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A meta-analysis of coffee consumption and pancreatic cancer

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Background: Since when in 1981 a case–control study showed a positive association between coffee and pancreatic cancer, several studies reported inconsistent results on this issue.

Materials and methods: We conducted a systematic bibliography search updated March 2011 to identify observational studies providing quantitative estimates for pancreatic cancer risk in relation to coffee consumption. We used a meta-analytic approach to estimate overall relative risk (RR) and 95% confidence interval (CI) for the highest versus the lowest coffee consumption categories, using random-effects models.

Results: Based on 37 case–control and 17 cohort studies (10 594 cases), the pooled RR for the highest versus lowest intake was 1.13 (95% CI 0.99–1.29). Considering only the smoking-adjusting studies, the pooled RRs were 1.10 (95% CI 0.92–1.31) for the 22 case–control, 1.04 (95% CI 0.80–1.36) for the 15 cohort, and 1.08 (95% CI 0.94–1.25) for all studies. The pooled RR for the increment of one cup of coffee per day was 1.03 (95% CI 0.99–1.06) for the 28 smoking-adjusting studies reporting three or more coffee consumption categories. No significant heterogeneity was observed across strata of study design, sex, geographic region, and other selected characteristics.

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Conclusions: This meta-analysis provides quantitative evidence that coffee consumption is not appreciably related to pancreatic cancer risk, even at high intakes.
Key words: coffee, meta-analysis, pancreatic cancer

introduction

The possible relation between coffee consumption and pancreatic cancer has been of considerable interest since the early 1980s, when a case–control study from New England showed a positive association [40]. In that study, consumption of three or more cups of coffee per day was associated with almost a threefold increased risk, independent of cigarette smoking. More than 50 studies have been published thereafter, with inconsistent results. Few of them showed some positive association between coffee drinking and pancreatic cancer, irrespective of study design or geographic area [46, 47, 53, 59, 66, 68, 71, 84, 87]. Thus, although a strong association between coffee and cancer of the pancreas may be excluded, the issue of a weak relation is still open for consideration.

To provide updated results on this topic, we combined all published data on coffee and pancreatic cancer risk from case–control and cohort studies, using a meta-analytic approach.

materials and methods

literature search and identification of the publications

In March 2011, we carried out a PubMed search using the string '(coffee OR caffeine OR diet OR dietary OR beverages OR drinks) AND (pancreas OR pancreatic) AND (cancer OR neoplasm) AND risk', following the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [1]. We limited our search to human studies written in English. Two of the authors (FT and CG) independently selected the articles reporting information on the association between coffee consumption and pancreatic cancer incidence or mortality, and checked the reference list of the publications retrieved and those of some reviews [2–5]. All case–control and cohort studies providing estimates of relative risk (RR) and corresponding confidence interval (CI), or information sufficient to calculate them, were included in the meta-analysis. No study was excluded a priori for weakness of design or data quality. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis only the most recent or informative one. The flow chart of the selection of publications included in the meta-analysis is shown in Figure 1.

For each study, we extracted data on study design, country, number of subjects (cases, controls, or cohort size), duration of follow-up (for cohort studies) or study calendar years of subject inclusion (for case–control studies), sex, variables adjusted for in the analysis, RR estimates for categories of coffee intake and corresponding 95% CIs, and, when available, number of cases and non-cases for each level of coffee consumption. Discrepancies between the two authors extracting this information (FT and CG) were discussed and adjudicated.

