Dietary folate intake and pancreatic cancer risk:

Results from the European Prospective Investigation into Cancer and Nutrition

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Novelty and impact statement: This large investigation with 865 incident pancreatic cancer cases from the EPIC study showed no significant association between dietary folate intake and pancreatic cancer risk. Dietary folate intake was ascertained using the standardised folate dataset compiled for EPIC which provided comparable folate data across the participating countries with minimum influence of folic acid fortification or supplementation.

Abstract

Pancreatic cancer (PC) has an exceptionally low survival rate and primary prevention strategies are limited. Folate plays an important role in one-carbon metabolism and has been associated with the risk of several cancers, but not consistently with PC risk. We aimed to investigate the association between dietary folate intake and PC risk, using the standardised folate database across 10 European countries. A total of 477,206 participants were followed up for 11 years, during which 865 incident primary PC cases were recorded. Folate intake was energy-adjusted using the residual method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. In multivariable analyses stratified by age, sex, study centre and adjusted for energy intake, smoking status, BMI, educational level, diabetes status, supplement use and dietary fibre intake, we found no significant association between folate intake and PC risk: the HR of PC risk for those in the highest quartile of folate intake (≥353 μg/d) compared with the lowest (<241 μg/d) was 0.81 (95% CI: 0.51, 1.31; P_{trend} = 0.38). In current smokers, a positive trend was observed in PC risk across folate quartiles (HR=4.42 (95% CI: 1.05, 18.62) for ≥353 μg/d vs. <241 μg/d, P_{trend} = 0.01). Nonetheless, there was no significant interaction between smoking and dietary folate intake ($P_{interaction}$= 0.99). We found no association between dietary folate intake and PC risk in this large European study.

Introduction

The diagnosis of pancreatic cancer (PC) is rarely made at an early stage and it has an exceptionally low survival rate due to a late diagnosis and limited treatment options, making it the seventh leading cause of cancer death worldwide with an almost equal number of new cases diagnosed each year[1]. The burden of this cancer is increasing with an aging population, and is particularly high in more developed countries. The incidence of pancreatic cancer varies greatly across regions, which suggests a role of environmental, dietary or lifestyle factors [2, 3]. Consistently identified risk factors for pancreatic cancer include tobacco smoking, body fatness, conditions characterized by high insulin secretion, chronic pancreatitis, heavy alcohol intake and family history of the disease[4-6]. Nonetheless, the aetiology of the cancer is largely unknown and prevention strategies are limited.

Folate, naturally available in a wide variety of foods including fruits and vegetables, is a water-soluble vitamin B that plays an important role in the synthesis and methylation of DNA as a crucial cofactor in one-carbon metabolism together with other B vitamins such as vitamin B2, vitamin B6 and vitamin B12[7]. Inadequate folate status may contribute to carcinogenesis through aberrations in DNA methylation and uracil misincorporation, leading to DNA instability [7-9].

Previous epidemiological studies have shown inconsistent results for associations between folate status and pancreatic cancer risk suggesting a weak inverse association with dietary folate intake from natural sources, but not from supplements [10-14]. A recent meta-analysis supported this observation[15] whereas a large pooled analysis of 14 prospective cohort studies found no association [16]. In the former meta-analysis, the overall estimates were from both case-control and prospective cohort studies, and a significant heterogeneity was found across those studies. In the latter pooled analyses, folate data might not be comparable across studies and countries due to the use of various databases and analytical methods, thus

attenuating potential relationships with pancreatic cancer. A recent meta-analysis of randomised trials of folic acid supplementation with an average duration of 5 years of treatment found no significant effect on overall or site-specific cancer incidence including pancreatic cancer [17]. The results from plasma measurements of folate intake in association with pancreatic cancer were also inconclusive [18-20]. In a more recent nested case-control study in the EPIC cohort, including 463 incident pancreatic cancer case, a weak U-shaped association was observed between plasma folate and pancreatic cancer risk[18].

The aim of this study was to investigate the association between dietary folate intake and pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, benefitting from a large number of cases with an extended follow-up time and standardised dietary folate intake data from a comprehensive EPIC Nutrient DataBase (ENDB) where folate information was harmonized using common procedures and guidelines, with support from the local national compilers in 10 countries participating in EPIC[21].

Subjects and Methods

Study population

The EPIC study is a multicentre prospective cohort study designed to investigate the associations between diet and various lifestyle, environmental risk factors and the incidence of different cancers and other chronic diseases. The full rationale and methods of the study were reported elsewhere [22, 23]. Briefly, the EPIC cohort consists of 23 study centres in 10 European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK), with over 521,330 participants. EPIC participants were mostly recruited from the general population residing within defined geographical areas between

1992 and 2000, with some exceptions: women members of a health insurance for school employees (France); women attending breast cancer screening (Utrecht, the Netherlands, Florence, and Italy); blood donors (centres in Italy and Spain) and a cohort with a large proportion (approximately 50%) of vegetarians ('health conscious' cohort in Oxford, UK). The participants completed dietary and lifestyle questionnaires and had their anthropometric measurements recorded by trained health professionals (self-reported in France, Norway and Oxford). All participants gave their written informed consent, and the study was approved by the local ethics committee in the participating countries and the Ethics Committee of the Internal Agency for Research on Cancer, Lyon, France.

Our study is based on data from 477,206 participants (142,228 men and 334,978 women) after a priori exclusion of individuals with prevalent cancer at recruitment, missing diagnosis or censoring date, missing dietary or lifestyle information, and implausible extreme values in the top and bottom one percent of the distribution of the ratio of reported total energy intake to estimated energy requirement (estimated from age, sex, and body weight and height).

Diet and lifestyle data

Diet including folate and other B vitamins over the previous 12 months was measured by country/centre-specific validated dietary assessment methods, mostly food frequency questionnaire designed to capture local dietary habits and to allow high compliance. The relative validity and reproducibility of the questionnaires has previously been published [24]. The questionnaire, validated within each count ry, was self-administered in all centres, except in Greece, two Italian centres, and Spain, where it was administered by interviewers.

Dietary folate intake was estimated using the updated EPIC Nutrient DataBase (ENDB)[21]. The ENDB project was initiated and nutrient databases were harmonized using common

93 procedures and guidelines, with support from the local national compilers in 10 countries in
94 EPIC [25]. The ENDB was first completed for 26 priority components to provide a standardised
95 reference instrument for calibrating the EPIC dietary measurements at the nutrient level [26].
96 This work has been extended to cover other nutrients including folate and other B vitamins[21]
97 Although the ENDB values were obtained from country-specific food composition tables,
98 they were standardized as much as possible across the EPIC countries by matching of EPIC
99 foods to the national databases according to the recommendation given in a recent review[21].
100 In particular, a microbiological assay was chosen as the reference analytical method for folate
101 values in the ENDB. Folate values of unavailable foods were derived by recipe calculation or
102 borrowed from similar foods[21]. During the ENDB compilation for folate, to address the issue
103 of voluntary fortification of breakfast cereals particularly in the UK and France where cereal
104 consumption was substantially higher, aggregation was re-done taking into account the brand
105 names and folic acid fortification levels of cereals[21].

