Original Article

Dietary fiber intake is inversely associated with risk of pancreatic cancer: a meta-analysis

Qi-qi Mao PhD, Yi-wei Lin PhD, Hong Chen PhD, Jie Qin PhD, Xiang-yi Zheng PhD, Xin Xu PhD, Li-ping Xie MD

Department of Urology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China

Background and Objectives: The association between fiber intake and pancreatic cancer risk is conflicting and poorly explored. The aim of study was to investigate the association between dietary fiber intake and the risk of pancreatic cancer by conducting a meta-analysis of epidemiological studies. **Methods and Study Design:** Systematic search of PubMed and Embase databases up to April 2015 were conducted to identify relevant studies. Adjusted odds ratios (ORs) were combined using random-effects models to assess the risk of pancreatic cancer when comparing extreme categories of fiber intake. Dose-response meta-analysis was performed for studies reporting categorical risk estimates for at least 3 exposure levels. **Results:** One cohort and thirteen case-control studies were identified. The overall analysis revealed a strong inverse association between risk of pancreatic cancer and high fiber intake (OR 0.52; 95% CI 0.44-0.61). No publication bias was detected by Egger's or Begg's test. The dose-response analyses showed that the summary OR for an increment of 10 g daily intake of fiber was 0.88 (0.84 to 0.92). **Conclusion:** A high intake of dietary fiber was associated with a reduced risk of pancreatic cancer. Further well-designed prospective studies are warranted to confirm the inverse association and to identify the dietary fiber types involved.

Key Words: dietary fiber, epidemiology, meta-analysis, nutrition, pancreatic cancer

INTRODUCTION

Pancreatic cancer is a highly aggressive cancer and represents the 7th most frequent cause of cancer death worldwide with an approximate 265,000 deaths in 2008.[1] The increasing incidence in recent decades, together with the very high fatality rate, make this cancer a major contributor to cancer mortality.[2,3] Because there is no effective screening for pancreatic cancer, the prevention of this malignancy through identifying modifiable risk factors becomes very important. The striking variation in pancreatic cancer incidence across the world[4] and the migrant studies[5] have indicated the probable importance of lifestyle and environmental factors in the etiology of this disease.

It has been long hypothesized that plant foods or their components could protect against cancer. Fiber, which is found in high amounts in fruit, vegetables, and whole grains, is also hypothesized to have several anti-carcinogenic biological activities. Epidemiologic studies and meta-analyses have showed that dietary fiber is associated with reduced risk of several cancers, such as colorectal, breast, endometrial and upper aero-digestive tract cancers.[6-9] However, scanty and inconsistent studies are available on the relation between dietary fiber intake and pancreatic cancer. However, the World Cancer Research Fund[10] stated that there is insufficient evidence to draw a conclusion on the association between dietary fiber intake and pancreatic cancer risk. Therefore, the purpose of the present study was to summarize evidence on the association between dietary fiber intake and the risk of pancreatic cancer and to quantify the potential dose-response relationship by conducting a meta-analysis on all relevant published epidemiological studies.

METHODS
Publication search
The literature search was conducted in April 2015 using PubMed, EMBASE and Web of Science. We used the following search algorithm in the any field: (fiber or fibre) and AND (pancreas OR pancreatic) AND (neoplasm OR cancer). All potentially relevant publications were evaluated by examining their titles and abstracts, and full texts of the studies matching the inclusion criteria were retrieved. Reference lists of the retrieved articles were also reviewed to identify any additional relevant studies. This systematic review was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analyses.[11] The study was performed with the ap-

Corresponding Author: Dr Qi-qi Mao, Department of Urology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Qingchun Road 79, Hangzhou, Zhejiang Province, China.
Tel:+86 571 87236286; Fax: +86 571 87072577
Email: uromao@126.com

proval of the ethics committee of the First Affiliated Hospital of Zhejiang University.

Study selection and data extraction

Studies were included in the meta-analyses if they 1) had a prospective cohort or case-control study design; 2) the exposure of interest was intake of total dietary fiber, including fiber from cereal, fruit, vegetable, and other foods; 3) the endpoint of interest was pancreatic cancer incidence; and 4) the relative risk (RR) or odds ratio (OR) and the corresponding 95% CI for the highest compared with the lowest category of dietary fiber intake were reported. When multiple reports were published on the same study population, we included the most informative one.

Data were extracted using a standardized data-collection form. Information was recorded as follows: the name of the first author, publication year, study location, study design, year of follow-up (cohort studies) or year of data collection (case-control studies), number of cases and participants, dietary assessment, range of dietary fiber intake, study quality, and adjusted covariates. Data extraction was conducted independently by 2 authors, with disagreements resolved by consensus. Considering that pancreatic cancer is a relatively rare disease, the RR was assumed approximately the same as OR, and the OR was used as the study outcome. If studies reported sex-stratified, we calculated the overall sex-adjusted OR by combining these estimates with the method of Mantel and Haenszel.[12] If a study provided several ORs, we extracted the RRs reflecting the greatest degree of control for potential confounders.

