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Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies

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Background: Dietary carbohydrates, glycemic load and glycemic index have been hypothesized to influence pancreatic cancer risk, but epidemiological studies have been inconsistent. We conducted a systematic review and meta-analysis of prospective studies to clarify these results.
Methods: PubMed and several other databases were searched for prospective studies of intake of carbohydrates, glycemic index and glycemic load and pancreatic cancer up to September 2011. Summary relative risks were estimated using a random effects model.
Results: Ten cohort studies (13 publications) were included in the meta-analysis. The summary relative risk (RR) per 10 glycemic index units was 1.02 [95% confidence interval (CI): 0.93–1.12, $I^2 = 0\%$], per 50 glycemic load units was 1.03 (95% CI: 0.93–1.14, $I^2 = 10\%$), per 100 g/day of total carbohydrates was 0.97 (95% CI: 0.81–1.16, $I^2 = 35\%$), and per 25 g/day of sucrose intake was 1.05 (95% CI: 0.85–1.23, $I^2 = 53\%$). A positive association was observed with fructose intake, summary RR = 1.22 (95% CI: 1.08–1.37, $I^2 = 0\%$) per 25 g/day.
Conclusions: This meta-analysis does not support an association between diets high in glycemic index, glycemic load, total carbohydrates or sucrose and pancreatic cancer risk. The finding of an increased risk with fructose intake warrants further investigation in studies with better adjustment for confounding and in non-American populations.
Key words: carbohydrates, glycemic index, glycemic load, fructose, pancreatic cancer, sucrose

introduction

Pancreatic cancer is the ninth most common cause of cancer with 277 000 new cases diagnosed in 2008 worldwide, accounting for ∼2.2% of all cancer cases [1]. The survival of pancreatic cancer patients is very poor and 5-year survival rates are 2%–8% [2]. Currently, there are no established methods for screening or early detection; thus, primary prevention by altering modifiable risk factors will probably be the most effective way of reducing the pancreatic cancer burden at present. Ecological studies have suggested that modifiable risk factors are likely to be important in pancreatic cancer etiology [3]. However, with the exception of tobacco smoking, which explains ∼20%–25% of pancreatic cancer cases [4, 5], and diabetes [relative risk (RR) = 1.8] [6] and body fatness (RR = 1.10 per 5 kg/m^2) [7], relatively few modifiable risk factors have been firmly established. Dietary factors have been hypothesized to be involved in the etiology of pancreatic cancer, but to date no convincing dietary risk factors for pancreatic cancer have been established [8].

Several lines of evidence indicate that insulin resistance may play a role in the etiology of pancreatic cancer. Some established or possible risk factors for pancreatic cancer including overweight and obesity, low physical activity and type 2 diabetes are linked to insulin resistance [6, 8, 9]. Epidemiological studies have reported increased pancreatic cancer risk with elevated blood glucose or C-peptide [10–12] and dietary carbohydrates are the main dietary component affecting an individual's insulin secretion and glycemic response [13]. Several studies have investigated the association between diets high in carbohydrates, glycemic index (GI) or glycemic load (GL) and pancreatic cancer risk; however, the results have been inconsistent [14–26]. Also, it is not known whether specific types of carbohydrates (e.g. fructose, glucose or sucrose) are associated with pancreatic cancer risk. Some experimental and epidemiological studies have suggested that high fructose intake may increase risk of insulin resistance, type 2 diabetes and obesity [27–29]; however, data regarding

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fructose intake and pancreatic cancer are inconsistent [14, 15, 17, 19–22]. Studies on sucrose intake and pancreatic cancer risk have also been inconsistent with inverse [25], null [14, 15, 17, 19, 20, 22, 23] and positive [21] associations reported. To clarify the association between intake of carbohydrates, GI, GL and pancreatic cancer risk, we conducted a systematic review and dose–response meta-analysis of prospective studies.

methods

data sources and searches

The literature search and data extraction up to December 2005 were conducted by several reviewers at University of Leeds. Initially, several databases were searched including Pubmed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane Library, CINAHL, AMED, National Research Register and In Process Medline. Because all the relevant studies were identified through searches in PubMed, a change in the protocol was made and only PubMed was used for the updated searches from January 2006 to September 2011. We followed a predefined protocol for the review (http://www.dietandcancerreport.org/cancer_resource_center/downloads/SLR_Manual.pdf), which includes details of the search terms. Standard criteria for conducting and reporting meta-analyses were followed [30]. We also searched the reference lists of all the studies that were included in our analysis as well as those listed in the published systematic reviews and meta-analyses [31, 32].

study selection

To be included, the study had to have a prospective cohort, case-cohort or nested case-control study design and to investigate the association between dietary carbohydrates (excluding fiber), GI or GL and pancreatic cancer risk. Estimates of the relative risk (hazard ratio, risk ratio) had to be available with the 95% confidence intervals in the publication. For the dose–response analysis, a quantitative measure of intake had to be provided. We identified 13 relevant publications in the search [14–26]. One duplicate publication [26] was excluded from the main analysis, but its results were included in analyses stratified by gender as the publication used for the main analysis [19] did not report sex-specific results and one publication was excluded from the dose–response analysis of sucrose and fructose intake because only the highest versus the lowest intake was reported [17], so no dose–response could be estimated for this publication.

data extraction and quality assessment

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), exposure, quantity of intake, RRs and 95% CIs for the highest versus the lowest level of intake and variables adjusted for in the analysis. The search and data extraction up to December 2005 were conducted by JEC, DSMC, VJB and several other reviewers at the University of Leeds. These data were checked for accuracy by DA. The search and data extraction from January 2006 to September 2011 was conducted by DA and was checked for accuracy by TN.

data synthesis and analysis

We used random effects models to calculate summary RRs and 95% CIs for the highest versus the lowest level of carbohydrate and GI/GL intake and for the dose-response analyses [33]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $P < 0.05$ was considered statistically significant. For one study [17] that reported results separately for men and women, we combined the results using a fixed-effects model to obtain an overall combined estimate for both genders.

