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Short Report

Consumption of nuts and seeds and pancreatic ductal adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition

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Four epidemiologic studies have assessed the association between nut intake and pancreatic cancer risk with contradictory results. The present study aims to investigate the relation between nut intake (including seeds) and pancreatic ductal adenocarcinoma (PDAC) risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Cox proportional hazards models were used to estimate hazards ratio (HR) and 95% confidence intervals (95% CI) for nut intake and PDAC risk. Information on intake of nuts was obtained from the EPIC country-specific dietary questionnaires. After a mean follow-up of 14 years, 476,160 participants were eligible for the present study and included 1,283 PDAC cases. No association was observed between consumption of nuts and PDAC risk (highest intake *vs* nonconsumers: HR, 0.89; 95% CI, 0.72–1.10; *p*-trend = 0.70). Furthermore, no evidence for effect-measure modification was observed when different subgroups were analyzed. Overall, in EPIC, the highest intake of nuts was not statistically significantly associated with PDAC risk.

What's new?
Environmental and lifestyle factors probably play a major role in the development—or prevention—of pancreatic cancer (PC). For example, might the inclusion of nuts in one's diet reduce the risk of PC? Results of previous studies have been contradictory. In this analysis of data from the large, prospective EPIC study, the authors found no significant protective role for nuts or seeds against PC.

Introduction

Pancreatic cancer (PC) is one of the most aggressive human cancers, and it is projected to be the second leading cause of cancer mortality by 2030.[1] The most frequent histological type is pancreatic ductal adenocarcinoma (PDAC), and accounts for almost 95% of all exocrine pancreatic tumors.[2] PC incidence is increasing, and 5-year survival is the worst (<8%) of all common cancers since it is usually diagnosed at late stages, and few treatment improvements have been achieved in recent years.[3] Thus, scientific evidence for primary prevention is crucial.[4]

Chronic pancreatitis and long-standing diabetes are associated with higher PC risk, while family history and genetic syndromes account for <10% of all PC cases, suggesting that environmental and lifestyle factors play a major role in PC development.[5–7] Tobacco smoking, heavy alcohol consumption and body fatness are considered lifestyle risk factors.[6] Red and processed meat intakes have also been associated with PC risk, but scientific evidence remains unclear. Likewise, inconsistent results have been reported for *Helicobacter pylori*, physical activity, adherence to the Mediterranean diet and dietary intakes of fruits, vegetables, magnesium and folate.[6–8]

Nuts (comprising tree nuts and peanuts) are a food group that has largely been associated with beneficial health effects including reduced total and cause-specific mortality, cardiovascular disease, hypertension, diabetes, insulin resistance and cancer risk.[9–12] The characteristic nutritional composition of nuts (rich in fiber, vitamins, minerals, mono- and polyunsaturated fatty acids and bioactive compounds) makes them an ideal food group to be studied as a preventive factor for PC.[10,13]

One prospective epidemiologic study from the United States found evidence for an inverse association between nut intake and PC risk in women,[14] whereas one case–control and one prospective cohort study, both from the Netherlands, observed no statistically significant associations.[15,16] A third prospective cohort study from Iran also found no clear association.[17] The purpose of the present study was to investigate the relation between the consumption of nuts and seeds and PDAC risk accounting for dietary and lifestyle factors in one of the largest prospective cohort studies of nutrition and chronic diseases.

Methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a multicenter study that started between 1992 and 1998 and comprises 23 research centers in ten European countries. The study was approved by the International Agency for Research on Cancer ethical review boards and/or all local ethics committees. The design and methodology of the EPIC study has been published elsewhere.[18]

Of the 521,324 participants, a total of 45,164 were excluded because they had prevalent cancer other than nonmelanoma skin cancer at recruitment (n = 25,184), had incomplete follow-up data (n = 4,128), had missing data of diagnosis (n = 20), had no lifestyle or dietary information at recruitment (n = 6,259) or had an extreme ratio of energy intake to energy requirement (top or bottom 1%; n = 9,573); resulting in 476,160 participants (70% women) for the present analysis.

Identification of PC cases

PC incidence was ascertained through population-based cancer registries or active follow-up (Germany, Greece and France) and confirmed through a mixture of methods that included health insurance records, and cancer and pathology registries. Participants were followed until cancer diagnosis, death or last complete follow-up, whichever occurred first. Fifty-seven neuroendocrine PC cases were censored. After a mean follow-up of 14 years, 1,283 first incidence PDAC cases were available for analysis and were classified according to International Classification of Diseases for Oncology third edition codes C25.0-C25.3 and C25.7-C25.9.

