Dietary total antioxidant capacity and pancreatic cancer risk: an Italian case–control study

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Background: Pancreatic cancer is one of the leading causes of cancer mortality. Diet may be associated with pancreatic cancer, but it is unknown whether specific dietary components contribute to its risk. The potential differential role of dietary antioxidants warrants further investigation.

Methods: We analysed data from a case–control study of 326 pancreatic cancer cases and 652 controls conducted between 1991 and 2008 in Northern Italy. Subjects’ usual diet was assessed through a validated and reproducible food frequency questionnaire. Using this information and an Italian food composition database, we calculated three indices of dietary total antioxidant capacity (TAC): Trolox equivalent antioxidant capacity (TEAC), total radical-trapping antioxidant parameter (TRAP) and ferric-reducing antioxidant power (FRAP). We estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer using multiple logistic regression models conditioned on study centre, sex and age, and adjusted for major known pancreatic cancer risk factors.

Results: Significant inverse associations were found for the highest tertile of TAC compared with the lowest tertile for both TEAC and FRAP. The ORs were 0.61 (95% CI 0.39–0.94, P-value for trend 0.03) and 0.63 (95% CI 0.41–0.99, P-value for trend 0.05), respectively. Total radical-trapping antioxidant parameter was inversely, but not significantly, associated with pancreatic cancer risk, with an OR of 0.78 (95% CI 0.49–1.24, P-value for trend 0.27).

Conclusions: Diet high in TAC, as measured by TEAC and FRAP, is inversely associated with pancreatic cancer risk.
Vegetables have been positively associated with the risk of pancreatic cancer; consumption of red meat and low consumption of fruit and vegetables have been associated with decreased overall cancer risk, but have not been definitively associated with decreased pancreatic cancer risk (Romagueri et al., 2012; Lucas et al., 2015). Although elevated consumption of red meat and low consumption of fruit and vegetables have been positively associated with the risk of pancreatic cancer (Anderson et al., 2002, 2005; Polesel et al., 2010; World Cancer Research Fund/American Institute for Cancer Research, 2012; Bosetti et al., 2013; Lucas et al., 2015), the evidence is inconsistent to draw conclusions. A common theme to these more comprehensive dietary approaches is that they are high in dietary antioxidants.

Total antioxidant capacity (TAC) is a marker of dietary antioxidant potential, and is defined as the moles of oxidants neutralised by 1 l plasma, food extracts or single molecules (Serafini et al., 2006). According to WCRF/AICR recommendations, TAC provides a more comprehensive overview of dietary patterns as opposed to analysis of single dietary antioxidants (World Cancer Research Fund/American Institute for Cancer Research, 2012). We hypothesised that dietary TAC would be inversely associated with pancreatic cancer risk in a case–control study of pancreatic cancer subjects.

**MATERIALS AND METHODS**

We analysed data from a case–control study of pancreatic cancer conducted between 1991 and 2008 in Milan and Pordenone, Italy (Polesel et al., 2010). Cases were 326 subjects (174 men, 152 women, median age 63 years, range 34–80 years) with incident pancreatic cancer admitted to major general hospitals in the study centres. Controls were 652 subjects (348 men, 304 women, frequency-matched according to age (+ 5 years), sex and study centre) with a 2:1 ratio. Controls were admitted to the same teaching or general hospitals as cases for a variety of acute non-neoplastic diagnoses, including acute surgical conditions (28%), traumatic orthopaedic conditions (31%), other orthopaedic conditions (31%) and other miscellaneous conditions (10%). Over 95% of cases and controls who were approached agreed to participate. All enrolled subjects signed an informed consent, according to the recommendations of the Board of Ethics of each participating centre.