106 In the Scandinavian countries and in the Netherlands, folate fortification was not allowed
107 at the time of data collection. In other EPIC countries, breakfast cereal consumption was very
108 low and the information on folic acid-fortified foods was not always available[21]. It was
109 therefore, decided not to adopt the dietary folate equivalent (DFE) conversion which
110 considers lower bioavailability of naturally occurring folate compared to synthetic folic acid.
111 Information on dietary intakes of other nutrients including other B vitamins was also
112 estimated using the ENDB.

113 Self-reported data on lifestyle factors, including total physical activity, educational level,
114 smoking history, diabetes status and ever use of vitamin or mineral supplements considered
115 in the analysis were collected at baseline through standardised questionnaires and clinical
116 examinations, and have been described elsewhere [23, 27-30].
117

Endpoints

Incident pancreatic cancer cases were identified through population cancer registries (Denmark, Italy, Netherlands, Norway, Spain, Sweden, and the UK) or by active follow-up (France, Germany, Naples, and Greece). The active follow-up procedure used a combination of different strategies, including health insurance records, cancer and pathology registries, and contacts with participants and their next of kin [23]. Participants were followed up from study entry until cancer diagnosis (except non-melanoma skin cancer), death, emigration or until the end of the follow-up period, whichever occurred first. Forty-five cases were censored because the tumours were neuroendocrine (n = 42), benign (n = 1), carcinoma in situ (n = 1), or with uncertain primary origin (n = 1). After a mean follow-up of approximately 11 years, 865 first incident pancreatic cancers were available for analysis and were classified corresponding to the International Classification of Diseases 10th revision as C25 (C25.0–C25.3 and C25.7–C25.9).

Statistical analysis

Multivariable Cox proportional hazard models were fitted to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Disease models were fitted with intake of folate and other B vitamins as continuous variables and categorisation of the variables in quartiles based on the distribution of the whole study population. Dietary folate intake and other nutrients were energy adjusted using the residual method [31]. To preserve the geographical specificity in the dietary assessment in EPIC, centre-specific residuals for total dietary folate were computed. Centre-specific mean values were then added to residuals to recuperate the original scale and ease interpretability.

The following potential confounders were considered based on the literature review: total energy intake (kcal/d), BMI (kg/m^2), physical activity (<moderately inactive/≥moderately

active), smoking status (never/former/current), education (<secondary school/ ≥secondary school), ever use of vitamin or mineral supplements (no/yes), history of diabetes (no/yes) and intake of other dietary factors (g/day) including dietary fibre, carbohydrate, and alcohol. In the multivariable models, the variables that changed the unadjusted risk estimate by at least ~10% were considered as confounders and adjusted for. These include smoking status, BMI, educational level, history of diabetes, supplement use and dietary fibre intake. Energy intake was further included in the model for complete energy adjustment [31] even though it did not alter the unadjusted risk substantially.

Quartiles of dietary folate intake were determined on the basis of the whole cohort, with the lowest quartile as the reference. Disease models were stratified by age at recruitment, sex, and study centre (Model 1) and adjusted for smoking status, total energy intake and BMI, education, diabetes status, supplement use and dietary fibre intake (Model 2). A test for trend was made by modelling a score variable using quartile-specific medians as a continuous variable. In addition, the association between dietary folate and the risk of pancreatic cancer was examined using four-knot restricted cubic splines[32] with the median of the fifth decile of folate intake as the reference category.

Alcohol intake was not considered as a covariate in the models as it did not change the unadjusted risk estimates. However, alcohol has a role as a folate antagonist and has been shown to have suppressive effects on methyl group metabolism [33], and we investigated the association according to tertiles of alcohol consumption. Likewise, we further explored the association between dietary folate intake and pancreatic cancer risk stratified by smoking status as smoking has been the most consistently known risk factor for pancreatic cancer and current smoking status was related to lower dietary folate intake [34]. Models with main effects and cross-product terms were fitted to test for interactions.

The effect of very high (≥500 µg/d) or very low folate intake (<150 µg/d) in relation to pancreatic cancer risk was additionally explored, with the reference category set at 200-300 µg/d, which was observed to be the average intake range in a previous EPIC study comparing standardised dietary folate intake across ten participating countries[34].

A model including the combined effects of folate tertiles and three smoking categories in relation to overall pancreatic cancer risk was developed and the joint effects was presented in comparison with never smokers in the highest folate tertile as a reference.

Sensitivity analyses were performed 1) excluding any dietary supplement users to examine a possible impact of supplement use on the association between dietary folate and pancreatic cancer risk 2) excluding the cases diagnosed within the first 2 years of follow-up to assess possible influence of preclinical factors that might cause a change in diet among participants and 3) excluding the microscopically non-confirmed cases (n = 257) to minimize possible misclassification of tumours.

All statistical tests were two-sided and analyses were performed using STATA (version 13, Stata Corporation, College Station, Texas).

Results

A total of 477,206 participants without any history of cancer and with complete dietary folate information were included in the analysis among which 397 men and 468 women developed a first primary pancreatic cancer during an average of 11 years of follow-up. **Table 1** shows baseline characteristics of the participants according to quartiles of energy-adjusted dietary folate intake. Participants in the highest category of folate intake tended to be more educated, were less likely to report being a current smoker and more likely to be physically active or

dietary supplement users; and consumed more dietary fibre, fruit and vegetables compared with those with lower dietary folate intake.

When we investigated energy-adjusted folate intake as a continuous variable in association with pancreatic cancer in the fully adjusted model, we found an HR of 1.03 (95% CI: 0.83, 1.28; *P*=0.78*)* for an increment of 100 μg/day of dietary folate intake (approximately 1 SD). When folate intake was categorised into quartiles, higher dietary folate intake showed a borderline statistically significant association with lower risk of pancreatic cancer (Model 1, **Table 2**). The trend became attenuated and did not reach statistical significance in Model 2 after multivariable adjustment (**Table 2**): the multivariable HR of pancreatic cancer for those in the highest category of folate intake (≥353 μg/day) compared with the lowest category of intake (<241 μg/day) was 0.81 (95% CI: 0.51, 1.31; P_{trend} = 0.38). Among the variables included in the Model 2, smoking and dietary fibre intake changed the unadjusted risk estimate most. Our non-linear multivariable modelling of the association using cubic spline confirmed no significant trend (**Figure 1**). Further analysis using continuous folate intake with a quadratic term provided no evidence of a non-linear association between folate intake and pancreatic cancer risk ($P_{quadratic\ term}$=0.56).