When a study analyzed both caffeinated and decaffeinated coffee separately, we collected both these information distinctly. If a study reported more than one RR estimate, we used the one adjusted for the larger number of available potential confounding factors. In particular, whenever possible, we selected smoking-adjusted risk estimates. When a study reported only the number of cases and controls for each coffee consumption category, we calculated from these frequencies the crude RRs and the corresponding 95% CIs. Moreover, when a study reported the adjusted RRs but not the corresponding adjusted 95% CIs, we used the distribution of cases and controls to calculate the standard errors of the corresponding crude RRs. Then, as the crude RRs were similar to the corresponding adjusted ones, we built up the approximate CIs for the reported adjusted RRs using the standard errors. For a few case–control studies based on both hospital and population controls and providing risk estimates separately for the two types of controls, we opted for the RRs based on population controls [45, 48, 64].

statistical analyses

We pooled the RRs for the highest versus the lowest exposure categories of coffee consumption from each study using random-effects models, which consider both within- and between-study variation [6]. Studies reporting risk estimates for two categories (e.g. coffee drinkers versus nondrinkers) were also included. When a study reported risk estimates for men and women separately, we first pooled them using fixed-effects models. Statistical heterogeneity among studies was assessed using the chi-square test (results were defined as heterogeneous for a P value <0.10) [7], and the potential inconsistency was quantified through the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance [8]. Usually, values of the I^2 statistic <25% are indicative of low heterogeneity, those ranging between 25% and 75% of moderate heterogeneity, and those >75% of high heterogeneity.

As smoking is a major confounder for the possible relationship between coffee and risk for pancreatic cancer [9, 10], and given the inconsistency between results from studies with and without tobacco-adjusting risk estimates, in most analyses we considered separately the 37 studies providing smoking-adjusted RRs [40, 42–45, 50–59, 62, 63, 67, 69, 70, 73–76, 79–91].

To obtain the information on a dose–response relationship, we considered the increment of one cup per day. Different measurements of coffee consumption in the original studies were converted into approximate cups per day. We defined 180 g of coffee equal to one cup in a cohort study from Finland [88]. In a study reporting risk estimates for weekly and daily coffee consumption, we redefined these exposure categories as less then one cup and one or more cups per day, respectively [44]. We also excluded studies showing two categories of exposure only (e.g. coffee drinkers versus nondrinkers) [42, 51, 62, 76, 80, 89] and studies with cumulative lifetime consumption expressed as liters per life [57, 58, 63]. We used the method proposed by Greenland and Longnecker [11, 12] to estimate study-specific slopes, when this measure was not reported in the original articles. This method estimates, in each study, the RR for the increment of one unit of consumption by relating the natural logarithm of the RR to the corresponding mean value of intake across exposure categories, taking into account, when possible, that estimates of risk for successive levels of intake are correlated. For the open-ended upper category, we considered it of the same amplitude as the previous one. Then, we obtained the overall RR for an increment of one cup of coffee per day pooling the corresponding study-specific RRs with random-effects models.

We also carried out a cumulative meta-analysis over time and conducted stratified analyses by selected covariates, considering both case–control and cohort studies, to investigate the possible sources of heterogeneity among studies.