All subjects were interviewed by centrally trained interviewers using a structured questionnaire that included socio-demographic and lifestyle habits (including history of tobacco use, alcohol use and physical activity), anthropometric measures (e.g., self-reported height and weight at different ages), personal medical history of selected diseases (e.g., diabetes) and history of cancer in first-degree relatives. Subject’s usual diet two years before cancer diagnosis (cases) or hospital admission (controls) was assessed though a validated (Decarli et al., 1996) and reproducible (Franceschi et al., 1993) food frequency questionnaire (FFQ), which included data on 83 foods and beverages grouped into seven sections: (1) bread and cereal dishes; (2) meat, fish and other main dishes; (3) potatoes and vegetables; (4) fruit; (5) sweets, desserts and soft drinks; (6) dairy and hot beverages (including tea and coffee); and (7) alcohol consumption. Subjects indicated average weekly consumption of each item; those with intermediate use were assigned frequency of 0.5.

The most commonly used measures of TAC are the Trolox equivalent antioxidant capacity (TEAC), the total radical-trapping antioxidant parameter (TRAP) and the ferric-reducing antioxidant power (FRAP) (Prior et al., 2005). TEAC and FRAP are based on single electron transfer mechanism and measure the ability of antioxidants to scavenge to the stable radical cation ABTS+ (2,2’-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) and to reduce Fe3+/2 (ferric ion) to Fe2+/3 (ferrous ion). Total radical-trapping antioxidant parameter measures the chain-breaking potential to reduce peroxyl radicals generated by AAPH (2,2-azobis(2-aminopropane) dihydrochloride) or ABAP (2,2’azobis(2-amidinopropane) dihydrochloride) and represents a measurement of the hydrogen atom transfer mechanism (Re et al., 1999).

Using the Italian food composition database (Gnagnarella et al., 2004), an ad hoc database was developed to calculate TAC for each of the three indices (i.e., TEAC, TRAP and FRAP) based on experimental assessment of the food extracts (Pellegrini et al., 2003, 2006). A total of 64 items contribute to the assessment of TEAC, 57 to TRAP and 59 to FRAP in this study. Coffee was excluded from the TAC estimate, since the main contributors to in vitro antioxidant capacity of coffee are the Maillard reaction products (creating during the coffee roasting of beans) (Delgado-Andrade and Morales, 2005), whose absorption and antioxidant capacity in vivo have not been demonstrated (Morales et al., 2012). In addition, due to their high molecular weight, they may function in a different manner from other antioxidants. Intake of total energy was computed using an Italian food composition database (Gnagnarella et al., 2004).

Energy-adjusted TEAC, TRAP and FRAP were categorised into tertiles based on the control distribution. We estimated the corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer using conditional multiple logistic regression models, controlled for study centre (Milan, Pordenone), sex, age (5-year intervals) and adjusted for year of interview (continuous), years of education (<7, 7–11, ≥12, categorically), body mass index (BMI) (<25, 25–30, ≥30 kg m⁻², categorically), tobacco use (never smoker, ex-smoker, current smoker <15 and ≥15 cigarettes per day, categorically), alcohol intake (non-drinkers, <28 g of ethanol per day, >28 g of ethanol per day, categorically) and diabetes (yes, no). Energy intake was adjusted for using the residual model (Willett and Stampfer, 1986). We also fitted models in strata of sex, age, BMI, tobacco smoking, alcohol use and history of diabetes, and assessed the heterogeneity of the risk estimates across strata using the Wald χ²-test.

**RESULTS**

The distribution of 326 pancreatic cancer cases and 652 controls according to sex, age and other selected characteristics is shown in Table 1. No significant differences were noted for education, BMI and alcohol consumption. Compared with controls, cases were more often smokers and more frequently had a history of diabetes. When analysing the distribution of these characteristics among tertiles of the three energy-adjusted TAC indices, subjects in the higher tertiles were more frequently men, current smokers and alcohol drinkers; moreover, they had a higher intake of fruit and vegetables and a lower consumption of cereals (Supplementary Table 1).

Table 2 provides the distribution of pancreatic cancer cases and controls with the corresponding ORs and 95% CIs by tertiles of energy-adjusted dietary TAC indices. Significant inverse associations were noted between TEAC and FRAP and pancreatic cancer risk; the OR for the highest tertile of TEAC compared with the lowest tertile was 0.61 (95% CI 0.39–0.94, P-value for trend 0.03), and the OR for FRAP was 0.63 (95% CI 0.41–0.99, P-value for trend 0.05). TRAP was inversely but not significantly associated.
with pancreatic cancer risk, with an OR of 0.78 (95% CI 0.49–1.24, P-value for trend 0.27).