When we investigated the association according to alcohol consumption, there was no evidence of a differential relationship according to levels of alcohol intake ($P_{interaction}$= 0.82, **Table 2**). In a subgroup analysis by smoking status we observed an increased risk of pancreatic cancer with increasing folate intake in current smokers while no significant associations were observed in never and former smokers: the multivariable HR of pancreatic cancer among current smokers and those who had folate intake between 292 and 352 μg/day and those who consumed more than 353 μg/day compared with the lowest category were 4.52 (95% CI: 1.59, 12.88) and 4.42 (95% CI: 1.05, 18.62), respectively (P_{trend} = 0.01, **Table 2**). The results did not differ when alcohol was additionally adjusted for. Nonetheless, an

interaction test with smoking and folate intake for the risk of pancreatic cancer was not statistically significant ($P_{interaction}$= 0.99).

The characteristics of the participants in this study varied according to their smoking status. Current smokers were younger, more likely to be men, to have a lower educational level, and less likely to be diabetic at baseline, tended to have lower folate, fibre, fruit and vegetable intakes and consumed more alcohol compared to never smokers (data not shown). Further alcohol adjustment in the main models did not change the risk estimates stratified by smoking status. When we considered smoking intensity in current smokers by adjusting for number of cigarettes smoked per day, the results showed a greater than five-fold increased risk in those who had a folate intake of more than 292 μg/d (data not shown).

The observed increased risk of pancreatic cancer with higher folate intake in current smokers was further explored by choosing one single reference category (≥330 μg/day of dietary folate intake and never smoker) and combined effects were determined for tertiles of folate intakes in combination with categories of smoking status in relation to pancreatic cancer risk (**Figure 2**). A more than 50% increase in pancreatic cancer risk was observed in current smokers regardless of the levels of folate intake, although a significantly higher risk was observed among those who consumed more than 258 μg/day of folate.

We also explored the effect of very high (≥500 μg/d) or very low folate intake (<150 μg/d) in relation to pancreatic cancer risk, and we did not observe any significant associations in the multivariable adjusted model, possibly due to limited statistical power (**Table 3**).

When we conducted a sensitivity analysis among those who reported not to take any dietary supplements (n=237,113), the results did not change substantially (HR of 0.90, 95% CI: 0.60, 1.35; P=0.61 for an increment of 100 μg/day folate, HR for the highest quartile vs. lowest: 0.61, 95% CI: 0.26, 1.44; P_{trend} = 0.28). Similarly, the results hardly changed when

we excluded the pancreatic cancer cases incident within the first 2 years of follow-up (n=90 cases) and repeated the analyses (HR of 1.03, 95% CI: 0.82, 1.29; P=0.79 for an increment of 100 µg/day, HR for the highest quartile vs. lowest: 0.79, 95% CI: 0.48, 1.30; P_{trend} = 0.32). A sensitivity analysis restricting the analyses to the microscopically confirmed cases did not alter the results.

Discussion

To our knowledge, this study that analysed 865 incident pancreatic cancer cases, is the largest single study so far that investigated the association between dietary folate intake and pancreatic cancer risk. Within a unique international setting of European populations with diverse dietary habits and lifestyle characteristics, we found no overall association between dietary folate intake and pancreatic cancer risk.

There have been relatively few published single prospective studies that examined the association between dietary folate intake and pancreatic cancer risk (summarised in **Table 4**). Previous studies showed inconsistent results: they were heterogeneous by sex, ranges of dietary folate intake, supplement use, and confounding factors that were adjusted for in the analyses (**Table 4**). Including studies conducted in the US, where dietary supplement use is widespread, there is little evidence that folic acid intake from supplements was associated with pancreatic cancer risk, while dietary folate intake was shown to be possibly related with lower risks in some, but not in all studies (**Table 4**). Only one study from the US was able to distinguish the difference in dietary folate intake from natural sources and from folic acid fortification [12]. In this study, no association was found in men, while women in the highest quartile of food folate intake showed a significant 53% reduction in pancreatic cancer risk

compared with those in the lowest quartile. No significant association was found between supplemental folic acid use and pancreatic cancer risk [12].

Three meta-analyses[15, 35, 36] have reported a generally decreased risk of pancreatic cancer with increasing dietary folate intake based on the above mentioned cohort studies together with case-control studies, with significant heterogeneity reported in the two[15, 36]. The 2012 Continuous Update Project (CUP) Report of the WCRF/AICR Export Report weakened the conclusions from the 2007 Expert Report, after reviewing evidence from five prospective cohort studies, concluding the evidence is too inconsistent to allow a firm conclusion to be drawn[4].

A large pooled analysis of 14 prospective cohort studies showed that dietary folate intake was not associated with overall risk of pancreatic cancer [16]. The summary relative risk for the highest vs. the lowest quintile of folate intake was 1.06 (95% CI: 0.90-1.25, $P_{heterogeneity}$=0.15) [16]. In the pooled analysis, folate data may be heterogeneous across studies and countries as studies rely on each country's own food-composition data which tend to vary in terms of availability and quality of folate values [37, 38]. This may have an influence in a potential relationship. It has been pointed out that there is a lack of clarity and consistency in the terminology and definitions used for folate information in the food composition tables available in Europe due to the specific complexity of folate [39]. A recent critical evaluation of folate data in 18 European and international databases concluded that a lack of comparability still exists between countries [40]. To overcome this, our study results came from the standardised food and nutrient data linked to the ENDB with recently updated folate information.

Despite the recent increasing use of dietary supplements in many European countries, the use of folic acid supplement was not a common practice when our baseline data were collected [10, 41]. Indeed, folic acid-containing supplements were not among the most frequently

consumed types of supplements in the EPIC study according to the 24 hour-recall data that were collected in a sub group of participants with more detailed information on supplement use at the baseline [41]. In addition, folic acid fortification was not widespread at the time of the baseline information collection in Europe[21]. Thus, we had the unique opportunity to assess the association between baseline dietary folate intake and pancreatic cancer risk, with minimum influence of folic acid fortification or supplementation in the EPIC study. This was confirmed when we conducted a sensitivity analysis excluding ever users of vitamin and mineral supplements and the results did not materially change.

