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Macronutrients, fatty acids, cholesterol and pancreatic cancer

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ABSTRACT

A role of diet and nutrition in pancreatic carcinogenesis has been suggested, but the association between selected macronutrients, fatty acids, cholesterol and pancreatic cancer remains controversial. We analysed data from a hospital-based case-control study conducted in Italy between 1991 and 2008, including 326 cases (174 men and 152 women) with incident pancreatic cancer, and 652 controls (348 men and 304 women) frequency-matched to cases by sex, age and study centre. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multiple logistic regression models conditioned on age, sex and study centre, and adjusted for year of interview, education, tobacco smoking, history of diabetes and energy intake. A positive association was found for animal proteins (OR = 1.85 for the highest versus the lowest quintile of intake; 95% CI: 1.15–2.96; p for trend = 0.039), whereas a negative association was observed for sugars (OR = 0.52; 95% CI: 0.31–0.86; p for trend = 0.003). Non-significant negative associations emerged for vegetable proteins (OR = 0.69) and polyunsaturated fatty acids (OR = 0.67). In conclusion, a diet poor in animal proteins and rich in sugars (mainly derived from fruit) appears to have a beneficial effect on pancreatic cancer risk.

1. Introduction

In Europe, pancreatic cancer is the fifth cause of cancer death in men and the sixth in women.[1]

Tobacco is the major established risk factor for pancreatic cancer[2]; family history of pancreatic cancer[3] and a history of diabetes[4] have also been consistently associated with the risk. Some aspects of diet and nutrition-including obesity, physical activity, low intake of fruit and vegetables and possible high intake of meat-appear to have an effect on pancreatic cancer risk.[5–9]

With reference to macronutrients, the evidence from both case-control and adequately powered cohort studies is still inconclusive.[10–26] Case-control[10,15] and cohort[20,21] studies found no association between total protein intake and pancreatic cancer risk, while the results on sugars[15,18,19,22,24,26] and carbohydrates[10,13–20,22,24–26] were mixed and inconsistent. Case-control[10,16,23] and cohort[20,21] studies found a positive association with (total) fat intake, but the results for different types of fats,[13–15,20,21,23] as well as cholesterol[11,13–15,18,20,21,23] were inconsistent.

In order to further assess the role of selected macronutrients, fatty acids and cholesterol on the risk of pancreatic cancer, we analysed data from a hospital-based case-control study conducted in Italy, where diet was assessed using a validated food frequency questionnaire (FFQ).[27,28]

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2. Materials and methods

Between 1991 and 2008, we conducted a hospital-based case-control study of pancreatic cancer in the province of Pordenone and in the greater Milan area, Northern Italy.[29]

Cases were 326 subjects (174 men and 152 women, median age 63 years, range 34–80) with incident (83% diagnosed 3 months before interview) cancer of the pancreas (excluding neuroendocrine tumours), admitted to major teaching and general hospitals in the study areas, diagnosed no longer than 1 year before the interview, and with no previous diagnosis of cancer. Controls were 652 subjects (348 men and 304 women, median age 63 years, range 34–80) admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, not related to smoking, alcohol consumption nor long-term modifications of diet. They were admitted for traumatic orthopaedic disorders (31%), other orthopaedic disorders (31%), acute surgical conditions (28%) and miscellaneous other illnesses, including eye, nose, ear, skin or dental disorders (10%). Controls were frequency-matched to cases by sex, age and study centre with a control-to-case ratio of 2:1. Less than 5% of cases and controls approached refused to be interviewed.

For both cases and controls, data were collected during their hospital stay by trained interviewers using a structured questionnaire. This included information on socio-demographic characteristics, anthropometric measures, selected lifestyle habits (e.g. tobacco smoking, alcohol and coffee drinking), a personal medical history, family history of cancer, and, for women, menstrual and reproductive factors, and use of exogenous hormones.