Table 3 gives the ORs for pancreatic cancer according to tertiles of TEAC and FRAP by strata of selected covariates. The association between TEAC and FRAP and pancreatic cancer risk was apparently stronger (although not significantly) in subjects with a history of tobacco use. No differences were noted across strata of sex, age, BMI, alcohol use and history of diabetes. Given the low number of diabetic subjects, we also computed continuous OR for an increment equal to 1 s.d. For TEAC, the continuous OR was 0.81 (95% CI, 0.75–1.10) among non-diabetic subjects. The continuous OR for FRAP was 0.69 (95% CI, 0.56–1.35) among diabetic subjects and 0.93 (95% CI, 0.77–1.12) among non-diabetic subjects.

### DISCUSSION

The association between antioxidants and pancreatic cancer risk is complex, with overall mixed results. Dietary intake of single antioxidants such as vitamin C (Bueno de Mesquita et al, 1991; Gong et al, 2010), α-tocopherol (Stozenberg-Solomon et al, 2009; Bravi et al, 2011; Jeurnink et al, 2015), β-carotene (Olsen et al, 1991; Jeurnink et al, 2015), flavonoids (Nothlings et al, 2008; Rossi et al, 2012; Arem et al, 2013) and selenium (Banim et al, 2013) has been associated with decreased risk of pancreatic cancer. However, the intake of individual antioxidant supplements has failed to demonstrate a protective effect in pancreatic cancer (Rautalalhti et al, 1999; Heinen et al, 2012; Han et al, 2013). We hypothesised that antioxidants may have an important role in pancreatic cancer risk, but that there may be interactions between antioxidant supplements and other dietary components that abrogate a beneficial effect.

Plant-based diets, rich in dietary antioxidants, have been associated with decreased pancreatic cancer risk (Anderson et al, 2005; Polesel et al, 2010; Bosetti et al, 2013). Also the Mediterranean diet has been associated with decreased pancreatic cancer risk and is rich in antioxidants (Bosetti et al, 2013). Thus, these data are in line with our findings suggesting that a diet high in TAC is associated with decreased pancreatic cancer risk.

Antioxidants are thought to reduce oxidative DNA damage and subsequent genetic mutations, and therefore may provide a protective effect against cancer (Foksinski et al, 2007). Tobacco smoke promotes cancer by a variety of different mechanisms, including genetic mutations in tumour suppressors and oncogenes, gene promoter hypermethylation and protein kinase activation (U.S. Department of Health and Human Services, 2010) and therefore may modify the effect of antioxidants on cancer risk (Woodson et al, 1999; Wu et al, 2015). Our data indicating that the association between dietary antioxidant and pancreatic cancer may be stronger in subjects with a history of tobacco exposure could suggest that those exposed to increased oxidative stress may benefit the most from a diet high in antioxidants (Lettieri-Barbato et al, 2013). Further studies are warranted, as our results did not reach statistical significance.

All three indices were inversely related to pancreatic cancer, but the association was not significant for TRAP. Apart from the play of chance, this might be because of the fact that TRAP is more strongly influenced by the consumption of alcoholic beverages as compared with FRAP and TEAC (Praud et al, 2015), and alcohol use is positively related to pancreatic cancer risk (Gapstur et al, 2013). Further studies are warranted, as our results did not reach statistical significance.

