06)

[a]Median intake in the subcohort.

[b]Adjusted for age (years; continuous); cigarette smoking [status (never/former/current), frequency (n/d; continuous, centered) and duration (years; continuous, centered)]; BMI (kg/m^2; continuous); family history of pancreatic cancer (no/yes); history of diabetes (no/yes); educational level (low/medium/high); total energy intake (kcal/d; continuous) and alcohol consumption (g/d; continuous).

[c]Adjusted for [b] and sex (male/female).

significant decreasing risks were found with increasing intake in men (P_{trend} = 0.106 and 0.293, respectively), and a statistically significant reduced risk for the category of 0.1–<5 g tree nut consumption/day compared to nonconsumers [HR (95% CI) = 0.68 (0.48–0.95)]. In women, tree nut consumption was not associated with total pancreatic cancer risk. When looking at the results of both the categorical and continuous analyses, the relation for peanut intake was not clear in women. In the total population, nonstatistically significant inverse associations were found for tree nut and peanut intake. Because the number of cases in the highest intake category of tree nuts was small in both sexes, categories were merged into consumers (0.1+ g/d) and nonconsumers. The HR (95% CI) for total pancreatic cancer for tree nut consumers versus nonconsumers was 0.67 (0.49–0.92) in men and 0.95 (0.70–1.28) in women. Associations for peanut butter intake were not clear.

Table 3 presents the HRs for MCPC according to nut and peanut butter consumption. Overall, associations with nut consumption categories were stronger when cases were restricted to MCPC cases, and some became significant in men. Increased total nut consumption was associated with a nonsignificantly decreased MCPC risk in men (P_{trend} = 0.163). Although intake of 5–<10 g total nuts/day was related to a significantly reduced risk in men [HR (95% CI) = 0.56 (0.32–0.99)], intake of 10+ g/d was not. No clear association was found for total nut consumption in women, and a nonsignificant inverse trend in the total population. For tree nut and peanut consumption, nonsignificant inverse associations were observed in men (P_{trend} = 0.214 and 0.407, respectively), although peanut consumption of 5–<10 g/d compared with nonconsumption was associated with a significantly reduced risk [HR (95% CI) = 0.44 (0.23–0.85)]. In women, no association was found for tree nut consumption and no clear association for peanut consumption. In the total population, nonsignificant inverse trends were found for both tree nuts and peanuts. When comparing tree nut consumers (0.1+ g/d) to nonconsumers, the HR (95% CI) for MCPC was 0.68 (0.47–1.00) in men and 0.89 (0.60–1.33) in women. Peanut butter intake was related to a significantly reduced MCPC risk in men [HR (95% CI) for 5+ g/d vs. nonconsumers = 0.53 (0.28–1.00), P_{trend} = 0.047], but this relation was not clear in women and in the total population.

Because of the higher diagnostic certainty and the, in general, stronger associations in MCPC cases, subsequent analyses were performed using this case definition.

No significant interaction was observed between gender and total nut intake (Table 4, $P_{interaction}$ = 0.377). For the nut types separately, no significant interactions with gender were found either. For this reason, and to increase statistical power, men, and women were combined in subsequent analyses. In restricted cubic spline analyses, evidence for a nonlinear dose–response relation was found for tree nut intake ($P_{nonlinearity}$ = 0.005), but not for total nut, peanut, and peanut butter intake ($P_{nonlinearity}$ = 0.669, 0.598, and 0.778, respectively). In both sexes combined, MCPC risk was significantly decreasing with increasing tree nut intake from 0.1 to 7.5 g/d, but this association weakened somewhat for intakes above 7.5 g/d. Increasing total nut, peanut, and peanut butter intake were associated with a nonsignificantly decreasing MCPC risk. In Fig. 2, nonparametric regression curves are shown.

Table 4 presents the associations between total nut consumption and MCPC risk in strata of potential effect modifiers. To increase statistical power, the two highest intake categories were merged. No significant interactions were found for any of the potential effect modifiers: *P* values for interaction were ≥0.082. In most subgroups, associations were inverse or not clear, although significant inverse trends were found in men, in participants with a normal BMI (18.5–<25 kg/m^2), and in former smokers.