Quality assessment

We assessed the quality of individual studies using the 9-star Newcastle-Ottawa Scale (The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses. Ottawa, Canada: Dept of Epidemiology and Community Medicine, University of Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). NOS is an eight-item instrument that allows for the assessment of the patient selection, study comparability, and exposure (for case-control study) or outcome (for cohort study). The range of possible scores is 0-9. The study with score more than 6 was considered of high quality.

Statistical analysis

Random effects models[13] were used to calculate summary ORs and 95% CIs for the highest versus the lowest level of fiber intake. Subgroup analyses were performed according to study design, sex, the study location, study quality, and method of exposure assessment. To conduct dose-response meta-analyses, we included studies that considered at least 3 levels of fiber intake. We used the method proposed by Greenland[14] and Orsini[15] to back-calculate and pool the risk estimates. For each study, we assigned the midpoint of the upper and lower boundaries in each category as the average value of fiber intake. When the highest category was open-ended, we assumed the width of the interval to be the same as in the preceding category. We quantified the extent of heterogeneity using Q-test and I^2 score[16] and statistical significance was considered while $p<0.05$. Publication bias was assessed using the tests of Egger[17] and Begg.[18] All statistical analyses were done with Stata Statistical Software, version 11.0.

RESULTS

Search results and study characteristics

The detailed steps of our literature search are shown in Figure 1. Thirteen case-control studies[19-31] and one cohort study[32] were included in the analysis of dietary fiber intake and pancreatic cancer risk. Overall, this meta-analysis included 3,287 cases of pancreatic cancer. Six of the studies were from North America,[20,27-29,31,32] five from Europe,[22,23,25,26,30] two from Asia[19,24] and one from Australia.[21] Eleven studies obtained information on fiber intake by interview,[19,20,22-30] the remaining three studies used self-administered questionnaire.[21,31,32]
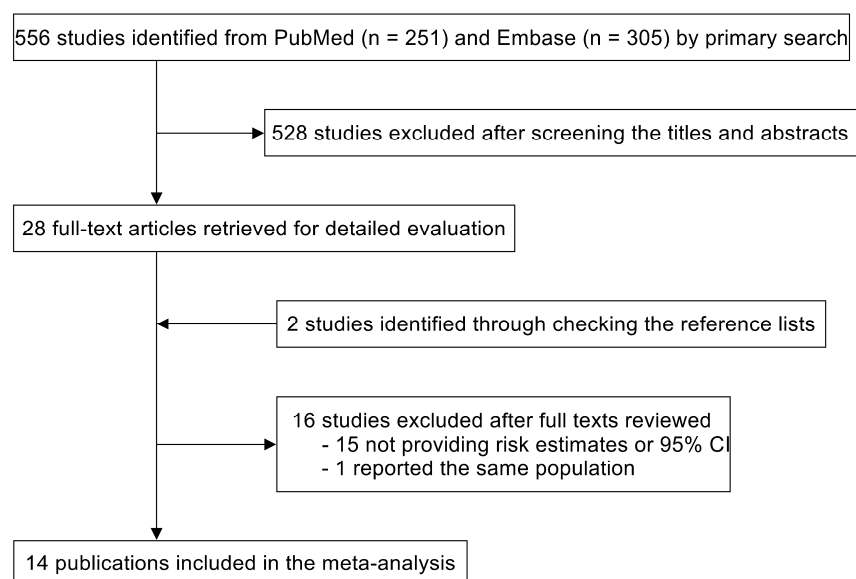