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

| Characteristics | Cases | Controls |
|-----------------|-------|----------|
| Study centre    | No.   | %        | No.   | %        |
| Milan           | 151   | 46.3     | 302   | 46.3     |
| Pordenone       | 175   | 53.7     | 350   | 53.7     |
| Sex             |       |          |       |          |
| Men             | 174   | 53.4     | 348   | 53.4     |
| Women           | 152   | 46.6     | 304   | 46.6     |
| Age (years)     |       |          |       |          |
| <50             | 32    | 9.8      | 64    | 9.8      |
| ≥50–<55         | 31    | 9.5      | 62    | 9.5      |
| ≥55–<60         | 58    | 17.8     | 116   | 17.8     |
| ≥65–<70         | 65    | 19.9     | 130   | 19.9     |
| ≥70             | 57    | 17.5     | 114   | 17.5     |
| Education (years) |     |          |       |          |
| <7              | 166   | 51.2     | 350   | 53.9     |
| 7–<12           | 86    | 26.5     | 192   | 29.5     |
| ≥12             | 72    | 22.2     | 108   | 16.6     |
| Body mass index (kg m−2) | | | | |
| <25             | 139   | 42.9     | 264   | 40.7     |
| 25–<30          | 135   | 41.7     | 296   | 45.6     |
| ≥30             | 50    | 15.4     | 89    | 13.7     |
| Smoking status |       |          |       |          |
| Never smokers   | 137   | 42.4     | 328   | 50.5     |
| Ex-smokers      | 86    | 26.6     | 189   | 29.1     |
| Current smokers |       |          |       |          |
| <15 Cigarettes per day | 36 | 11.2     | 60    | 9.2      |
| ≥15 Cigarettes per day | 64 | 19.8     | 72    | 11.1     |
| Alcohol drinkers (tertiles) | | | | |
| I               | 96    | 29.5     | 218   | 33.4     |
| II              | 108   | 33.1     | 218   | 33.4     |
| III             | 122   | 37.4     | 216   | 33.2     |
| History of diabetes | | | | |
| No              | 279   | 85.6     | 615   | 94.3     |
| Yes             | 47    | 14.4     | 37    | 5.7      |

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

*On the basis of the control distribution. Tertiles of alcohol were calculated in grams of ethanol per day.

Limitations of the study include the hospital-based case–control design. Pancreatic cancer subjects and hospitalised controls may differ from those in the general population. We attempted to minimize selection bias by selecting controls that were admitted for reasons such as trauma and acute surgical conditions, and excluding those with a cancer diagnosis. We additionally attempted to limit bias by having the same trained interviewers administering the questionnaire to both cases and controls under similar conditions. Responses to dietary questionnaires may introduce some bias for those with a recent diagnosis of cancer. To minimise this, we asked about diet in the 2 years before cancer diagnosis. We also excluded controls with long-term diagnoses that required hospitalisation. At the time of study enrolment, limited data was available on pancreatic cancer risk factors; therefore, recall bias should be minimal. Data were not available on dietary supplements, which may be contributors to TAC; however, their use was infrequent in this study population during the study period (Sette et al, 2013). Our dietary TAC assay measures in vitro antioxidant activity which may not fully represent in vivo activity, due to still
Table 2. Distribution of 326 pancreatic cancer case and 652 control patients and corresponding ORs and 95% CIs by tertiles of three energy-adjusted TAC indices. Italy, 1991–2008

| Tertilesb | Mean (SD)c | I | II | III | P for trend |
|-----------|------------|---|----|-----|-------------|
| TEAC      |            |   |    |     |             |
| Cases:controls | 4.39 (2.30) |   |    |     |             |
| Upper cutoff points (mmol Trolox per day)d | | 119.217 | 105.218 | 102.217 |             |
| OR (95% CI)e | 3.67 | 4.77 | — | 0.61 (0.39–0.94) | 0.028 |
| TRAP      |            |   |    |     |             |
| Cases:controls | 4.51 (2.81) |   |    |     |             |
| Upper cutoff points (mmol Trolox per day)d | | 114.217 | 105.218 | 107.217 |             |
| OR (95% CI)e | 3.47 | 5.00 | — | 0.78 (0.49–1.24) | 0.27 |
| FRAP      |            |   |    |     |             |
| Cases:controls | 11.23 (5.98) |   |    |     |             |
| Upper cutoff points (mmol Fe$^{2+}$ per day)d | | 117.218 | 111.217 | 98.217 |             |
| OR (95% CI)e | 9.17 | 12.29 | — | 0.63 (0.41–0.99) | 0.048 |

Abbreviations: CI = confidence interval; OR = odds ratio; FRAP = ferric-reducing antioxidant power; SC = standard deviation; TAC = total antioxidant capacity; TEAC = Trolox equivalent antioxidant capacity; TRAP = trapping antioxidant parameter.

aMean and s.d. among controls.
bOn the basis of the control distribution.
cComputed as the sum of the upper cutoff points of energy-adjusted TAC tertiles plus the means of TAC.
dEstimates from logistic regression models, conditioned on study centre, sex and age, and adjusted for year of interview, education, body mass index, tobacco smoking, alcohol intake, diabetes and energy intake according to the residual method.
eReference category.