For the dose–response analyses, we used the method by Greenland and Longnecker [34] to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of carbohydrate and GI/GL intake. The method requires that the distribution of cases and person-years or noncases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases/person-years, for example, the total number of person-years was divided by 5 when data were analyzed by quintiles in order to derive the number of person-years in each quintile. The median or mean level of intake in each category of intake was assigned to the corresponding relative risk for each study. We estimated the midpoint in each category by calculating the average of the lower and upper bound for studies that reported intakes by ranges. When the highest or lowest category was open ended, we assumed the open-ended interval length to be the same as the adjacent interval. If the intakes were reported in densities (e.g. gram per 1000 kcal), we recalculated the reported intakes to absolute intakes using the mean or median energy intake [19, 21, 22]. The dose–response results in the forest plots are presented for a 10- and 50-unit increment per day for GI and GL, respectively, and for a 100 g/day increment for total carbohydrates and 25 g/day increment for sucrose/fructose intake (the approximate mean difference between the highest and lowest intake across studies). We examined a potential nonlinear dose–response relationship by using fractional polynomial models [35]. The best fitting second-order fractional polynomial regression model was determined, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [36].

Heterogeneity between studies was assessed by the Q test and I^2 (a measure of the proportion of total variation in study estimates that is due to heterogeneity) [37]. Subgroup and meta-regression analyses by sex, duration of follow-up, number of cases, geographic location and adjustment for potential confounding factors such as body mass index (BMI), smoking, alcohol, physical activity, intake of fruit and vegetables, energy and red and processed meat were conducted to investigate potential sources of heterogeneity. Small study effects, such as publication bias, was assessed by inspection of the funnel plots and with Egger's test [38] and with Beggapos;s test [39], and the results were considered to indicate small study effects when $P < 0.10$. We conducted sensitivity analyses excluding one study at a time to clarify whether the results were simply due to one large study or a study with an extreme result. Results from these sensitivity analyses are reported for the two studies that had the most positive and negative influence on the summary estimate.

results

We identified 10 cohort studies (13 publications) [14–26], one of which was a case-cohort study [18], that were included in the analysis of carbohydrate, GI and GL intake and pancreatic cancer risk [Table 1, supplementary Figure S1 (available at *Annals of Oncology* online)]. One of these publications was only included in subgroup analyses by sex [26] as it was superseded by another publication from the same study [19]. Eight studies were from North America and two were from Europe.

Table 1. Prospective cohort studies of intake of carbohydrates, glycemic index and glycemic load and pancreatic cancer risk

Author, year, country	Study name	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Simon et al., 2010, USA [20]	Women's Health Initiative	1993/1998–, 8 years follow-up	139 503 postmenopausal women, age 50–79 years: 287 cases	Validated FFQ, 122 food items	Glycemic load	150 versus 105 units/day	0.80 (0.55–1.15)	Age, race, income, BMI, physical activity, DM, alcohol use, smoking status, energy intake
					Glycemic index	56 versus 48 units/day	1.13 (0.78–1.63)	
					Dietary total carbohydrates	285 versus 203 g/day	0.80 (0.56–1.15)	
					Dietary sucrose	60 versus 32 g/day	1.30 (0.89–1.89)	
					Dietary fructose	33 versus 13 g/day	0.79 (0.54–1.17)	
Meinhold et al., 2010, USA [21]	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	1998–2006, 6.5 years follow-up	109 175 men and women, age 55–74 years: 266 cases	Validated FFQ, 124 food items	Glycemic load	≥73.57 versus ≤54.28 g/1000 kcal/day	1.41 (0.97–2.07)	Age, sex, total energy, BMI, cigarette smoking status
					Glycemic index	≥56.17 versus ≤50.89 units/day	1.00 (0.69–1.47)	
					Available carbohydrates	≥137.00 versus ≤102.02 g/1000 kcal/day	1.56 (1.06–2.30)	
					Starch	≥56.27 versus ≤38.68 g/1000 kcal/day	1.12 (0.76–1.65)	
					Sucrose	≥29.71 versus ≤17.04 g/1000 kcal/day	1.55 (1.06–2.27)	
					Fructose	≥17.48 versus ≤7.59 g/1000 kcal/day	1.20 (0.83–1.75)	
Jiao et al., 2009, USA [19]	NIH-AARP Diet and Health Study	1995/1996–2003, 7.2 years follow-up	482 362 men and women, age 50–71 years: 1151 cases	Validated FFQ, 124 food items	Glycemic index	≥52.6 versus 24.5–46.2 units/day	1.09 (0.90–1.32)	Age, sex, total energy intake, smoking, alcohol, SFA, red meat, BMI
					Total carbohydrate	≥151.5 versus 9.0	1.12 (0.84–1.50)	
					Available carbohydrate	≥138.9 versus 8.7	1.11 (0.84–1.46)	
					Glycemic load	≥74.9 versus 4.0	0.95 (0.74–1.22)	
					Starch	≥59.0 versus 0.55	0.95 (0.78–1.16)	
					Sucrose	≥30.0 versus 0.45	0.95 (0.78–1.16)	
					Lactose	≥12.2 versus 0	0.89 (0.73–1.09)	
					Maltose	≥2.34 versus 0	1.07 (0.88–1.29)	
					Free fructose	≥18.4 versus 0.10	1.29 (1.04–1.59)	
					Free glucose	≥17.4 versus 0.45	1.35 (1.10–1.67)	
					Galactose	≥0.18 versus 0	0.91 (0.75–1.11)	
					Total sugar	≥75.8 versus 2.16	1.10 (0.88–1.38)	