Figure 1. Flowchart of study selection

Table 1. Characteristics of included epidemiological studies

Authors and publication year	Study design	Country	Study period	Sex	Age	Cases/subjects	Exposure range	Study quality	Variables of adjustment	Exposure assessment
Howe et al 1990	PCC	Canada	1983-1986	M/W	35-79	249/754	> 29.3 vs < 15.9 g/day	7	Age, sex, caloric intake, and life-time cigarette consumption.	Interview
Baghurst et al 1991	PCC	Australia	1984-1987	M/W	Not mentioned	104/357	The highest vs the lowest quartile	7	Age, total energy, cigarette usage, alcohol consumption	Self-administered questionnaire.
De Mesquite et al 1991	PCC	Netherland	1984-1988	M/W	35-79	164/644	The highest vs the lowest quintile	8	Age, sex, total smoking, and dietary intake of energy.	Interview
Ghadirian et al 1991	PCC	France	1984-1988	M/W	35-79	179/418	> 26.4 vs < 16.1 g/day	6	Age, sex, lifetime cigarette consumption, response status, and energy.	Interview
Zatonski et al 1991	PCC	Poland	1985-1988	M/W	Not mentioned	110/305	> 34.8 vs < 21.5 g/day	7	Age, sex, cigarette lifetime consumption and calories	Interview
Kalapothaki et al 1993	HCC	Greece	1991-1992	M/W	Not mentioned	181/362	Ever vs none	5	Age, smoking, and energy intake	Interview
Lyon et al 1993	PCC	USA	1984-1987	M/W	40-79	149/542	High vs low intake	7	Age, cigarette smoking, and consumption of coffee and alcohol	Interview
Ji et al 1995	PCC	China	1990-1993	M/W	30-79	451/2003	Men: ≥ 12.4 vs ≤ 7.0 g/day Women: ≥ 10.5 vs ≤ 6.0 g/day	5	Age, sex, income, smoking, green tea drinking, response status, and total calories	Interview
Stolzenberg-Solomon et al 2002	Cohort	USA	1985-1997	M	50-69	163/27111	> 31.0 vs ≤ 18.8 g/day	7	Age, smoking, energy intake	Self-administered questionnaire.
Lin et al 2005	PCC	Japan	2000-2002	M/W	40-79	109/327	> 15.1 vs < 11.5 g/day	7	Age, smoking, energy intake	Interview
Chan et al 2007	PCC	USA	1995-1999	M/W	21-85	532/2233	≥ 26.5 vs ≤ 15.6 g/day	8	Age, sex, total energy intake, BMI, race, education, smoking, and history of diabetes.	Interview
Zhang et al 2009	PCC	USA	1994-1998	M/W	Above 20	186/740	The highest vs the lowest quartile	8	Age, sex, race, education, cigarette smoking, alcohol intake, physical activity, fruit intake, vegetable intake and fat intake	Interview
Jasen et al 2011	HCC	USA	2004-2009	M/W	19-92	384/1367	The highest vs the lowest quintile	7	Age, sex, energy, smoking, BMI, and drinks of alcohol per week	Self-administered questionnaire.
Bidoli et al 2012	HCC	Italy	1991-2008	M/W	34-80	326/978	The highest vs the lowest quintile	5	Age, study center, sex, period of interview, BMI, education, tobacco smoking, alcohol consumption, diabetes, dietary folate intake, and total energy intake	Interview

