Coffee and gastric cancer: systematic review and meta-analysis

Café e câncer gástrico: revisão sistemática e meta-análise

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Abstract

We systematically reviewed the literature on the association between coffee consumption and gastric cancer and performed a meta-analysis of the results. Published cohort and case-control studies were identified in PubMed and reference lists. Random effects meta-analysis was used to pool effects from 23 studies, and heterogeneity was explored by stratification and meta-regression. The odds ratio (OR) for the overall association between coffee and gastric cancer (highest vs. lowest category of exposure) was 0.97 (95%CI: 0.86-1.09), similar for cohort (OR = 1.02; 95%CI: 0.76-1.37) and case-control studies (population-based: OR = 0.90; 95%CI: 0.70-1.15; hospital-based: OR = 0.97; 95%CI: 0.83-1.13). The OR was 1.26 (95%CI: 1.02-1.57) when considering five studies conducted in the USA, 0.97 (95%CI: 0.82-1.14) for the five Japanese studies, 0.98 (95%CI: 0.81-1.17) for the six studies from Europe, and 0.64 (95%CI: 0.47-0.86) for the two studies from South America. In this meta-analysis we found no adverse effect of coffee associated with gastric cancer. Knowledge on the level of exposure to different coffee constituents may provide a deeper understanding of this reassuring result and the real role of coffee on cancer risk.

Coffee; Gastric Neoplasms; Meta-analysis

Introduction

Coffee is one of the most popular beverages, with a yearly world average consumption of 1.1kg per capita, which reaches 4.5kg in industrialized countries [1].

Roasted coffee is a complex mixture of more than a thousand chemicals. These constituents have been described as having genotoxic and mutagenic properties, but also antimutagenic and antioxidant activities and the capacity to inhibit cancer-promoting agents [2,3]. Caffeine appears to disturb cell cycle checkpoint integrity, alter mechanisms of DNA repair, modify the apoptotic response, and potentiate a variety of DNA-damaging agents [2,3]. However, it can also inhibit carcinogenesis *in vivo* and alter carcinogen metabolism, decreasing the cytotoxic, cytostatic, or mutagenic activity of aromatic DNA-damaging compounds through a decrease in the concentration of free aromatic procarcinogens available for cytochrome activation [4,5]. The protective effects of coffee were partially ascribed to the potential for kahweol and cafestol palmitates to convert rapid acetylators into a slow acetylator phenotype [6]. These diterpenes may also have anti-inflammatory and anti-carcinogenic properties by interfering with nitric oxide [7], prostaglandin E2 production, and cyclooxigenase-2 expression [8]. The antioxidant attributes of coffee may contribute to a protective role against cancer [9,10].

These contrasting effects parallel the results of previous epidemiological studies that disclosed no clear-cut effect of coffee consumption on cancer. Reviews and meta-analyses of available studies showed a 20% increased urinary tract cancer risk in coffee consumers [11], no effect on pancreatic cancer risk [12], and a 25% reduction in colorectal cancer risk [13,14].

Investigation of other cancer sites has been less extensive. An earlier review of the association between coffee and gastric cancer identified two cohort studies and nine case-control studies published until 1996 [15] and underscored the contradictory nature of the results. Coffee is such a common exposure that any small effect can result in a large population impact. Therefore, we systematically reviewed and performed a meta-analysis of the published data addressing the association between coffee consumption and gastric cancer.

Material and methods

We performed a systematic review of case-control and cohort studies evaluating the association between coffee consumption and gastric cancer. We used PubMed (http://www.ncbi.nlm.nih.gov/entrez) to identify studies published through December 2004, under the searching expression "*(stomach cancer OR gastric cancer OR cardia cancer) AND (coffee OR lifestyle OR tea)*". The reference lists provided by the identified papers was additionally hand-searched. We evaluated full papers published in English, Spanish, French, Portuguese, and Italian, and English abstracts of full papers written in other languages.