Information on lifestyle, dietary and nut intake

Anthropometric measures were assessed at baseline, and participants also answered a lifestyle questionnaire.[18] Country-specific validated dietary questionnaires, with the timeframe referring to the preceding year, were used to assess dietary information at baseline.[18] The determination of nut and seed intake in EPIC has been previously published.[19,20] Briefly, the term "nut" denotes a combination of three terms: tree nuts (including almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios and walnuts), peanuts (including peanut butter) and nonspecific nuts (not specified by the participant). Generally, in the EPIC cohort, there was a low intake of specific seeds (i.e., sunflower, linseed and pumpkin), thus "seeds" were combined as a sum total variable. Finally, total intake of nuts and seeds was used as the main exposure variable (herein referred to as "total nut intake"). Consumers were defined as those who reported an intake >0 g per day on average.

Statistical analysis

Cox proportional hazards models were used to estimate hazards ratio (HR) and 95% confidence intervals (95% CIs) for total nut intake and overall PDAC risk. Total nut intake was analyzed both as a continuous variable (15 g/day; 15 g-increments correspond to half a standard serving),[21] and as categorical variable with all nonconsumers as the reference category and consumers categorized in quartiles based on the distribution of total nut intake in the EPIC cohort. All statistical models had age as the primary time variable, were stratified by study center to control for center effects and by age at recruitment in 1-year categories. Covariates of gender, smoking status, diabetes, alcohol consumption, body mass index (BMI) and total energy intake were included in final models as they were known PC risk factors or potential confounders. Other variables such as physical activity using the Cambridge index, education level, magnesium (mg/day), red and processed meat, fiber, vegetable and fruit intake (all in g/day) were evaluated but not included as they did not change the HR estimates ≥10%. We also evaluated sex-specific and country-specific categorical variables for total nut intake; however, since HRs for total nut intake and PDAC risk did not vary from those of the main model, results were not shown.

Analyses for effect-measure modification were carried out by known PC risk factors: smoking (never, ever), diabetes (yes, no) and BMI (<25, ≥25 kg/m^2). Heavy alcohol consumption (>60, 0.1–4.9 g/day) was evaluated for men and women combined.[22] Stratified analyses by sex (male, female), by geographic region (northern: Norway, Denmark and Sweden; central: Germany, The Netherlands, the United Kingdom and northern of France; southern: southern of France, Italy, Spain and Greece) and by country intake (countries over *vs* countries below the EPIC median nut intake) were also investigated.

Sensitivity analyses were performed: (*i*) exclusion of PDAC cases that were diagnosed during the first 2 years of follow-up to minimize the possible effect of preclinical disease on dietary intake; (*ii*) restriction to microscopically confirmed PDAC cases ($n = 910$) to reduce a possible disease misclassification; (*iii*) adjustment for the *adapted-relative* Mediterranean diet score (removing nuts from the score)[23]; (*iv*) evaluation of nut intake in quartiles of frequency (never/almost never, 0.2–1 times/month, 0.25 to ≤1 times/week, >1 times/week), rather than absolute intake.[24] This analysis was performed excluding 47,171 participants from Cambridge and Malmö, as frequency data were not available; (*v*) removing BMI and diabetes from the multivariable model and (*vi*) modeling waist-to-hip ratio instead of BMI.

The proportional hazards assumption was evaluated using Schoenfeld residuals, which was satisfied in all models. The median value for each category was estimated and included in a score test to evaluate dose–response trends. The likelihood ratio test *p*-value was used to evaluate statistical significance of effect-measure modification based on the continuous intake variable. All analyses were performed using SAS v.9.3 and STATA v.14 was used to test the proportional hazards assumption. An α-level of 0.05 was used to set the cutoff for statistical significance.

Results

Basic information on cohort members

After a mean follow-up of 14 years, 1,283 PDAC cases (57% women) were observed. More than 90% of the populations from The Netherlands, Germany and Greece reported consuming nuts and seeds, whereas only 38.8% of the Spanish population reported nut/seed consumption. However, the highest median of intake among consumers was observed in Spain (5.9 g/day), followed by Greece (5.3 g/day) and the Netherlands (5.0 g/day) (Table 1). Even though the distributions of intake were skewed, means of intake by country are presented in Table 1 to compare to some previously published reports.