Mutual adjustment for tree nut, peanut, and peanut butter did not importantly alter the results for the associations with total pancreatic cancer and MCPC, and neither did choosing nonconsumers of both nuts and peanut butter as the reference category. Median total nut, tree nut, peanut, and peanut butter intake of MCPC cases diagnosed in the first 2 years of follow-up were similar to the intakes of MCPC cases diagnosed later in time ($P \geq$ 0.233). Exclusion of patients diagnosed during the first two years of follow-up did not importantly alter the results. Excluding respondents with diabetes at baseline gave comparable results as well. Repeating the analyses of peanut butter consumption, restricted to participants who had stated having had a constant intake of peanut butter during the 5 years before baseline, gave similar results as when all participants were included. Additional adjustment for the adapted aMed score did not essentially alter the results.

The sensitivity analyses regarding the assumptions in restricted cubic spline analyses showed that including an additional knot or using different knot positions did not improve the performance of the model with three fixed knots at 0, 5, and 10 g nut intake/day, as measured with the AIC score.

For the array approach sensitivity analysis, the observed HR for MCPC was set at 0.78 (HR for 5+ g total nut consumption/day vs. nonconsumers in males and females combined, Table 4) and the prevalence of the unmeasured confounder among nonconsumers at 0.3. The analysis showed that the true, adjusted HR would exceed the value of one if the prevalence of the unmeasured confounder in the category of 5+ g total nut consumption/day were ≤0.1 and the HR for MCPC according to the unmeasured confounder ≥2.0, or if the prevalence were ≥0.5 and the HR ≤0.5 (Supplementary Fig. S1). Nevertheless, most estimates of the adjusted HR were smaller than 1.0.

Discussion

In this large prospective cohort study, we have found nonsignificant inverse trends between total nut, tree nut, and peanut consumption and microscopically confirmed pancreatic cancer risk in males, but no or unclear associations in females. Increased peanut butter consumption was related to a significantly reduced MCPC risk in men, whereas this association was not clear in women. These associations were weaker in both genders when looking at total pancreatic cancer. Evidence for a nonlinear dose–response relation with MCPC was found for tree nut intake only. Furthermore, no significant interactions between total nut consumption and potentially effect modifying pancreatic cancer risk factors were identified.

The restriction to MCPC cases resulted in stronger associations between nut consumption and pancreatic cancer risk. This finding indicates that a lack of microscopic confirmation might have led to disease misclassification and to an attenuation of the results towards the null. Therefore, restriction to MCPC cases should be preferred.

Table 3. Age-and sex-adjusted and multivariable-adjusted HRs (and 95% CIs) for microscopically confirmed pancreatic cancer according to nut consumption; NLCS, 1986–2006

