

Coffee, decaffeinated coffee, tea, and pancreatic cancer risk: a pooled-analysis of two Italian case-control studies

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To evaluate the association between coffee, decaffeinated coffee, and tea consumption and pancreatic cancer risk in a pooled analysis of two Italian case-control studies, between 1983 and 2008, we conducted two case-control studies in Northern Italy, including a total of 688 pancreatic cancer cases and 2204 hospital controls with acute, non-neoplastic diseases. We computed multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for coffee drinking (mostly espresso and mocha), adjusting for age, sex, center, year of interview, education, body mass index, tobacco smoking, alcohol drinking, and diabetes.

Compared with coffee nondrinkers, the multivariate OR for coffee drinkers was 1.34 (95% CI: 1.01–1.77). However, there was no trend in risk with respect to dose and duration. The OR for an increment of one cup per day was 1.05 (95% CI: 0.98–1.11). There was no heterogeneity in strata of age, sex, and other covariates, including tobacco smoking. No association emerged for decaffeinated coffee (for drinkers the OR was 0.87, 95% CI: 0.60–1.26, compared with decaffeinated coffee

nondrinkers) or tea (for tea drinkers the OR was 0.92, 95% CI: 0.75–1.14). The lack of relationship with dose and duration weighs against a causal association between coffee and pancreatic cancer, which is in agreement with most evidence on the issue. *European Journal of Cancer Prevention* 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The relation of coffee consumption with pancreatic cancer risk has long been investigated since a case-control study in the early 1980s showed a strong positive association (MacMahon *et al.*, 1981).

Since then, 17 cohort studies have been published. Two of these found a significant increased risk (Harnack *et al.*, 1997; Lin *et al.*, 2002) and one a significant decreased risk (Isaksson *et al.*, 2002) for the highest versus the lowest coffee drinking categories. The remaining 14 cohort studies found relative risks close to unity (Nomura *et al.*, 1981; Whittemore *et al.*, 1983; Snowdon and Phillips, 1984; Jacobsen *et al.*, 1986; Hiatt *et al.*, 1988; Mills *et al.*, 1988; Zheng *et al.*, 1993; Shibata *et al.*, 1994; Stensvold and Jacobsen, 1994; Michaud *et al.*, 2001; Stolzenberg-Solomon *et al.*, 2002; Khan *et al.*, 2004; Luo *et al.*, 2007; Nilsson *et al.*, 2010). Of the 35 case-control studies (Jick and Dinan, 1981; Kessler, 1981; Goldstein, 1982; Severson *et al.*, 1982; Wynder *et al.*, 1983, 1986; Kinlen and McPherson, 1984; Gold *et al.*, 1985; Hsieh *et al.*, 1986; Mack *et al.*, 1986; Norell *et al.*, 1986; Falk *et al.*, 1988; Gorham *et al.*, 1988; Clavel *et al.*, 1989; Cuzick and Babiker, 1989; Olsen *et al.*, 1989; Farrow and Davis, 1990;

Ghadirian *et al.*, 1991; Jain *et al.*, 1991; Bueno de Mesquita *et al.*, 1992; Lyon *et al.*, 1992; Mizuno *et al.*, 1992; Stefanati *et al.*, 1992; Friedman and Van den Eeden, 1993; Kalapothaki *et al.*, 1993; Sciallero *et al.*, 1993; Zatonski *et al.*, 1993; Gullo *et al.*, 1995; Partanen *et al.*, 1995; Kokic *et al.*, 1996; Nishi *et al.*, 1996; Silverman *et al.*, 1998; Mori *et al.*, 1999; Alguacil *et al.*, 2000; Villeneuve *et al.*, 2000), seven found a significant positive association between the highest category of coffee intake and pancreatic cancer risk (Hsieh *et al.*, 1986; Mack *et al.*, 1986; Clavel *et al.*, 1989; Lyon *et al.*, 1992; Gullo *et al.*, 1995; Kokic *et al.*, 1996; Mori *et al.*, 1999), in the absence, however, of a dose-risk relation in most of them. Thus, it is possible that the observed positive association is not causal but due to selection bias, residual confounding with cigarette smoking (the major recognized risk factor for pancreatic cancer) (Anderson *et al.*, 2006), or other sources of bias. The odds ratios (ORs) were below unity in approximately 12 case-control studies (Jick and Dinan, 1981; Kessler, 1981; Kinlen and McPherson, 1984; Olsen *et al.*, 1989; Ghadirian *et al.*, 1991; Jain *et al.*, 1991; Bueno de Mesquita *et al.*, 1992; Mizuno *et al.*, 1992; Friedman and Van den Eeden, 1993; Kalapothaki *et al.*, 1993; Sciallero *et al.*, 1993; Zatonski *et al.*, 1993; Partanen *et al.*, 1995; Silverman *et al.*,