HCC: hospital-based case-control study; PCC: population-based case-control study; BMI: body mass index.
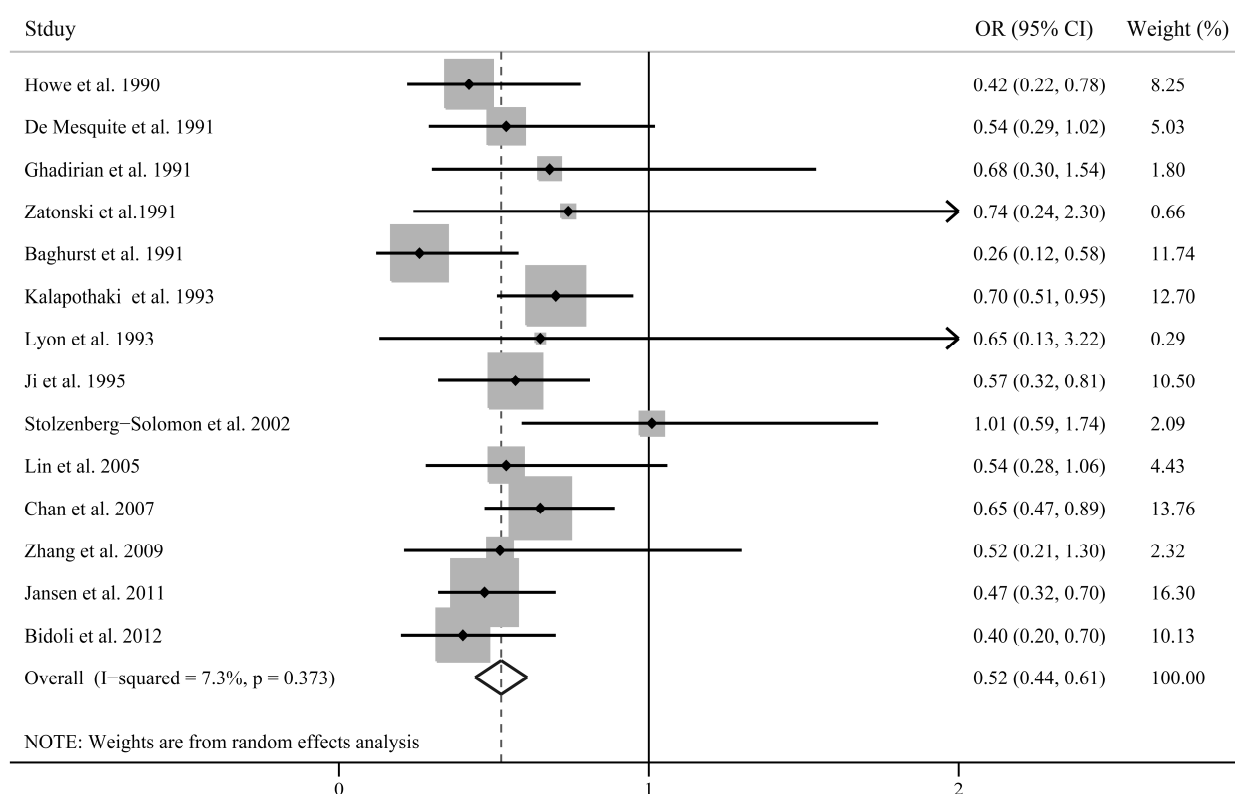
Stduy	OR (95% CI)	Weight (%)
Howe et al. 1990	0.42 (0.22, 0.78)	8.25
De Mesquite et al. 1991	0.54 (0.29, 1.02)	5.03
Ghadirian et al. 1991	0.68 (0.30, 1.54)	1.80
Zatonski ct al.1991	0.74 (0.24, 2.30)	0.66
Baghurst et al. 1991	0.26 (0.12, 0.58)	11.74
Kalapothaki et al. 1993	0.70 (0.51, 0.95)	12.70
Lyon et al. 1993	0.65 (0.13, 3.22)	0.29
Ji et al. 1995	0.57 (0.32, 0.81)	10.50
Stolzenberg−Solomon et al. 2002	1.01 (0.59, 1.74)	2.09
Lin et al. 2005	0.54 (0.28, 1.06)	4.43
Chan et al. 2007	0.65 (0.47, 0.89)	13.76
Zhang et al. 2009	0.52 (0.21, 1.30)	2.32
Jansen et al. 2011	0.47 (0.32, 0.70)	16.30
Bidoli et al. 2012	0.40 (0.20, 0.70)	10.13
Overall (I−squared = 7.3%, p = 0.373)	0.52 (0.44, 0.61)	100.00

NOTE: Weights are from random effects analysis

Figure 2. Pooled results for 14 epidemiological studies of dietary fiber intake and pancreatic cancer risk

Table 2. Subgroup analysis by study design, sex, geographical region, study quality, exposure assessment and solubility

Outcome of interest	No. of studies	OR (95% CI)	$p_{heterogenity}$	I^2 (%)
Study design				
Cohort	1	1.01 (0.59, 1.74)	NA	NA
PCC	11	0.49 (0.39, 0.58)	0.629	0
HCC	2	0.58 (0.35, 0.80)	0.121	58.4
Sex				
Men	3	0.82 (0.34, 1.29)	0.131	50.8
Women	2	0.43 (0.06, 0.80)	0.160	49.3
Geographical region				
Europe	7	0.57 (0.43, 0.72)	0.498	0
North America	6	0.55 (0.43, 0.67)	0.433	0
Asia	2	0.56 (0.35, 0.77)	0.898	0
Study quality				
High	10	0.50 (0.39, 0.60)	0.359	9.1
Low	4	0.57 (0.43, 0.71)	0.357	7.2
Exposure assessment				
Interview	11	0.57 (0.47, 0.66)	0.885	0
Questionnaire	3	0.48 (0.19, 0.77)	0.046	67.6
Solubility				
Soluble fiber	3	0.66 (0.51, 0.80)	0.336	8.3
Insoluble fiber	3	0.65 (0.44, 0.87)	0.074	61.6

PCC: population-based case-control studies; HCC: hospital-based case-control studies.

Total fiber intake

As shown in Figure 2, the summary OR for highest versus lowest categories of fiber intake was 0.52 (95% CI 0.44-0.61), with no evidence of heterogeneity, I^2=7.3% and $p_{heterogeneity}$=0.373, indicating that high fiber intake was inversely associated with pancreatic cancer. The summary OR ranged from 0.50 (95% CI 0.41-0.58) when the study by Kalapothaki et al[26] was excluded, to 0.56 (95% CI 0.47-0.64) when the study by Baghurst et al[21] was excluded. There was no evidence of publication bias with Egger's test, p=0.743, or with Begg's test, p=0.334 (Figure 3).