In our study, we observed a greater than four-fold elevated risk in current smokers with higher dietary folate intake while in never or former smokers the risks were lower and non-significant. Current smokers have a higher chance to harbour precursor lesions in the pancreas, and increased availability of folate may promote proliferation of already existing neoplastic cells [42, 43]. We investigated this further by excluding cases diagnosed within the first two or three years of follow-up which did not alter the results. Previous studies have shown inconsistent results with regards to smoking status. While a previous EPIC nested case-control study that investigated plasma folate levels in relation to pancreatic cancer risk did not show any heterogeneity across smoking status[18], an inverse association with pancreatic cancer risk was reported with both dietary folate intake[14] and serum folate levels[19] in a cohort of Finnish male smokers. In the large pooled analysis of cohort studies, there was no effect modification by smoking status with dietary folate intake[16]. Although increased pancreatic cancer risk observed in current smokers in our study, especially in participants with dietary folate intake higher than 292 μg/day may be worth exploring further in future studies, few cases included, no statistically significant interaction found, potential role of residual confounding or chance require cautious interpretation of the results.

The current study has limitations. We did not have information on occurrence of pancreatitis in the study population which might have affected pancreatic cancer risk. Neither did we have repeated information during the follow-up period to assess any potential changes in dietary intakes over time. In addition, we relied on self-reported dietary folate intake. However, the overall results did not substantially differ from the previous EPIC study that investigated plasma folate level in association with pancreatic cancer risk[18]. In our study, the range of dietary folate intake was quite narrow, as shown previously in the results using the 24-hour dietary recall methods [34], with too few participants with either very low or very high intakes. It was therefore not possible to explore the effect of extreme folate intake on pancreatic cancer risk with sufficient statistical power. We used self-reported smoking status which might be inaccurate. However, a recent EPIC study of plasma cotinine level and pancreatic cancer risk compared the cotinine level against self-reported smoking status and concluded that self-reported smoking status was sufficient to establish a causal relationship and did not underestimate its relationship with pancreatic cancer risk [44].

In conclusion, using standardised data from this large, multi-centre prospective study, we found no association between dietary folate intake and pancreatic cancer risk.

Data sharing statement: 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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Reference List

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 6/February/2018., 2013.

2. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 2015;44: 186-98.

3. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009;6: 699-708.

4. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Pancreatic Cancer. Available at http://www.dietandcancerreport.org, 2012.

5. Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. Clin Gastroenterol Hepatol 2008;6: 275-82.

6. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005;294: 2872-8.

7. Kim YI. Folate and DNA Methylation: A Mechanistic Link between Folate Deficiency and Colorectal Cancer? Cancer Epidemiol Biomarker Prev 2004;13: 511-9.

8. Blount BC, Mack MM, Wehr CM, MacGregor JT, Hiatt RA, Wang G, Wickramasinghe SN, Everson RB, Ames BN. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: Implications for cancer and neuronal damage. Proc Natl Acad Sci U S A 1997;94: 3290-5.

9. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA Methylation: A Review of Molecular Mechanisms and the Evidence for Folate's Role. Adv Nutr 2012;3: 21-38.

10. Keszei AP, Verhage BA, Heinen MM, Goldbohm RA, van den Brandt PA. Dietary folate and folate vitamers and the risk of pancreatic cancer in the Netherlands cohort study. Cancer Epidemiol Biomarkers Prev 2009;18: 1785-91.

11. Larsson SC, Hakansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. J Natl Cancer Inst 2006;98: 407-13.

12. Oaks BM, Dodd KW, Meinhold CL, Jiao L, Church TR, Stolzenberg-Solomon RZ. Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr 2010;91: 449-55.

13. Skinner HG, Michaud DS, Giovannucci EL, Rimm EB, Stampfer MJ, Willett WC, Colditz GA, Fuchs CS. A prospective study of folate intake and the risk of pancreatic cancer in men and women. Am J Epidemiol 2004;160: 248-58.

14. Stolzenberg-Solomon RZ, Pietinen P, Barrett MJ, Taylor PR, Virtamo J, Albanes D. Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers. Am J Epidemiol 2001;153: 680-7.

15. Lin HL, An QZ, Wang QZ, Liu CX. Folate intake and pancreatic cancer risk: an overall and dose–response meta-analysis. Public Health 2013;127: 607-13.

16. Bao Y, Michaud DS, Spiegelman D, Albanes D, Anderson KE, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Goldbohm RA, Hakansson N, Horn-Ross PL, Jacobs EJ, Kitahara CM, Marshall JR, Miller AB, Robien K, Rohan TE, Schatzkin A, Stevens VL, Stolzenberg-Solomon RZ, Virtamo J, Wolk A, Ziegler RG, Smith-Warner SA. Folate Intake and Risk of Pancreatic Cancer: Pooled Analysis of Prospective Cohort Studies. Journal of the National Cancer Institute 2011;103: 1840-50.

17. Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, Armitage J, Manson JE, Hankey GJ, Spence JD, Galan P, Bonaa KH, Jamison R, Gaziano JM, Guarino P, Baron JA, Logan RF, Giovannucci EL, den Heijer M, Ueland PM, Bennett D, Collins R, Peto R. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50000 individuals. The Lancet 2013;381: 1029-36.

18. Chuang SC, Stolzenberg-Solomon R, Ueland PM, Vollset SE, Midttun O, Olsen A, Tjonneland A, Overvad K, Boutron-Ruault MC, Morois S, Clavel-Chapelon F, Teucher B, Kaaks R, Weikert C, Boeing H, Trichopoulou A, Benetou V, Naska A, Jenab M, Slimani N, Romieu I, Michaud DS, Palli D, Sieri S, Panico S, Sacerdote C, Tumino R, Skeie G, Duell EJ, Rodriguez L, Molina-Montes E, Huerta JM, Larranaga N, Gurrea AB, Johansen D, Manjer J, Ye W, Sund M, Peeters PH, Jeurnink S, Wareham N, Khaw KT, Crowe F, Riboli E, Bueno-de-Mesquita B, Vineis P. A U-shaped relationship between plasma folate and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Eur J Cancer 2011;47: 1808-16.

19. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, Hartman TJ, Tangrea JA, Rautalahti M, Sehlub J, Virtamo J, Taylor PR. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. J Natl Cancer Inst 1999;91: 535-41.

20. Schernhammer E, Wolpin B, Rifai N, Cochrane B, Manson JA, Ma J, Giovannucci E, Thomson C, Stampfer MJ, Fuchs C. Plasma folate, vitamin B6, vitamin B12, and homocysteine and pancreatic cancer risk in four large cohorts. Cancer Res 2007;67: 5553-60.

21. Nicolas G, Witthöft CM, Vignat J, Knaze V, Huybrechts I, Roe M, Finglas P, Slimani N. Compilation of a standardised international folate database for EPIC. Food Chem 2016;193: 134-40.

22. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26: S6.

23. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, Overvad K, Tjonneland A, Clavel-Chapelon F, Thiebaut A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-de-Mesquita HB, Peeters PHM, Lund E, Engeset D, Gonzalez CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R. European prospective investigation into cancer and nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5: 1113-24.

24. Kaaks R, Slimani N, Riboli E. Pilot phase studies on the accuracy of dietary intake measurements in the EPIC project: overall evaluation of results. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26: S26.

25. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, Salvini S, Parpinel M, Moller A, Ireland J, Becker W, Farran A, Westenbrink S, Vasilopoulou E, Unwin J, Borgejordet A, Rohrmann S, Church S, Gnagnarella P, Casagrande C, van Bakel M, Niravong M, Boutron-Ruault MC, Stripp C, Tjonneland A, Trichopoulou A, Georga K, Nilsson S, Mattisson I, Ray J, Boeing H, Ocke M, Peeters PH, Jakszyn P, Amiano P, Engeset D, Lund E, de Magistris MS, Sacerdote C, Welch A, Bingham S, Subar AF, Riboli E. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. Eur J Clin Nutr 2007;61: 1037-56.

26. Slimani N, Margetts Be. Nutrient intake and patterns in the EPIC cohorts from 10 European countries. Eur J Clin Nutr 2009;63.

27. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, Bellegotti M, Ocke MC, Peeters PHM, Engeset D, Lund E, Agudo A, Larranaga N, Mattisson I, Andren C, Johansson I, Davey G, Welch AA, Overvad K, Tjonneland A, van Staveren WA, Saracci R, Riboli E. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr 2002;5: 1125-45.

28. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S, Linseisen J, Rohrmann S, Boeing H, Pischon T, Tjonneland A, Halkjaer J, Overvad K, Mendez M, Redondo ML, Garcia CM, Larranaga N, Tormo MJ,

Gurrea AB, Bingham S, Khaw KT, Allen N, Key T, Trichopoulou A, Vasilopoulou E, Trichopoulos D, Pala V, Palli D, Tumino R, Mattiello A, Vineis P, Bueno-de-Mesquita HB, Peeters PHM, Berglund G, Manjer J, Lundin E, Lukanova A, Slimani N, Jenab M, Kaaks R, Riboli E. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control 2007;18: 399-413.

29. Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H, Giurdanella MC, Krogh V, Bueno-de-Mesquita H, Peeters PHM, Skeie G, Hjartaker A, Rodriguez M, Quiros JR, Berglund G, Janlert U, Khaw KT, Spencer EA, Overvad K, Tjonneland A, Clavel-Chapelon F, Tehard B, Miller AB, Klipstein-Grobusch K, Benetou V, Kiriazi G, Riboli E, Slimani N. Overweight, obesity and fat distribution in 50-to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5: 1147-62.

30. Haftenberger M, Schuit AJ, Tormo N, Boeing H, Wareham N, Bueno-de-Mesquita HB, Kumle M, Hjartaker A, Chirlaque MD, Ardanaz E, Andren C, Lindahl B, Peeters PHM, Allen NE, Overvad K, Tjonneland A, Clavel-Chapelon F, Linseisen J, Bergmann MM, Trichopoulou A, Lagiou P, Salvini S, Panico S, Riboli E, Ferrari P, Slimani N. Physical activity of subjects aged 50-64 years involved in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5: 1163-77.

31. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65: 1220S-8S; discussion 9S-31S.

32. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Comput Methods Programs Biomed 1997;54: 201-8.

33. Halsted CH, Villanueva JA, Devlin AM, Chandler CJ. Metabolic interactions of alcohol and folate. J Nutr 2002;132: 2367S-72S.

34. Park JY, Nicolas G, Freisling H, Biessy C, Scalbert A, Romieu I, Chajes V, Chuang SC, Ericson U, Wallstrom P, Ros MM, Peeters PHM, Mattiello A, Palli D, Huerta JM, Amiano P, Halkjaer J, Dahm CC, Trichopoulou A, Orfanos P, Teucher B, Feller S, Skeie G, Engeset D, Boutron-Ruault MC, Clavel-Chapelon F, Crowe F, Khaw KT, Vineis P, Slimani N. Comparison of standardised dietary folate intake across ten countries participating in the European Prospective Investigation into Cancer and Nutrition. Br J Nutr 2012;108: 552-69.

35. Larsson SC, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. Gastroenterology 2006;131: 1271-83.

36. Tio M, Andrici J, Cox MR, Eslick GD. Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis. J Gastroenterol Hepatol 2014;29: 250-8.

37. deBree A, vanDusseldorp M, Brouwer IA, vanhetHof KH, SteegersTheunissen RPM. Folate intake in Europe: recommended, actual and desired intake. Eur J Clin Nutr 1997;51: 643-60.

38. Elmadfa I, Meyer A, Nowak V, Hasenegger V, Putz P, Verstraeten R, Remaut-DeWinter AM, Kolsteren P, Dostalova J, Dlouhy P, Trolle E, Fagt S, Biltoft-Jensen A, Mathiessen J,

Velsing Groth M, Kambek L, Gluskova N, Voutilainen N, Erkkila A, Vernay M, Krems C, Strassburg A, Vasquez-Caicedo AL, Urban C, Naska A, Efstathopoulou E, Oikonomou E, Tsiotas K, Bountziouka V, Benetou V, Trichopoulou A, Zajkas G, Kovacs V, Martos E, Heavey P, Kelleher C, Kennedy J, Turrini A, Selga G, Sauka M, Petkeviciene J, Klumbiene J, Holm Totland T, Andersen LF, Halicka E, Rejman K, Kowrygo B, Rodrigues S, Pinhao S, Ferreira LS, Lopes C, Ramos E, Vaz Almeida MD, Vlad M, Simcic M, Podgrajsek K, Serra Majem L, Roman Vinas B, Ngo J, Ribas Barba L, Becker V, Fransen H, Van Rossum C, Ocke M, Margetts B. European Nutrition and Health Report 2009. Forum Nutr 2009;62: 1-405.

39. Deharveng G, Charrondiere UR, Slimani N, Southgate DA, Riboli E. Comparison of nutrients in the food composition tables available in the nine European countries participating in EPIC. European Prospective Investigation into Cancer and Nutrition. Eur J Clin Nutr 1999;53: 60-79.