Participants classified at the highest levels of total nut intake were more likely to have higher energy, dietary fiber, vegetable and fruit intakes, while nonconsumers had higher intakes of processed meat. Furthermore, nonconsumers compared to high consumers tended to be nonalcohol drinkers, had higher BMI and a higher proportion of smokers and were more likely to report diabetes at baseline (Table 2).

Overall PDAC risk

No associations and no evidence for linear dose–response trends were observed between total nut intake and PDAC risk in EPIC (highest intake *vs* nonconsumers: HR, 0.89; 95% CI, 0.72–1.10; *p*-trend = 0.70) (Table 3). The continuous total nut intake variable, assessed in 15 g/day increments, was nonsignificantly inversely associated ($HR_{15g/day}$, 0.94; 95% CI, 0.84–1.07).

Table 1. Estimated total nut[1] intake and pancreatic ductal adenocarcinoma cases by country in the EPIC cohort

Country	Cohort sample *n*	Person-years	Total PDAC cases *n* (%)[2]	Male PDAC cases *n* (%)[2]	Female PDAC cases *n* (%)[2]	Microscopically confirmed cases *n* (%)	Consumers of total nuts *n* (%)	Total nuts among consumers (g/day)	
								Median (p25–p75)	Mean ± SD
France	67,403	869,372	56 (4.4)		56 (7.7)	26 (2.9)	48,381 (71.8)	4.8 (2.1–8.6)	7.7 ± 9.0
Italy	44,545	630,951	104 (8.1)	35 (6.3)	69 (9.5)	66 (7.3)	39,667 (89.0)	0.2 (0.2–1.0)	1.0 ± 2.1
Spain	39,989	637,947	106 (8.3)	55 (9.9)	51 (7.0)	80 (8.8)	15,200 (38.8)	5.9 (2.1–13.7)	11.3 ± 15.6
United Kingdom	75,416	1,122,765	188 (14.7)	69 (12.4)	119 (16.4)	19 (2.1)	63,134 (83.7)	2.3 (0.5–7.0)	7.1 ± 12.3
The Netherlands	36,539	524,671	93 (7.3)	20 (3.6)	73 (10.0)	67 (87.4)	34,402 (94.2)	5.0 (1.8–11.9)	9.3 ± 12.8
Greece	26,048	281,284	44 (3.4)	25 (4.5)	19 (2.6)	18 (2.0)	24,173 (92.8)	5.3 (0.2–8.0)	6.3 ± 8.5
Germany	48,557	504,479	116 (9.0)	72 (13.0)	44 (6.1)	88 (9.7)	43,597 (89.9)	1.5 (0.6–3.7)	3.9 ± 7.7
Sweden	48,674	801,130	204 (15.9)	93 (16.7)	111 (15.3)	197 (21.6)	30,489 (62.6)	0.3 (0.0–0.8)	1.5 ± 4.2
Denmark	55,014	815,097	325 (25.3)	187(33.6)	138 (19.0)	303 (33.3)	40,815 (74.2)	0.8 (0.8–1.6)	2.4 ± 4.5
Norway	33,975	452,171	47 (3.7)		47 (6.5)	46 (5.10)	16,105 (47.4)	3.0 (3.0–6.4)	4.6 ± 3.9
Total	476,160	6,639,867	1,283 (100)	556 (100)	727 (100)	910 (100)	355,963 (74.8)	2.3 (0.7–5.7)	5.3 ± 9.5

[1]Total nut intake is the sum of the total intake of nuts and seeds.
[2]Percentages are calculated by country.
Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

Table 2. Estimated total nut[1] intake and covariates at baseline used in the analyses