A cumulative meta-analysis was also done by sorting the studies in the sequence of publication year. Figure 4 shows the results from the cumulative meta-analysis of the association between fiber intake and pancreatic cancer risk in chronologic order. The 95% CIs became increasingly narrower with the addition of each study, indicating that the precision of the estimates was progressively boosted by the continual addition of more cases.

In Table 2, we pooled the OR estimates by study design (cohort, HCC and PCC), sex (men and women), geographical region (US/Canada, Europe and Asia), study quality (high and low quality), and exposure assessment (interview and self-administered questionnaire). The OR

Figure 3. Publication bias which was estimated by Begg's test (A) and Egger's test (B)

estimates from subgroup analysis varied little, showing fiber intake was consistently associated with reduced risk of pancreatic cancer, expect in men's group.

We further performed the dose-response analysis between fiber intake and pancreatic cancer risk, which included 7 studies.[19,20,23,24,28,29,32] Figure 5 shows the dose-response relationship between risk of pancreatic cancer and fiber intake. The pooled OR of pancreatic cancer risk per 10 g/day increment in total dietary fiber was 0.88 (95 % CI 0.84-0.92, $p_{heterogenity}$<0.001).

Other fiber-related exposures included crude fiber, soluble and insoluble fiber, and fiber categorized by food group: grain fiber, fruit fiber, and vegetable fiber. Two studies evaluated crude fiber, one study[26] found a suggestion of an inverse association, whereas no evidence of an association was found in the other study.[23] Three studies provided information for soluble and insoluble fiber.[30-32] The combined results of the three studies showed significant inverse associations between soluble and insoluble fiber intake and pancreatic cancer risk (Table 2). Fiber intake by food source was evaluated by only one study.[30] No association was observed for vegetable and grain fiber, whereas high fruit fiber intake was inversely associated with the risk of pancreatic cancer (OR: 0.5; 95% CI: 0.3, 0.8).

DISCUSSION
The findings of the present meta-analysis supported the hypothesis that dietary fiber intake is inversely associated with the risk of pancreatic cancer. The risk of pancreatic cancer was reduced by 48% in a comparison of the highest with the lowest category of dietary fiber intake. There was no evidence of heterogeneity throughout our study. Furthermore, the dose-response analysis showed that the
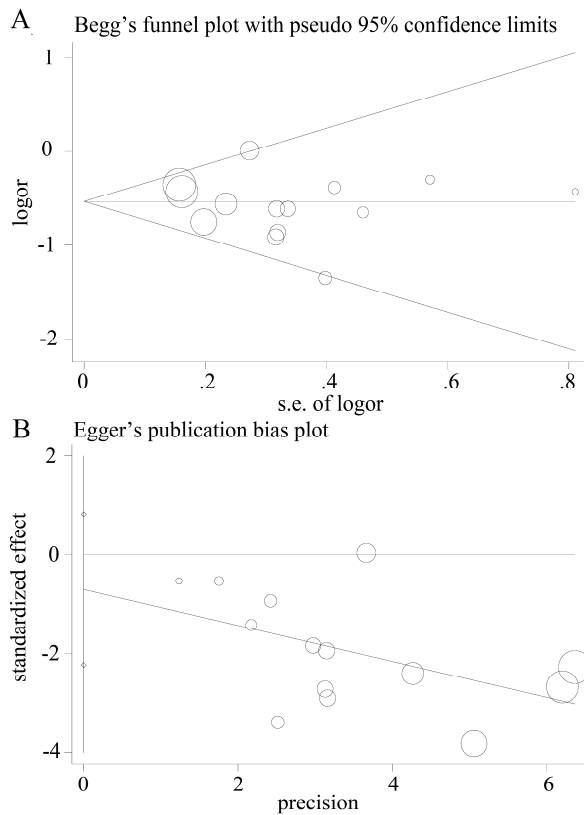