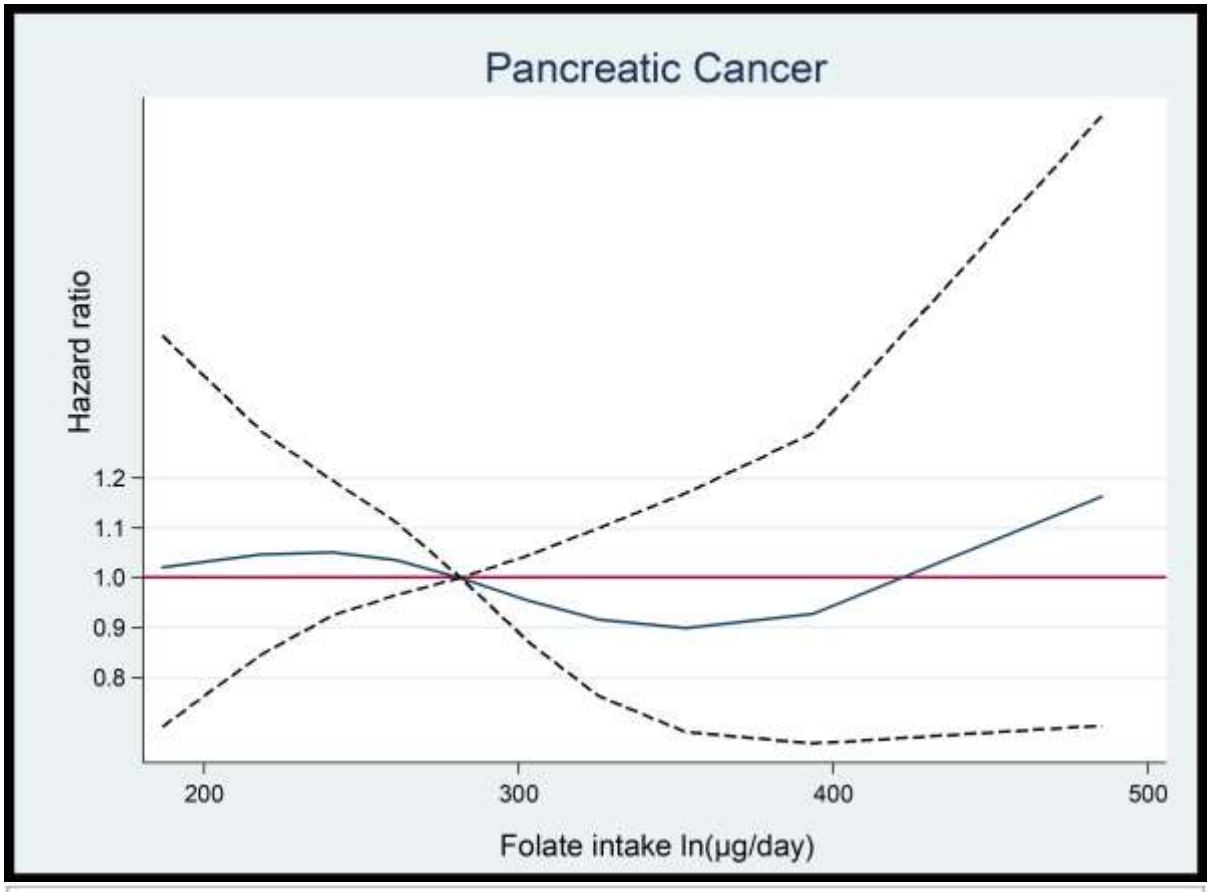
40. Bouckaert KP, Slimani N, Nicolas G, Vignat J, Wright AJ, Roe M, Witthoft CM, Finglas PM. Critical evaluation of folate data in European and international databases: recommendations for standardization in international nutritional studies. Mol Nutr Food Res 2011;55: 166-80.

41. Skeie G, Braaten T, Hjartaker A, Lentjes M, Amiano P, Jakszyn P, Pala V, Palanca A, Niekerk EM, Verhagen H, Avloniti K, Psaltopoulou T, Niravong M, Touvier M, Nimptsch K, Haubrock J, Walker L, Spencer EA, Roswall N, Olsen A, Wallstrom P, Nilsson S, Casagrande C, Deharveng G, Hellstrom V, Boutron-Ruault MC, Tjonneland A, Joensen AM, Clavel-Chapelon F, Trichopoulou A, Martinez C, Rodriguez L, Frasca G, Sacerdote C, Peeters PHM, Linseisen J, Schienkiewitz A, Welch AA, Manjer J, Ferrari P, Riboli E, Bingham S, Engeset D, Lund E, Slimani N. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. Eur J Clin Nutr 2009;63: S226-S38.

42. Smith AD, Kim YI, Refsum H. Is folic acid good for everyone? The American Journal of Clinical Nutrition 2008;87: 517-33.

43. Ulrich CM, Potter JD. Folate and cancer - Timing is everything. Jama-Journal of the American Medical Association 2007;297: 2408-9.

44. Leenders M, Chuang SC, Dahm CC, Overvad K, Ueland PM, Midttun O, Vollset SE, Tjonneland A, Halkjaer J, Jenab M, Clavel-Chapelon F, Boutron-Ruault MC, Kaaks R, Canzian F, Boeing H, Weikert C, Trichopoulou A, Bamia C, Naska A, Palli D, Pala V, Mattiello A, Tumino R, Sacerdote C, van Duijnhoven FJ, Peeters PH, van Gils CH, Lund E, Rodriguez L, Duell EJ, Perez MJ, Molina-Montes E, Castano JM, Barricarte A, Larranaga N, Johansen D, Lindkvist B, Sund M, Ye W, Khaw KT, Wareham NJ, Michaud DS, Riboli E, Xun WW, Allen NE, Crowe FL, Bueno-de-Mesquita HB, Vineis P. Plasma cotinine levels and pancreatic cancer in the EPIC cohort study. Int J Cancer 2012;131: 997-1002.