A FFQ was used to assess the usual diet during the 2 years before diagnosis (or hospital admission, for controls). This included 78 foods, food groups or recipes divided into six sections: (i) bread, cereals, first courses; (ii) second courses (i.e. meat, fish and other main dishes); (iii) side dishes (i.e. vegetables); (iv) fruits; (v) sweets, desserts and soft drinks; (vi) milk, hot beverages and sweeteners. At the end of each section, one or two open questions were used to include other foods eaten at least once per week. Subjects were asked to indicate the average weekly frequency of consumption for each dietary item; intakes lower than once a week, but at least once a month were coded as 0.5 per week. For 40 food items, the portion was defined in 'natural' units (e.g. 1 teaspoon of sugar, 1 egg), while for other items it was defined as small, average or large with the help of pictures. For fruit and vegetables subject to seasonal variation, consumption in season, and the corresponding duration, were elicited. Specific questions aimed to assess the fat intake pattern, e.g. the type of fat used for cooking or seasoning, and the avoidance of visible fat in meat and ham, were also included in the questionnaire. Intake of total energy and selected macronutrients was computed using an Italian food composition database,[30] which was periodically updated.[31] An additional section investigated lifelong consumption of alcoholic beverages.

Odds ratios (ORs) of pancreatic cancer and their corresponding 95% confidence intervals (CIs) were estimated using multiple logistic regression models[32] conditioned on age, sex and study centre, and adjusted for year of interview, education, tobacco smoking, history of diabetes and energy intake. To control for energy intake, the residuals of the linear regression of nutrients on energy were computed.[33] We used the estimate of energy intake only as an adjustment variable, and for this purpose ranking of subjects according to their level of intake is considered satisfactory.[33] The quintiles of energy-adjusted nutrients were computed on the distribution of controls; the unit for the continuous variables was set to one standard deviation (SD) of the distribution of controls. ORs according to energy-partitioned models – in which total energy intake was successively split into two terms, energy derived from the specific nutrients and energy derived from all other sources – were also computed.[33,34] This allowed to estimate the effect of adding the nutrient to diet instead of substituting it for other nutrients.

We also performed stratified analyses by sex, age (<60, $\geqslant$60 years), education (<7, $\geqslant$7 years) and tobacco smoking (never/ex, current smokers). To test for interactions, the differences in 2 log (likelihood) of the models with and without interaction term were compared with the χ^2 distribution with one degree of freedom.

3. Results

Table 1 shows the distribution of cases and controls according to sex, age and other selected variables. By design, cases and controls had the same distribution of sex, age and study centre. There was no significant association with education; cases reported more frequently a history of diabetes and higher tobacco consumption than controls.

Table 2 gives the median daily intake of selected macronutrients, fatty acids and cholesterol among controls and the corresponding ORs of pancreatic cancer according to quintile of intake, and continuously. There was a significant positive association with animal protein (OR = 1.85, 95% CI: 1.15–2.96 for the highest versus lowest quintile of intake; p for trend = 0.039), and a negative one with sugars (OR = 0.52, 95% CI: 0.31–0.86; p for trend = 0.003). Non significant negative associations were observed for vegetable proteins (OR = 0.69) and polyunsaturated fatty acids (OR = 0.67); no association was found for other macronutrients, fatty acids or cholesterol. Further adjustment for body mass index did not significantly change the ORs for various nutrients considered. Moreover, the risk estimates were similar when diabetic subjects were excluded from the analyses. For an increase in intake equal to one SD of the control distribution, the ORs were 0.89 (95% CI: 0.76–1.04) for vegetable proteins, 1.16 (95% CI: 1.00–1.35) for animal proteins, 0.80 (95% CI: 0.67–0.95) for sugars and 0.88 (95% CI: 0.74–1.06) for polyunsaturated fatty acids. Energy-partitioned models produced results similar to the residual energy-adjusted models. The OR relative to 100 kcal/d was 0.63 (95% CI: 0.32–1.25) for vegetable proteins, 1.30 (95% CI: 1.03–1.66) for animal proteins, 0.91 (95% CI: 0.82–1.00) for sugars, 1.04 (95% CI: 0.97–1.12) for starch, 1.00 (0.94–1.09) for total fats, 1.04 (95% CI: 0.82–1.32) for saturated fatty acids, 0.99 (95% CI: 0.89–1.11) for monounsaturated fatty acids and 0.83 (95% CI: 0.62–1.13) for polyunsaturated fatty acids.