George et al., 2009, USA [26]	NIH-AARP Diet and Health Study	1995/1996–2003, 7.2 years follow-up	262 642 men and 183–535 women, age 50–71 years: 601/348 cases	Validated FFQ, 124 food items	Glycemic index, men	≥57.02 versus ≤51.26 units/day	1.19 (0.92–1.55)	Age, race/ethnicity, education, marital status, BMI, family history of any cancer, physical activity, smoking, alcohol, total energy, menopausal hormone therapy (women)
					Glycemic load	≥164.44 versus ≤83.20 units/day	0.67 (0.42–1.08)	
					Glycemic index, women	≥56.56 versus ≤50.43 units/day	1.00 (0.71–1.40)	
					Glycemic load	≥135.31 versus ≤66.91 units/day	0.49 (0.26–0.94)	
Meinhold et al., 2009, Finland [25]	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	1985/1988–2004, 16.1 years follow-up	27 035 smoking men, age 50–69 years: 305 cases	Validated FFQ, 276 food items	Available carbohydrates	312 versus 221 g/day	0.65 (0.46–0.93)	Age, BMI, cigarettes per day, years of smoking, total energy, DM
					Sucrose	84.3 versus 24.9 g/day	0.68 (0.47–0.98)	
Heinen et al., 2008, The Netherlands [18]	Netherlands Cohort Study	1986–1999, 13.3 years follow-up	3980 men and women, age 55–69 years: 408 cases	Validated FFQ, 150 items	Glycemic load	156 versus 88 units/day	0.85 (0.58–1.24)	Age, sex, energy intake, smoking status, cigarettes per day, years of smoking, alcohol, DM, hypertension, BMI, vegetables, fruit, fiber
						Per 50 g/day	1.03 (0.77–1.39)	
					Glycemic index	64 versus 55 units/day	0.87 (0.59–1.29)	
						Per 5 units	0.98 (0.81–1.19)	
					Total carbohydrate	256 versus 155 g/day	1.03 (0.69–1.52)	
						Per 50 g/day	1.04 (0.85–1.27)	
Nothlings et al., 2007, USA [22]	Multiethnic Cohort Study	1993/1996–2002, 8 years follow-up	162 150 men and women, age 45–75 years: 434 cases	Validated FFQ, 180 food items	Glycemic load	≥82.3 versus < 63.3 g/1000 kcal/day	1.10 (0.80–1.52)	Age, race-ethnicity, smoking status, pack-yrs of smoking, family history of pancreatic cancer, energy intake, red and processed meat, BMI
					Carbohydrates	≥58.7 versus < 46.7 g/1000 kcal/day	1.04 (0.75-1.46)	
					Sucrose	≥22.1 versus < 13.7 g/1000 kcal/day	1.23 (0.91–1.65)	
					Fructose	≥15.4 versus < 7.3 g/1000 kcal/day	1.35 (1.02–1.80	
					Total sugar	≥62.6 versus < 40.0 g/1000 kcal/day	1.28 (0.95–1.73)	
					Added sugars	≥6.5 versus < 3.2 g/1000 kcal/day	1.08 (0.81–1.44)	