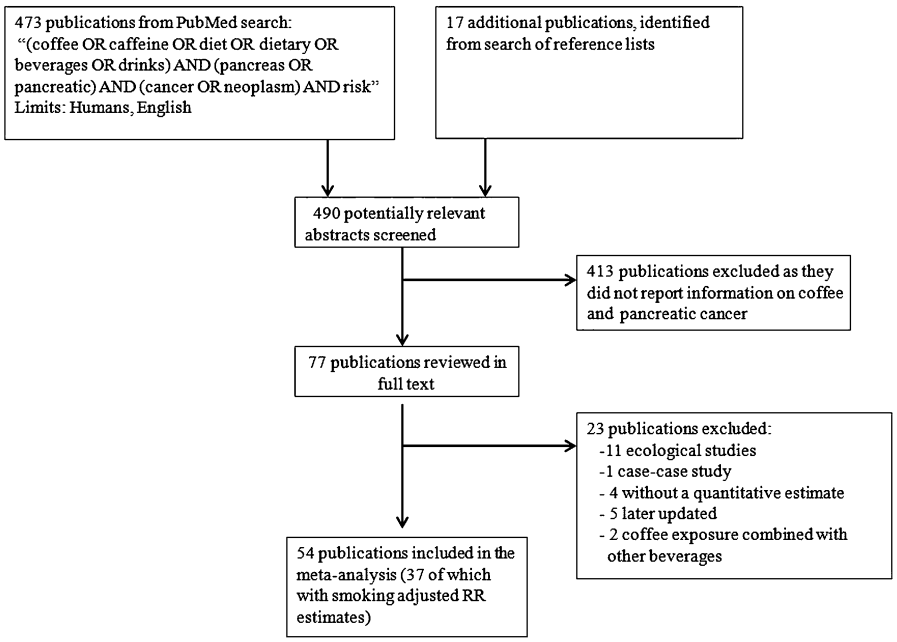

Figure 1. Flow chart of the selection of publications included in the meta-analysis. RR, relative risk.

Publication bias was evaluated through funnel plots [13] and with the Egger's and Begg's tests [14].

results

The main characteristics of the studies on pancreatic cancer and coffee included in the meta-analysis are reported in supplemental Table S1 (available at *Annals of Oncology* online). We summarized decisions and operations on original data for each study in the column 'notes'. We identified for the meta-analysis 37 case–control [38–74] and 17 cohort studies [75–91], for a total of 10 594 pancreatic cancer cases or deaths. There was no evidence of publication bias overall, as tested using Egger's ($P = 0.900$) and Begg's ($P = 0.988$) tests. Twenty-nine studies were conducted in North America (5643 cases), 10 in Northern Europe (1886 cases), 7 in Southern Europe (1932 cases), 2 in Eastern Europe (210 cases), and 6 in Asia (850 cases).

Figure 2 shows the RRs of pancreatic cancer for the highest versus the lowest coffee drinking categories, from studies with and without adjustment for smoking, and from all the studies combined. The overall RR for the 54 studies included in the meta-analysis was 1.13 (95% CI 0.99–1.29, P for heterogeneity <0.001, $I^2 = 50.2\%$). Considering the 17 studies not adjusting for tobacco smoking, the pooled RRs were 1.34 (95% CI 1.01–1.78, 15 studies) for case–control, 0.75 (95% CI 0.45–1.25, 2 studies) for cohort studies, and 1.25 (95% CI 0.96–1.63) for all the studies (P for heterogeneity for all the 17 studies = 0.003, $I^2 = 55.9\%$), based on ~800 cases exposed to the highest doses and >650 exposed to the lowest ones. A significant heterogeneity was detected between case–control and cohort design ($P = 0.054$). For the 37 studies adjusting for tobacco smoking, the pooled RRs for the highest versus lowest cateogory of intake were 1.10 (95% CI 0.92–1.31, 22 studies) for case–control, 1.04 (95% CI 0.80–1.36, 15 studies) for cohort studies, and 1.08 (95% CI 0.94–1.25) for all the studies (P for heterogeneity for all the 37 studies = 0.002, $I^2 = 44.9\%$), based on >1300 cases exposed to the highest doses and >1100 exposed to the lowest ones. No heterogeneity across study design was found ($P = 0.732$). When the hypothesis-generating article [40] was excluded from the meta-analysis, the pooled RR for all the smoking-adjusting studies was 1.04 (95% CI 0.91–1.19), and the one for the smoking-adjusting case–control studies was 1.05 (95% CI 0.90–1.22).

The pooled RRs for the increment of one cup of coffee per day based on the smoking-adjusting studies were 1.04 (95% CI 1.00–1.09) for case–control, 1.00 (95% CI 0.95–1.05) for cohort studies, and 1.03 (95% CI 0.99–1.06) for all the studies combined (P for heterogeneity for all the studies <0.001, $I^2 = 64.8\%$) (Figure 3). The exclusion of MacMahon et al. study [40] from the analysis led to an overall RR of 1.01 (95% CI 0.99–1.04) and to an RR of 1.02 (95% CI 0.99–1.04) for case–control studies.