	Median intake[a]		Men				Women				Total population	
Food item	Men	Women	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR[b] (95% CI)	Age- and sex-adjusted HR (95% CI)	Multivariable-adjusted HR[c] (95% CI)
Total nuts (g/d)												
0	0.0	0.0	8,888	68	1.00 (reference)	1.00 (reference)	13,529	60	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	2.5	2.1	9,675	62	0.84 (0.58–1.21)	0.86 (0.59–1.24)	12,393	67	1.24 (0.86–1.78)	1.23 (0.84–1.79)	1.02 (0.79–1.32)	1.03 (0.79–1.35)
5–<10	8.5	7.8	3,951	18	0.60 (0.35–1.03)	0.56 (0.32–0.99)	3,883	14	0.84 (0.46–1.55)	0.81 (0.43–1.54)	0.71 (0.47–1.06)	0.68 (0.45–1.04)
10+	21.4	15.7	7,124	40	0.75 (0.50–1.13)	0.72 (0.47–1.11)	4,280	20	1.08 (0.64–1.82)	0.99 (0.56–1.73)	0.88 (0.63–1.22)	0.85 (0.60–1.19)
P_{trend}					0.218	0.163			0.848	0.602	0.270	0.196
Continuous, per 5 g/d increment					0.96 (0.90–1.03)	0.95 (0.89–1.03)			0.98 (0.88–1.08)	0.96 (0.86–1.07)	0.96 (0.91–1.02)	0.96 (0.90–1.02)
Tree nuts (g/d)												
0	0.0	0.0	21,394	150	1.00 (reference)	1.00 (reference)	23,851	116	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	1.6	1.6	6,704	31	0.66 (0.44–0.99)	0.68 (0.45–1.03)	8,367	41	1.02 (0.70–1.47)	1.00 (0.67–1.49)	0.83 (0.63–1.08)	0.85 (0.64–1.13)
5+	8.6	8.9	1,542	7	0.65 (0.30–1.43)	0.68 (0.31–1.50)	1,866	4	0.45 (0.16–1.23)	0.42 (0.15–1.20)	0.56 (0.30–1.04)	0.56 (0.30–1.06)
P_{trend}					0.169	0.214			0.116	0.105	0.043	0.056
Continuous, per 5 g/d increment					0.91 (0.63–1.31)	0.92 (0.64–1.33)			0.96 (0.65–1.42)	0.95 (0.62–1.44)	0.93 (0.70–1.24)	0.94 (0.71–1.25)
Peanuts (g/d)												
0	0.0	0.0	9,995	72	1.00 (reference)	1.00 (reference)	15,938	70	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	2.5	2.1	10,542	69	0.92 (0.65–1.30)	0.92 (0.64–1.32)	12,639	62	1.14 (0.80–1.64)	1.15 (0.80–1.67)	1.03 (0.80–1.32)	1.04 (0.80–1.35)
5–<10	8.5	8.5	3,285	11	0.48 (0.25–0.92)	0.44 (0.23–0.85)	2,556	16	1.49 (0.83–2.65)	1.35 (0.73–2.47)	0.83 (0.53–1.28)	0.77 (0.50–1.21)
10+	21.4	17.1	5,816	36	0.89 (0.58–1.36)	0.85 (0.55–1.33)	2,951	13	1.03 (0.56–1.91)	0.98 (0.51–1.88)	0.97 (0.68–1.37)	0.94 (0.65–1.35)
P_{trend}					0.508	0.407			0.647	0.894	0.700	0.550
Continuous, per 5 g/d increment					0.96 (0.90–1.03)	0.95 (0.89–1.02)			0.98 (0.88–1.08)	0.95 (0.85–1.06)	0.96 (0.91–1.02)	0.95 (0.90–1.01)
Peanut butter (g/d)												
0	0.0	0.0	21,203	142	1.00 (reference)	1.00 (reference)	24,883	112	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<5	1.2	1.2	5,164	35	1.04 (0.70–1.53)	1.05 (0.70–1.57)	5,970	34	1.28 (0.86–1.91)	1.27 (0.84–1.93)	1.14 (0.86–1.51)	1.16 (0.87–1.55)
5+	9.6	6.9	3,272	11	0.51 (0.27–0.97)	0.53 (0.28–1.00)	3,232	15	1.04 (0.59–1.83)	1.05 (0.58–1.88)	0.73 (0.48–1.11)	0.73 (0.48–1.12)
P_{trend}					0.037	0.047			0.807	0.823	0.139	0.141
Continuous, per 5 g/d increment					0.86 (0.67–1.11)	0.87 (0.68–1.12)			0.96 (0.77–1.19)	0.94 (0.75–1.17)	0.90 (0.77–1.07)	0.90 (0.76–1.06)

[a]Median intake in the subcohort.

[b]Adjusted for age (years; continuous); cigarette smoking [status (never/former/current), frequency (n/day; continuous, centered) and duration (years; continuous, centered)]; BMI (kg/m^2; continuous); family history of pancreatic cancer (no/yes); history of diabetes (no/yes); educational level (low/medium/high); total energy intake (kcal/d; continuous) and alcohol consumption (g/d; continuous).

[c]Adjusted for [b] and sex (male/female).