Continued

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Table 1.. *Continued*

Author, year, country	Study name	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Patel et al., 2007, USA [17]	Cancer Prevention Study 2 Nutrition Cohort	1992/1997–2001, 9 years follow-up	124 907 men and women, age 50–74 years: 401 cases	Validated FFQ, 68 food items	Glycemic load, men	>169.88 versus ≤119.02 units/day	1.10 (0.73–1.64)	Age, sex, race, BMI, gallstones, smoking, total energy intake, family history of pancreatic cancer, location of weight gain, sedentary behavior
					Glycemic index	>81.83 versus ≤69.61 units/day	0.80 (0.53–1.20)	
					Carbohydrate intake	>218.93 versus ≤162.56 g/day	1.28 (0.83–1.96)	
					Glycemic load, women	>132.37 versus ≤95.13 units/day	0.89 (0.56–1.45)	
					Glycemic index	>79.96 versus ≤68.42 units/day	1.11 (0.71–1.74)	
					Carbohydrate intake	>177.15 versus ≤129.98 g/day	0.90 (0.56–1.45)	
					Sucrose, men and women	Quintile 5 versus 1	0.84 (0.62–1.14)	
					Fructose, men and women	Quintile 5 versus 1	1.00 (0.73–1.36)	
Johnson et al., 2005, USA [16]	Iowa Women's Health Study	1986–2002, 16 years follow-up	33 551 women, age 55–69 years: 181 cases	Validated FFQ, 126 food items	Glycemic index	>89 versus < 82 units/day	1.08 (0.74–1.58)	Age, smoking, pack-years, DM, multivitamin use
					Glycemic load	>188 versus < 151	0.87 (0.56–1.34)	
Silvera et al., 2005, Canada [15]	Canadian National Breast Screening Study	1980/1985–2000, 16.5 years follow-up	49 613 women: 112 cases	Validated FFQ, 86 food items	Glycemic index	>92 versus < 63 units/day	1.43 (0.56–3.65)	Age, BMI, alcohol, smoking, parity, energy intake, study center, randomization group
					Glycemic load	>169 versus < 125	0.80 (0.45–1.41	
					Total carbohydrate	>236 versus < 152 g/day	0.63 (0.31–1.26)	
					Total sugar	>96 versus < 64 g/day	0.99 (0.59–1.66)	
					Sucrose	>34 versus < 17 g/day	0.64 (0.35–1.17)	
					Fructose	>25 versus < 13 g/day	1.18 (0.65–2.13)	
Stolzenberg-Solomon 2002, Finland [24]	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	1985/1988–1997, 10.2 years follow-up	27 111male smokers, age 50–69 years: 163 cases	Validated FFQ, 276 food items	Carbohydrate	>330.2 versus ≤260.7 g/day	0.62 (0.37–1.03)	Energy, age, years of smoking
Michaud et al., 2002, USA [14]	Nurses' Health Study	1980–1998, 18 years follow-up	88 802 women, age 34–59 years: 180 cases	Validated FFQ, 61 food items	Glycemic load	167 versus 80 g/day	1.53 (0.96–2.45)	Age, height, BMI, pack-years of smoking, DM, cholecystectomy, calorie intake, physical activity
					Glycemic index	81 versus 65	1.16 (0.69–1.97)	
					Carbohydrates	202 versus 110 g/day	1.30 (0.81–2.09)	
					Sucrose	55 versus 17 g/day	1.34 (0.82–2.17)	
					Fructose	45 versus 11 g/day	1.57 (0.95–2.57)	
Harnack et al., 1997, USA [23]	Iowa Women's Health Study	1986–1994, 8 years follow-up	33 976 women, age 55–69 years: 66 cases	Validated FFQ, 126 food items	Carbohydrate	>238 versus ≤178 g/day	1.22 (0.67–2.20)	Age, smoking status, pack-years
					Sucrose	>47 versus ≤30 g/day	0.94 (0.50–1.75)	

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FFQ, food frequency questionnaire; NIH-AARP, National Institutes of Health - American Association of Retired Persons; RR, relative risk; SFA, saturated fatty acids.

glycemic index

high versus low analysis

Eight cohort studies [14–21] were included in the high versus low analysis of GI and pancreatic cancer risk and included 2986 cases among 1 031 893 participants. The summary RR for all studies was 1.04 [95% confidence interval (CI): 0.93–1.17, $I^2 = 0\%$, $P_{heterogeneity} = 0.92$] (supplementary Figure S2a, available at *Annals of Oncology* online).

dose–response analysis

Eight cohort studies [14–21] were included in the dose–response analysis. The summary RR per 10 units/day was 1.02 (95% CI: 0.93–1.12, $I^2 = 0\%$, $P_{heterogeneity} = 0.97$) (Figure 1a) [14–21]. The summary RR ranged from 1.01 (95% CI: 0.91–1.11) when the Canadian National Breast Cancer Screening Study was excluded to 1.05 (95% CI: 0.94–1.17) when the Cancer Prevention Study 2 Nutrition Cohort was excluded. There was no indication of small study effects with Eggerapos;s test, $P = 0.54$ or with Beggapos;s test, $P = 0.26$. There was no evidence for a nonlinear association between GI and pancreatic cancer risk, $P_{nonlinearity} = 1.00$ (supplementary Figure S3a, available at *Annals of Oncology* online).

glycemic load

high versus low analysis

Nine cohort studies [14–22] were included in the analysis of high versus low GL and pancreatic cancer risk and included a total of 3420 cases among 1 194 043 participants. The summary RR was 1.01 (95% CI: 0.88–1.15, $I^2 = 19\%$, $P_{heterogeneity} = 0.27$) (supplementary Figure S2b, available at *Annals of Oncology* online).

dose-response analysis

Nine cohort studies [14–22] were included in the dose–response analysis. The summary RR per 50 units/day was 1.03 (95% CI: 0.93–1.14, $I^2 = 10\%$, $P_{heterogeneity} = 0.35$) (Figure 1b). In a sensitivity analysis, the summary RR ranged from 1.01 (95% CI: 0.91–1.12) when excluding the Nurses' Health Study to 1.05 (95% CI: 0.95–1.16) when excluding the National Institutes of Health - American Association of Retired Persons (NIH-AARP) Diet and Health Study. There was no indication of small study effects with Eggerapos;s test, $P = 0.68$, or with Beggapos;s test, $P = 0.60$. There was no evidence for a nonlinear association between GL and pancreatic cancer risk, $P_{nonlinearity} = 0.51$ (supplementary Figure S3b, available at *Annals of Oncology* online).