Table 3. ORs of pancreatic cancer and 95% CIs by tertiles of TEAC and FRAP by selected covariates. Italy, 1991–2008

| OR, 95% Ci | TEAC, tertiles | FRAP, tertiles |
|-----------|---------------|---------------|
| Sex       |               |               |
| Men       | 174.338       | 0.70 (0.41–1.19) | 0.71 (0.43–1.24) | 0.68 (0.38–1.23) |
| Women     | 152.304       | 0.55 (0.28–1.10) | 0.61 (0.34–1.26) | 0.61 (0.30–1.26) |
| P valueb  | 0.71          | 0.64          |
| Age (years) |              |               |
| <65       | 186.372       | 0.85 (0.51–1.42) | 0.58 (0.32–1.08) | 0.91 (0.55–1.51) |
| >65       | 140.280       | 0.84 (0.47–1.51) | 0.75 (0.39–1.45) | 0.75 (0.39–1.47) |
| P valueb  | 0.48          | 0.49          |
| BMI (kg m$^{-2}$) |       |               |
| <25       | 139.264       | 0.93 (0.50–1.71) | 0.88 (0.42–1.82) | 1.06 (0.59–1.93) |
| >25       | 185.385       | 0.94 (0.55–1.60) | 0.61 (0.34–1.10) | 0.93 (0.54–1.59) |
| P valueb  | 0.98          | 0.70          |
| Smoking statusc |         |               |
| Never     | 137.330       | 0.68 (0.39–1.21) | 0.72 (0.36–1.44) | 0.88 (0.50–1.57) |
| Ever      | 188.322       | 0.96 (0.55–1.68) | 0.49 (0.27–0.91) | 0.83 (0.48–1.43) |
| P valueb  | 0.30          | 0.36          |
| Alcohol (tretiles)d |   |               |
| I         | 96.218        | 0.70 (0.36–1.34) | 0.34 (0.11–0.7) | 0.72 (0.38–1.37) |
| II        | 108.218       | 1.02 (0.54–1.93) | 0.70 (0.32–1.52) | 1.14 (0.60–2.16) |
| III       | 122.216       | 1.00 (0.38–2.64) | 0.65 (0.28–1.55) | 0.93 (0.35–2.44) |
| P valueb  | 0.76          | 0.96          |
| History of diabetes |     |               |
| No        | 269.615       | 0.87 (0.58–1.30) | 0.70 (0.44–1.12) | 0.90 (0.60–1.35) |
| Yes       | 57.37         | 0.60 (0.15–2.43) | 0.33 (0.05–2.35) | 0.74 (0.16–3.40) |
| P valueb  | 0.67          | 0.44          |

Abbreviations: BMI = body mass index; CI = confidence interval; FRAP = ferric-reducing antioxidant power; OR = odds ratio; TEAC = Trolox equivalent antioxidant capacity.

aEstimates from logistic regression models, conditioned on study centre, sex and age, and adjusted for year of interview, education, body mass index, tobacco smoking, alcohol intake, diabetes and energy intake according to the residual method. Reference category is the first tertile.
bP for heterogeneity.
cThe sum does not add up to the total because of some missing values.
dOn the basis of the control distribution.
unclear association between dietary and endogenous antioxidant and to the low bioavailability of flavonoids (Manach et al, 2004; Serafini et al, 2011). The FFQ was reproducible (Franceschi et al, 1993) and valid (Decarli et al, 1996), and the reproducibility of FFQ data provided by hospital controls was satisfactory (D’Avanzo et al, 1997). Strengths of the study include the ability to control for other known pancreatic cancer risk-factors, and near-complete data collection for both cases and controls.