	Total nut intake (g/day)				
		Consumers			
	Nonconsumers 0 g/day	Q1 >0–0.7 g/day Median: 0.3 g/day	Q2 >0.7–2.3 g/day Median: 1.0 g/day	Q3 >2.3–5.7 g/day Median: 3.5 g/day	Q4 >5.7 g/day Median: 11.8 g/day
Participants (*n*)	120,197	89,014	86,213	91,788	88,948
PDAC (*n*)	400	223	303	196	161
Female (%)	72.0	65.4	65.7	75.0	71.7
Age at recruitment	53.6 (47.9–60.2)[2]	50 (40.7–57.9)	53.7 (49.1–59)	49.8 (43.4–56.2)	49.2 (43.3–55.8)
Energy intake (Kcal/day)	1887 (1,536–2,315)	1908 (1,544–2,360)	2049 (1,695–2,467)	1964 (1,626–2,375)	2,216 (1,832–2,665)
Dietary fiber (g/day)	20.7 (16.4–25.8)	20.3 (16.1–25.2)	22.3 (17.9–27.6)	21.9 (17.8–26.8)	24.3 (19.8–29.7)
Magnesium (mg/day)	324.4 (266.6–394.1)	306.6 (251.3–372.8)	356.7 (297.7–426.2)	349.6 (293.2–416.5)	399.7 (333.5–479.7)
Vegetables (g/day)	169.3 (104.9–262.7)	143.7 (86.2–236.3)	163.3 (108.0–241.6)	203.7 (127.3–316.9)	207.3 (129.2–326.5)
Fruit (g/day)	185.2 (100.0–307.6)	206.8 (110.3–330.9)	170.7 (94.0–279.9)	200.9 (114.2–318.5)	210.6 (118.7–327.9)
Red meat (g/day)	35.1 (17.9–61.5)	26.2 (12.2–49.5)	49.5 (26.9–75.9)	31.4 (12.8–58.6)	35.6 (12.3–66.7)
Processed meat (g/day)	26.9 (13.4–46.4)	22.6 (9.7–41.0)	25.9 (14.2–45.0)	20.0 (5.0–40.6)	23.6 (6.5–45.4)
Body Mass Index (kg/m^2)	25.3 (22.8–28.4)	25.1 (22.7–27.9)	25.0 (22.6–27.8)	24.4 (22.1–27.3)	24.1 (21.9–27.1)
Time quitting smoking (year)	14.5 (6.5–23.0)	13.0 (6.5–21.0)	15.0 (7.0–23.5)	14.0 (6.5–22.0)	13.5 (96.5–21.5)
Smoking status (%)					
Never	48.4	53.0	44.8	50.3	48.4
Former	25.0	25.5	28.8	26.8	27.7
Smoker	24.0	20.6	25.1	20.4	21.4
Unknown	2.6	0.9	1.3	2.5	2.5
Diabetes (%)					
No	81.4	94.9	89.9	89.8	92.6
Yes	3.5	2.7	2.2	2.2	2.2
Do not know	0.5	0.0	1.6	0.2	0.1
Missing	14.5	2.4	6.3	7.7	5.1
Alcohol at recruitment					
Nondrinker (%)	26.7	9.6	8.1	9.5	8.6
Consumers among women (g/day)	4.4 (1.4–10.9)	2.9 (0.8–9.8)	6.9 (2.2–14.7)	5.3 (1.6–11.8)	7.0 (2.3–15.3)
Consumers among men (g/day)	14.1 (5.4–33.1)	8.0 (2.8–23.7)	17.2 (8.1–35.9)	15.1 (6.5–30.6)	16.6 (6.8–33.1)

[1]Total nut intake is the sum of the total intake of nuts and seeds.
[2]Median (p25–p75).
Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

Table 3. Hazard ratios and 95% confidence intervals for estimated total nut intake[1] and PDAC risk in EPIC

