European Journal of Nutrition (2022) 61:309–316
https://doi.org/10.1007/s00394-021-02646-5

ORIGINAL CONTRIBUTION

Diabetes risk reduction diet and the risk of pancreatic cancer

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Received: 29 March 2021 / Accepted: 19 July 2021 / Published online: 2 August 2021

Abstract

Purpose To evaluate the role of a diabetes risk reduction diet (DRRD) on pancreatic cancer risk.

Methods We used data from a hospital-based case–control study conducted in Italy between 1991 and 2008; the study included 326 incident pancreatic cancer cases and 652 controls matched by age, gender and study center. Subjects' usual diet was collected through a valid and reproducible food frequency questionnaire. A DRRD score was derived from 8 dietary components: cereal fiber, total fruit, coffee, polyunsaturated to saturated fats ratio and nuts (higher score for higher intake), and dietary glycemic index, red/processed meat and sugar-sweetened beverages/fruit juices (higher score for lower intake). The score ranged 8–37, with higher values indicating greater DRRD adherence. Odds ratios (ORs) of pancreatic cancer according to the DRRD score were estimated using multiple conditional logistic regression models.

Results After allowance for confounding factors, the DRRD score was inversely related to pancreatic cancer risk, with ORs of 0.55 (95% confidence interval, CI 0.38–0.80) for the highest versus the lowest score tertile (p for trend across tertiles = 0.002) and 0.84 (95% CI 0.75–0.95) for a 3-point score increment. The exclusion of diabetic subjects and additional adjustment for vegetable intake did not change the results. Inverse associations were observed in subgroups defined by age, gender, education, body mass index, smoking and total energy intake.

Conclusion Study findings suggest a protective role of high adherence to a DRRD on pancreatic cancer risk.

Keywords Pancreatic cancer · Case–control study · Diabetes · Diet · Prevention

Introduction

Pancreatic cancer is an aggressive tumor, frequently diagnosed at advanced stages, with an overall 5-year survival of less than 10%. According to GLOBOCAN 2018 estimates, pancreatic cancer is the seventh most common cause of cancer death in both males and females [1]. In contrast with most other cancers, mortality rates from pancreatic cancer have not been declined during the last years [2, 3], and it has been projected that the disease will become the third leading cause of cancer death in the European Union in the nearer future [4]. Primary prevention of pancreatic cancer is, therefore, crucial.

Tobacco smoking is the major identified risk factor for pancreatic cancer [5]. Other correlates of the disease include diabetes, history of (chronic) pancreatitis, obesity and the metabolic syndrome, and heavy alcohol consumption. Family history and genetic factors also play a role [6].

Diabetes mellitus has been associated with pancreatic cancer in multiple studies. The risk of pancreatic cancer is greatest early after the diagnosis of diabetes and then progressively declines, but remains elevated for many years [7]. This suggests a bidirectional causality, with diabetes being a predisposing factor for pancreatic cancer, and new-onset diabetes an early manifestation of the (subclinical) malignancy [8]. Patients with long-standing diabetes have an approximately 1.5- to twofold increased pancreatic cancer risk [9]. While overweight/obesity and the increased medical surveillance of diabetic patients may partly account for the association, possible mechanisms linking diabetes to

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pancreatic cancer include insulin resistance and the consequent hyperinsulinemia, increased circulating insulin-like growth factors (IGF) levels, hyperglycemia and low chronic inflammation [10].

Selected dietary factors have been associated with pancreatic cancer. High intake of red and processed meat and foods rich in saturated fats and fructose may increase the risk [11], while the intake of vegetables and fruit [12], and the related nutrients and compounds [13], and healthy dietary patterns [14], including the Mediterranean diet [15], may decrease the risk. High dietary glycemic index (GI) and load (GL) have also been related to pancreatic cancer [16, 17]. However, the issue of diet and pancreatic cancer is largely undefined.