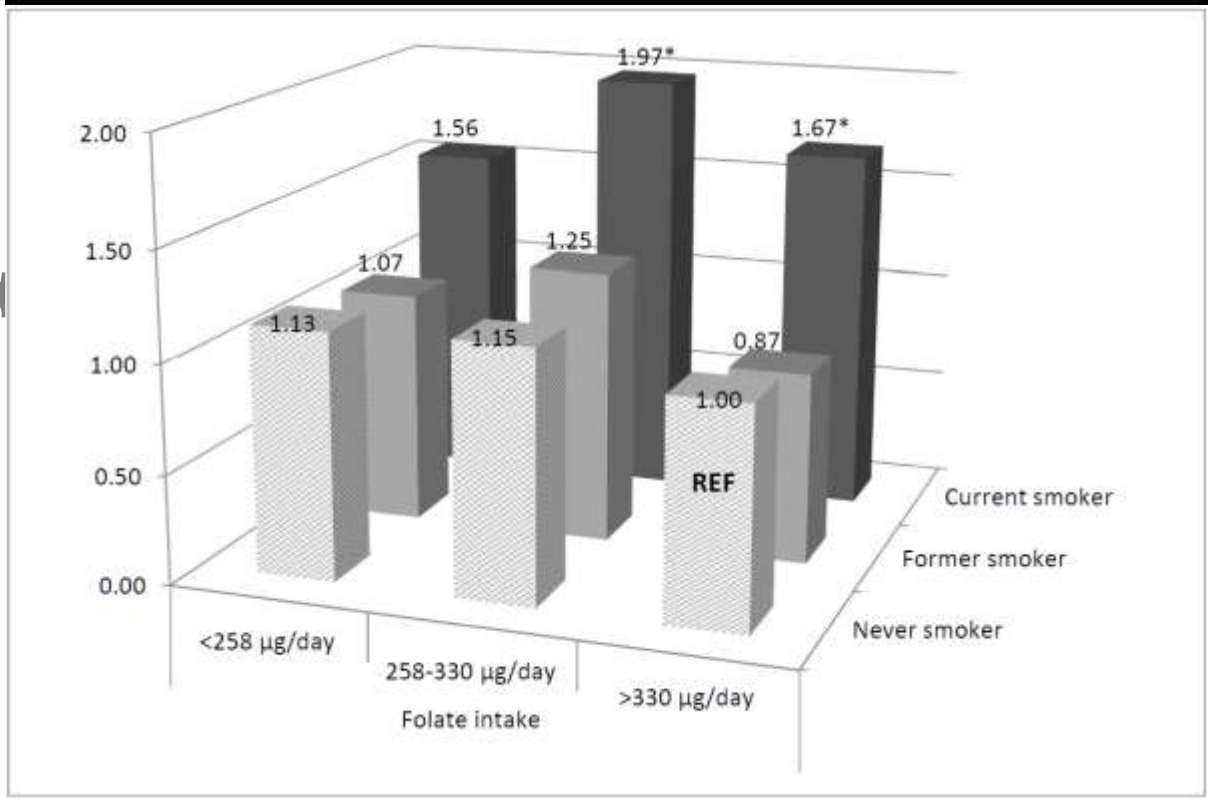


Table 1 Baseline characteristics of participants by energy-adjusted dietary folate intake, the EPIC study

	Energy-adjusted folate intake (µg/d)			
	Q1	Q2	Q3	Q4
Range	0-241	241-292	292-353	≥353
Cases/all participants	231/119,302	234/119,301	228/119,302	172/119,301
Men	133/44,758	106/38,789	95/33,284	63/25,397
Women	98/74,544	128/80,512	133/86,018	109/93,904
Person-years	1,320,250	1,321,789	1,309,460	1,313,115
Sex				
Men	37.5	32.5	27.9	21.3
Women	62.5	67.5	72.1	78.7
Age (years)	50.2 (9.0)	51.5 (9.3)	52.3 (9.9)	50.9 (11.3)
BMI (kg/m^2)	25.4 (4.1)	25.6 (4.3)	25.6 (4.4)	25.0 (4.4)
Smoking status				
Never (%)	42.4	46.6	53.1	58.2
Former (%)	27.4	27.8	26.0	27.4
Current (%)	30.2	25.6	20.9	14.4
Educational level				
<Secondary school (%)	62.1	57.5	53.7	42.7
≥Secondary school (%)	37.9	42.5	46.3	57.3
Physical activity				
< moderately inactive (%)	58.1	56.4	56.9	55.6
> moderately active (%)	41.9	43.6	43.1	44.4
Dietary supplement user				
No (%)	67.4	63.0	57.5	52.9
Yes (%)	32.6	37.0	42.5	47.1
Self-reported diabetes				
No (%)	98.1	97.4	96.6	96.4
Yes (%)	1.9	2.6	3.4	3.7
Energy intake (Kcal)	2,062 (678)	2,064 (614)	2,067 (602)	2,092 (611)
Alcohol intake (units/week)[1,2]	6.20 (15.27)	8.36 (16.15)	8.13 (13.89)	6.23 (11.17)
Fibre intake (g/day)[2]	18.39 (4.16)	21.61 (4.45)	23.59 (4.93)	27.54 (6.67)
Folate intake (µg/d)[1,2]	211.82 (35.04)	266.36 (25.44)	319.59 (29.62)	408.31 (89.83)
Vitamin B-12 intake (µg)[1,2]	5.51 (2.68)	5.96 (3.19)	6.09 (3.74)	6.02 (4.55)
Vitamin B-6 intake (mg)[2]	1.53 (0.32)	1.76 (0.31)	1.95 (0.33)	2.25 (0.44)
Riboflavin intake (mg)[2]	1.47 (0.36)	1.70 (0.42)	1.93 (0.50)	2.34 (0.72)
Meat and meat products intake (g/day)[1]	93.5 (68.3)	97.7 (69.2)	94.4 (71.6)	78.7 (91.9)
Vegetable intake (g/day)[1]	97.9 (69.6)	145.6 (94.8)	210.4 (134.1)	321.3 (192.7)
Fruits, nuts and seeds intake (g/day)[1]	123.5 (137.7)	178.9 (176.1)	232.9 (204.1)	292.5 (246.9)

[1]Intakes are all dietary and shown as median values with interquartile ranges, otherwise values are mean (SD) for continuous or percentages for categorical variables. [2] Nutrients were energy adjusted.

Table 1 Hazard ratios of pancreatic cancer, with 95% confidence intervals (CIs), according to quartiles of energy-adjusted dietary folate intake

	Quartile of energy-adjusted dietary folate intake[1]					
	>0 to <241 µg/d	241 to <292 µg/d	292 to <353 µg/d	≥353 µg/d	*P* for trend	*P* for interaction
No. of all participants	119,302	119,301	119,302	119,301		
Pancreatic cancer cases	231	234	228	172		
Person-years	1,320,250	1,321,789	1,309,460	1,313,115		
Model1[2]	1.00	0.94 (0.70 - 1.25)	0.86 (0.62 - 1.18)	0.70 (0.48 - 1.03)	0.06	
Model2[3]	1.00	1.01 (0.74 - 1.37)	0.97 (0.67 - 1.41)	0.81 (0.51 - 1.31)	0.38	
Sex						
Men	1.00	0.90 (0.57 - 1.42)	0.97 (0.54 - 1.75)	0.76 (0.35 - 1.65)	0.57	0.49
Women	1.00	1.13 (0.73 - 1.74)	0.98 (0.60 - 1.62)	0.80 (0.43 - 1.50)	0.38	
Tertiles of alcohol intake						
T1 (no. cases), Median 0.8 g/day P10-P90 (0-3.0)	77	69	57	63		
	1.00	1.24 (0.62 - 2.48)	1.50 (0.60 - 3.78)	1.37 (0.33 - 5.75)	0.52	0.82
T2 (no. cases), Median 7.2 g/day(4.3-11.1)	54	70	69	61		
	1.00	0.80 (0.33 - 1.94)	0.74 (0.25 - 2.20)	0.51 (0.11 - 2.43)	0.41	
T3 (no. cases), Median 22.5 g/day (13.6-50.9)	100	95	102	48		
	1.00	0.97 (0.48 - 1.97)	1.89 (0.83 - 4.33)	1.33 (0.45 - 3.94)	0.28	
Smoking status						
	71	79	100	86		
Never smokers (no. cases)	1.00	0.79 (0.41 - 1.51)	1.03 (0.48 - 2.18)	0.55 (0.21 - 1.41)	0.24	0.99
	67	65	55	52		
Former smokers (no. cases)	1.00	0.79 (0.31 - 2.02)	0.71 (0.23 - 2.12)	0.55 (0.13 - 2.27)	0.41	
	90	89	68	28		
Current smokers (no. cases)	1.00	1.85 (0.82 - 4.17)	4.52 (1.59 - 12.88)	4.42 (1.05 - 18.62)	0.01	

[1] Folate intake was adjusted for energy using the residual method. [2]Model1 was with stratification of sex, age and centre. [3] Model2 was adjusted for smoking status, energy intake and BMI, education, diabetes status (self-reported), supplement use and fibre intake, and age, sex and centre being included as stratification variables.