Table 1 – Distribution of 326 cases of pancreatic cancer and 652 controls according to age, education and other selected variables. Italy, 1991–2008.

Characteristic	Cases		Controls	
	No.	%	No.	%
Sex				
Men	174	53.4	348	53.4
Women	152	46.6	304	46.6
Centre				
Milan	151	46.3	302	46.3
Pordenone	175	53.7	350	53.7
Age (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 (years)[a]				
<7	166	51.2	350	53.9
7–11	86	26.5	192	29.5
⩾12	72	22.2	108	16.6
Smoking status[a]				
Never smokers	137	42.4	328	50.5
Ex-smokers	88	27.2	194	29.9
Current smokers				
<15 Cigarettes/day	35	10.8	59	9.1
⩾15 Cigarettes/day	63	19.5	68	10.5
History of diabetes				
No	269	82.5	615	94.3
Yes	57	17.5	37	5.7

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

The relation with vegetable and animal proteins, sugars and polyunsaturated fatty acids was further examined in strata of sex, age, education and tobacco smoking (Table 3). No significant heterogeneity was observed across any of the strata considered, although the negative association between vegetable proteins and pancreatic cancer risk was only observed in men, and the negative association with sugars was only observed in non-smokers. Likewise, no heterogeneity in risk estimates for these nutrients was observed across strata of body mass index (data not shown).

4. Discussion

Our study indicates that a diet rich in animal proteins was positively related with pancreatic cancer risk, while a negative relation emerged with sugars. Non significant negative associations were observed for vegetable proteins and polyunsaturated fatty acids. Total proteins, starch, total fats, as well as other fatty acids and cholesterol were not associated with risk.

In broad agreement with our results, no association between total protein intake and pancreatic cancer risk was observed in a few case-control studies,[10,15] as well as in the Alpha-tocopherol, Beta-carotene Cancer Prevention (ATBC) Study cohort from Finland,[20] and the Nurses' Health Study from the USA.[21] However, conflicting results were reported in other case-control studies.[11,13,14,16–18] At least one case-control[18] and two cohort[20,21] studies evaluated the role of types of proteins (i.e. vegetable and animal), and reported inconsistent results. In the Italian population, red meat is one of the main sources of animal proteins,[35] and the association between animal proteins and pancreatic cancer risk observed in our study is consistent with the positive relation with red meat observed in another hospital-based case-control study from Italy[36,37], as well as in a few cohort studies.[38,39] Meat and other protein-rich foods produce heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH) and N-nitroso compounds (NOC) when cooked at high temperature (e.g. grilling) or when heated for prolonged time (e.g. stewing).[40] Studies on animal models reported carcinogenic effects for several HCAs and PAHs,[41] and at least two epidemiological studies[39,42] associated high dietary intakes of HCAs and PHAs to elevated risk of pancreatic cancer.

With reference to sugars, the results from previous studies are inconsistent, some studies reporting positive associations,[19,24] and some null or inconsistent associations across subgroups or types of sugars.[15,18,22,26] The negative relation between sugars and pancreatic cancer risk in the present study is related to the fact that in this Italian population the main source of sugars was fruit (47%),[35] which has been found to be negatively related to the risk of pancreatic cancer risk in this study (OR = 0.60 for the highest versus the lowest quintile of intake) as well as in other case-control studies.[5–9,43] The negative association between sugars and pancreatic cancer risk was indeed attenuated after allowance for fruit intake.