A dietary pattern for diabetes prevention has been recently proposed (diabetes risk reduction diet, DRRD). The original version of the DRRD was based on high intakes of cereal fiber, coffee, and nuts, a high ratio of polyunsaturated to saturated fats, low dietary GI, low intakes of red/processed meat, sugar-sweetened beverages and *trans* fats [18]. The DRRD was subsequently modified by adding information on fruit (among the favorable components) and combining fruit juices to sugar-sweetened beverages [19]. The original DRRD has been inversely related to hepatocellular carcinoma in one study [20] and the modified one to breast cancer in the same database [19]. To our knowledge, no data are yet available for pancreatic cancer.

The aim of the present study is to assess the association between a score measuring adherence to the DRRD and the risk of pancreatic cancer using data from a multicentric Italian study.

Patients and methods

Data were derived from a multicentric case–control study of pancreatic cancer conducted between 1991 and 2008 in the provinces of Milan and Pordenone, northern Italy [21]. The study included 326 incident cases (174 men, 152 women; median age 63 years, range 34–80 years) and 652 controls (348 men, 304 women) frequency-matched by age (±5 years), sex and study center in a 2:1 ratio. Controls were admitted to the same teaching or general hospitals as cases for a wide spectrum of acute conditions other than neoplastic or digestive tract diseases; they were hospitalized for traumas (31%), other orthopedic disorders (31%), acute surgical conditions (28%), and miscellaneous other illnesses (10%). More than 95% of cases and controls approached agreed to study participation. All enrolled subjects signed an informed consent, according to the recommendations of the Board of Ethics of each participating center. All procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Cases and controls were interviewed in hospital by centrally trained interviewers, using a standard structured questionnaire. This included information on sociodemographic and anthropometric factors, lifestyle habits, such as tobacco smoking, alcohol drinking and physical activity, personal medical history, and family history of cancer. Usual diet during the 2 years before cancer diagnosis (for cases) or hospital admission (for controls) was assessed through a food frequency questionnaire (FFQ). Subjects were asked to indicate their average weekly consumption of 78 food items or food groups. Open questions were used to report foods/dishes eaten at least once a week not included in the FFQ list. The FFQ also included a few questions aiming at assessing fat intake pattern. Intakes lower than once a week, but at least once per month, were coded as 0.5 per week. Total energy intake and intake of nutrients and fiber were determined using an Italian food composition database [22]. For GI, we primarily used international nutritional tables [23]; Italian sources were used for a few local recipes [24]. The FFQ was tested for validity [25] and reproducibility [26, 27] with satisfactory results.

A score measuring adherence to the DRRD was calculated as proposed by Kang et al. [19], based on 8 dietary factors. We assigned subjects scores between 1 and 5 according to quintiles of consumption (derived among controls), in ascending order for cereal fiber, coffee, total fruit, and ratio of polyunsaturated to saturated fats (i.e., factors associated to decreased diabetes risk), and in descending order for GI and red/processed meat (i.e., factors associated with increased diabetes risk) (See Table S1, Supplementary Information, for quintile cut-points). Since the consumption of sugar-sweetened beverages and fruit juices was relatively infrequent in our population [i.e., 605 subjects (61.9%) did not drink either sugar-sweetened beverages or fruit juices], we assigned a score of 5 to non-drinkers, a score of 3 to drinkers of ≤2.5 drinks per week (i.e., the median value among drinking controls), and a score of 1 to drinkers of more than 2.5 drinks per week. The FFQ did not include a specific item for nuts consumption; subjects reporting nuts consumption in the open question of the FFQ [$n=21$ (2.2%)] were given a score of 2; otherwise, a score of 1 was assigned. For each subject, the overall DRRD score was obtained by summing up the scores in all the dietary components. Due to the lack of *trans* fats information within the Italian food composition tables, *trans* fats intake could not be derived. Consequently, the score ranged 8–37, with higher values indicating greater adherence to the DRRD. See Fig S1 (Supplementary Information) for a graphical representation example for a subject in the first and in the third tertile of the DRRD score.