Table 1 presents the pooled RRs derived from smoking-adjusting studies (both case–control and cohort studies), for the highest versus the lowest coffee drinking categories, according to selected covariates. No heterogeneity was observed across strata of sex, geographic region, and other selected characteristics, although both case–control and cohort studies were included. The pooled RRs in strata of smoking habits were 1.47 (95% CI 1.10–1.98) for never smokers and 1.74 (95% CI 1.02–3.01) for ever smokers (P for heterogeneity = 0.730). The study by MacMahon et al. [40] was excluded from this analysis as it did not report the CIs for the stratified estimates.

Figure 4 shows the cumulative meta-analysis for the highest versus the lowest coffee drinking from studies with smoking adjustment. The pooled cumulative RRs were 2.71 (95% CI 1.64–4.52) in 1981 (2 studies), 1.32 (95% CI 0.93–1.90) for studies published up to 1985 (7 studies), and 1.28 (95% CI 1.01–1.61) for those published up to 1990 (15 studies). For studies published after the mid-1990s, the pooled RRs were never statistically significant and ranged between 1.00 and 1.10.

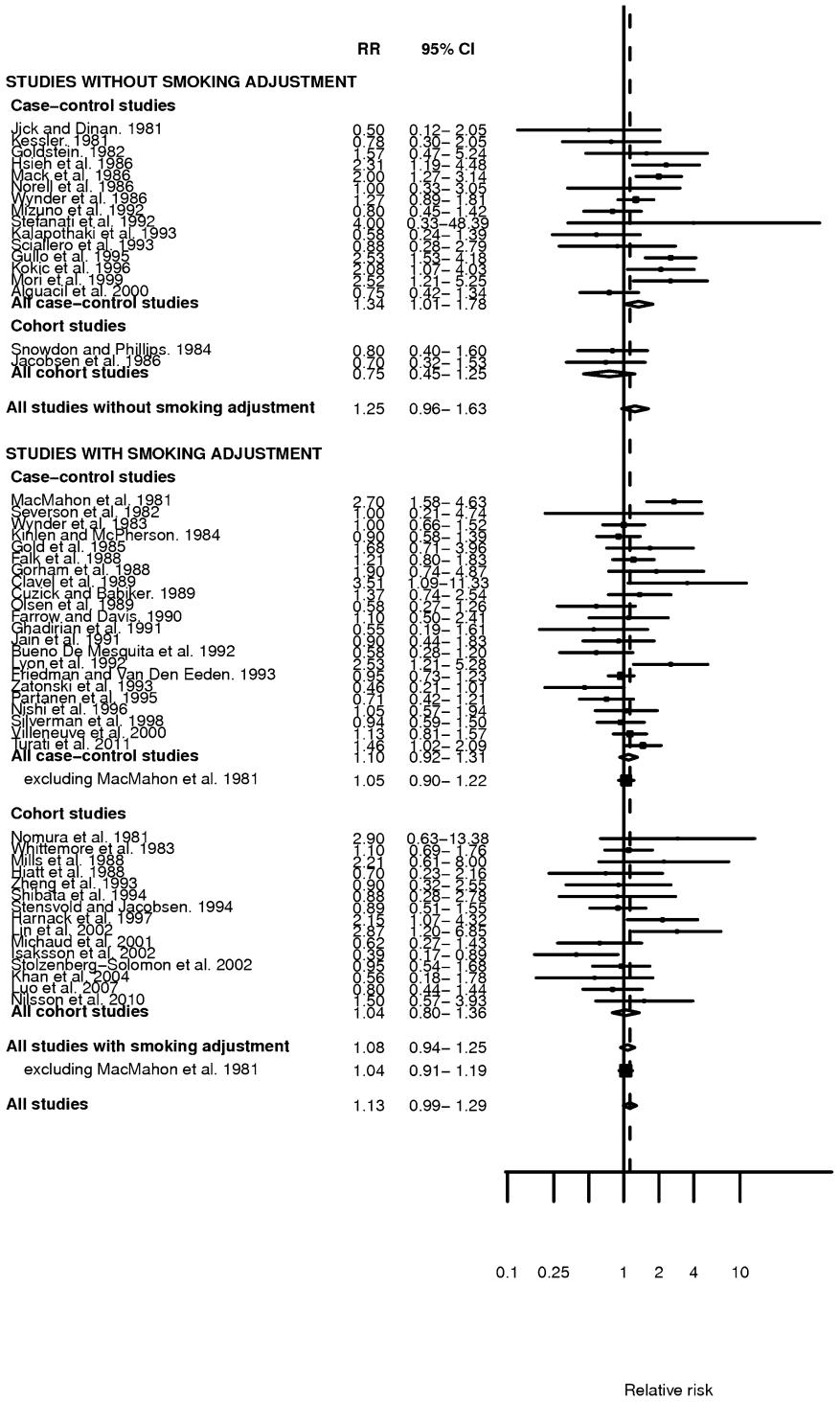

Figure 2. Relatives risks (RRs) and 95% confidence intervals (CI) of pancreatic cancer for the highest versus the lowest coffee drinking categories from studies with and without smoking adjustment, and from all the studies combined. The combined RRs and 95% CI were calculated using the random-effects models. A case–control study [62] nested within a cohort was analyzed as a case–control study.

discussion

The present meta-analysis, carried out on 54 studies and 10 594 cases, found no appreciable overall association between coffee consumption and pancreatic cancer risk. Results were consistent for case–control and cohort studies that included adjustment for smoking consumption in multiple regression models. We observed a weak association in case–control studies not adjusted for tobacco, which can be attributed to residual confounding by smoking. The lack of association is further supported, in smoking-adjusting studies, by the consistency of the results across strata of sex, geographic region, type of controls, and other covariates. The pattern observed in the cumulative meta-analysis, with the decrease of the pooled RR