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Table 4. HRs (95% CIs) for microscopically confirmed pancreatic cancer according to total nut intake in men and women combined in subgroups, in multivariable-adjusted analyses[a], the Netherlands Cohort Study, 1986–2006

	Total nut consumption (g/d; median[b])				
	0 g/day (0.0)	0.1–<5 g/d (2.5)	5+ g/d (11.5)	P_{trend}	$P_{interaction}$
Overall					
Cases/person-time at risk (years)	128/22,417	129/22,068	92/19,238		
HR (95% CI)	1.00 (reference)	1.03 (0.79–1.35)	0.78 (0.58–1.05)	0.060	
Sex					
Males					
Cases/person-time at risk (years)	68/8,888	62/9,675	58/11,075		
HR (95% CI)	1.00 (reference)	0.86 (0.59–1.24)	0.66 (0.45–0.98)	0.043	0.377
Females					
Cases/person-time at risk (years)	60/13,529	67/12,393	34/8,163		
HR (95% CI)	1.00 (reference)	1.23 (0.84–1.79)	0.90 (0.56–1.45)	0.451	
Total population					
BMI					
18.5–<25 kg/m^2					
Cases/person-time at risk (years)	64/11,288	56/12,036	39/11,210		
HR (95% CI)	1.00 (reference)	0.85 (0.57–1.26)	0.60 (0.39–0.94)	0.026	0.082
≥25 kg/m^2					
Cases/person-time at risk (years)	63/10,837	73/9,904	53/7,924		
HR (95% CI)	1.00 (reference)	1.24 (0.86–1.78)	0.97 (0.64–1.47)	0.597	
Cigarette smoking					
Never					
Cases/person-time at risk (years)	37/9,919	40/9,208	23/5,778		
HR (95% CI)	1.00 (reference)	1.12 (0.70–1.79)	0.92 (0.51–1.64)	0.662	0.260
Former					
Cases/person-time at risk (years)	50/6,461	46/7,954	35/8,511		
HR (95% CI)	1.00 (reference)	0.82 (0.52–1.27)	0.54 (0.34–0.87)	0.012	
Current					
Cases/person-time at risk (years)	41/6,037	43/4,907	34/4,948		
HR (95% CI)	1.00 (reference)	1.19 (0.73–1.92)	1.04 (0.62–1.76)	0.957	
Alcohol consumption					
0 g/day					
Cases/person-time at risk (years)	34/7,916	25/4,691	8/2,259		
HR (95% CI)	1.00 (reference)	1.26 (0.72–2.22)	0.69 (0.29–1.61)	0.357	0.757
0.1–<15 g/d					
Cases/person-time at risk (years)	63/10,028	69/12,731	44/10,348		
HR (95% CI)	1.00 (reference)	0.92 (0.64–1.33)	0.74 (0.48–1.13)	0.156	
≥15 g/day					
Cases/person-time at risk (years)	31/4,473	35/4,647	40/6,631		
HR (95% CI)	1.00 (reference)	1.12 (0.64–1.94)	0.83 (0.48–1.45)	0.335	
Educational level					
Low					
Cases/person-time at risk (years)	71/12,894	55/10,788	38/7,450		
HR (95% CI)	1.00 (reference)	1.00 (0.68–1.46)	0.87 (0.56–1.35)	0.500	0.716
Medium					
Cases/person-time at risk (years)	40/7,213	52/8,018	38/7,866		
HR (95% CI)	1.00 (reference)	1.16 (0.74–1.82)	0.83 (0.51–1.34)	0.246	
High					
Cases/person-time at risk (years)	17/2,310	22/3,263	16/3,921		
HR (95% CI)	1.00 (reference)	0.87 (0.43–1.78)	0.55 (0.25–1.21)	0.123	

[a]Adjusted for age (years; continuous); sex (male/female); cigarette smoking [status (never/former/current), frequency (n/day; continuous, centered) and duration (years; continuous, centered)]; BMI (kg/m^2; continuous); family history of pancreatic cancer (no/yes); history of diabetes (no/yes); educational level (low/medium/high); total energy intake (kcal/day; continuous) and alcohol consumption (g/d; continuous).
[b]Median intake in the subcohort.