Thus, we found that a diet high in antioxidant potential, as measured by dietary TEAC and FRAP, is associated with a decreased risk of pancreatic cancer. The association may be stronger in those with a history of tobacco exposure, although this was not statistically heterogeneous. Our findings provide evidence that a diet high in dietary antioxidants may be protective against pancreatic cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Anderson KE, Kadlubar FF, Kullimor D, Harnack L, Gross M, Lang NP, Barber C, Rothman N, Sinha R (2005) Dietary intake of hydrolyzable amines and benzo(a)pyrene: associations with pancreatic cancer. Cancer Epidemiol Biomarkers Prev 14(9): 2261–2265.

Anderson KE, Sinha R, Kadlubar FF, Kulldorff M, Harnack L, Gross M, Lang NP, Barber C, Rothman N, Sinha R (2005) Dietary intake of hydrolyzable amines and benzo(a)pyrene: associations with pancreatic cancer. Cancer Epidemiol Biomarkers Prev 14(9): 2261–2265.

Arem H, Bojicic P, Sampson J, Subar AF, Sampson J, Subar AF, Park Y, Risch H, Hollenbeck A, et al

Bosetti C, Turati F, Dal Pont A, Ferrari M, Polese J, Negri E, Serraino D, Talanini R, La Vecchia C, Zeegers MP (2013) The role of Mediterranean diet on the risk of pancreatic cancer. Br J Cancer 109(5): 1360–1366.

Bravi F, Polese J, Bosetti C, Talanini R, Negri E, Dal Maso L, Serraino D, La Vecchia C (2011) Dietary intake of selected micronutrients and the risk of pancreatic cancer: an Italian case-control study. Ann Oncol 22(1): 202–206.

Bueno de Mesquita HB, Maisonneuve P, Runia S, Moerman CJ (1991) Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in The Netherlands. Int J Cancer 48(4): 540–549.

D’Avanzo B, La Vecchia C, Katsouyanni K, Negri E, Trichopoulos D (1997) An assessment, and reproducibility of food frequency data provided by hospital controls. Eur J Cancer Prev 6(3): 288–293.

Decarli A, Franceschi S, Ferrari M, Gnagnarella P, Pappalini MT, La Vecchia C, Negri E, Saini S, Falchini F, Giaconia A (1996) Validation of a food-frequency questionnaire to assess dietary intake in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 6(2): 110–118.

Delgado-Andrade C, Morales FJ (2005) Unraveling the contribution of melanoedins to the antioxidant activity of coffee beans. J Agric Food Chem 53(5): 1403–1407.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5): E359–E386.

Foksinski M, Gackowski D, Rozalski R, Siomek A, Guz J, Szpila A, Dziatman M, Olinski R (2007) Effects of basal level of antioxidants on oxidative DNA damage in humans. Eur J Nutr 46(3): 174–180.

Franceschi S, Negri E, Saini S, Decarli A, Ferrari M, Filiberti R, Giaconia A, Talanini R, Nanni O, Panarello G et al. (1993) Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. Eur J Cancer 29A(16): 2298–2305.

Garst J, Jacobs EJ, Deek A, McCullough ML, Patel AV, Thun MJ (2011) Association of a diet with a high antioxidant potential with cancer mortality in never smokers. Arch Intern Med 171(5): 444–451.

Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Gnagnarella P, Parpinel M, Salvini S, Franceschi S, Palli D, Boyle P (2004) Intake of vegetables, fruits, carotenoids and vitamins C and E and pancreatic cancer risk in The Netherlands Cohort Study. Int J Cancer 109(5): 489–495.

Han X, Li J, Brasky TM, Xun P, Stevens J, White E, Gammon MD, He K (2012) Olives and total and breast cancer risk: a pooled analysis of 12 cohort studies of Mediterranean diets. Arch Intern Med 172(10): 1209–1214.

Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Zatonski W, Foretova L, Fontham E, Hamlet WR, Holly EA, Negri E, Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Trichopoulos D, Polese J, Duell EJ, Boffetta P, La Vecchia C (2014) Diabetes, antiobiotic medications, and pancreatic cancer risk: an analysis from the European Pancreatic Cancer Case-Control Consortium. Ann Oncol 25(10): 2065–2072.

Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Zatonski W, Foretova L, Fontham E, Hamlet WR, Holly EA, Negri E, Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Trichopoulos D, Polese J, Duell EJ, Boffetta P, La Vecchia C (2014) Diabetes, antiobiotic medications, and pancreatic cancer risk: an analysis from the European Pancreatic Cancer Case-Control Consortium. Ann Oncol 25(10): 2065–2072.

Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Zatonski W, Foretova L, Fontham E, Hamlet WR, Holly EA, Negri E, Hassan M, Prizment A, Cotterchio M, Cleary S, Kurtz RC, Maisonneuve P, Trichopoulos D, Polese J, Duell EJ, Boffetta P, La Vecchia C (2014) Diabetes, antiobiotic medications, and pancreatic cancer risk: an analysis from the European Pancreatic Cancer Case-Control Consortium. Ann Oncol 25(10): 2065–2072.

Heinen MM, Verheugen A, Goldbohm RA, van den Brandt PA (2012) Intake of vegetables, fruits, carotenoids and vitamins C and E and pancreatic cancer risk in The Netherlands Cohort Study. Int J Cancer 130(1): 147–158.

Idecid S, Gandini S, Maisonneuve P, Lowenfels AB (2008) Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg 394(4): 535–545.

Jernnik SM, Rot RM, Leenders M, van Duijnhoven FJ, Siersmenda PD, Janssen EJ, van Gils CH, Bakker MF, Overvad K, Roswall N, Tjonneland A, Boffetta P, La Vecchia C, Katsouyanni K, Negri E, Serraino D, Talanini R, Fratoni M, Polese J, Negri E, Serraino D, Talanini R, Ogunniyi AD, Frankoski A, Aquilina M, Trichopoulos D, Polese J, Duell EJ, Boffetta P, La Vecchia C (2014) Diabetes, antiobiotic medications, and pancreatic cancer risk: an analysis from the European Pancreatic Cancer Case-Control Consortium. Ann Oncol 25(10): 2065–2072.

Jernnik SM, Rot RM, Leenders M, van Duijnhoven FJ, Siersmenda PD, Janssen EJ, van Gils CH, Bakker MF, Overvad K, Roswall N, Tjonneland A, Boffetta P, La Vecchia C, Katsouyanni K, Negri E, Serraino D, Talanini R, Ogunniyi AD, Frankoski A, Aquilina M, Trichopoulos D, Polese J, Duell EJ, Boffetta P, La Vecchia C (2014) Diabetes, antiobiotic medications, and pancreatic cancer risk: an analysis from the European Pancreatic Cancer Case-Control Consortium. Ann Oncol 25(10): 2065–2072.
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Larsson SC, Hakansson N, Giovannucci E, Wolk A (2006) Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. J Natl Cancer Inst 98(6): 407–413.

lettieri-Barbato D, Tomei F, Sancini A, Morabito G, Serafini M (2013) Effect of plant foods and beverages on plasma non-enzymatic antioxidant capacity in human subjects: a meta-analysis. Br J Nutr 109(4): 1544–1556.

Luceteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, Allen N, Amundadottir L, Bergmann M, Boffetta P, Buring JE (2015) Adherence to World Cancer Research Fund/American Institute for Cancer Research recommendations and pancreatic cancer risk. Cancer Epidemiol 40: 15–21.

Malvezzi M, Caroli G, Bertuccio P, Rosso T, Boffetta P, Levi F, La Vecchia C, Negri E (2016) European cancer mortality predictions for the year 2016 with focus on leukaemias. Ann Oncol 27: 725–731.

Manach C, Sabclart A, Morand C, Remeys C, Jimenez L (2004) Polyphenols: food sources and bioavailability. Am J Clin Nutr 79(2): 727–747.

Michaud DS, Prior RL, Wu X, Schaich K (2005) Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements. J Agric Food Chem 53(10): 4290–4302.

Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM (2014) Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. Cancer Res 74: 2913–2921.

Rautalahti MT, Virtamo JR, Taylor PR, Heinonen OP, Albanes D, Haukkka JK, Edwards BK, Karkkainen PA, Stolzenberg-Solomon RZ, Huttunen J (1999) The effects of supplementation with alpha-tocopherol and betacarotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer 86(1): 37–42.

Re R, Pellegrini N, Proteggente A, Pannala A, Yang M, Rice-Evans C (1999) Antioxidant activity applying an improved ABTS radical cation decolorization assay. Free Radic Biol Med 26(9-10): 1231–1237.

Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, Romieu I, Jenab M, Slimani N, Clavel-Chapelon F, Fagherazzi G, Perquier F, Kaaks R, Teucher B, Boeing H, von Rutsen A, Tjonneland A, Olsen A, Dahn CC, Overvad K, Quirós JR, Gonzalez CA, Sanchez MJ, Navarro C, Barricarte A, Dorronsoro M, Khaw KT, Wareham NJ, Crowe FL, Key TJ, Trichopoulos A, Lagiou P, Barina C, Masala G, Vines P, Timunio R, Sierri S, Panico S, May AM, Bueno-de-Mesquita HB, Buchner FL, Wirfalt E, Manjer J, Johansson I, Hallmans G, Skeie G, Benjamensen Borch K, Parr C, Riboli E, Norat T (2012) Is Concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 96(1): 150–163.

Rossi M, Lugo A, Lagiou P, Zucchetto A, Pelleli I, Serrano D, Negri E, Trichopoulos D, La Vecchia C (2012) Proanthocyanidins and other flavonoids in relation to pancreatic cancer: a case-control study in Italy. Ann Oncol 23(6): 1488–1493.

Serafini M, Miglio C, Peluso I, Petrozino T (2011) Modulation of plasma non-enzymatic antioxidant capacity (NEAC) by plant foods: the role of polyphenols. Curr Top Med Chem 11(14): 1821–1846.

Serafini M, Villano D, Spera G, Pellegrini N (2006) Redox molecules and cancer prevention: the importance of understanding the role of the antioxidant network. Nutr Cancer 56(2): 232–240.

Sette S, Le Donne C, Piccinelli R, Mistura L, Ferrari M, Leclercq C, group I-Ss (2013) The third National Food Consumption Survey, INRAN-SCAI 2005-06: major dietary sources of nutrients in Italy. Int J Food Sci Nutr 64(8): 1014–1021.

Skinner HG, Michaud DS, Giovannucci EL, Rimm EB, Stawder MJ, Willett WC, Colditz GA, Fuchs CS (2004) A prospective study of dietary intake and the risk of pancreatic cancer in men and women. Am J Epidemiol 160(3): 248–258.

Stolzenberg-Solomon RZ, Shefler-Collins S, Weinstein S, Garabrant DH, Mannisto S, Taylor P, Virtamo J, Albanes D (2009) Vitamin E intake, alpha-tocopherol status, and pancreatic cancer in a cohort of male smokers. Am J Clin Nutr 89(2): 584–591.

U.S. Department of Health and Human Services (2010) How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA, USA. Available at http://www.ncbi.nlm.nih.gov/pubmed/21452462.

Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H (2010) Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clin Cancer Res 16(20): 5028–5037.

Willett WC, Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 124(1): 17–27.

Woodson K, Tangrea JA, Barrett MJ, Virtamo J, Taylor PR, Albanes D (1999) Serum alpha-tocopherol and subsequent risk of lung cancer among male smokers. J Natl Cancer Inst 91(20): 1738–1743.

World Cancer Research Fund/American Institute for Cancer Research (2012) Continuous Update Project Summary. Food, Nutrition, Physical Activity, and the Prevention of Pancreatic Cancer.

Wu QJ, Xiang YB, Yang G, Li HL, Lan Q, Gao YT, Zheng W, Shu XO, Fowke JH (2015) Vitamin E intake and the lung cancer risk among female nonsmokers: a report from the Shanghai Women’s Health Study. Int J Cancer 136(3): 610–617.

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