Two reviewers extracted information from each study following a previously defined data collection procedure. Discrepancies in the evaluation of the articles were resolved by consensus, involving a third researcher. The protocol for data extraction covered: study design (case-control, population-based or hospital-based, or cohort, with respective follow-up time; number of subjects); histological confirmation of cases; histological type and location of gastric neoplasias; evaluation of exposure (interviewer or self-administered questionnaire as measuring instrument; type of coffee, reference class, exposure strata, timing of exposure); risk estimates for the association between coffee consumption and gastric cancer, considering two exposure levels (lowest vs. highest); precision estimates (confidence intervals, P values, and number of participants in each exposure category); control of confounding factors; and country of origin.

In one study [16] there were only one case and one control in the upper exposure category and we opted for the results based on the immediate class of consumption.

We excluded from meta-analysis studies that did not provide relative risk estimates and respective variance, or the information needed to calculate it. When a study provided more than one estimate, we selected the one adjusted for the largest set of variables, and when results were available according to gender or ethnicity we included all estimates in the final analysis as if obtained from different studies.

Combined risk estimates and 95% confidence intervals were computed using the random effects method, and statistical tests for homogeneity [17] were performed. Heterogeneity was investigated by subgroup analysis, looking at the magnitude of the combined risk estimates in each stratum as well as to the respective tests of heterogeneity, and meta-regression, to assess the independent contribution of each variable to explain heterogeneity. Publication bias was examined through funnel plot visual analysis, the Begg adjusted rank correlation test [18], and the Egger's regression asymmetry test [19]. A 0.1 level of significance was used in the statistical tests. The software STATA version 8.0 (Stata Corporation, College Station, USA) was used in all analyses.

Results

We identified 40 publications. The English abstracts of two articles published in Chinese [20,21], two in Russian [22,23], one in Japanese [24] and one in Serbian [25] provided insufficient information to be included in the final analysis. One of these studies [25] described a negative correlation and another stated that in large amounts coffee increased the risk [23]. Three publications [26,27,28] provided no quantitative risk estimates but stated that no statistically significant association was found. One study [29] only stated the finding of a non-statistically significant association in males, and a significant association in females (hazard ratio = 2.54) without providing any further statistical estimates. Two studies [30,31] were later reported in more detail [32,33], and the more recent publications were used. Four reports were excluded from analysis because tea and coffee were considered combined (OR = 3.2) [34], coffee assessed as a preference (OR = 1.02) [35], only cardia cancers (OR = 1.3) [36] were evaluated, or results were presented separately for intestinal (OR = 0.50) and diffuse (OR = 1.98) type gastric cancer using the same control group [37].

One case-control study was not considered for meta-analysis because no precision estimates were available [38]. Table 1 briefly characterizes the 17 studies excluded from the final analysis.

Twenty-three studies [16,32,33,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58] remained for quantitative data synthesis (Figure 1 and Table 2). There were 7 cohort studies, with follow-ups ranging from 4.3 to 15 years, and 16 case-control studies, 10 hospital-based, 5 population-based, and one with no specified study base. Seven studies were European, 5 were conducted in the USA (3 on Japanese in Hawaii), and 5 in Japan. The remaining studies described other Asian (n = 4) and South American samples (n = 2).

Fourteen studies used only histologically confirmed cases, two [40,50] stated that respectively "most" and 90.6% of cases had histological confirmation, five [46,52,54,56,57] only indicated having used cancer registries to identify cases, and two [16,58] did not provide this information.

Six studies [45,47,52,54,55,57] used a self-administered questionnaire, one [16] did not specify the measuring instrument, and the remaining 16 collected information by interview. Among the 16 case-control studies, three evaluated coffee exposure five or more years prior to the interview [44,48,51], two did not specify the timing of exposure [16,42], and the rest assessed coffee consumption within five years before onset of disease. In 14 studies, the reference category was non-coffee drinkers, but 9 included subjects drinking more than one cup of coffee per week in the reference group. Nine studies presented results considering only two groups of exposure, and 14 defined three or more categories of consumption. Only two reports specified the type of coffee consumed as being Turkish coffee [16] and caffeine-containing coffee [30]. One study evaluated the consumption of hot coffee [32].

From 9 studies only crude risk estimates could be used, 10 controlled for the potential confounding effect of tobacco smoking, and 4 provided results adjusted for the consumption of fruit or vegetables.