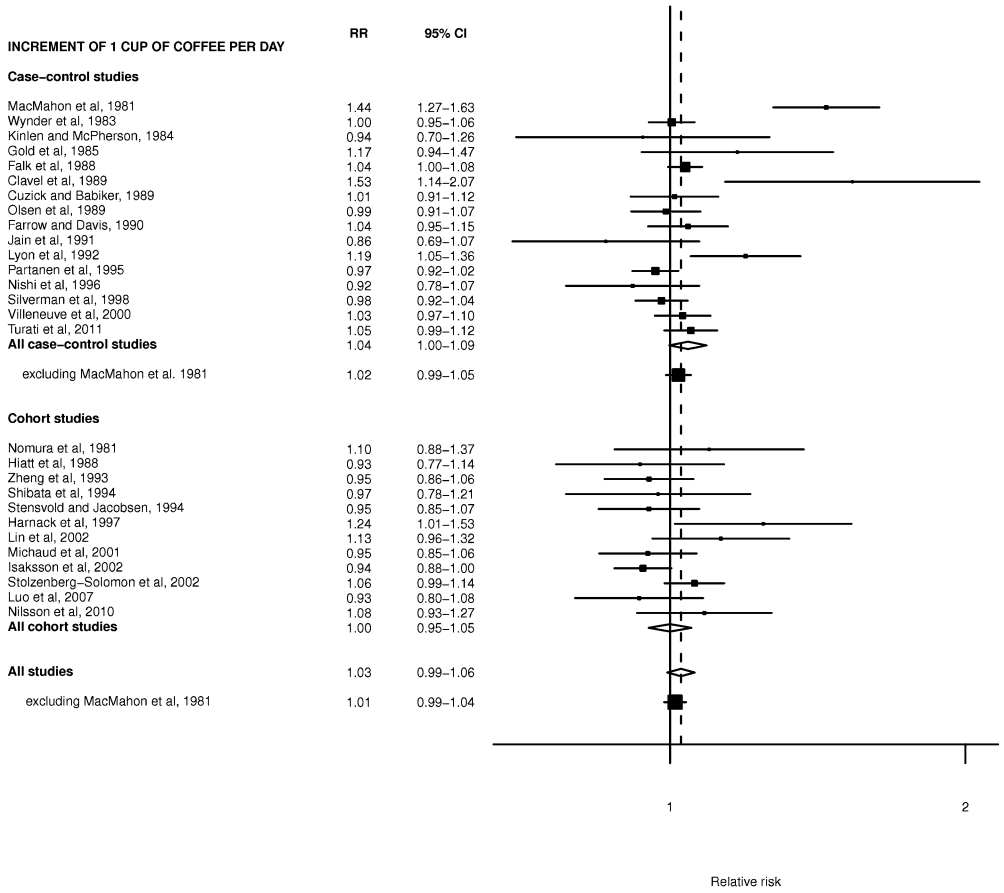

Figure 3. Relative risks (RRs) and 95% confidence intervals (CI) of pancreatic cancer for the increment of one cup of coffee per day. The combined RRs and 95% CI were calculated using the random-effects models. The 37 smoking-adjusting studies were considered.

over time to approach unity since the mid-1900s, is likely due to false-positive results in earlier studies [15, 16]. Besides the role of chance, the exclusion from the control group of subjects with diseases related to cigarette smoking and alcohol intake (positively correlated to coffee consumption [17]) may have led to an overestimation of the real association in cases only in the MacMahon et al. study [40]. Other studies with apparently positive findings included cancer controls [53], were based on proxy interviewers [59], or on a limited number of cases (66) [84]. However, only a few studies were positive, thus reflecting at least in part random variation.

The exclusion of any study from the analysis did not materially change the summary estimates, and *P* values from Begg's and Egger's tests, together with the absence of significant asymmetry in the funnel plot, indicate that publication bias is unlikely to have appreciably influenced our results.

Besides the original hypothesis-generating article [40], among the 37 smoking-adjusting studies, only 5 found significant increased risks. Among these, a cohort study of postmenopausal women [84], a case–control study from France [53], and one from the United States [59] found increased risks for pancreatic cancer for successive levels of coffee consumption. The remaining two, a Japanese cohort study [87] and a recent Italian case–control study [74], found increased risks for pancreatic cancer without an exposure–response trend. The Italian study also showed a lack of significant association with the duration of coffee consumption [74]. The only study that found decreased risks for pancreatic cancer for increasing coffee intakes was a Swedish twin cohort study [86], including 176 incident cases of pancreatic cancer.