Statistical analysis

Conditional logistic regression models were used to estimate the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of pancreatic cancer for approximate tertiles (derived among controls) of the DRRD score, using the lowest category as the reference one. ORs for a 3-point increment in the score were also estimated. We fitted models conditioned on center, age and sex and adjusted for year of interview (continuous variable), years of education (< 7, 7–11, ≥ 12), body mass index (BMI, < 25, 25 to < 30, ≥ 30 kg/m^2), tobacco smoking (never smoker, former smoker, current smoker of < 15 and ≥ 15 cigarettes per day), history of diabetes (yes, no), alcohol intake (never drinker, ever drinker of 1 to < 21 and ≥ 21 drinks per week) and total energy intake (tertiles). A few missing data in education (< 1%), BMI (< 1%), tobacco smoking (< 1%) and alcohol intake (< 1%) were replaced by the median value (for continuous variables) or mode category (for categorical variables) according to case/control status and sex.

We conducted sensitivity analyses by (1) excluding diabetic subjects, (2) adjusting for total vegetables intake, and (3) excluding each score component in turn from the DRRD score calculation. We conducted subgroup analyses in strata of age, sex, education, BMI, smoking status and total energy intake. Heterogeneity across strata was evaluated using the likelihood ratio test comparing the models with and without interactions terms for the score tertile variables and the subgroup factors.

All the analyses were conducted using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the distribution of pancreatic cancer cases and controls according to age and other selected factors. By design, cases and controls had a similar age, center and sex distribution. Cases were more educated and more frequently smokers and drinkers of ≥ 21 drinks/week than controls; they also reported more frequently a history of diabetes. The distribution of BMI and energy intake was similar between the two groups.

Table 2 provides the ORs of pancreatic cancer, with the corresponding 95% CIs, according to the DRRD score. The DRRD score was inversely related to the risk of pancreatic cancer. Based on the multivariable model, the ORs were 0.55 (95% CI 0.38–0.80) for the third versus the first tertile of the score (p for trend across tertiles 0.002), and 0.84 (95% CI 0.75–0.95) for a 3-point increment in the score. Further adjustment for vegetable intake (OR_{T3vsT1}: 0.56, 95% CI 0.38–0.82, p for trend across DRRD score tertiles 0.003) and exclusion of diabetic subjects from the analyses (OR_{T3vsT1}: 0.61, 95% CI 0.41–0.91, p for trend across DRRD score tertiles = 0.017) did not appreciably influence the results. The association between the DRRD score and the risk of pancreatic cancer persisted when removing from the score each dietary component in turn (Supplementary Information, Fig S2); the ORs for the third versus the first tertile ranged from 0.45, after excluding the cereal fiber or the coffee component, to 0.66 (statistically significant), with the exclusion of the fruit component.

When single score components were analyzed separately, inverse associations were observed for total fruit

Table 1 Distribution of 326 pancreatic cancer cases and 652 controls by age and other selected factors (Italy, 1991–2008)

	Cases, *n* (%)	Controls, *n* (%)
Center		
Aviano/Pordenone	175 (53.7)	350 (53.7)
Milano	151 (46.3)	302 (46.3)
Sex		
Men	174 (53.4)	348 (53.4)
Women	152 (46.6)	304 (46.6)
Age group (years)		
< 50	32 (9.8)	64 (9.8)
50–59	89 (27.3)	178 (27.3)
60–69	122 (37.4)	244 (37.4)
≥ 70	83 (25.5)	166 (25.5)
Education[a] (years)		
< 7	166 (51.2)	350 (53.9)
7–11	86 (26.5)	192 (29.5)
≥ 12	72 (22.2)	108 (16.5)
Body mass index[a] (kg/m^2)		
< 25.0	139 (42.9)	264 (40.7)
25.0–29.9	135 (41.7)	296 (45.6)
≥ 30	50 (15.4)	89 (13.7)
Smoking habits[a]		
Never	137 (42.0)	328 (50.4)
Ex	86 (26.4)	189 (29.0)
Current, < 15 cigarettes/day	36 (11.2)	60 (9.2)
Current, ≥ 15 cigarettes/day	64 (19.8)	72 (11.1)
Alcohol drinking[a]		
Never	42 (13.0)	100 (15.4)
< 21 drinks/week	155 (48.1)	342 (52.6)
≥ 21 drinks/week	125 (38.8)	208 (32.0)
History of diabetes		
No	279 (85.6)	615 (94.3)
Yes	47 (14.4)	37 (5.7)
Total energy intake (kcal)		
< 1993	98 (30.1)	218 (33.4)
1993–2610	106 (32.5)	216 (33.1)
≥ 2611	122 (37.4)	218 (33.4)