When all studies were combined, coffee intake showed no effect on gastric cancer (OR = 0.97; 95%CI: 0.86-1.09, heterogeneity test: p = 0.08) (Figure 1).

The combined risk estimate was 1.02 (95%CI: 0.76-1.37, heterogeneity test: p = 0.12) for cohort studies, 0.90 for population-based case-control studies (95%CI: 0.70-1.15, heterogeneity test: p = 0.19), and 0.97 for hospital-based case-control studies (95%CI: 0.83-1.13, heterogeneity test: p = 0.14).

The studies that adjusted coffee effect for smoking resulted in a combined odds ratio of 0.91 (95%CI: 0.75-1.11, heterogeneity test: p = 0.02), and 0.94 (95%CI: 0.79-1.12, heterogeneity test: p = 0.99) for the studies adjusting for fruit or vegetable consumption. The combined risk estimates including only the studies with all cases histologically confirmed was 0.97 (95%CI: 0.84-1.12, heterogeneity test: p = 0.06).

The common odds ratio for the 9 studies including coffee drinkers in the reference category was 0.86 (95%CI: 0.67-1.11, heterogeneity test: p = 0.007) and 1.02 (95%CI: 0.90-1.14, heterogeneity test: p = 0.77) for the remaining 14 studies. The association was 1.11 (95%CI: 0.95-1.30, heterogeneity test: p = 0.37) when considering only the studies that described exposure to coffee in two categories and 0.89 (95%CI: 0.76-1.03, heterogeneity test: p = 0.15) for those using more strata. The OR was 1.00 (95%CI: 0.81-1.23, heterogeneity test: p = 0.25) for the studies using a self-administered questionnaire, and 0.96 (95%CI: 0.83-1.12, heterogeneity test: p = 0.06) for those assessing exposure by interview. Among the case-control studies, the combined risk estimate was 0.93 (95%CI: 0.66-1.31, heterogeneity test: p = 0.05) for those assessing exposure five or more years before interview, and 0.95 (95%CI: 0.83-1.09, heterogeneity test: p = 0.31) when coffee consumption was evaluated closer to the time of the study.

The OR was 1.26 (95%CI: 1.02-1.57, heterogeneity test: p = 0.59) when considering studies conducted in the USA (OR = 1.28, 95%CI: 0.99-1.67, for those three conducted in populations of Japanese ancestry). It was 0.97 (95%CI: 0.82-1.14, heterogeneity test: p = 0.52) for the 5 Japanese studies, 0.98 (95%CI: 0.81-1.17, heterogeneity test p = 0.34) for the 7 studies from Europe, and 0.64 (95%CI: 0.47-0.86, heterogeneity test: p = 0.27) for the two studies from South America.

A multivariate analysis including all the above variables showed that risk estimates differed significantly according to country of origin, with North America studies presenting a significantly higher risk (coefficient = 0.45, p = 0.003), number of exposure strata (coefficient = -0.21, p = 0.06, for 3 or more groups compared with two), and reference category (coefficient = -0.27, p = 0.02, for some drinking in reference group compared to non-exposed to coffee).

Neither visual inspection nor tests of statistical significance resulted in funnel plot asymmetry (Figure 2).

As described above, most of the studies excluded from the meta-analysis were not considered simply because they did not provide the necessary risk and precision estimates, were duplicate publications, or analyzed exposures