Table 2 – Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) among 326 pancreatic cancer and 652 controls according to intake of selected macronutrients, fatty acids and cholesterol. Italy, 1991–2008.

	Median (p20-p80)[b]	Quintile of intake, OR[a] (95% CI)					χ^2 trend (*p*-value)	OR continuous[d] (95% CI)
		1[c]	2	3	4	5		
Macronutrients (g)								
Total proteins	87.5 (67.8–110.1)	1	1.05 (0.64–1.72)	0.91 (0.55–1.50)	1.14 (0.70–1.85)	1.47 (0.91–2.29)	2.760 (0.097)	1.12 (0.96–1.30)
Vegetable proteins	29.9 (23.4–37.8)	1	0.78 (0.49–1.25)	0.61 (0.38–0.98)	0.63 (0.39–1.02)	0.69 (0.43–1.12)	3.150 (0.076)	0.89 (0.76–1.04)
Animal proteins	55.7 (42.6–73.2)	1	1.35 (0.83–2.21)	1.05 (0.63–1.76)	1.05 (0.62–1.76)	1.85 (1.15–2.96)	4.251 (0.039)	1.16 (1.00–1.35)
Sugars	97.3 (66.4–135.6)	1	1.18 (0.76–1.84)	0.79 (0.49–1.25)	0.74 (0.46–1.18)	0.52 (0.31–0.86)	9.166 (0.003)	0.80 (0.67–0.95)
Starch	168.8 (121.1–225.5)	1	1.03 (0.63–1.68)	1.14 (0.70–1.85)	1.19 (0.74–1.92)	0.94 (0.57–1.55)	0.006 (0.938)	1.02 (0.88–1.20)
Total fats	79.2 (55.5–108.5)	1	1.23 (0.75–2.01)	1.69 (1.05–2.72)	1.04 (0.75–2.17)	0.84 (0.51–1.38)	0.784 (0.376)	0.92 (0.79–1.08)
Vegetable fats	39.7 (24.9–58.1)	1	1.10 (0.69–1.77)	1.27 (0.79–2.07)	0.87 (0.54–1.42)	0.76 (0.47–1.25)	1.886 (0.170)	0.91 (0.78–1.06)
Animal fats	38.1 (26.0–54.3)	1	1.08 (0.65–1.78)	1.45 (0.90–2.36)	1.26 (0.76–2.08)	1.17 (0.72–1.91)	0.643 (0.423)	1.03 (0.88–1.20)
Fatty acids (g) and cholesterol (mg)								
Saturated fatty acids	25.8 (17.9–35.7)	1	1.62 (0.98–2.69)	2.38 (1.44–3.95)	1.68 (1.00–2.82)	1.19 (0.70–2.02)	0.195 (0.659)	1.00 (0.86–1.18)
Monounsaturated fatty acids	35.0 (24.3–50.1)	1	1.08 (0.66–1.79)	1.11 (0.66–1.86)	1.40 (0.86–2.28)	0.82 (0.50–1.07)	0.047 (0.829)	0.95 (0.82–1.10)
Oleic acid	33.0 (22.4–47.8)	1	0.88 (0.53–1.46)	1.17 (0.70–1.96)	1.22 (0.76–1.98)	0.76 (0.47–1.25)	0.128 (0.721)	0.95 (0.82–1.10)
Polyunsaturated fatty acids	10.6 (7.6–17.3)	1	0.61 (0.38–0.99)	0.77 (0.48–1.23)	0.84 (0.52–1.35)	0.67 (0.40–1.10)	1.040 (0.308)	0.88 (0.74–1.06)
Linoleic acid	8.5 (5.9–14.2)	1	0.59 (0.37–0.97)	0.81 (0.51–1.28)	0.85 (0.52–1.38)	0.67 (0.41–1.12)	0.853 (0.356)	0.88 (0.74–1.06)
Linolenic acid	1.3 (0.9–2.0)	1	0.97 (0.61–1.54)	0.95 (0.60–1.52)	0.90 (0.55–1.47)	0.68 (0.41–1.13)	1.904 (0.168)	0.88 (0.74–1.05)
Cholesterol	273.3 (195.3–381.1)	1	1.15 (0.72–1.84)	0.83 (0.50–1.37)	1.14 (0.70–1.84)	1.10 (0.68–1.77)	0.118 (0.732)	0.96 (0.82–1.12)