[a]The sum does not add up to the total because of some missing values

Table 2 Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of pancreatic cancer according to approximate tertiles of the diabetes risk reduction diet (DRRD) score (Italy, 1991–2008)

	Cases, *N* (%)	Controls, *N* (%)	OR[a] (95% CI)
DRRD score, tertiles			
I (< 21)	134 (41.1)	223 (34.2)	1[b]
II (22–24)	110 (33.7)	208 (31.9)	0.79 (0.56–1.12)
III (> 24)	82 (25.2)	221 (33.9)	0.55 (0.38–0.80)
χ^2 Trend (*p* value)			9.6 (*0.002*)
3-point increment			0.84 (0.75–0.95)

[a]Estimated from logistic regression models, conditioned on center, age and sex, and adjusted for year of interview, education, body mass index, tobacco smoking, history of diabetes, alcohol intake and total energy intake

[b]Reference category

intake and the ratio polyunsaturated:saturated fats, and direct associations with dietary GI and red/processed meat; the intake of cereal fiber, coffee, sugar-sweetened beverages/fruit juices and nuts was not appreciably associated to the risk of pancreatic cancer (data not shown).

Figure 1 shows the association between the DRRD score (third versus first tertile) and the risk of pancreatic cancer in strata of selected factors. Inverse associations were observed in subgroups defined by age, sex, education, BMI, smoking and total energy intake, although the ORs did not reach statistical significance in women, more educated and non-overweight subjects, and never smokers. Tests for interaction did not reveal significant heterogeneity across strata.

Discussion

In this study, a score measuring adherence to a diet aiming at diabetes prevention was inversely related with the risk of pancreatic cancer. After allowance for a number of potential confounders, including overweight/obesity, total energy intake and smoking, subjects with the highest DRRD adherence score had a 45% reduced risk of pancreatic cancer, as compared to those with the lowest adherence.

To our knowledge, this is the first study showing that a diet that reduces the risk of diabetes might also have a preventive effect on pancreatic cancer risk. One prior study examined the association of such antidiabetic diet with breast cancer [19] and one with hepatocellular carcinoma [20], finding inverse associations, stronger for hepatocellular carcinoma than breast cancer.

To date, no strong dietary correlates of pancreatic cancer have been identified [11]. As for the dietary components of the DRRD score, fruit intake may decrease the risk of pancreatic cancer [12]. However, evidence for an inverse association mostly derives from case–control studies, while cohort studies generally reported weaker or null associations [28, 29], casting some doubts on the relationship. Again, total fiber and whole grain intakes were inversely related to pancreatic cancer in case–control studies [30, 31]; in