Table 1

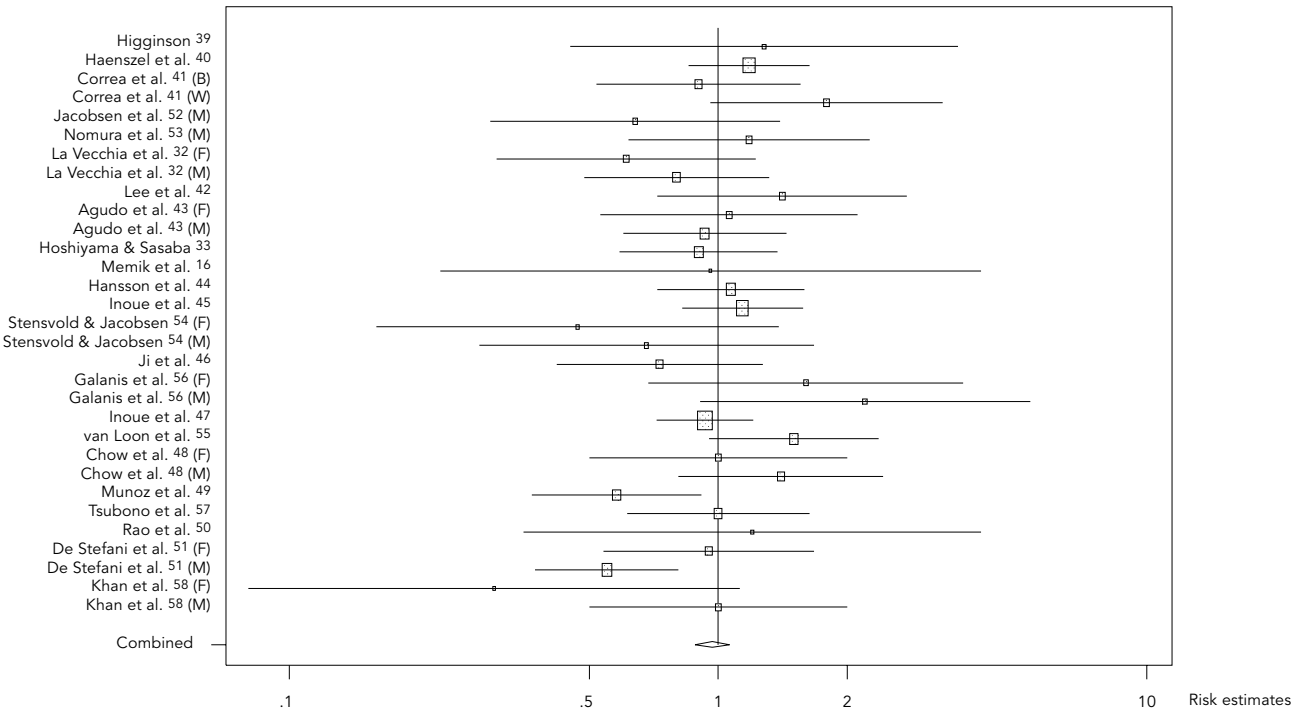
Summary characteristics of studies excluded from the meta-analysis.

Reference	Publication year	Country	Type of study	Coffee ("highest" vs. "lowest")	OR (95%CI)	Control for confounders	Reason for exclusion
Graham et al. [26]	1967	USA	Case-control Hospital based	ns	No statistically significant association	ns	Does not present any results
Graham et al. [27]	1972	USA	Case-control Hospital based	ns	No statistically significant association	ns	Does not present any results
Salimov [22]	1984	USSR	–	–	–	–	Article in Russian
Trichopoulos et al. [34]	1985	Greece	Case-control Hospital based	Quintiles	3.2 (0.39-37.82)*	ns	Combines coffee and tea
Risch et al. [28]	1985	Canada	Case-control Population based	ns	"Little relationship"	ns	Does not present any results
Tajima et al. [38]	1985	Japan	Case-control Hospital based	Every day vs. no drinking habit	1.02	Age, sex	Does not present precision estimates
Tajima & Tominaga [24]	1986	Japan	Case-control Hospital based	–	–	–	Article in Japanese
La Vecchia et al. [30]	1987	Italy	Case-control Hospital based	Tertiles	1.00	Age, sex	Same study as La Vecchia et al. [32]
Jarebinski et al. [23]	1989	Yugoslavia	Case-control Hospital based	–	"coffee in large amounts... ...increases the risk"	–	Article in Russian
Jarebinski et al. [25]	1992	Yugoslavia	Case-control	–	"negative correlation"	–	Article in Serbian
Hoshiyama & Sasaba [31]	1992	Japan	Case-control Population based	≥ 10 cups/week vs. ≤1 cup/week	0.8 (0.5-1.3)	Age, sex, smoking, administrative division	Same as Hoshiyama & Sasaba [33]
Ye et al. [20]	1998	China	Case-control	–	–	–	Article in Chinese
Komoto et al. [37]	1998	Japan	Case-control Hospital based	Consumption vs. non-consumption	0.50 (0.24-1.01) Intestinal 1.98 (0.71-5.46) Diffuse	*H. pylori* infection, alcohol, smoking, blood group, family history of gastric carcinoma	Stratified in intestinal and diffuse without any global analysis
Wang et al. [21]	1999	China	Case-control	–	–	–	Article in Chinese
Terry et al. [36]	2000	Sweden	Case-control Population based	Quartiles	1.3 (0.8-2.0)	Age, sex, body mass index, total energy, energy adjusted alcohol, fruits and vegetable intake, smoking, use of anti-acids	Only gastric cardia
Huang et al. [35]	2000	Japan	Controls were hospital visitors	Preference for coffee	1.02 (0.83-1.24)	Age, sex	Exposure was preference for coffee
Nagata et al. [29]	2002	Japan	Cohort (mortality) Follow-up: 7 years	Daily vs. rare/ never	No statistically significant association (men) Statistically significant association, HR=2.54 (women)	Age, total energy	Does not present precision estimates Caffeinated coffee