			Total nut intake						
				Consumers					
		15 g/day increments	Nonconsumers 0 g/day	Q1 >0–0.7 g/day Median: 0.3 g/day	Q2 >0.7–2.3 g/day Median: 1.0 g/day	Q3 >2.3–5.7 g/day Median: 3.5 g/day	Q4 >5.7 g/day Median: 11.8 g/day	Trend test *p*-value[2]	LRT *p*-value[3]
Final model	Final model								
	N cases	1,283	400	223	303	196	161		
	HR (95% CI)[4]	0.94 (0.84–1.07)	1.00 (ref)	0.92 (0.74–1.14)	0.92 (0.77–1.09)	0.99 (0.82–1.20)	0.89 (0.72–1.10)	0.70	
Sensitivity analysis	Cases diagnosed ≥2 years after recruitment								
	N cases	1,195	374	208	284	181	148		
	HR (95% CI)	0.95 (0.84–1.08)	1.00 (ref)	0.93 (0.74–1.17)	0.92 (0.77–1.10)	0.99 (0.81–1.20)	0.89 (0.72–1.10)	0.75	
	Microscopically confirmed cases								
	N cases	910	229	140	242	125	104		
	HR (95% CI)	0.95 (0.66–1.38)	1.00 (ref)	0.72 (0.46–1.13)	0.87 (0.65–1.15)	0.99 (0.71–1.37)	0.68 (0.44–1.04)	0.28	
	Mediterranean diet score								
	N cases	1,283	400	223	303	196	161		
	HR (95% CI)[5]	0.94 (0.84–1.07)	1.00 (ref)	0.92 (0.74–1.14)	0.92 (0.77–1.09)	0.99 (0.82–1.20)	0.89 (0.72–1.10)	0.70	
Analyses of effect-measure modification	Alcohol consumption								
	Light drinkers (>0.1–4.9 g/day)								
	N cases	373	111	99	75	53	35		
	HR (95% CI)[6]	0.72 (0.52–1.01)	1.00 (ref)	0.91 (0.62–1.32)	1.10 (0.79–1.54)	0.82 (0.57–1.19)	0.65 (0.42–0.99)	0.19	0.74
	Heavy drinkers (>60 g/day)								
	N cases	71	26	4	24	7	10		
	HR (95% CI)[6]	0.79 (0.43–1.47)	1.00 (ref)	0.53 (0.14–1.99)	0.76 (0.40–1.46)	0.45 (0.17–1.19)	0.61 (0.25–1.52)	0.57	
	Diabetes								
	No								
	N cases	1,075	316	195	260	159	145		
	HR (95% CI)[7]	0.94 (0.82–1.07)	1.00 (ref)	0.82 (0.65–1.04)	0.85 (0.71–1.03)	0.91 (0.73–1.13)	0.89 (0.71–1.12)	0.38	0.77
	Yes								
	N cases	74	23	19	14	12	6		
	HR (95% CI)[7]	0.93 (0.58–1.51)	1.00 (ref)	1.96 (0.83–4.62)	1.28 (0.57–2.86)	1.35 (0.60–3.07)	0.72 (0.26–1.99)	0.40	

(Continues)

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Table 3. Hazard ratios and 95% confidence intervals for estimated total nut intake and PDAC risk in EPIC (Continued)

		Total nut intake						
			Consumers					
	15 g/day increments	Nonconsumers 0 g/day	Q1 >0–0.7 g/day Median: 0.3 g/day	Q2 >0.7–2.3 g/day Median: 1.0 g/day	Q3 >2.3–5.7 g/day Median: 3.5 g/day	Q4 >5.7 g/day Median: 11.8 g/day	Trend test *p*-value[2]	LRT *p*-value[3]
Body Mass Index								
<25 kg/m^2								
N cases	535	169	88	118	82	78		
HR (95% CI)[8]	0.98 (0.82–1.16)	1.00 (ref)	0.80 (0.56–1.14)	0.84 (0.65–1.10)	0.92 (0.69–1.24)	0.90 (0.66–1.22)	0.66	
≥25 kg/m^2								0.34
N cases	748	231	135	185	114	83		
HR (95% CI)[8]	0.91 (0.77–1.09)	1.00 (ref)	0.98 (0.74–1.31)	0.97 (0.77–1.21)	1.03 (0.80–1.33)	0.87 (0.66–1.15)	0.81	
Smoking Status								
Never smokers								
N cases	465	142	90	99	73	61		
HR (95% CI)[9]	0.91 (0.73–1.14)	1.00 (ref)	0.91 (0.64–1.28)	0.97 (0.72–1.30)	0.99 (0.72–1.37)	0.94 (0.66–1.32)	0.98	
Ever smokers[10]								0.88
N cases	783	244	128	197	120	94		
HR (95% CI)[9]	0.89 (0.75–1.05)	1.00 (ref)	0.92 (0.68–1.23)	0.88 (0.71–1.09)	1.00 (0.78–1.27)	0.81 (0.62–1.06)	0.47	