Table 3 Hazard ratios of pancreatic cancer, with 95% confidence intervals (CIs), according to different categories of energy-adjusted dietary folate intake, with 200-300 µg/d of folate intake being a reference

	Energy-adjusted folate intake[1]					
	<150 µg/d	150 to <200 µg/d	200 to <300 µg/d	300 to <500 µg/d	≥500 µg/d	*P* for trend
No. of all participants	4,013	36,330	216,143	200,438	20,282	
Pancreatic cancer cases	17	58	420	344	26	
Person-years	45,102	401,302	2,392,501	2,200,878	224,725	
Model1[2]	2.72 (1.16 - 6.39)	0.81 (0.53 - 1.24)	1.00	0.82 (0.64 - 1.05)	1.17 (0.55 - 2.52)	0.34
Model2[3]	1.82 (0.70 - 4.73)	0.73 (0.47 - 1.14)	1.00	0.89 (0.67 - 1.18)	1.61 (0.67 - 3.86)	0.77

[1] Folate intake was adjusted for energy using the residual method. [2]Model1 was with stratification of sex, age and centre. [3] Model2 was adjusted for smoking status, energy intake and BMI, education, diabetes status (self-reported), supplement use and fibre intake, and age, sex and centre being included as stratification variables.

Table 4 Previous prospective studies that investigated the associations between dietary folate intake and pancreatic cancer risk

Study	Study data	Study participants		Exposure of interest	Average follow-up time (years)	Study outcome	Main statistical methods	Confounding factors adjusted	Main results	Conclusions	Comments on folic acid supplements
		Number (as in the analysis)	Age at baseline (years)								
Oaks et al, 201[illegible] (US)	The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort	51,988 men and 57,187 women	55-74	Dietary food folate (natural + fortified) intake (124-item FFQ data)	6.5	266 incident pancreatic cancer cases	Cox proportional hazard models	Age, total energy intake, smoking, self-reported diabetes, BMI, and saturated fat intake	0.47 (95% CI, 0.23-0.94; P_{trend}=0.09) for Q4 (>253.3 μg/d) vs. Q1 (<179.1 μg/d) in women and 1.20 (0.70-2.04; P_{trend}=0.67) for Q4 (>229.6 μg/d) vs. Q1 (<158.0 μg/d) in men	The results supoprt an association between higher food (natural+fortified) and total folate intakes and decreased risk of pancreatic cancer in women but not in men	The findings show no association between folic acid added to foods and pancreatic cancer risk (and also do not support the hypothesis that folic acid fortification increases the risk of pancreatic cancer)
[illegible]eszei et al, 2009 (The Netherlands)	The Netherlands Cohort Study	5,000 men and women (case-cohort design)	55-69	Dietary folate intake (150-item FFQ data)	13.3	363 incident pancreatic cancer cases	Cox proportional hazard models	Age, sex, smoking status, number of years smoked, number of cigarettes smoked, intake of vegetables and added sugar	1.37 (95% CI, 0.97-1.94; P_{trend}=0.07) for Q5 (>259.1 μg/d in men, >233.1 μg/d in women) vs. Q1 (<176.3 μg/d in men, <154.1 μg/d in women)	The results do not support a protective association of total dietary folate intake on the risk of pancreatic cancer	Folic acid in vitamin supplements was not allowed until the mid nineties, the effect of folic acid supplementation is therefore negligible
Larsson et al, 2006 [illegible]weden)	The Swedish Mammography Cohort+the Cohort of Swedish Men	81,922 men and women	45-83	Dietary folate intake (96-item FFQ data)	6.8	135 incident pancreatic cancer cases	Cox proportional hazard models	Age, sex, smoking status, pack-years of somking, education, BMI, exercise, history of diabetes, intakes of total energy, alcohol, and carbohydrate and fruit and vegetable consumption	0.25 (95% CI, 0.11-0.59; P_{trend}=0.002) for Q5 (>350 μg/d) vs. Q1 (<200 μg/d)	The results support an association between increased intake of food folate **and** a reduced risk of pancreatic cancer	An inverse association was observed between intake of folate from foods (combining dietary and supplemental sources), but not from supplements, and the risk of pancreatic cancer
Skinner et al, 200[illegible] (US)	The Nurses' Health Study + the Health Professionals Follow-up Study	77,640 women and 47,840 men	30-75	Dietary folate intake (131-item FFQ data)	14	326 incident pancreatic cancer cases	Cox proportional hazard models	Age, energy intake, cigarette smoking, BMI, diabetes and height	0.66 (95% CI, 0.37-1.18; P_{trend}=0.17) for Q5 (>500 μg/d) vs. Q1 (<300 μg/d)	The results from two large cohorts do not support a strong association between energy-adjusted folate intake and the risk of pancreatic cancer	No influence of supplemental folic acid, a nonsignificant inverse trend for folate from food sources
Stolzenberg-Solom[illegible]n et al, 2001 [illegible]inland)	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	27,101 male smokers	50-69	Dietary folate intake (276-item FFQ data)	13	157 incident pancreatic cancer cases	Cox proportional hazard models	Age and intervention adjusted	0.52 (95% CI, 0.31-0.87; P_{trend}=0.05) for Q5 (>373 μg/d) vs. Q1 (<280 μg/d)	The results support an inverse association between energy-adjusted dietary folate intake and the risk of pancreatic cancer in male smokers	No significant association found between folic acid supplement consumption and pancreatic cancer risk

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Inadequate folate intake is suspected of playing a role in the development of anomalies in DNA methylation, thereby contributing to carcinogenesis. In the case of pancreatic cancer, however, associations with folate status are unclear. The present investigation examined incident pancreatic cancer and dietary folate intake among subjects enrolled in the EPIC study, a multicentre prospective cohort study in Europe. Overall, no significant association was identified between dietary folate and pancreatic cancer risk. While a positive trend in risk association was detected among current smokers with high dietary folate, interactions between smoking and folate intake were not statistically significant.