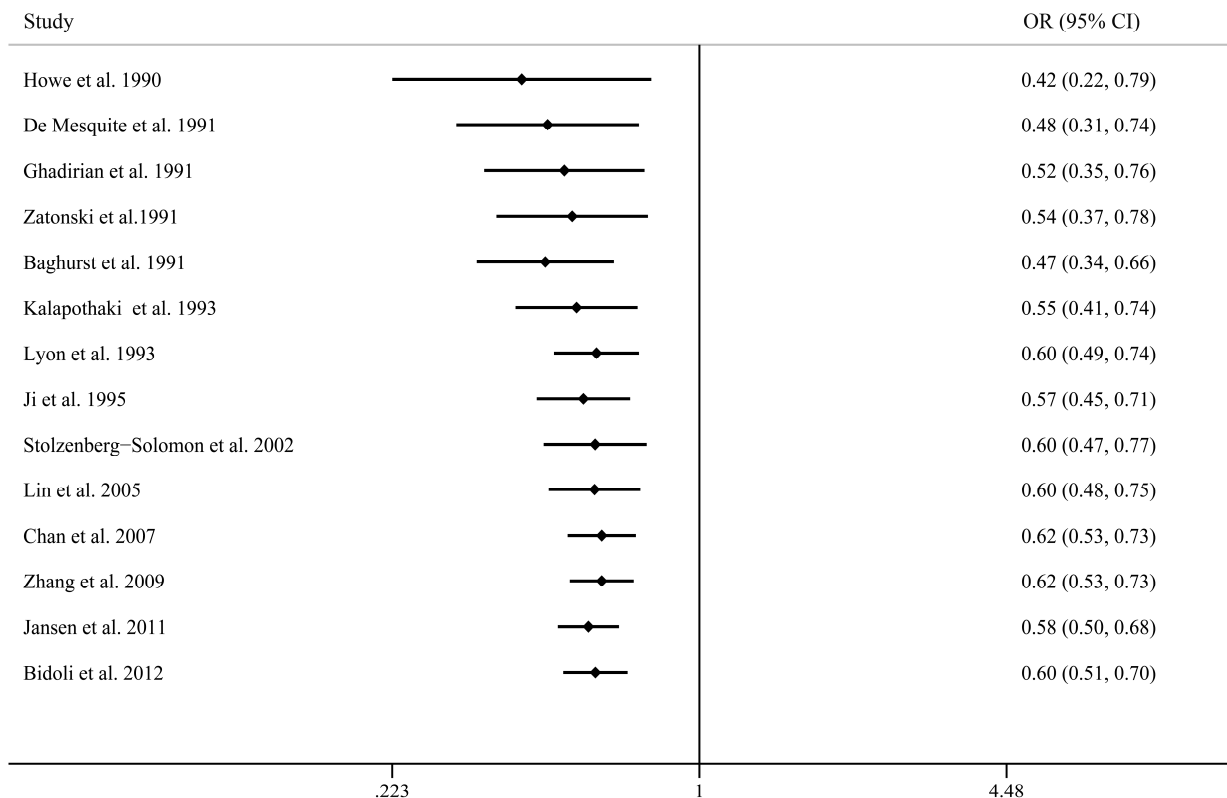| Study		OR (95% CI)
Howe et al. 1990		0.42 (0.22, 0.79)
De Mesquite et al. 1991		0.48 (0.31, 0.74)
Ghadirian et al. 1991		0.52 (0.35, 0.76)
Zatonski et al.1991		0.54 (0.37, 0.78)
Baghurst et al. 1991		0.47 (0.34, 0.66)
Kalapothaki et al. 1993		0.55 (0.41, 0.74)
Lyon et al. 1993		0.60 (0.49, 0.74)
Ji et al. 1995		0.57 (0.45, 0.71)
Stolzenberg−Solomon et al. 2002		0.60 (0.47, 0.77)
Lin et al. 2005		0.60 (0.48, 0.75)
Chan et al. 2007		0.62 (0.53, 0.73)
Zhang et al. 2009		0.62 (0.53, 0.73)
Jansen et al. 2011		0.58 (0.50, 0.68)
Bidoli et al. 2012		0.60 (0.51, 0.70)

Figure 4. A forest plot showing cumulative meta-analysis of fiber intake and pancreatic cancer risk
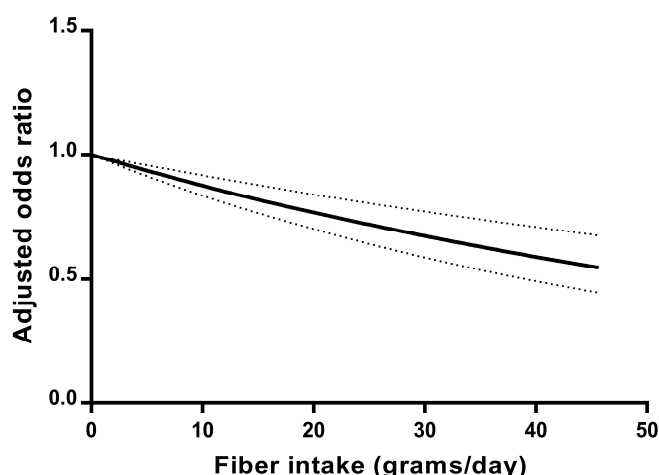
Figure 5. Odds ratio for prostate cancer by doses of fiber intake based on the results of the dose-response meta-analyses. Solid line represents the estimated odds ratios, and the dotted lines represent the 95% confidence intervals.

risk of pancreatic cancer decreased significantly, by 12% for every 10 g/d increment of dietary fiber intake.