[1]Total nut intake is the sum of the total intake of nuts and seeds.
[2]All *p*-values for trend are based on the quintile medians.
[3]All LRT *p*-values for effect measure modification are based on the continuous total nut intake variable.
[4]Stratified by age at recruitment and center. Adjusted for gender, total energy intake (1,000 kcal/day), BMI (kg/m^2), smoking status (never smokers, current pipe or cigar or occasional smokers, current cigarette smokers: 1–15, 16–25, or ≥26 cigarettes/day, former cigarette smokers who quit >20 years, 11–20 years or ≤10 years before recruitment), diabetes (no, yes, do not known, missing) and alcohol consumption (nondrinkers, drinkers of 0–6 g/day, >6–12 g/day, >12-24 g/day, >24–60 g/day, female drinkers with >60 g/day, male drinkers >60–96 g/day, male drinkers >96 g/day).
[5]Final model further adjusted by the adapted relative Mediterranean diet score.
[6]Stratified by age at recruitment and center. Adjusted for gender, total energy intake (1,000 kcal/day), BMI (kg/m^2), smoking status (never smokers, current pipe or cigar or occasional smokers, current cigarette smokers: 1–15, 16–25 or ≥26 cigarettes/day, former cigarette smokers who quit >20 years, 11–20 years or ≤10 years before recruitment) and diabetes (no, yes, do not known, missing).
[7]Stratified by age at recruitment and center. Adjusted for gender, total energy intake (1,000 kcal/day), BMI (kg/m^2), smoking status (never smokers, current pipe or cigar or occasional smokers, current cigarette smokers: 1–15, 16–25 or ≥26 cigarettes/day, former cigarette smokers who quit >20 years, 11–20 years or ≤10 years before recruitment) and alcohol consumption (nondrinkers, drinkers of 0–6 g/day, >6–12 g/day, >12-24 g/day, >24–60 g/day, female drinkers with >60 g/day, male drinkers >60–96 g/day, male drinkers >96 g/day).
[8]Stratified by age at recruitment and center. Adjusted for gender, total energy intake (1,000 kcal/day), smoking status (never smokers, current pipe or cigar or occasional smokers, current cigarette smokers: 1–15, 16–25 or ≥26 cigarettes/day, former cigarette smokers who quit >20 years, 11–20 years or ≤10 years before recruitment), diabetes (no, yes, do not known, missing) and alcohol consumption (nondrinkers, drinkers of 0–6 g/day, >6–12 g/day, >12-24 g/day, >24–60 g/day, female drinkers with >60 g/day, male drinkers >60–96 g/day, male drinkers >96 g/day).
[9]Stratified by age at recruitment and center. Adjusted for gender, total energy intake (1,000 kcal/day), BMI (kg/m^2), diabetes (no, yes, do not known, missing) and alcohol consumption (nondrinkers, drinkers of 0–6 g/day, >6–12 g/day, >12-24 g/day, >24–60 g/day, female drinkers with >60 g/day, male drinkers >60–96 g/day, male drinkers >96 g/day).
[10]Ever smokers: former and current smokers.
Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazards ratio; LRT, likelihood ratio test; PDAC, pancreatic ductal adenocarcinoma.

The three sensitivity analyses performed excluding cases with follow-up of <2 years, restricting to microscopically confirmed cases and adjusting for adapted relative Mediterranean diet score showed similar results (Table 3). Likewise, when total nut intake was analyzed using frequency of consumption, no statistically significant inverse association was observed (p-trend = 0.23; data not shown). Results remained unchanged when diabetes and BMI were not included in final models, and when BMI was replaced by waist-to-hip ratio (data not shown).

Effect-measure modification

No effect-measure modification was observed for any of the stratified analyses according to heavy alcohol consumption, diabetes, smoking status or BMI (Table 3). There was also no evidence for modification of HRs for total nut intake and PDAC by sex, geographic region or country intake (likelihood ratio test p-value = 0.31, 0.42 and 0.50 respectively; data not shown).

Discussion

The present study prospectively assessed the association between total nut intake and PDAC risk in the EPIC cohort. Although all relative risk estimates were below the null value, our study failed to detect any statistically significant inverse associations for men and women. Likewise, relative risks were somewhat lower when we restricted the analysis to microscopically confirmed PDAC cases, but no statistically significant associations were observed. Results for total nut intake and PDAC remained unchanged when we evaluated effect-measure modification by various subgroups.

Regular nut consumption has been associated with health benefits in both epidemiological and clinical studies. Regular nut consumption may play a role in reducing insulin resistance, inflammation, hyperglycemia and oxidative stress among others.[12,24] Despite differences in nutritional composition by nut subtypes (i.e., walnuts have the highest content in linoleic acid and α-linolenic acid, hazelnuts in fiber, peanuts in protein and folate, pine nuts in polyunsaturated fatty acids), they are considered highly nutritious.[25] Therefore, nuts have been postulated as a food group that might have potential in cancer prevention and in lowering cancer mortality; however, the epidemiologic evidence remains limited, particularly for specific cancers.[9–11]

