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

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Running head: Consumption of nuts and seeds and pancreatic cancer risk in EPIC
Keywords: pancreatic cancer, nuts, seeds, diet, intake, EPIC, prospective cohort study
Number of Tables: 3
Abbreviations: 95%CI; 95% confidence intervals; arMED, adapted relative Mediterranean Diet; BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; GCS, Golestan Cohort Study; HR, hazards ratio; HR, hazards ratio; LRT, likelihood ratio test, MED; mediterranean diet; NLCS, Netherlands Cohort Study; NHS, Nurses' Health Study; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; RR, relative risk; United States, US; Waist-to-hip ratio, WHR.
Novelty and impact: Knowledge of pancreatic cancer (PC) risk factors and preventive factors is incomplete. Nuts have been evaluated as a potential preventive factor for PC cancer risk in four epidemiologic studies, with inconclusive results. The authors have assessed this association in one of the largest European prospective cohorts, the European Prospective Investigation into Cancer and nutrition (EPIC) study. Nut intake does not appear to play a role in PC incidence, at least not at the levels of consumption observed in EPIC.
Conflicts of Interest: None of the authors declared a conflict of interest. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they

do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

ABSTRACT:

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, 476160 participants were eligible for the present study and included 1283 PDAC cases. No association was observed between consumption of nuts and PDAC risk (highest intake vs non-consumers: HR:0.89, 95%CI:0.72-1.10, *P*-trend:0.70). Further, 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.

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 is still unclear. Likewise, inconsistent results have been reported for *Helicobacter pylori*, physical activity, adherence to the Mediterranean Diet (MED), 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 (US) 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 1992-1998 and comprises 23 research centers in 10 European countries. The study was approved by the IARC ethical review boards and/or all local ethics committees. The design and methodology of the EPIC study has been published elsewhere[18].

Of the 521324 participants, a total of 45164 were excluded because they had prevalent cancer other than non-melanoma skin cancer at recruitment (n=25184), had incomplete follow-up data (n=4128), had missing data of diagnosis (n=20), had no lifestyle or dietary information at recruitment (n=6259), or had an extreme ratio of energy intake to energy requirement (top or bottom 1%; n=9573); resulting in 476160 participants (70% women) for the present analysis.

Identification of pancreatic cancer cases

Pancreatic cancer 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, 1283 first incidence PDAC cases were available for analysis, and were classified according to ICD-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 non-specific nuts (not specified by the participant). Generally, in the EPIC cohort, there was a low intake of specific seeds (i.e., sunflower, linseed, 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 >0g per day on average.

Statistical analysis

Cox proportional hazards models were used to estimate hazards ratio (HR) and 95% confidence intervals (95%CI) for total nut intake and overall PDAC risk. Total nut intake was analyzed both as a continuous variable (15g/day; 15g-increments correspond to half a standard serving)[21], and as categorical variable with all non-consumers 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 UK 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: 1) Exclusion of PDAC cases that were diagnosed during the first two years of follow-up to minimize the possible effect of pre-clinical disease on dietary intake; 2) Restriction to microscopically confirmed PDAC cases (n=910) to reduce a possible disease misclassification; 3) Adjustment for the *adapted-relative* MED (arMED) score (removing nuts from the score)[23]; 4) Evaluation of nut intake in quartiles of frequency (never/almost never, 0.2-1 times/month", 0.25-≤1 times/week, >1 times/week), rather than absolute intake[24]. This analysis was performed excluding 47171 participants from Cambridge and Malmö, as frequency data were not available; 5) Removing BMI and diabetes from the multivariable model; 6) Modeling waist-to-hip ratio (WHR) 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 (LRT) *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 v14 was used to test the proportional hazards assumption. An α-level of 0.05 was used to set the cut-off for statistical significance.

RESULTS

Basic information on cohort members. After a mean follow-up of 14 years, 1283 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 Table1 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, whilst non-consumers had higher intakes of processed meat. Further, non-consumers compared to high consumers, tended to be non-alcohol drinkers, had higher BMI, and a higher proportion of smokers and were more likely to report diabetes at baseline (Table2).

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 non-consumers: HR:0.89, 95%CI:0.72-1.10, *P*-trend:0.70) (Table3). The continuous total nut intake variable, assessed in 15g/day increments, was non-significantly inversely associated ($HR_{15g/day}$:0.94, 95%CI:0.84-1.07). The three sensitivity analyses performed excluding cases with follow-up <2 years, restricting to microscopically confirmed cases, and adjusting for arMED score, showed similar results (Table3). 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 WHR (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 (Table3). There was also no evidence for modification of HRs for total nut intake and PDAC by sex, geographic region or country-intake (LRT *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 (RR) estimates were below the null value, this study failed to detect any statistically significant inverse associations for men and women. Likewise, RRs 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 is still 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 (NHS) of 75680 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 (GCS; Iran), included 50045 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 (NLCS) 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 RRs for higher consumers compared to non-consumers (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 NLCS and the GCS studies, but not with the NHS. 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 NHS 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 non-consumers[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. Further, 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 NLCS and the NHS[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 this study is its prospective design, in which recall bias is less likely than in case-control studies, and EPIC is a multi-country cohort with heterogeneity in diets and lifestyle factors. We performed a sensitivity analysis excluding cases diagnosed within the first two years of follow-up to avoid any influence of pre-diagnostic 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.

ACKNOWLEDGEMENTS

Research support: We thank the CERCA Program/Generalitat de Catalunya for their institutional support. Mireia Obón-Santacana received a post-doctoral fellow from "Fundación Científica de la Asociación Española Contra el Cáncer (AECC)", and is part of the group 55 of CIBERESP. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the Health Research Fund (FIS) of the Spanish Ministry of Health, Regional Governments of Andalucía, Asturias, Basque Country, Murcia [no. 6236], Navarra and the Catalan Institute of Oncology, La Caixa [BM 06-130], Danish Cancer Society (Denmark); Ligue contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum (DKFZ) and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF) and Statistics Netherlands (The Netherlands); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK (C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (MR/M012190/1 to EPIC-Oxford) (United Kingdom).

Availability of data and materials: For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

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