In our meta-analysis, we pooled risk estimates for the highest versus the lowest coffee drinking categories in each study, although the cut-offs for high exposure varied between studies, as the pattern of coffee consumption differs by geographic area. This approach has been previously adopted by other meta-analyses of coffee in relation to cancer, and combining RRs for the highest versus the lowest coffee drinking categories has previously shown inverse associations between coffee and cancers of the colorectum [18, 19], liver [20], and endometrium [21]. When we considered only the 21 smoking-adjusted studies with consistent highest consumption categories (intakes of at least four cups of coffee per day) [43, 50, 52–55, 59, 62, 67, 70, 73–75, 79, 81–83, 85–87, 91], the pooled RR was 1.08 (95% CI 1.01–1.29) which was similar to that obtained from the highest versus the lowest consumption from all the smoking-adjusted studies. Moreover, findings from the five available smoking-adjusted studies from Asia, where coffee consumption is lower than in Europe and North America, were similar to those from studies conducted in North America and Europe. The pooled RR per unit increase of coffee intake indicates no material association, in agreement with the results obtained from the

Table 1. Combined relative risks (RRs) and 95% confidence intervals (CI) of pancreatic cancer from both case–control and cohort studies for the highest versus the lowest coffee drinking categories, according to selected study characteristics (the 37 smoking-adjusted studies are considered)