To our knowledge, only four published studies have evaluated the potential preventive role of nut intake on PC risk, with inconclusive results. The first study was conducted in the Netherlands and encompassed 164 PC cases and 480 controls from both genders. The authors concluded that there was no association between the intake of "nuts and tasty snacks" (including peanuts and other nuts, peanut butter and chips among others) and PC risk.[15] The second study was performed in the prospective Nurses' Health Study of 75,680 women, where the frequency of nut consumption (defined by the sum of peanuts and other nuts) was statistically significantly inversely associated with PC risk showing an HR of 0.65 (95% CI, 0.47–0.92; p-trend = 0.007).[14] The third study, from the Golestan Cohort Study (Iran), included 50,045 participants and 54 PC cases, and found no association between nut intake and PC risk.[17] The most recent study was conducted in the Netherlands Cohort Study and evaluated the association between consumption of nuts (sum of peanuts and tree nut), tree nuts, and peanut butter and the risk of PC overall and by sex. Despite observing lower relative risks for higher consumers compared to nonconsumers (HR, 0.84; 95% CI, 0.63–1.11; p-trend = 0.17), none of the associations or trend tests were statistically significant.[16]

Our results are consistent with those from the case–control study, the Netherlands Cohort Study and the Golestan Cohort Study studies, but not with the Nurses' Health Study. Nonetheless, we advise caution when comparing results across studies since nut consumption was assessed differently, and the types of nuts consumed differed between studies. In EPIC, as discussed by Jenab *et al.*, the exposure variable was a combination of tree nuts and seeds (≈90% nuts, of which walnuts, almonds and hazelnuts were the most regularly consumed),[19,20] whereas in both the Nurses' Health Study and the NCLS, peanuts were more frequently consumed than tree nuts. Similarly, in EPIC-Netherlands, peanuts composed more than half of total nut and seed intake, but no associations with PDAC were observed in our investigation when country-specific analyses were performed, including EPIC-Netherlands. Nuts and peanuts have different nutritional composition, and thus, they may play different roles in human health. In the present study, we could not analyze them as a unique variable, but additional studies should try to evaluate these foods items separately.

Dietary guidelines recommend a minimum portion of 30 g/day of nuts, seeds and legumes as they may have beneficial effects on human health.[21] In the present study, only 2% of nut consumers reported an intake >30 g/day. The general population may have a misconception about nut consumption, that they are thought to increase weight due to their high caloric value; however, in our study, as well as in other published prospective and clinical studies, it has been observed that high nut consumers have lower BMI and less weight gain compared to nonconsumers.[24,26] Some studies have suggested a lower risk of Type-2 diabetes among nut consumers as well, although data have not been consistent.[12] Both excess weight and Type-2 diabetes are established risk factors for PC; however, removing BMI or diabetes from the multivariable model, or analyzing waist-to-hip ratio as a measure of abdominal fatness instead of BMI, did not materially alter our results.

The present study had the following limitations: although we tried to control for confounding effects, we could not adjust our models for all known PC risk factors (i.e., family history, ABO blood group, chronic pancreatitis) because this information was not collected in EPIC. Some but not all EPIC dietary questionnaires were designed to capture nut consumption, thus misclassification of the exposure and the possibility that some foods that contribute to total nut intake in EPIC were not assessed (i.e., *turrón* in Spain) could have also influenced our results. Furthermore, as mentioned before, specific analyses by type of nut could not be performed, including for peanut butter. The range of total nut intake in EPIC was narrower than reported by the Netherlands Cohort Study and the Nurses' Health Study.[14,16] Lastly, there is only one dietary assessment on all EPIC participants (which was conducted at baseline), thus we were not able to evaluate changes in diet over time.

One of the strengths of our study is its prospective design, in which recall bias is less likely than in case–control studies, and EPIC is a multicountry cohort with heterogeneity in diets and lifestyle factors. We performed a sensitivity analysis excluding cases diagnosed within the first 2 years of follow-up to avoid any influence of prediagnostic PC on dietary intakes, which showed similar results to the overall model. Moreover, this is the largest study evaluating the association between total nut intake and PDAC risk to date (including men and women and over a thousand of PC cases), which allowed us to evaluate effect measure modification by several parameters.

In conclusion, the results of the present study indicate that there were no statistically significant inverse associations between total nut intake and PDAC risk within a large European cohort.

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Availability of Data and Materials

For information on how to submit an application for gaining access to European Prospective Investigation into Cancer and Nutrition (EPIC) data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

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