1998; Alguacil *et al.*, 2000), in the absence, however, of any significant association. Thus, overall, the available data indicate no consistent association between coffee drinking and pancreatic cancer risk, leaving a few inconsistencies and open issues.

Data on decaffeinated coffee are scantier and show no overall association (IARC, 1991; Tavani and La Vecchia, 2000).

Tea contains several antioxidants and has been hypothesized to have a favorable impact on human carcinogenesis (Yang *et al.*, 2009). However, there is no consistent evidence of any relationship between tea drinking and pancreatic cancer risk (La Vecchia *et al.*, 1992; Luo *et al.*, 2007; Lin *et al.*, 2008).

In this study, we assessed the relationship between regular coffee, decaffeinated coffee, and tea consumption and pancreatic cancer risk in a pooled analysis of two Italian case-control studies.

Methods

We analyzed data from two hospital-based case-control studies. The first one, conducted between 1983 and 1992 in Milan (Northern Italy), included 362 incident cases of pancreatic cancer (229 men, 133 women, median age: 60 years, range: 18–86 years) and 1552 controls (1114 men, 411 women, median age: 56 years, range: 18–84) (La Vecchia *et al.*, 1990; Soler *et al.*, 1998). The second study, conducted between 1992 and 2008 in two Italian areas (i.e. Milan and Pordenone, Northern Italy), included 326 incident cases (174 men, 152 women, median age: 62 years, range: 34–80 years) and 652 controls (348 men, 304 women, median age: 62 years, range: 34–80 years), frequency matched with cases by age and sex (ratio: 1:2) (Rossi *et al.*, 2010). Histological confirmation was available for 60% of cases, whereas the remaining cases were diagnosed on ultrasound and/or tomography. Neuroendocrine tumors of the pancreas were excluded.

In both studies, controls were admitted to the same network of hospitals as cases for a wide spectrum of acute conditions other than neoplasia or diseases of the digestive tract (overall, 30% had trauma, 21% other orthopedic disorders, 33% acute surgical conditions, 16% other illnesses including eye, nose, ear, or skin diseases). Less than 5% of cases and controls refused to participate in the interview.

Cases and controls were interviewed by centrally trained interviewers using a structured questionnaire including information on sociodemographic characteristics, anthropometric measures, personal medical history of selected diseases, tobacco smoking, alcohol drinking, and frequency of consumption of several food items during the 2 years before the onset of the disease that led to hospital admission. The information on coffee (mostly espresso and mocha), decaffeinated coffee, and tea (mostly black

tea) included the daily frequency of consumption (cups per day) and the duration of the habit in the first study (Soler *et al.*, 1998), and the weekly frequency of consumption (cups per week) in the second study (Lucenteforte *et al.*, 2010; Rossi *et al.*, 2010). A satisfactory level of reproducibility and validity of consumption of the three beverages has been reported in both studies (D'Avanzo *et al.*, 1996; Ferraroni *et al.*, 2004).

Statistical analysis

ORs and corresponding 95% confidence intervals (CIs) for coffee and tea intake were estimated using multiple logistic regression models. We used two models: the first one included terms for center, age (quintennia), sex, and year of interview; the second model included further terms for education, body mass index, tobacco smoking, alcohol drinking, and diabetes.