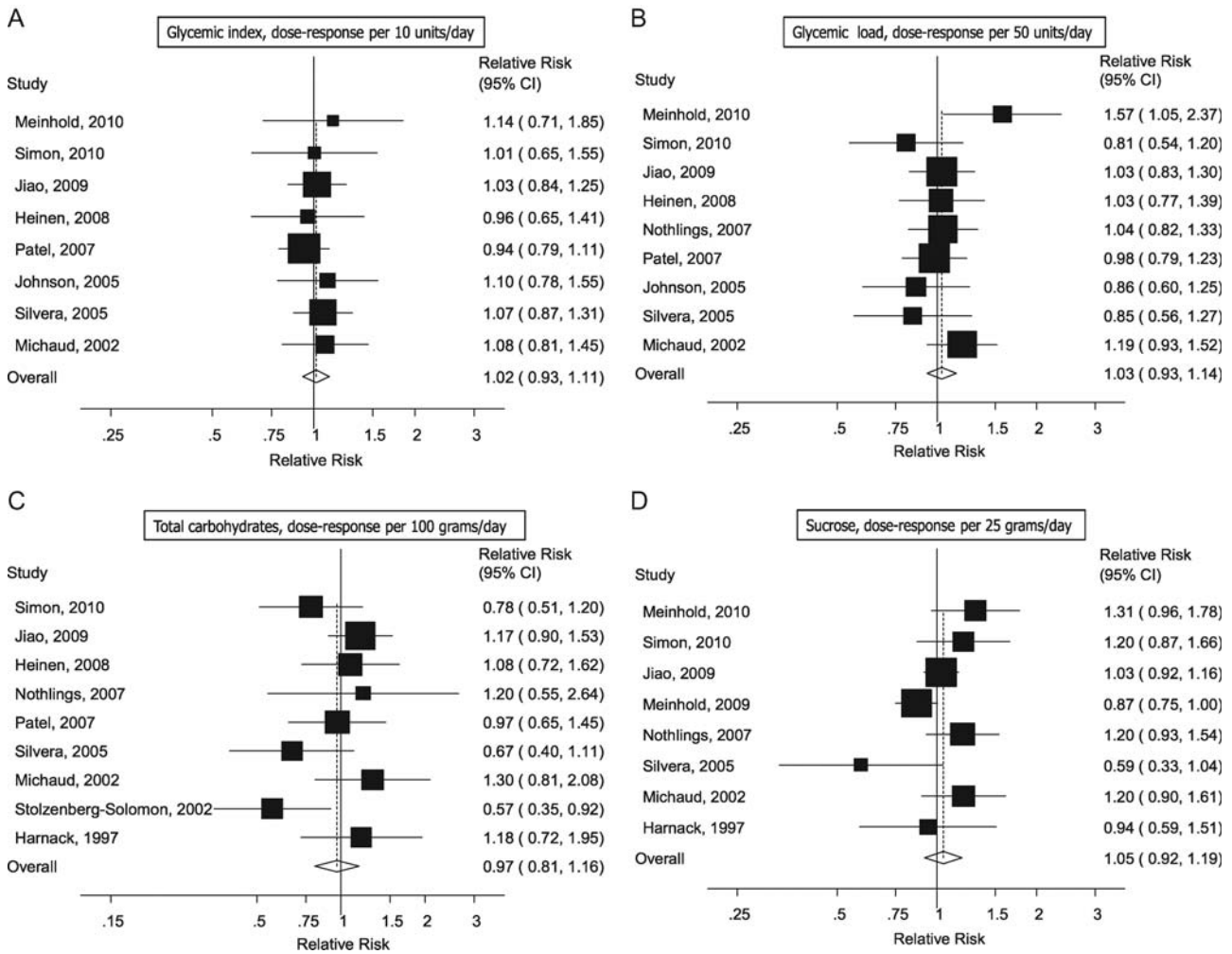

Figure 1.. Glycemic index, glycemic load, total carbohydrates and sucrose intake and pancreatic cancer, dose–response analysis.

total carbohydrates

high versus low analysis

Nine cohort studies [14, 15, 17–20, 22–24] were included in the high versus low analysis of total carbohydrate intake and pancreatic cancer risk and included 3202 cases among 1 112 404 participants. The summary RR was 1.00 (95% CI: 0.86–1.15, $I^2 = 35\%$, $P_{heterogeneity} = 0.14$) (supplementary Figure S2c, available at *Annals of Oncology* online).

dose–response analysis

Nine cohort studies [14, 15, 17–20, 22–24] were included in the dose–response analysis. The summary RR per 100 g/day was 0.97 (95% CI: 0.81–1.16, $I^2 = 35\%$, $P_{heterogeneity} = 0.14$) (Figure 1c). The summary RR ranged from 0.92 (95% CI: 0.75–1.13) when excluding the NIH-AARP Diet and Health Study to 1.04 (95% CI: 0.90–1.21) when excluding the Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study. There was no evidence of small study effects with Eggerapos;s test, $P = 0.42$, or with Beggapos;s test, $P = 0.47$. There was no evidence for a nonlinear association between carbohydrates and pancreatic cancer risk, $P_{nonlinearity} = 0.32$ (supplementary Figure S3c, available at *Annals of Oncology* online).

sucrose

high versus low analysis

Nine cohort studies [14, 15, 17, 19–23, 25] were included in the high versus low analysis of sucrose intake and pancreatic cancer and included 3202 cases among 1 217 523 participants. The summary RR was 1.02 (95% CI: 0.85–1.23, $I^2 = 56\%$, $P_{heterogeneity} = 0.02$) (supplementary Figure S2d, available at *Annals of Oncology* online).