ns = not specified.
* estimated using data available in the article.

Figure 1

Meta-analysis of studies evaluating the association between coffee consumption and gastric cancer*.



* Heterogeneity test (p = 0.08).
M = Male; F = Female; B = Black; W = White.

to coffee and tea together. Relaxing the inclusion criteria to accommodate the remaining studies [35,36,37] the summary risk estimate was 1.05 (95%CI: 0.90-1.23, heterogeneity test: $p < 0.001$), similar to that obtained in our main analysis.

Discussion

This meta-analysis of studies published during the last three decades showed no overall effect of coffee consumption on gastric cancer risk. However, we observed substantial methodological differences between studies that have potential effect on the risk estimates.

Most studies presented results on the association between coffee and gastric cancer as secondary data analysis or part of confounder evaluation [17,33,38,39,40,41,42,46,47,49,50,51,56,57,58], and it is unlikely that this specific result influenced publication. The studies excluded from the analysis presented non-significant associations between coffee and gastric cancer, and after changing our inclusion criteria, enlarging the number of studies combined, the results remained virtually unchanged. Publication bias is an improbable cause of our findings, as supported by the funnel plot analysis and the result of the regression asymmetry test, and it is unlikely that unpublished results would change our conclusions, because the bias is due to the over-publication of positive findings [59].

In this analysis, several sources of heterogeneity are likely, even if most risk estimates from individual reports were not significantly different as assessed by statistical tests.

In case-control studies, coffee consumption among controls may not represent the target population, and bias is even more probable with hospital controls. However, considering the results from hospital- and population-based studies, this appears unlikely. Symptoms, namely heartburn, are associated with coffee intake, and cases might avoid coffee. This differential information bias could lead to a misleading

Table 2

Summary characteristics of studies included in the meta-analysis.