	No. of studies	RR (95% CI)
Sex[a]		
Men	19	1.00 (0.83–1.19)
Women	14	1.15 (0.94–1.41)
P for heterogeneity = 0.312		
Geographic region[b]		
North America	20	1.14 (0.96–1.36)
Asia	5	1.21 (0.69–2.12)
Europe	11	0.93 (0.70–1.23)
P for heterogeneity = 0.448		
Direct interviews		
Yes	23	1.12 (0.93–1.34)
No	14	1.01 (0.78–1.30)
P for heterogeneity = 0.519		
Reference category[c]		
Non/occasional drinking[d]	27	1.12 (0.94–1.33)
Different from non/occasional drinking	8	0.99 (0.76–1.30)
P for heterogeneity = 0.449		
Type of controls (for case–control studies)[e]		
Population	15	1.00 (0.82–1.22)
Hospital	8	1.21 (0.94–1.56)
P for heterogeneity = 0.246		
Smoking habits[f]		
Never smokers	9	1.47 (1.10–1.98)
Ever smokers	8	1.75 (1.02–3.01)
P for heterogeneity = 0.730		

[a]Six studies were carried out on men only [54, 55, 75, 76, 81, 88] and one study on women only [84]; another 13 studies presented risk estimates separately for sex.

[b]A study on USA Adventists [80] was excluded from the analysis stratified by geographic area. One study from Hawaii [75] was considered Asiatic because it included a cohort of men of Japanese ancestry.

[c]Two studies [58, 80] were excluded from this analysis because information on coffee drinking in the lowest category was not available.

[d]Non/occasional drinking was defined as consumption of less than one cup per day.

[e]A study with 212 hospital controls and 67 controls randomly selected from the registries of three general practices was considered in the category of hospital-based studies [52]. The study by Gold et al. [45] was included in both strata, in this table only, because it provides smoking-adjusted RRs for hospital and population controls separately.

[f]Never smokers stratum included only studies reporting risk estimates for subjects who never smoked in their life. The study by Mack et al. [47], which provides risk estimates for subjects who never smoked cigarettes or stopped ≥10 years before, and the one by Stefanati et al. [61], which presents results for a combination of never smokers and nondrinkers, were also included in the analysis. Ever smokers stratum included studies reporting risk estimates for subjects who ever smoked in their life. When the risk estimates for ex and current smokers were reported separately, we pooled them before their inclusion in the meta-analysis. When the definition of smoking was ambiguous in the article [69], we excluded it from this analysis.

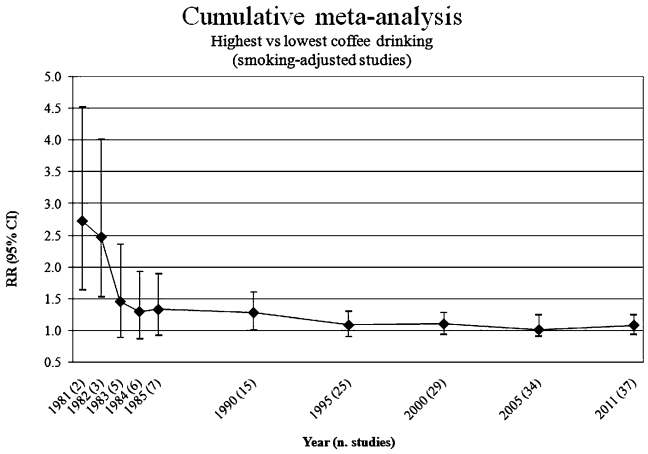

Figure 4. Cumulative meta-analysis for the highest versus the lowest coffee drinking categories in case–control and cohort studies with smoking adjustment. Estimated relative risks (RRs) are shown with the corresponding 95% confidence intervals (CIs) (error bars) by year of publication of subsequent reports. The numbers of studies included in the cumulative meta-analyses for each year are reported in parentheses.

analysis with the highest versus the lowest drinking categories.