dose–response analysis

Eight cohort studies [14, 15, 19–23, 25] were included in the dose–response analysis. The summary RR per 25 g/day was 1.05 (95% CI: 0.92–1.19, $I^2 = 53\%$, $P_{heterogeneity} = 0.04$) (Figure 1d). The summary RR ranged from 1.02 (95% CI: 0.89–1.16) when the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial study was excluded to 1.10 (95% CI: 0.97–1.24) when the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was excluded. There was no evidence of small study effects with Eggerapos;s test, $P = 0.71$, or Beggapos;s test, $P = 0.71$. There was no evidence of a nonlinear association between sucrose and pancreatic cancer risk, $P_{nonlinearity} = 0.14$ (supplementary Figure S3d, available at *Annals of Oncology* online).

fructose

high versus low analysis

Seven cohort studies [14, 15, 17, 19–22] were included in the high versus low analysis of fructose intake and pancreatic cancer and included 2831 cases among 1 156 512 participants. The summary RR was 1.18 (95% CI: 1.01–1.37, $I^2 = 25\%$, $P_{heterogeneity} = 0.24$) (supplementary Figure S4, available at *Annals of Oncology* online).

dose–response analysis

Six cohort studies [14, 15, 19–22] were included in the dose–response analysis of fructose intake and pancreatic cancer risk. The summary RR for a 25 g/day increment was 1.22 (95% CI: 1.08–1.37, $I^2 = 0\%$, $P_{heterogeneity} = 0.43$) (Figure 2a). The summary RR ranged from 1.16 (95% CI: 0.99–1.36) when excluding the NIH-AARP Diet and Health study to 1.26 (95% CI: 1.12–1.42) when excluding the Women's Health Initiative. There was no evidence of small study effects with Eggerapos;s test, $P = 0.22$, although some evidence with Beggapos;s test, $P = 0.06$. When excluding one study [20] from the analysis, Beggapos;s test showed $P = 0.22$, but the summary RR remained similar, 1.26 (95% CI: 1.12–1.42). There was no evidence for a nonlinear association between fructose intake and pancreatic cancer, $P_{nonlinearity} = 1.00$ (Figure 2b).

other carbohydrates

Few studies investigated the association between intake of other carbohydrates and pancreatic cancer risk. The summary RR for high versus low intake was 1.14 (95% CI: 0.96–1.35, $I^2 = 0\%$, $P_{heterogeneity} = 0.62$, $n = 3$) for total sugar [15, 19, 22], 1.04 (95% CI: 0.65–1.64, $I^2 = 82\%$, $P_{heterogeneity} = 0.004$, $n = 3$) for available carbohydrates (total carbohydrates minus fiber) [19, 21, 25] and 0.98 (95% CI: 0.82–1.17, $I^2 = 0\%$, $P_{heterogeneity} = 0.46$, $n = 2$) for starch (results not shown) [19, 21]. There were not enough studies to conduct analyses of lactose, maltose, glucose, or galactose.

Subgroup, meta-regression and sensitivity analyses

In subgroup analyses, the results were consistent in showing no association between intake of GI, GL, total carbohydrates or sucrose and pancreatic cancer risk (supplementary Tables S1 and S2, available at *Annals of Oncology* online). There was a significant association for fructose intake in the subgroups of studies that adjusted for smoking [14, 15, 19–22], BMI [14, 15, 19–22], red and processed meat intake [19, 22] and energy intake [14, 15, 19–22], but there was no association in the subgroups of studies that adjusted for intake of alcohol [15, 19, 20], diabetes status [14, 20] or physical activity [14, 20], although the number of studies was low in some of these subgroups (Table 2). In meta-regression analyses, there was, however, no evidence of heterogeneity between the subgroups with and without adjustment for these factors, neither in the fructose analysis (Table 2) nor in the analysis of total carbohydrates, GI, GL or sucrose (supplementary Tables S1 and S2, available at *Annals of Oncology* online). Because not all studies reported on all types of carbohydrates, we conducted further sensitivity analyses using the same dataset to clarify if there was a 'study effect'. When the analyses were restricted to the studies that were common for the analyses of total carbohydrates, sucrose and fructose [14, 15, 19, 20, 22], the summary RR was 1.00 (95% CI: 0.78–1.29, $I^2 = 37\%$, $P_{heterogeneity} = 0.17$) for total carbohydrates, 1.08 (95% CI: 0.93–1.25, $I^2 = 38\%$, $P_{heterogeneity} = 0.17$) for sucrose and 1.21 (95% CI: 1.05–1.40, $I^2 = 16\%$, $P_{heterogeneity} = 0.32$) for fructose.

discussion

We found no statistically significant association between intake of total carbohydrates, sucrose, GI or GL and pancreatic cancer risk in categorical and dose–response meta-analyses. However, to our knowledge, this is the first meta-analysis to report an

