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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.

Pancreatic cancer is one of the leading causes of cancer mortality worldwide (Rahib *et al*, 2014; Ferlay *et al*, 2015; Malvezzi *et al*, 2016). Known risk factors include tobacco use (Iodice *et al*, 2008), high levels of alcohol consumption (Michaud *et al*, 2010; Gapstur *et al*, 2011; Lucenteforte *et al*, 2012), obesity (Arslan *et al*, 2010; Genkinger *et al*, 2011), family history (Verna *et al*, 2010) and diabetes (Ben *et al*, 2011; Bosetti *et al*, 2014). Several analyses have been performed of individual nutrients and compounds on pancreatic cancer risk, but the evidence remains uncertain as to which aspect of diet is related to pancreatic cancer risk (World Cancer Research Fund/American Institute for Cancer Research, 2012). Heterocyclic amines (Anderson *et al*, 2002, 2005) have been suggested as risk factors for pancreatic cancer, while folate (Skinner *et al*, 2004; Larsson *et al*, 2006), β-carotene (Jeurnink *et al*, 2015),

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α-tocopherol (Stolzenberg-Solomon *et al*, 2009; Jeurnink *et al*, 2015), vitamin C (Bueno de Mesquita *et al*, 1991; Gong *et al*, 2010), selenium (Banim *et al*, 2013) and flavonoids (Rossi *et al*, 2012; Jeurnink *et al*, 2015) may protect against pancreatic cancer.

Dietary patterns have also been associated with pancreatic cancer risk and may provide a more relevant dietary measure of cancer potential than analysis of individual dietary components. Adherence to dietary and lifestyle recommendations such as the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations to reduce cancer risk have been associated with decreased overall cancer risk, but have not been definitively associated with decreased pancreatic cancer risk (Romaguera *et al*, 2012; Lucas *et al*, 2015). Although elevated consumption of red meat and low consumption of fruit and vegetables have been positively associated to 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 ($\pm$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 factors, 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 Fe^{3+} (ferric ion) to Fe^{2+} (ferrous ion). Total radical-trapping antioxidant parameter measures the chain-breaking potential to reduce peroxyl radicals generated by AAPH ((2,2-azobis(2-amidinopropane) 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, $\geq 30\,kg\,m^{-2}$, 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 χ^2-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

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

	Cases		Controls	
Characteristics	**No.**	**%**	**No.**	**%**
Study centre				
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
⩾50–<65	65	19.9	130	19.9
⩾65–<70	57	17.5	114	17.5
⩾70	83	25.5	166	25.5
Education (years)[a]				
<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})[a]				
<25	139	42.9	264	40.7
25–<30	135	41.7	296	45.6
⩾30	50	15.4	89	13.7
Smoking status[a]				
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)[b]				
I	96	29.5	218	33.4
II	108	33.1	218	33.4
II	122	37.4	216	33.2
History of diabetes				
No	279	85.6	615	94.3
Yes	47	14.4	37	5.7

[a]The sum does not add up to the total because of some missing values.
[b]On the basis of the control distribution. Tertiles of alcohol were calculated in grams of ethanol per day.

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, 0.41–1.62) among diabetic subjects and 0.91 (95% CI, 0.75–1.10) among non-diabetic subjects. The continuous OR for FRAP was 0.69 (95% CI, 0.36–1.35) 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 (Stolzenberg-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 (Rautalahti *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*, 2011; Lucenteforte *et al*, 2012). In addition, the TRAP assay has a high specificity for antioxidant behaviour, such as peroxyl radical scavenging activity, compared with FRAP and TEAC, respectively addressing iron reduction and scavenging of the not physiological ABTS +. Trapping antioxidant parameter provides more direct evidence of the canonical antioxidant activity, but at the same time since it is more specific, the test requires evidence of a redox condition (Serafini *et al*, 2006).

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 minimise 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 dietary modifications. 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[a] and 95% CIs by tertiles of three energy-adjusted TAC indices. Italy, 1991–2008

		Tertiles[b]			
	Mean (SD)[a]	**I**	**II**	**III**	***P* for trend**
TEAC	4.39 (2.30)				
Cases:controls		119:217	105:218	102:217	
Upper cutoff points (mmol Trolox per day)[c]		3.67	4.77	—	
OR (95% CI)[d]		1[e]	0.82 (0.56–1.20)	0.61 (0.39–0.94)	0.028
TRAP	4.51 (2.81)				
Cases:controls		114:217	105:218	107:217	
Upper cutoff points (mmol Trolox per day)[c]		3.47	5.00	—	
OR (95% CI)[d]		1[e]	0.84 (0.57–1.24)	0.78 (0.49–1.24)	0.27
FRAP	11.23 (5.98)				
Cases:controls		117:218	111:217	98:217	
Upper cutoff points (mmol Fe^{2+} per day)[c]		9.17	12.29	—	
OR (95% CI)[d]		1[e]	0.88 (0.61–1.29)	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.
[a]Mean and s.d. among controls.
[b]On the basis of the control distribution.
[c]Computed as the sum of the upper cutoff points of energy-adjusted TAC tertiles plus the means of TAC.
[d]Estimates 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.
[e]Reference 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[a]			
		TEAC, tertiles		FRAP, tertiles	
	Cases:controls	**II**	**III**	**II**	**III**
Sex					
Men	174:338	1.00 (0.57–1.78)	0.71 (0.39–1.29)	1.04 (0.59–1.83)	0.68 (0.38–1.23)
Women	152:304	0.70 (0.41–1.19)	0.55 (0.28–1.10)	0.73 (0.43–1.24)	0.61 (0.30–1.26)
P value[b]		*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)	0.62 (0.34–1.15)
⩾65	140:280	0.84 (0.47–1.51)	0.75 (0.39–1.45)	0.90 (0.50–1.61)	0.75 (0.39–1.47)
P value[b]		*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)	0.78 (0.38–1.63)
⩾25	185:385	0.94 (0.55–1.60)	0.61 (0.34–1.10)	0.93 (0.54–1.59)	0.67 (0.37–1.21)
P value[b]		*0.98*		*0.70*	
Smoking status[c]					
Never	137:330	0.68 (0.39–1.21)	0.72 (0.36–1.44)	0.88 (0.50–1.57)	0.84 (0.42–1.57)
Ever	188:322	0.96 (0.55–1.68)	0.49 (0.27–0.91)	0.83 (0.48–1.43)	0.46 (0.25–0.86)
P value[b]		*0.30*		*0.36*	
Alcohol (tertiles)[d]					
I	96:218	0.70 (0.36–1.34)	0.34 (0.11–1.07)	0.72 (0.38–1.37)	0.54 (0.17–1.70)
II	108:218	1.02 (0.54–1.93)	0.70 (0.32–1.52)	1.14 (0.60–2.16)	0.70 (0.32–1.54)
III	122:216	1.00 (0.38–2.64)	0.65 (0.28–1.55)	0.93 (0.35–2.44)	0.63 (0.27–1.49)
P value[b]		*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)	0.74 (0.47–1.19)
Yes	57:37	0.60 (0.15–2.43)	0.33 (0.05–2.35)	0.74 (0.16–3.40)	0.14 (0.02–1.19)
P value[b]		*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.
[a]Estimates 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.
[b]*P* for heterogeneity.
[c]The sum does not add up to the total because of some missing values.
[d]On 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.

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