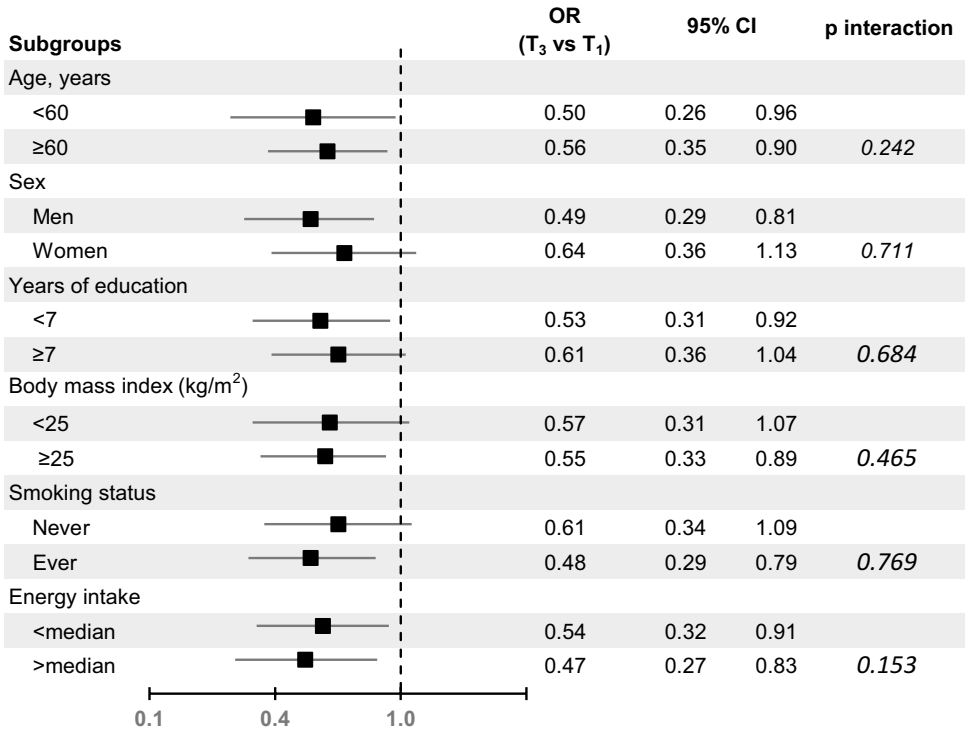

Fig. 1 Odds ratios[a] (ORs) of pancreatic cancer for the highest versus the lowest tertile of the diabetes risk reduction diet (DRRD) score, with corresponding 95% confidence interval (CIs), in selected subgroups[b] (Italy, 1991–2008). [a]Estimated from logistic regression models, conditioned on center, age and sex, and adjusted for year of interview, education, body mass index, tobacco smoking, history of diabetes, alcohol intake and total energy intake, unless the covariate was the stratification factor. The lowest DRRD score tertile was the reference category in the analyses. [b]Test for interaction considered all the three tertiles of the DRRD score

contrast, the few available cohort studies did not support such associations [32, 33]. In this dataset, fiber from grain was not related to pancreatic cancer [34]; to our knowledge, no other study has addressed the topic. Although earlier investigations suggested a possible detrimental role of coffee on pancreatic cancer [35, 36], several subsequent epidemiological studies clearly indicated that coffee consumption is not appreciably related to pancreatic cancer risk [37, 38]. As for nuts consumption, evidence is limited and inconsistent, with some studies showing null results [39] and other inverse associations [40], possibly restricted to selected subgroups of the population [41]. Investigations on dietary fats have provided inconclusive results. Findings from a meta-analysis based on 13 case–control and 7 cohort studies showed lack of association for dietary saturated and monounsaturated fatty acids, while a moderate inverse association of borderline significance was observed for polyunsaturated fatty acids, which was smaller in cohort studies [42]. In cohort studies using biomarkers of fatty acids exposure, higher circulating n-3 polyunsaturated fatty acids appeared to lower pancreatic cancer risk [43, 44]. Among the unfavorable score components, recent meta-analyses showed no association with pancreatic cancer for dietary GI (though the pooled relative risk for GI was above unity), as well as dietary GL [45], and sugar-sweetened beverages consumption [46]; evidence on red and processed meat is unclear, with some studies showing positive associations of small magnitude, possibly restricted to men, and other a lack of association [47, 48].