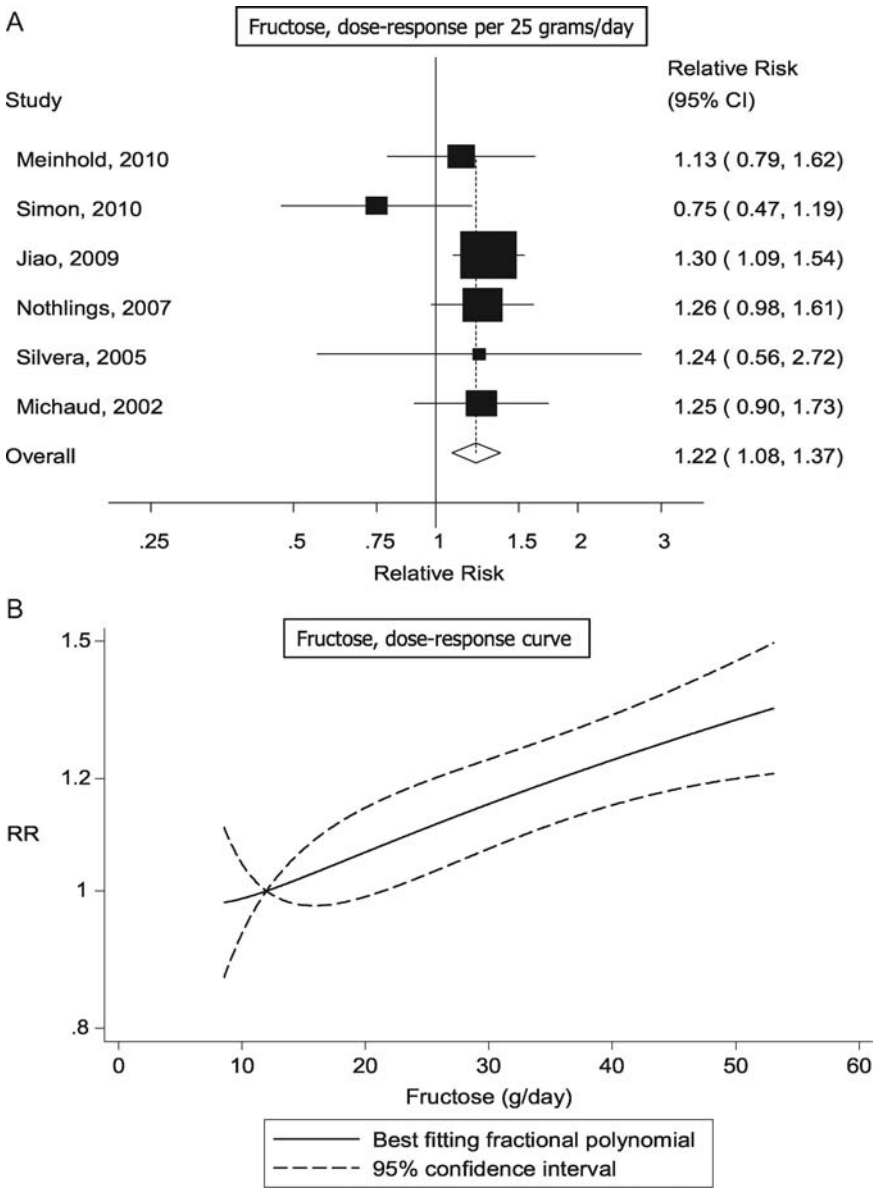

Figure 2.. Fructose and pancreatic cancer, dose–response analysis.

association between intake of fructose and increased pancreatic cancer risk.

Our meta-analysis may have several limitations which must be taken into consideration. Intake of diets high in fructose, carbohydrates, GI and GL may be associated with other behaviors including physical activity, overweight and obesity, smoking and intake of alcohol and red and processed meat, which possibly could confound associations we observed. The results for fructose intake persisted in studies that adjusted for smoking [14, 15, 19–22], BMI [14, 15, 19–22], intake of red and processed meat [19, 22] and energy intake [14, 15, 19–22]; however, there was no association in the few studies that adjusted for alcohol [15, 19, 20], diabetes [14, 20] and physical activity [14, 20]. Because of the few studies in some of these subgroup analyses interpretation of these analyses is difficult. There was no evidence of heterogeneity between these subgroups with and without adjustment for these potentially confounding factors. For the other exposures, the results were similar across subgroups and there was no evidence of heterogeneity between the subgroups. We found little evidence of small study effects in this analysis and in the one analysis where there was some indication of small study effects this was caused by only one study [20] and exclusion of that study did not change the results.

Measurement errors in the assessment of dietary intake are known to bias effect estimates; however, none of the studies included in this meta-analysis made any corrections for measurement errors. Any measurement errors would, however, most likely result in bias toward the null and, thus, underestimate the association between fructose and carbohydrate intake and pancreatic cancer risk. Assessment of GI or GL may be particularly challenging because these measures are based on their postprandial blood glucose response and are not concentration values of nutrients in the

Table 2. Subgroup analyses of fructose intake and pancreatic cancer, dose–response analysis

	Fructose					
		n	RR (95% CI)	I^2 (%)	P_h[a]	P_h[b]
All studies		6	1.22 (1.08–1.37)	0	0.43	
Sex						
Men		0				NC
Women		3	1.05 (0.73–1.49)	38.6	0.20	
Duration of follow-up						
< 10 years follow-up		4	1.17 (0.98–1.40)	38.6	0.18	0.89
≥10 years follow-up		2	1.25 (0.92–1.69)	0	0.98	
Geographic location						
Europe		0				NC
America		6	1.22 (1.08–1.37)	0	0.43	
Number of cases						
Cases < 300		4	1.09 (0.87–1.36)	9.5	0.35	0.29
Cases 300 to < 499		1	1.26 (0.98–1.61)			
Cases ≥500		1	1.30 (1.09–1.54)			
Adjustment for confounding factors						
Alcohol	Yes	3	1.08 (0.74–1.58)	57.2	0.10	0.77
	No	3	1.23 (1.03–1.46)	0	0.89	
Smoking	Yes	6	1.22 (1.08–1.37)	0	0.43	NC
	No	0				
Diabetes	Yes	2	1.00 (0.60–1.64)	67.9	0.08	0.31
	No	4	1.26 (1.11–1.44)	0	0.93	
Body mass index	Yes	6	1.22 (1.08–1.37)	0	0.43	NC
	No	0				
Physical activity	Yes	2	1.00 (0.60–1.64)	67.9	0.08	0.31
	No	4	1.26 (1.11–1.44)	0	0.93	
Red, processed meat	Yes	2	1.28 (1.11–1.48)	0	0.85	0.28
	No	4	1.09 (0.87–1.36)	9.5	0.35	
Fruits, vegetables	Yes	0				NC
	No	6	1.22 (1.08–1.37)	0	0.43	
Energy intake	Yes	6	1.22 (1.08–1.37)	0	0.43	NC
	No	0				