Reference	Publication year	Country	Study characteristics	Coffee ("highest" vs. "lowest")	Number of subjects	Evaluation of coffee consumption	OR/RR (95%CI)	Control for confounders	Notes
Higginson [39]	1966	USA	Case-control Hospital based	> 3 cups/day vs. never/irregularly	54:152*,** 5:18*,***	Previous 2 years	1.28 (0.45-3.61)#	No#	
Haenszel et al. [40]	1972	USA	Case-control Hospital based	≥ 2 cups/day vs. < 2 cups/day	102:186*,** 118:253*,***	Current	1.18 (0.85-1.63)# 2.0 (Issei) 0.74 (Nisei)	Matching for sex Sex- and nativity-adjusted OR is 1.21, but no precision estimate is available	Japanese in Hawaii No differences by histological type
Correa et al. [41]	1985	USA	Case-control Hospital based	Above median vs. below median	171:157*,** White 159:150*,** Black 23:38*,*** White 38:45*,*** Black	Before illness	1.79 (0.96-3.35) White 0.9 (0.52-1.56) Black	Age, sex, education, income, tobacco, and alcohol use	
La Vecchia et al. [32]	1989	Italy	Case-control Hospital based	≥ 4 cups/day vs. 0 cups/day	42:24*,** Men 17:790*,** Women 41:194*,*** Men 33:106*,*** Women	Current	0.80 (0.49-1.32) Men# 0.61 (0.30-1.21) Women#	No OR adjusted for age, sex, social class, education, marital status, smoking, alcohol consumption (≥ 3 vs. ≤ 1 cups/day) is 1.26, but no precision estimate is available	Caffeine-containing coffee
Lee et al. [42]	1990	Taiwan	Case-control Hospital based	Drinker vs. non-drinker	14:39*,** 196:771*,***	ns	1.41 (0.72-2.75)#	Matching for age and sex	
Hoshiyama & Sasaba [33]	1992	Japan	Case-control Population based	≥ 10 cups/week vs. ≤ 1 cup/week	251:483*,##	Current	0.9 (0.6-1.4)	Age, smoking, dietary items (fruit, vegetables, preference for salty foods etc.)	Hot coffee
Memik et al. [16]	1992	Turkey	Case-control	2-3 cups/day vs. ≤ 1 cup/day	3:24*,** 76:584*,***	ns	0.96 (0.18-3.28)#	Matching for age	Turkish coffee No methods section
Agudo et al. [43]	1992	Spain	Case-control Hospital based	Drinker vs. non-drinker	228:227*,##	1 year before	0.93 (0.60-1.44) Men 1.06 (0.53-2.11) Women	Age, sex, area residence, total calories, fruits, vegetables, cold cuts, preserved fish	
Hansson et al. [44]	1993	Sweden	Case-control Population based	≥ 3,100ml/week vs. none	338:669 *,##	20 years before	1.07 (0.72-1.59)	Age, sex, social class	Exposure during adolescence OR = 1.35 (95%CI: 0.84-2.16)

(continues)

Table 2 (continued)

Reference	Publi-cation year	Country	Study charac-teristics	Coffee ("highest" vs. "lowest")	Number of subjects	Evaluation of coffee consumption	OR/RR (95%CI)	Control for confounders	Notes
Inoue et al. [45]	1994	Japan	Case-control Hospital based	Ever drinker vs. non-drinker	668/668*,##	Before illness	1.14 (0.82-1.57)	Sex	Cardia, OR = 0.94, 95%CI: 0.52-1.69); Middle stomach, OR = 1.04, 95%CI: 0.66-1.64); Antrum, OR = 1.32, 95%CI: 0.88-1.97)
Ji et al. [46]	1996	China	Case-control Population based	Drinker vs. non-drinker	21:32*,** 1103: 1217*,***	1 year before	0.73 (0.42-1.27)#	Matching for age and sex	
Inoue et al. [47]	1998	Japan	Case-control Hospital based	≥ 3 cups/day vs. rarely	84:1085*,** 149: 1274*,***	Before illness	0.93 (0.72-1.21)	Age, sex, smoking, alcohol, tea, physical exercise, fruit, beef, rice, year and season at first hospital visit	
Chow et al. [48]	1999	Poland	Case-control Population based	≥ 7 cups/week vs. none	63:68*,** Women 95:85*,** Men 27:39*,*** Women 52:65*,*** Men	5 years before	1.0 (0.5-2.0) Women 1.4 (0.8-2.4) Men	Age, smoking, education, years lived on a farm, family history of cancer	No differences by tumor location or Lauren's histological type
Munoz et al. [49]	2001	Venezuela	Case-control Population based	Quartiles	292:485*,##	Current	0.58 (0.37-0.92)	Age, sex, smoking, alcohol, total energy intake, social class	
Rao et al. [50]	2002	India	Case-control Hospital based	Daily vs. never/rarely	3:35*,** 116: 1542*,***	Current	1.2 (0.3-3.5)	Age, sex	
De Stefani et al. [51]	2004	Uruguay	Case-control Hospital based	Highest vs. lowest tertile	240:960*,##	5 years before	0.55 (0.38-0.82) Men 0.95 (0.54-1.67) Women	Age, residence, urban/rural status, education, body mass index, smoking, alcohol, total energy intake	
Jacobsen et al. [52]	1986	Norway	Cohort (incidence) Follow-up: 11.5 yrs	≥ 7 cups/day vs. ≤ 2 cups/day	10: 3375###,** 24: 1763###,***	Baseline	0.64, p = 0.13, Men	Age, residence, smoking. Results age-, sex- and residence-adjusted are available (RR = 1.46, p = 0.21)	
Nomura et al. [53]	1986	USA	Cohort (incidence) Follow-up: 15 yrs	≥ 5 cups/day vs. none	26#: 1,850###,** 14#: 1,178###,***	Baseline	1.18 (0.62-2.26)# Men	Age	Japanese men in Hawaii