Thus, although individual dietary components of the score have been only marginally associated with the risk of pancreatic cancer, the overall DRRD dietary pattern showed a strong inverse association with the disease in the present study. The dietary pattern approach allows to capture a broad picture of food and nutrient intake considering the biologic interactions among nutrients [49]. Dietary patterns may be more strongly related to disease risk than individual foods or nutrients, and are particularly useful when the standard approach of focusing on individual foods or nutrients have not revealed important associations [50], as in the case of pancreatic cancer.

An association between the DRRD and pancreatic cancer is plausible, as diabetes and overweight/obesity are recognized risk factors and selected aspects of diet may influence insulin resistance, hyperinsulinemia, hyperglycemia and inflammation. Notably, high intake of cereal fiber [51] and whole grain [52], nuts [53], fruit [54], polyunsaturated fats [55] and coffee [56] may decrease the risk of diabetes, while high dietary GI and GL [57], high intake of sugar-sweetened beverages [58], red and processed meat [59] and *trans* fats [55] may increase the risk. However, we could not assess whether the observed association of the DRRD score is due to a direct effect of this antidiabetic diet on glycemia and related factors, or to other beneficial effects of the healthy components of the dietary pattern and their combination.

Italian food composition tables do not provide information on the content of *trans* fats, and we were, therefore, unable to include *trans* fats in the DRRD score [19]. However, major sources of *trans* fats include margarine, fried fast foods, and highly industrially processed foods, such as packaged snacks and baked products, which consumption is relatively infrequent in Italy as compared to other Western countries [60]. Our FFQ collected information on fats and oils use in cooking. Margarine was used as the main fat source for cooking vegetables, cooking meat, frying or seasoning pasta only by, respectively, 0.4%, 1.2%, 0.5% and 1.5% of study participants. Additionally, most of the studies investigating FFQ-derived estimates of *trans* fats intake in relation to pancreatic cancer did not find direct associations [61–63], although a cohort investigating separately different sources of *trans* fats reported an inverse association for *trans* fats from partially hydrogenated vegetable oils in men only [64], and another cohort a direct association with *trans* 16:1 fatty acid but not with other more common *trans* fatty acids [65]; further, one study assessing measures of plasma fatty acids found a direct significant association with industrial *trans* fatty acids in men [43].

This is a retrospective study, and selection and information bias should be considered. In particular, recall bias is possible since we asked for habitual diet in the 2 years prior to pancreatic cancer diagnosis. However, the exclusion from the control group of patients admitted for chronic conditions or diseases related to alcohol, tobacco or diet modifications or known risk factors for pancreatic cancer, the near complete participation rate (> 95% for both cases and control), the matched data collection, the similar catchment areas and interview setting for cases and controls, the use of a FFQ with satisfactory results in terms of validity and reproducibility [25–27], and the lack of awareness in this population of a possible role of diet on pancreatic cancer has minimized such biases. We were able to adjust our relative risk estimates for a number of possible confounding factors; however, we cannot exclude that part of the observed association may be explained by residual confounding by a general healthy lifestyle or other factors.

In conclusion, the findings of this study suggest a favorable impact of adherence to a diabetes prevention diet on pancreatic cancer risk, offering a scenario of prevention through dietary choices in a disease with a dramatically poor prognosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-021-02646-5.

Author contributions FT analyzed the data and drafted the manuscript; CLV and EN conducted research; CLV, EN, MR and FB contributed

substantially to the interpretation of data; all authors contributed to manuscript revision and approved the final version of the manuscript.

Funding Fondazione AIRC, Associazione Italiana per la Ricerca sul cancro, Milano; FIRC, Fondazione Italiana Ricerca sul Cancro.

Availability of data and material The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Code availability SAS code is available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interests.

Ethics approval The study was approved by the local ethics committees according to the rules at the time of data collection and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate All enrolled subjects signed an informed consent, according to the recommendations of the Board of Ethics of each participating center.

Consent for publication Not applicable.

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