Despite the strong inverse association between fiber intake and the risk of pancreatic cancer, our finding was based on one cohort study and a large number of case-control studies, which were more likely subjected to selection and recall bias. The only one cohort study by Stolzenberg-Solomon et al[32] showed no significant association between fiber intake and pancreatic cancer. However, this study was conducted in Finland in male smokers, a group of persons with high risk for pancreatic cancer. Therefore, caution should be exercised when the findings from this prospective study are extrapolated to the general population. In addition, we found a significant dose-response relation between dietary fiber intake and risk of pancreatic cancer, and subgroup analyses consistently showed a significant inverse association, which thereby further strengthened this conclusion.

Although our results suggested that high intake of fiber might have a favourable role in pancreatic carcinogenesis, the mechanisms involved remain unclear. Currently, there are two main hypotheses as to how fiber intake could influence pancreatic cancer development and progression. First, dietary fiber intake could affect insulin insensitivity or insulin resistance pathways,[33,34] which has been implicated in pancreatic cancer etiology.[35] The second hypothesized mode of action is that fiber may confer effective protection due to its anti-inflammatory properties.[36] It has been suggested that chronic pancreatitis is a risk factor for pancreatic cancer.[37,38] Experimental studies showed that dietary fiber exert a down-regulation role on inflammation,[39] probably through the fermentation products, particularly butyrate[40] and propionate,[41] which have shown anti-inflammatory properties.

Our study also has some limitations. First, as a meta-analysis of observational studies, residual confounders are always of concern which might distort the association between dietary fiber intake and risk of pancreatic cancer. For example, high fiber intake is also characteristic of diets high in fruits and vegetables, low fat intake and increased physical activity, which are associated with lower pancreatic cancer risk, although most studies included in the present meta-analysis were adjusted for large numbers

of major confounders. Second, dietary fiber refers to a complex group of molecules, and all types of fibers may not have the same properties with regard to modulation of cancer risk. For instance, it has been suggested that resistant starch might be more protective against cancer than non-starch polysaccharides (major components of dietary fiber).[42] However, fiber intake was generally not the main focus of the included studies, and results for specific types of fiber and/or their fermentation properties were not available except for one study by Bidoli et al,[30] preventing us from distinguish the different types of fiber in the meta-analysis. Third, most enrolled studies were based on data from Western populations, so whether the significant relationship could be applied to low-income areas is unknown. This may limit the generalizability of the results from our meta-analysis. Fourth, all adjusted ORs were estimated on the basis of the highest compared with the lowest category of dietary fiber intake, and the fact that the studies did not compare the same absolute intake levels could have influenced our results, though no heterogeneity was detected across studies. Finally, because of the difficulty of early diagnosis, and the poor survival, some case-control studies examining the relationship had to rely on interviews with surrogates. This may have led to bias and inaccurate risk estimation.

In conclusion, in the present meta-analysis, we demonstrated that an increased fiber intake is associated with a reduced risk of pancreatic cancer. Considering the limitation of included studies, further well-designed prospective studies are needed to confirm the inverse association and to identify the dietary fiber types involved.

AUTHOR DISCLOSURES
No competing interests are reported.

REFERENCES
1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-917. doi: 10.1002/ijc.25516.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5-29. doi: 10.3322/caac.21254.
3. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252-61.

doi: 10.1053/j.gastro.2013.01.068.

4. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20:197-209. doi: 10.1016/j.bpg.2005.10.001.

5. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. Epidemiology of cancer of the pancreas. J Natl Cancer Inst. 1973;50:645-67.

6. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet. 2003;361:1496-501. doi: 10.1016/S0140-6736(03)13174-1.

7. Dong JY, He K, Wang P, Qin LQ. Dietary fiber intake and risk of breast cancer: a meta-analysis of prospective cohort studies. Am J Clin Nutr. 2011;94:900-5. doi: 10.3945/ajcn.111.015578.

8. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Association between dietary fiber and endometrial cancer: a dose-response meta-analysis. Am J Clin Nutr. 2007;86:1730-7.

9. Coleman HG, Murray LJ, Hicks B, Bhat SK, Kubo A, Corley DA, Cardwell CR, Cantwell MM. Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutr Rev. 2013;71:474-82. doi: 10.1111/nure.12032.

10. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008;11:253-6. doi: 10.1017/S002966510800712X.

11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097.

12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719-48.

13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. doi: 10.1016/0197-2456(86)90046-2.

14. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301-9.

15. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012;175:66-73. doi: 10.1093/aje/kwr265.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58. doi: 10.1002/sim.1186.

17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34. doi: 10.1136/bmj.315.7109.629.

18. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101.