Results

The distribution of cases and controls according to sex, age, and selected covariates is shown in Table 1. The ORs adjusted for all the covariates reported in the table were 1.06 (95% CI: 0.83–1.35) for 12 or more years of education compared with less than 7 years of education, 1.43 (95% CI: 1.10–1.86) for current smokers of 15 or more cigarettes/day compared with never smokers, 1.47 (95% CI: 1.09–1.99) for ever drinkers of 22 or more

Table 1 Distribution of 688 cases of pancreatic cancer and 2204 controls according to sex, age, and other selected variables, Italy (1983–2008)

	Cases	Controls
	Number (%)	Number (%)
Sex		
Males	403 (58.6)	1489 (67.6)
Females	285 (41.4)	715 (32.4)
Age (years)		
<50	92 (13.4)	519 (23.6)
50–59	208 (30.1)	678 (30.8)
60–69	247 (35.9)	686 (31.0)
≥70	141 (20.5)	321 (14.6)
Education (years) ^a		
<7	358 (52.5)	1087 (49.6)
7–11	181 (26.5)	646 (29.5)
≥12	143 (21.0)	459 (20.9)
Smoking habit ^a		
Never smokers	274 (39.0)	913 (41.5)
Exsmokers	173 (25.2)	521 (23.7)
Current smokers (cigarettes/day)		
<15	76 (11.2)	278 (12.5)
≥15	163 (23.8)	490 (22.3)
Alcohol consumption		
Never	126 (18.3)	417 (18.9)
Ever drinkers (drinks/week)		
<7	123 (17.9)	378 (17.2)
8–14	122 (17.7)	388 (17.6)
15–21	69 (10.0)	261 (11.8)
≥22	248 (36.1)	760 (34.5)
Diabetes		
No	585 (85.0)	2078 (94.3)
Yes	103 (15.0)	126 (5.7)

^aThe sum does not add up to the total because of some missing values.

alcoholic drinks/week compared with nondrinkers, and 2.89 (95% CI: 2.15–3.88) for individuals with diabetes compared with those without diabetes.

Compared with coffee nondrinkers, the OR for regular coffee drinkers, obtained from the fully adjusted model, was 1.34 (95% CI: 1.01–1.77) (Table 2). The ORs for less than or equal to one, more than one to two, more than two to three, and more than three cups per day were 1.41, 1.29, 1.23, and 1.46, respectively, with no significant trend in risk (P for trend = 0.232). The OR of pancreatic cancer for an increase of one cup per day of regular coffee was 1.05 (95% CI: 0.98–1.11). No association emerged for decaffeinated coffee and tea. The OR for decaffeinated coffee drinkers was 0.87 (95% CI: 0.60–1.26) compared with decaffeinated coffee nondrinkers. Drinkers of various combinations of regular and decaffeinated coffee had ORs of pancreatic cancer risk close to unity, compared with nondrinkers of any type of coffee. Compared with tea nondrinkers, the ORs for tea drinkers were 0.92 (95% CI: 0.75–1.14), and 1.31 (95% CI: 0.86–2.01) for those drinking more than one cup per day, based on 39 cases.

Table 3 shows the ORs of pancreatic cancer in relation to the duration of regular coffee drinking, based only on the study conducted in 1983–1992, in which the information on duration was available. The multivariate ORs were 1.73 (95% CI: 1.07–2.80) for individuals drinking coffee for 25 years or less, and 1.46 (95% CI: 0.91–2.36) for individuals drinking coffee for 36 years or longer.

There was no heterogeneity in the strata of age, sex, body mass index, tobacco smoking, alcohol drinking, and diabetes, although the association with coffee appeared slightly stronger in more educated people (Table 4).

Discussion

In this pooled analysis of two Italian case-control studies, coffee drinking (mainly espresso and mocha) showed no consistent association with pancreatic cancer risk. Indeed, the lack of a relationship with the amount of coffee and duration of the habit weighs against the hypothesis of

Table 3 Distribution of 362 cases of pancreatic cancer and 1552 controls, odds ratios, and corresponding 95% confidence intervals according to duration of coffee drinking, Italy (1983–1992)^a

	Cases		Controls		OR ^b (95% CI)	OR ^c (95% CI)
	Number (%)	Number (%)	Number (%)	Number (%)		
Duration (years) ^d						
Nondrinkers	50 (13.9)	228 (14.7)			1 ^e	1 ^e
≤ 25	111 (30.9)	493 (31.8)			1.39 (0.94–2.06)	1.73 (1.07–2.80)
26–35	95 (26.5)	497 (32.1)			0.91 (0.61–1.35)	1.08 (0.68–1.74)
≥ 36	103 (28.7)	332 (21.4)			1.29 (0.87–1.93)	1.46 (0.91–2.36)

CI, confidence interval; OR, odds ratio.

^aOn the basis of the study conducted in Milan in 1983–1992 (La Vecchia *et al.*, 1990; Soler *et al.*, 1998).

^bAdjusted for age, sex, and year of interview.