RR, relative risk; CI, confidence interval; '*n*', denotes the number of studies; NC, not calculable because no studies were present in one of the subgroups.
[a]*P* for heterogeneity within each subgroup.
[b]*P* for heterogeneity between subgroups with meta-regression analysis.

foods consumed. Most dietary questionnaires have estimated usual GI or GL values based on a limited number of food items, which may not have been specifically selected and validated for dietary GI or GL. However, studies using similar questionnaires have been able to detect associations between GI or GL and risk of type 2 diabetes [40] and cardiovascular disease [41], although we cannot exclude the possibility that a weak association with pancreatic cancer may have been obscured due to measurement errors.

The specific mechanism that may explain an association between fructose intake and pancreatic cancer remains speculative, but the metabolism of fructose differs from other carbohydrates such as glucose. Recently, it has been shown that the contribution of fructose to nucleic acid synthesis through the pentose phosphate pathway (catalyzed by transketolase) is greater than glucose [42]. Synthesis of nucleic acids and nucleotides is necessary for proliferating tissues and in particular, cancer cells. It has been shown that suppression of transketolase-like protein 1 reduces cancer cell proliferation [43, 44] while activation of transketolase stimulates tumor growth [45]. The contribution of fructose to the generation of nucleic acids is further illustrated by increased production of uric acid [42], a by-product of purine metabolism, and increased risk of gout among high fructose consumers [46]. Interestingly, one study reported an elevated pancreatic cancer risk among men with high serum uric acid levels, although no association was observed in women [47]. In addition, experimental studies have shown that chronic fructose feeding in animals leads to insulin resistance and obesity [27]. Several [28, 48–50], but not all [51] epidemiological and experimental studies have reported positive associations between fructose intake and type 2 diabetes and obesity in humans as well, both of which are established risk factors for pancreatic cancer; however, all the studies included in the analysis of fructose and pancreatic cancer risk adjusted for BMI, suggesting an association independent of BMI.

Our meta-analysis also has several strengths. Because we based our analyses on prospective studies, we have effectively

avoided recall bias and reduced the possibility of selection bias. Our meta-analysis is consistent with two previous meta-analyses that found no association between GI and GL and pancreatic cancer risk based on five to six cohort studies [31, 32]. However, with three additional studies, our meta-analysis included a total of ~1–1.2 million participants, depending on the exposure, and ~3000 cases. Thus, we had statistical power to detect moderate associations. In addition, we conducted more detailed subgroup analyses and dose–response analyses. Our results suggest that only specific types of carbohydrates may increase pancreatic cancer risk. It is possible that the association may reflect certain foods or drinks with a high fructose content. Fructose is a monosaccharide found naturally in fruits and vegetables, but data regarding fruit intake and pancreatic cancer risk have indicated a reduced risk, although the evidence was considered only limited suggestive in the World Cancer Research Fund/American Institute for Cancer Research report from 2007, while data on vegetable intake were even more limited or conflicting [8]. In addition, prospective data on specific types of fruits and vegetables pancreatic cancer risk are sparse. Fructose has also largely replaced sucrose as a sweetener in soft drinks in the past 10–20 years in the United States, although not in Europe. The third National Health and Nutrition Examination Survey reported that over 10% of Americanapos;s daily calories come from fructose, of which the largest part came from sugar-sweetened beverages (30%), followed by grains (22%) and fruit or fruit juice (19%) [52]. Some studies have reported elevated risk of pancreatic cancer with high intake of sugar-sweetened beverages [53–55] which can be high in high-fructose corn syrup, although the data are not completely consistent [22, 56, 57]. A meta-analysis found a summary RR of 1.21 (95% CI: 0.90–1.63) for heavy soft drink consumers among five cohort studies [57], while a more recent pooled analysis of 14 cohort studies reported a nonsignificant increase in risk for ≥250 versus 0 g/day of soft drink intake, RR = 1.19 (95% CI: 0.98–1.46), which reached significance on a continuous scale, RR = 1.06 (95% CI: 1.02–1.12) per 175 g/day [58]. These estimates are of similar size as our results for fructose intake. Further studies of fructose intake and specific sources of fructose and pancreatic cancer risk are warranted since all the studies reporting on fructose intake were American and it is not known whether these findings apply to other populations.

In conclusion, our results indicate that intake of fructose, but not total carbohydrates, sucrose, GI or GL, increases the risk of pancreatic cancer. Given the few established dietary risk factors for pancreatic cancer, further studies of fructose intake and pancreatic cancer risk with better adjustment for confounding factors are warranted to confirm or refute these findings and to clarify whether the results reflect the effect of specific foods or drinks.

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disclosure

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