19. Ji BT, Chow WH, Gridley G, McLaughlin JK, Dai Q, Wacholder S, Hatch MC, Gao YT, Fraumeni JF, Jr. Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai China. Cancer Epidemiol Biomarkers Prev. 1995;4:885-93.

20. Howe GR, Jain M, Miller AB. Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case-control study. Int J Cancer. 1990;45:604-8. doi: 10.1002/ijc.2910450405.

21. Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM. A case-control study of diet and cancer of the pancreas. Am J Epidemiol. 1991;134:167-79.

22. Bueno de Mesquita HB, Maisonneuve P, Runia S, Moerman CJ. Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in The Netherlands. Int J Cancer. 1991;48:540-9. doi: 10.1002/ijc.2910480411.

23. Ghadirian P, Simard A, Baillargeon J, Maisonneuve P, Boyle P. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. Int J Cancer. 1991;47:1-6.

24. Lin Y, Tamakoshi A, Hayakawa T, Naruse S, Kitagawa M, Ohno Y. Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan. J Gastroenterol. 2005;40:297-301. doi: 10.1007/s00535-004-1537-0.

25. Zatonski W, Przewozniak K, Howe GR, Maisonneuve P, Walker AM, Boyle P. Nutritional factors and pancreatic cancer: a case-control study from south-west Poland. Int J Cancer. 1991;48:390-4. doi: 10.1002/ijc.2910480314.

26. Kalapothaki V, Tzonou A, Hsieh CC, Karakatsani A, Trichopoulou A, Toupadaki N, Trichopoulos D. Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece. Cancer Causes Control. 1993;4:383-9. doi: 10.1007/BF00051342.

27. Lyon JL, Slattery ML, Mahoney AW, Robison LM. Dietary intake as a risk factor for cancer of the exocrine pancreas. Cancer Epidemiol Biomarkers Prev. 1993;2:513-8.

28. Chan JM, Wang F, Holly EA. Whole grains and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area, California. Am J Epidemiol. 2007;166:1174-85. doi: 10.1093/aje/kwm194.

29. Zhang J, Dhakal IB, Gross MD, Lang NP, Kadlubar FF, Harnack LJ, Anderson KE. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. Nutr Cancer. 2009;61:457-65. doi: 10.1080/01635580902718941.

30. Bidoli E, Pelucchi C, Zucchetto A, Negri E, Dal Maso L, Polesel J et al. Fiber intake and pancreatic cancer risk: a case-control study. Ann Oncol. 2012;23:264-8. doi: 10.1093/annonc/mdr060.

31. Jansen RJ, Robinson DP, Stolzenberg-Solomon RZ, Bamlet WR, de Andrade M, Oberg AL et al. Fruit and vegetable consumption is inversely associated with having pancreatic cancer. Cancer Causes Control. 2011;22:1613-25. doi: 10.1007/s10552-011-9838-0.

32. 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. doi: 10.1093/aje/153.7.680.

33. Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. Am J Clin Nutr. 2005;82:559-67.

34. Johnston KL, Thomas EL, Bell JD, Frost GS, Robertson MD. Resistant starch improves insulin sensitivity in metabolic syndrome. Diabet Med. 2010;27:391-7. doi: 10.1111/j.1464-5491.2010.02923.x.

35. Wolpin BM, Bao Y, Qian ZR, Wu C, Kraft P, Ogino S et al. Hyperglycemia, insulin resistance, impaired pancreatic beta-cell function, and risk of pancreatic cancer. J Natl Cancer Inst. 2013;105:1027-35. doi: 10.1093/jnci/djt123.

36. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ 3rd, Li W, Pagoto SL, Hafner AR, Ockene IS. Association between dietary fiber and serum C-reactive protein. Am J Clin Nutr. 2006;83:760-6.

37. Dite P, Hermanova M, Trna J, Novotny I, Ruzicka M, Liberda M, Bartkova A. The role of chronic inflammation: chronic pancreatitis as a risk factor of pancreatic cancer. Dig Dis. 2012;30:277-83. doi: 10.1159/000336991.

38. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. Gastroenterology. 1995;109:247-51. doi: 10.1016/0016-5085(95)90291-0.

39. King DE, Egan BM, Woolson RF, Mainous AG, 3rd, Al-Solaiman Y, Jesri A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. Arch Intern Med. 2007;167:502-6. doi: 10.1001/archinte.167.5.502.

40. Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. Nutrients. 2011;3:858-76. doi: 10.3390/nu3100858.

41. Al-Lahham S, Roelofsen H, Rezaee F, Weening D, Hoek A, Vonk R, Venema K. Propionic acid affects immune status and metabolism in adipose tissue from overweight subjects. Eur J Clin Invest. 2012;42:357-64. doi: 10.1111/j.1365-2362.2011.02590.x.

42. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev. 2001;81:1031-64.