^cFurther adjusted for education, body mass index, smoking habits, alcohol drinking, diabetes, and amount of coffee consumption (continuous).

^dThe sum does not add up to the total because of some missing values.

^eReference category.

Table 2 Distribution of 688 cases of pancreatic cancer and 2204 controls, odds ratios, and corresponding 95% confidence intervals according to coffee and tea drinking habits, Italy (1983–2008)

	Cases		Controls		OR ^a (95% CI)	OR ^b (95% CI)
	Number (%)	Number (%)	Number (%)	Number (%)		
Caffeinated coffee ^c						
Nondrinkers	78 (11.3)	308 (14.0)			1 ^d	1 ^d
Drinkers	610 (88.7)	1892 (86.0)			1.25 (0.95–1.64)	1.34 (1.01–1.77)
Cups/day						
> 0–≤ 1	171 (24.9)	512 (23.3)			1.27 (0.93–1.73)	1.41 (1.02–1.94)
> 1–≤ 2	199 (28.9)	622 (28.3)			1.22 (0.90–1.65)	1.29 (0.94–1.77)
> 2–≤ 3	133 (19.3)	432 (19.6)			1.17 (0.85–1.62)	1.23 (0.88–1.72)
> 3	107 (15.6)	326 (14.8)			1.40 (0.99–1.97)	1.46 (1.02–2.10)
P for trend					0.195	0.232
Increment of one cup/day					1.05 (0.99–1.11)	1.05 (0.98–1.11)
Decaffeinated coffee ^c						
Nondrinkers	643 (93.5)	2063 (93.7)			1 ^d	1 ^d
Drinkers	45 (6.5)	140 (6.3)			0.86 (0.60–1.24)	0.87 (0.60–1.26)
Type of coffee ^c						
Any type of coffee nondrinkers	63 (9.2)	260 (11.8)			1 ^d	1 ^d
Only caffeinated coffee drinkers	580 (84.2)	1799 (81.6)			1.26 (0.93–1.69)	1.33 (0.97–1.81)
Only decaffeinated coffee drinkers	15 (2.2)	48 (2.2)			0.94 (0.49–1.81)	0.90 (0.45–1.77)
Drinkers of both type	30 (4.4)	92 (4.2)			1.13 (0.68–1.88)	1.27 (0.75–2.15)
Tea ^c						
Nondrinkers	469 (68.4)	1626 (73.8)			1 ^d	1 ^d
Drinkers	217 (31.6)	577 (26.2)			0.93 (0.76–1.15)	0.92 (0.75–1.14)

CI, confidence interval; OR, odds ratio.

^aAdjusted for center, age, sex, and year of interview.

^bFurther adjusted for education, body mass index, smoking habits, alcohol drinking, and diabetes.

^cThe sum does not add up to the total because of some missing values.

^dReference category.

Table 4 Distribution of 688 cases of pancreatic cancer and 2204 controls, odds ratios, and corresponding 95% confidence intervals according to coffee drinking in strata of selected covariates, Italy (1983–2008)