Only two other studies have investigated the relation between nut consumption and pancreatic cancer, but neither looked at peanut butter consumption or at males specifically (16, 17). One case–control study found no association between "nut and tasty snack" consumption and pancreatic cancer risk (16). However, because it did not examine nut consumption separately, its results cannot be directly compared with ours. In the prospective Nurses' Health Study (NHS), the HRs for a nut consumption frequency of ≥2×/week versus never/almost never (95% CI) for pancreatic cancer in women were 0.68 (0.48–0.96), 0.89 (0.57–1.39), and 0.63 (0.39–1.03) for total nut, peanut, and other nut consumption, respectively (17). These results are in contrast with our results in women, for whom we found no or unclear associations. One possible explanation for this discrepancy might be the range of nut intake. In the women in our study, the mean total nut intake was 4.3 g/day, and the median intake in the highest consumption category 15.7 g/d. In the NHS, the number of (28 g) servings per day in the highest consumption category was ≥0.20, which equals ≥5.6 g nuts/day (17). Therefore, it seems that the range of nut consumption is larger in the NLCS than in the NHS, and that the mean nut intake is higher. However,

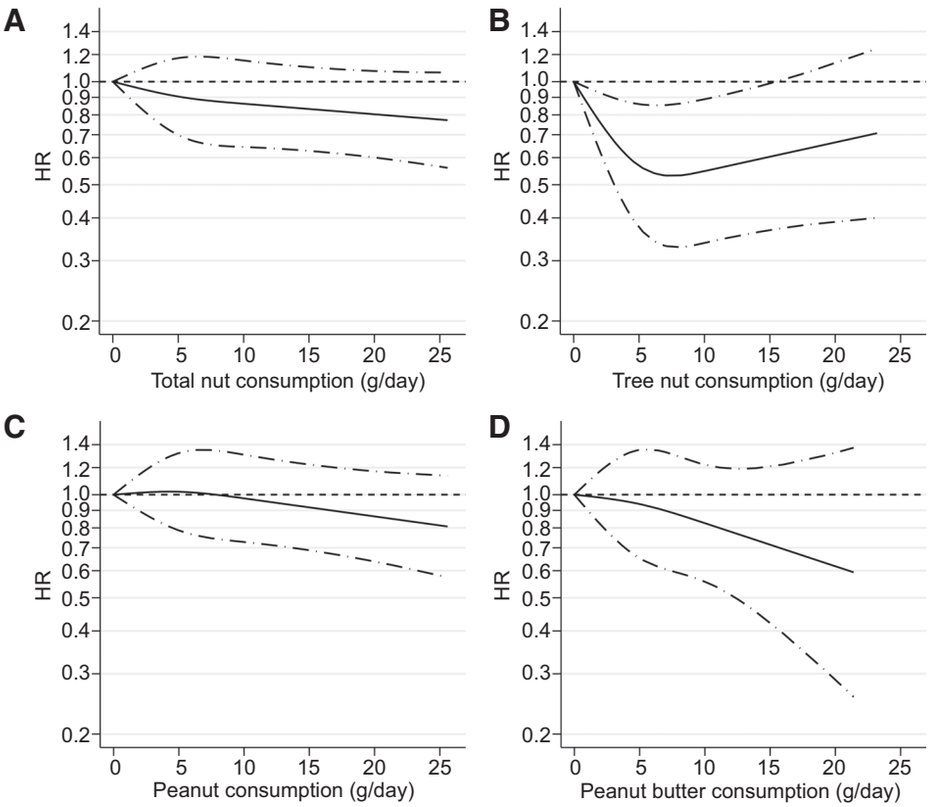

Figure 2.
Nonparametric regression curves for the associations between nut and peanut butter consumption and microscopically confirmed pancreatic cancer. It presents the nonparametric regression curves for the associations between (**A**) total nut, (**B**) tree nut, (**C**) peanut, and (**D**) peanut butter consumption and microscopically confirmed pancreatic cancer risk. Solid lines represent point estimates, dashed lines represent 95% CIs. *P* values for nonlinearity were 0.669 for total nuts, 0.005 for tree nuts, 0.598 for peanuts, and 0.778 for peanut butter. Multivariable-adjusted HRs were calculated using restricted cubic splines with three fixed knots (consumption of 0, 5, and 10 g/d), adjusted for age (years; continuous); sex (male/female); cigarette smoking [status (never/former/current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)]; BMI (kg/m^2; continuous); family history of pancreatic cancer (no/yes); history of diabetes (no/yes); educational level (low/medium/high); total energy intake (kcal/d; continuous) and alcohol consumption (g/d; continuous).

because the shape of the exposure–response curve for women in our study fluctuates over the entire intake range, the difference in nut intake between the two studies does not explain the discrepancy in the results. Furthermore, we included 161 female MCPC cases, whereas 424 (91% of the 466) female cases in the NHS were microscopically confirmed, resulting in more statistical power to detect significant differences.