a Estimates from logistic regression models, conditioned on age, sex and centre and adjusted for year of interview, education, tobacco smoking, history of diabetes and total energy intake, according to the residual model.

b Among controls, per day.

c Reference category.

d ORs for a difference in intake equal to one standard deviation of the distribution of controls. p20: 20th percentile. p80: 80th percentile.

Table 3 – Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) among 326 pancreatic cancer and 652 controls according to intake of vegetable proteins, animal proteins and sugars in strata of sex, age and other selected covariates. Italy, 1991–2008.

	Continuous OR[a] (95% CI)			
	Vegetable proteins	Animal proteins	Sugars	Polyunsaturated fatty acids
Sex				
Men	0.81 (0.67–0.98)	1.21 (0.99–1.46)	0.91 (0.73–1.13)	0.94 (0.75–1.18)
Women	1.10 (0.83–1.46)	1.08 (0.84–1.39)	0.63 (0.47–0.85)	0.80 (0.60–1.07)
p for interaction	0.07	0.51	0.06	0.39
Age (years)				
<60	0.92 (0.73–1.16)	1.30 (1.01–1.65)	0.88 (0.68–1.14)	0.99 (0.75–1.30)
⩾60	0.86 (0.70–1.07)	1.08 (0.89–1.31)	0.74 (0.58–0.93)	0.82 (0.65–1.04)
p for interaction	0.68	0.27	0.32	0.32
Education (years)				
<7	0.94 (0.75–1.17)	1.26 (1.02–1.56)	0.81 (0.64–1.02)	0.89 (0.71–1.11)
⩾7	0.85 (0.69–1.05)	1.05 (0.85–1.30)	0.79 (0.61–1.02)	0.86 (0.65–1.15)
p for interaction	0.52	0.23	0.90	0.86
Tobacco smoking				
Never-/ex-smokers	0.86 (0.71–1.03)	1.14 (0.95–1.36)	0.74 (0.60–0.91)	0.85 (0.69–1.05)
Current Smokers	0.97 (0.72–1.31)	1.23 (0.94–1.62)	1.00 (0.72–1.40)	0.98 (0.72–1.33)
p for interaction	0.48	0.64	0.13	0.45

a Estimates from logistic regression models, conditioned on age, sex and centre and adjusted for year of interview, education, tobacco smoking, history of diabetes and total energy intake, according to the residual model. ORs for a difference in intake equal to one standard deviation of the distribution of controls.

With respect to other carbohydrates, our results are consistent with those from other case-control[13,15,17] and cohort[24–26] studies that found no associations between starch and/or total carbohydrates and the risk of pancreatic cancer, although a few case-control studies[14,16,18] and at least one cohort study[19] reported positive associations, and at least one case-control study[10] and two cohort studies[20,22] reported negative associations.

In our study, as in previous case-control studies,[11–15,36] intake of total fat was not associated with pancreatic cancer risk. However, other studies[10,16,20,21,23] observed a positive association between total fat and the risk of pancreatic cancer, while a few others[17,18] reported negative associations.

Polyunsaturated fatty acids were negatively – although not significantly – associated with pancreatic cancer risk in our study. This is in broad agreement with a previous case-control study from Italy, which found a moderate negative relation with (olive) oil intake.[44] A negative association between polyunsaturated fat and pancreatic cancer risk was also observed in a case-control study from the USA,[13] in a collaborative case-control study within the SEARCH programme,[14] and in the Nurses' Health Study.[21] However, a case-control study from Greece,[15] as well as the ABTC Study cohort[20] reported positive associations, while a population-based case-control study from the USA[23] reported no association.