	Coffee drinking (cups per day), cases : controls, OR ^a (95% CI)			<i>P</i> for trend
	0	>0–≤ 3	>3	
Age (years)				
<60	26 : 165 1 ^b	209 : 797 1.79 (1.11–2.89)	65 : 232 1.93 (1.12–3.32)	0.037
≥ 60	52 : 143 1 ^b	294 : 769 1.11 (0.77–1.59)	42 : 94 1.29 (0.77–2.16)	0.337
<i>P</i> for heterogeneity=0.203				
Sex				
Male	45 : 181 1 ^b	282 : 1062 1.01 (0.69–1.47)	76 : 242 1.16 (0.74–1.82)	0.457
Female	33 : 127 1 ^b	221 : 504 1.75 (1.13–2.73)	31 : 84 1.87 (1.01–3.44)	0.027
<i>P</i> for heterogeneity=0.107				
Education (years) ^c				
<7	50 : 148 1 ^b	264 : 806 0.97 (0.67–1.41)	44 : 132 1.16 (0.70–1.92)	0.603
≥ 7	26 : 158 1 ^b	236 : 750 2.14 (1.34–3.43)	62 : 194 2.14 (1.24–3.71)	0.017
<i>P</i> for heterogeneity=0.018				
Body mass index (kg/m ²) ^c				
<25	48 : 175 1 ^b	301 : 749 1.52 (1.06–2.18)	57 : 149 1.64 (1.03–2.63)	0.037
≥ 25	30 : 129 1 ^b	198 : 809 1.02 (0.63–1.64)	50 : 177 1.23 (0.69–2.19)	0.434
<i>P</i> for heterogeneity=0.554				
Smoking status ^c				
Never	36 : 178 1 ^b	215 : 652 1.68 (1.10–2.56)	23 : 83 1.93 (1.03–3.63)	0.017
Ex	13 : 55 1 ^b	133 : 391 1.58 (0.80–3.11)	24 : 74 1.71 (0.76–3.85)	0.243
Current	29 : 74 1 ^b	155 : 523 0.77 (0.46–1.27)	55 : 168 0.87 (0.49–1.55)	0.986
<i>P</i> for heterogeneity=0.311				
Alcohol drinking (drinks/week)				
Nondrinkers	13 : 93 1 ^b	92 : 260 3.25 (1.61–6.55)	21 : 63 4.05 (1.71–9.61)	0.001
1–14	27 : 96 1 ^b	184 : 560 1.23 (0.75–2.00)	34 : 110 1.35 (0.72–2.53)	0.355
≥ 15	38 : 119 1 ^b	227 : 746 1.00 (0.65–1.53)	52 : 153 1.08 (0.64–1.82)	0.763
<i>P</i> for heterogeneity=0.131				
Diabetes				
No	66 : 238 1 ^b	428 : 1483 1.26 (0.93–1.71)	91 : 308 1.45 (0.98–2.13)	0.056
Yes	12 : 25 1 ^b	75 : 83 2.15 (0.84–5.46)	16 : 18 1.57 (0.47–5.30)	0.431
<i>P</i> for heterogeneity=0.875				

CI, confidence interval; OR, odds ratio.

^aAdjusted for center, age, sex, year of interview, education, body mass index, smoking habits, alcohol drinking, and diabetes.^bReference category.^cThe sum does not add up to the total because of some missing values.

a causal association. These results are in agreement with the overall evidence on the relation of coffee intake with pancreatic cancer.

With reference to potential sources of bias, hospital controls may not be representative of the general population, and it is possible that their coffee drinking differs from that of the general population. However, 86.0% of our controls were coffee drinkers, which is comparable with the 84.3% estimated from a population with similar sex and age in an Italian National Health Survey [National Institute of Statistics (ISTAT), 1984]. We selected controls from the major teaching and general hospitals of the areas under surveillance and excluded

from the comparison group those patients admitted to hospital for any chronic condition and for diseases related to alcohol drinking, tobacco smoking, or major modification in diet. The participation rate of cases and controls was almost complete (more than 95% for both groups). Under-reporting of coffee drinking may have occurred in the highest category of consumption, but the risk estimates were similar for low and high intakes. Moreover, the general population is unaware of a possible relationship between coffee intake and pancreatic cancer, and hence the reporting of coffee should not have been influenced by the disease status. The information on coffee and tea drinking from the questionnaires of the two studies was satisfactorily valid, and the reliability of

information collected from hospital controls proved to be satisfactory in this population (D'Avanzo *et al.*, 1996; Ferraroni *et al.*, 2004). The strengths of this study include the relatively large sample size, the similar interview settings of cases and controls, the availability of information on several covariates, and the use of data from a population with a peculiar coffee drinking habit. With reference to confounding, our estimates did not materially change after adjustment for tobacco smoking, alcohol drinking, socioeconomic characteristics, and other risk factors for pancreatic cancer risk, such as diabetes. Moreover, against a major role of confounding there is lack of heterogeneity in the relationship of coffee with pancreatic cancer risk across strata of age, sex, and other relevant covariates, including smoking, which is the major potential confounder of such a relation (Anderson *et al.*, 2006). Thus, it is unlikely that these results were severely affected by bias.

No association emerged with the intake of decaffeinated coffee consumption; however, the results were based on a few exposed cases drinking small amounts of the beverage, and are consequently only indicative. Our results also show a lack of association with tea intake, but also tea is drunk infrequently and in small amounts in the study population. Consequently, our data have a limited statistical power and are not adequate to address the high intake.

Our data provide no evidence that consumption of coffee, decaffeinated coffee, or tea is causally associated with pancreatic cancer risk.

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There is no conflict of interest to declare.

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