Restricted cubic splines showed evidence for nonlinearity for tree nut intake in the NLCS, with a decreasing pancreatic cancer risk with increasing nut intake up to approximately 7.5 g tree nuts/day. We found no other studies that have examined the optimal daily dosage of nut consumption or the linearity of the relation between nut consumption and pancreatic cancer risk.

Differences in associations between men and women in our study might be explained by the mean amount of nuts consumed: on average, males consumed more total nuts than women, which was mainly due to their higher peanut intake. Tree nut and peanut butter intake were low in both sexes.

Although peanuts are botanically legumes, their nutrient composition is similar to that of tree nuts (12, 36). However, peanuts contain more proteins than, for example, almonds, cashew nuts, hazelnuts, and walnuts (36). Furthermore, compared with peanuts, peanut butter sold in the Netherlands in 1986 contained more vitamin B6, sodium, and partially hydrogenated fatty acids, but less niacin (36). Moreover, unlike nut consumers, respondents who consumed more peanut butter consumed less alcohol in our study.

In this study, we found a significant inverse trend in participants with a normal BMI, and no association in overweight participants. Nevertheless, the test for interaction by BMI was not significant ($P_{\text{Interaction}} = 0.082$). It has often been mentioned that nut consumption might contribute to weight gain and obesity because of their high caloric density, and that these negative health effects may outweigh the beneficial effects of nuts. However, we found no studies demonstrating a positive association between nut intake and weight gain or obesity. Recent prospective studies have actually shown that higher nut consumption is associated with less weight gain and a lower risk of obesity (37–39), which was seen in several cross-sectional studies and RCTs as well (39). Moreover, we also found that participants with a higher nut intake were leaner in this study (Table 1).

Even though our results have been adjusted for confounders, residual confounding by unmeasured confounders still might occur. Nevertheless, additional adjustments for the investigated potential confounders and the aMed score did not alter our results. Furthermore, the array-approach sensitivity analysis showed that most estimates of the adjusted HR were smaller than 1.0. Therefore, and because of the large number of potential confounders we have considered, it seems not very likely that an unmeasured confounder exists that would dramatically alter our results.

The chance of reversed causation was minimized by excluding cases with prevalent cancer. Moreover, exclusion of pancreatic cancer cases diagnosed during the first two years of follow-up did not alter our results, and nut consumption of newly diagnosed cases was relatively constant over time. Furthermore, restricting the analyses of peanut butter to participants who had stated having had a constant peanut butter intake during the five years before baseline also showed that reversed causation is unlikely.

Strengths of this study include the prospective design, the high completeness of data, and the long duration of the follow-up, which make information and selection bias unlikely. Moreover, this was the first prospective cohort study that investigated the association of nut consumption and pancreatic cancer in men separately. Another strength is the high mean nut intake in our study population compared to other populations in Europe and Asia (40, 41). Potential limitations include possible measurement error, which might have attenuated the associations, and the fact that only baseline measurements were performed. However, nut intake appeared to be constant in other studies with repeated measurements (42), and a reproducibility study showed that dietary habits in our cohort were stable for at least 5 years (43). Furthermore, the complete case analysis approach may have resulted in biases if the missing data were not missing completely at random. For future research, we recommend to investigate the relation between nut consumption and pancreatic risk in participants without peanut or other nut allergies, because these allergies might potentially confound the observed associations. Unfortunately, we do not have information on these allergies.

In conclusion, total nut, tree nut, and peanut intake were associated with a nonsignificantly reduced MCPC risk in men, whereas peanut butter intake was associated with a significantly lowered MCPC risk. In women, no associations were found for total nut and tree nut consumption with MCPC, and unclear associations for peanut and peanut butter intake.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.A. van den Brandt
Development of methodology: P.A. van den Brandt
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.A. van den Brandt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Nieuwenhuis, P.A. van den Brandt
Writing, review, and/or revision of the manuscript: L. Nieuwenhuis, P.A. van den Brandt
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.A. van den Brandt
Study supervision: P.A. van den Brandt

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