We found no association between cholesterol intake and pancreatic cancer risk. This result is in agreement with other studies,[11,15,20,21] though at least three case-control studies found positive associations,[13,14,23] and another one found a positive association in men, but a negative one in women.[18]

The study size and the collection of extensive dietary information using a reproducible and valid FFQ[27,28] are the major strengths of this study. Further strengths include the comparable catchment areas of cases and controls, the high participation rate and the possibility of allowance for several covariates in the analyses, including energy intake. Moreover, these associations were consistent across strata of age, sex, education and tobacco smoking, thus showing that they are independent from the major risk factors for pancreatic cancer.

As in most case-control studies, recall and selection biases are possible. A recent cancer diagnosis and prediagnostic symptoms may have influenced diet and its recall for cases. However, we asked for dietary habits 2 years prior to the diagnosis of cancer. Moreover, awareness of dietary hypotheses in pancreatic cancer aetiology was unknown to the general population and to the interviewers, and the comparability of information between cases and controls was improved by interviewing subjects in the same hospital setting. Although some aspects of diet could have changed over time, the nutrient database used for macronutrients computation has been continuously updated in order to capture possible modification in the intake.[31] Further, dietary habits of hospital controls may differ from those of the general population, but we excluded from the control group any subject admitted for conditions associated with long-term modifications of diet.

Further epidemiological studies of nutrient and pancreatic cancer are warranted. Such studies should comprise large populations with broad exposure contrasts. Pooled analyses and multicentre studies would represent the best approach. Special focus should be given to the investigation in cohort studies of possible excess risk of pancreatic cancer in groups of population with high intake of animal protein.

Conflict of interest statement

None declared.