Sources of variability among studies that might influence the chemical composition of the beverage include type of coffee beans (Robusta versus Arabica), brewing methods, preparation and cup size. Most of the studies included in this meta-analysis, however, did not provide information about coffee characteristics. Only a cohort study from Sweden investigated separately the role of filtered and boiled coffee on pancreatic cancer risk [91]. It showed a positive association with boiled (unfiltered) coffee only, which has been reported to contain higher amounts of the lipid components (diterpenes, such as cafestol and kahweol) and has been previously related to the cholesterol-raising effect [22].

We were unable to estimate the association between decaffeinated coffee and pancreatic cancer risk, as data were scanty, it was not possible to separate drinkers of both caffeinated and decaffeinated coffee from drinkers of decaffeinated coffee only, and drinkers generally consumed low amount of this type of beverage. However, the few studies analyzing decaffeinated coffee consumption [46, 49, 51, 55–58, 74, 85] found no relation with pancreatic cancer risk. Two studies considered also caffeine intake [59, 85], reporting a lack of association with the risk for cancer of the pancreas.

There are difficulties in the diagnosis and classification of pancreatic cancer. In most studies, only ~50% of cases were histologically confirmed, whereas the rest was based on imaging, which is considered valid in most cases [9, 10]. Any possible misclassification of pancreatic cancer cases is therefore limited and would have only marginal effect on the RR estimates.

Coffee drinking has been inversely related to diabetes [23] and also inversely related to the few neoplasms [19–21, 24] known to be positively associated with diabetes, such as colorectal, liver, and endometrial cancers [25–30]. Type 2 diabetes has been directly related with pancreatic cancer [26, 27, 29, 30], with an overall RR of 1.82 (95% CI 1.66–1.99) in

a meta-analysis of 17 case–control and 19 cohort studies [31] and with an excess risk for diabetes diagnosed up to 10 years before pancreatic cancer diagnosis [32]. The apparent absence of association with cancer of the pancreas leaves therefore open the question of a combination of favorable and unfavorable effects of coffee on pancreatic cancer. However, the pooled risk estimates were similar for studies with adjustment for diabetes (RR = 0.99, 95% CI 0.76–1.28, based on 7 studies within the smoking-adjusting ones) and for those without adjustment for diabetes (RR = 1.12, 95% CI 0.93–1.33, based on 30 studies within the smoking-adjusting ones).

The observational studies included in our meta-analysis may have various sources of bias. An important issue concerns the assessment of coffee intake, which is always based on patients' self-reporting. However, recall of coffee drinking has been shown to be satisfactorily valid [33–36] and should not be different among cases and controls, as coffee is not widely considered as associated to pancreatic cancer. A reduction in coffee consumption because of early symptoms of pancreatic cancer in cases may have weakened a potential positive relation in case–control studies that consider more recent exposures. However, the similar risk estimates in case–control (pooled RR = 1.10) and prospective (pooled RR = 1.04) studies, where information is collected long time before pancreatic cancer symptoms, are against such hypothesis. More in general, case–control studies may be more subject to selection bias than cohort ones. However, the consistency of the results between hospital- and population-based case–control studies and cohort ones argues against the presence of major information or selection bias.

With reference to confounding, apart from smoking, the other recognized risk factors for pancreatic cancer are diabetes, pancreatitis, and family history [37]. Whenever possible, we included in our meta-analysis multivariate RRs adjusted for all available covariates. Tea may be a substitute for coffee. However, similar RRs of pancreatic cancer were reported in a study from Poland that considered models with and without adjustment for tea consumption [63].

In conclusion, this systematic meta-analysis of case–control and cohort studies provides quantitative evidence that coffee consumption is not appreciably related to pancreatic cancer risk, even at high doses.

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disclosure

The authors declare no conflict of interest.

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