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REFERENCES

1. Bosetti C, Bertuccio P, Levi F, et al. Cancer mortality in the European Union, 1970–2003, with a joinpoint analysis. *Ann Oncol* 2008;**19**:631–40.
2. IARC. *IARC Monographs on the evaluation of carcinogenic risks to humans. Tobacco smoke and involuntary smoking*, vol. 83. Lyon: International Agency for Research on Cancer; 2004.
3. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. *Fam Cancer* 2008;**1**:1–2.
4. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005;**92**:2076–83.
5. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition and the prevention of cancer: a global prospective*. Washington, DC: AICR; 1997.
6. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004;**363**:1049–57.
7. Anderson KE, Mack TM, Silverman DT. Cancer of the pancreas. In: Schottenfeld D, Fraumeni Jr JF, editors. *Cancer epidemiology and prevention*. 3rd ed. New York: Oxford University Press; 2006. p. 721–62.
8. van den Brandt PA, Goldbohm RA. Nutrition in the prevention of gastrointestinal cancer. *Best Pract Res Clin Gastroenterol* 2006;**20**:589–603.
9. World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global prospective*. Washington, DC: AICR; 2007.
10. Durbec JP, Chevillotte G, Bidart JM, Berthezene P, Sarles H. Diet, alcohol, tobacco and risk of cancer of the pancreas: a case-control study. *Br J Cancer* 1983;**47**:463–70.
11. Farrow DC, Davis S. Diet and the risk of pancreatic cancer in men. *Am J Epidemiol* 1990;**132**:423–31.
12. La Vecchia C, Negri E, D'Avanzo B, et al. Medical history, diet and pancreatic cancer. *Oncology* 1990;**47**:463–6.
13. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. *Cancer Causes Control* 1991;**2**:291–7.
14. Howe GR, Ghadirian P, Bueno de Mesquita HB, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. *Int J Cancer* 1992;**51**:365–72.
15. Kalapothaki V, Tzonou A, Hsieh CC, et al. Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece. *Cancer Causes Control* 1993;**4**:383–9.
16. 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.
17. Ji BT, Chow WH, Gridley G, et al. Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai China. *Cancer Epidemiol Biomarkers Prev* 1995;**4**:885–93.
18. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst* 1998;**90**:1710–9.
19. Michaud DS, Liu S, Giovannucci E, et al. Dietary sugar, glycemic load and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst* 2002;**94**:1293–300.
20. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol* 2002;**155**:783–92.
21. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol* 2003;**157**:1115–25.
22. Silvera SA, Rohan TE, Jain M, et al. Glycemic index, glycemic load and pancreatic cancer risk (Canada). *Cancer Causes Control* 2005;**16**:431–6.
23. Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control* 2007;**18**:1153–67.
24. Nothlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Dietary glycemic load, added sugars carbohydrates as risk factors for pancreatic cancer: the Multiethnic Cohort study. *Am J Clin Nutr* 2007;**86**:1495–501.
25. Heinen MM, Verhage BA, Lumey L, et al. Glycemic load, glycemic index and pancreatic cancer risk in the Netherlands cohort study. *Am J Clin Nutr* 2008;**87**:970–7.
26. Jiao L, Flood A, Subar AF, et al. Glycemic index, carbohydrates, glycemic load and the risk of pancreatic cancer in a prospective cohort study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:1144–51.
27. Decarli A, Franceschi S, Ferraroni M, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. *Ann Epidemiol* 1996;**6**:110–8.
28. Franceschi S, Barbone F, Negri E, et al. Reproducibility of an Italian food frequency questionnaire for cancer studies. Results for specific nutrients. *Ann Epidemiol* 1995;**5**:69–75.
29. Talamini R, Polesel J, Gallus S, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. *Eur J Cancer* 2010;**46**:370–6.
30. Salvini S, Parpinel MT, Gnagnarella P, Maisonneuve P, Turrini A. *Banca dati di composizione degli alimenti per studi epidemiologici in Italia*. Milano: Istituto Europeo di Oncologia; 1998.
31. Gnagnarella P, Parpinel M, Salvini S, et al. The update of the Italian food composition database. *J Food Comp Anal* 2004;**17**:509–22.
32. Breslow NE, Day NE. *Statistical methods in cancer research. The analysis of case-control studies*, vol. I. IARC Scientific Publications No. 32, Lyon: IARC; 1980.
33. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;**124**:17–27.
34. Decarli A, Favero A, La Vecchia C, et al. Macronutrients, energy intake and breast cancer risk: implications from different models. *Epidemiology* 1997;**8**:425–8.
35. Favero A, Salvini S, Russo A, et al. Sources of macro- and micronutrients in Italian women: results from a food frequency questionnaire for cancer studies. *Eur J Cancer Prev* 1997;**6**:277–87.
36. Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E. Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev* 1998;**7**:455–60.
37. Tavani A, La Vecchia C, Gallus S, et al. Red meat intake and cancer risk: a study in Italy. *Int J Cancer* 2000;**86**:425–8.
38. Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. Meat and fat intake and pancreatic cancer risk in the Netherlands cohort study. *Int J Cancer* 2009;**125**:1118–26.
39. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT, et al. Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:2664–75.
40. Sugimura T. Nutrition and dietary carcinogens. *Carcinogenesis* 2000;**21**:387–95.

41. Wei D, Xiong HQ, Abbruzzese JL, Xie K. Experimental animal models of pancreatic carcinogenesis and metastasis. *Int J Gastrointest Cancer* 2003;**33**:43–60.
42. Anderson KE, Kadlubar FF, Kulldorff M, et al. Dietary intake of heterocyclic amines and benzo(a)pyrene: associations with pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2261–5.
43. La Vecchia C, Altieri A, Tavani A. Vegetables, fruit, antioxidants and cancer: a review of Italian studies. *Eur J Nutr* 2001;**40**:261–7.
44. La Vecchia C, Negri E. Fats in seasoning and the relationship to pancreatic cancer. *Eur J Cancer Prev* 1997;**6**:370–3.