(continues)

Table 2 (continued)

Reference	Publi-cation year	Country	Study charac-teristics	Coffee ("highest" vs. "lowest")	Number of subjects	Evaluation of coffee consumption	OR/RR (95%CI)	Control for confounders	Notes
Stensvold & Jacobsen [54]	1994	Norway	Cohort (incidence) Follow-up: 10.1 yrs	≥ 7 cups/day vs. ≤ 2 cups/day	14: 71,923§,** Men 6:47,530§,** Women 7:24,576§,*** Men 7:25,906§,*** Women	Baseline	0.68 (0.28-1.69)# Men 0.47 (0.16-1.39)# Women	No RR adjusted for age, smoking and county of residence is 0.5 for men and 0.5 for women, but no precision estimates are available	
van Loon et al. [55]	1998	Nether-lands	Cohort (incidence) Follow-up: 4.3 yrs	> 4 cups/day vs. ≤ 3 cups/day	29:216§§,** 117: 1,309§§,***	Baseline	1.5 (0.95-2.36)#	No	
Galanis et al. [56]	1998	USA	Cohort (incidence) Follow-up: 14.8 yrs	≥ 2 cup/day vs. none	32: 2,584###,** Men 19:2703##,** Women 6:1,647###,*** Men 8:1,868###,*** Women	Baseline	2.2 (0.9-5.3) Men 1.6 (0.7-3.8) Women	Age, sex, education, Japanese place of birth, smoking (only in men)	Japanese in Hawaii
Tsubono et al. [57]	2001	Japan	Cohort (incidence) Follow-up: 9 yrs	≥ 3 cups/day vs. never	419: 19,9748§,##|	Baseline	1.0 (0.6-1.6)	Sex, age, tea, smoking, consumption of alcohol, rice, meat, vegetables, fruits, bean-past soup, type of health insurance	
Khan et al. [58]	2004	Japan	Cohort (mortality) Follow-up: Men, 13.8 years; Women, 14.8 years	≥ several times/ week vs. ≤ several times/month	36 cases##| in men 927:595§§§ Men 15 cases## in women 992:641§§§ Women	Baseline	1.0 (0.5-2.0) Men 0.3 (0.1-1.4) Women	Age, smoking (men); age, smoking, health status, health education, health screening (women)	

ns = not specified.
* cases:controls;
** highest level of exposure;
*** lowest level of exposure;
# estimated using data available in the article;
data stratified by exposure category not available;
cases:number of respondents;
§ cases:person-years of follow-up;
§§ cases:subcohort subjects;
§§§ subjects in reference:comparison groups.

protective effect. Again, similar summary estimates for case-control and cohort studies argue against this hypothesis.

The classification of exposure differs considerably across the reviewed studies, and the results were shown to be significantly different according to the number of consumption categories evaluated or the characteristics of the reference class regarding consumption. The lower risk estimates when consumption is evaluated in several categories could be explained if coffee had a protective effect that would be stronger when the difference between the groups of highest and lowest exposure was larger. On the other hand, in opposition to what is observed, if coffee had some effect on cancer risk we would expect the combined estimates to approach the null when the reference class includes coffee drinkers, and this is likely to be a chance finding. The method of questionnaire administration and the timing of exposure evaluation did not significantly influence our results, and our conclusions of lack of positive association between coffee and cancer do not appear to be affected by the specificities of exposure evaluation.

In the meta-analysis, we opted for individual risk estimates based on exposure categories with different cut-off points, and a dose-response analysis would have given more information on the underlying association. However, more than one-third of the studies allowed no such analysis, and we opted to include the 9 studies providing data for only two consumption categories. This option proved to be adequate, since the combined risk estimates differed across studies presenting results for two or more groups of exposure.

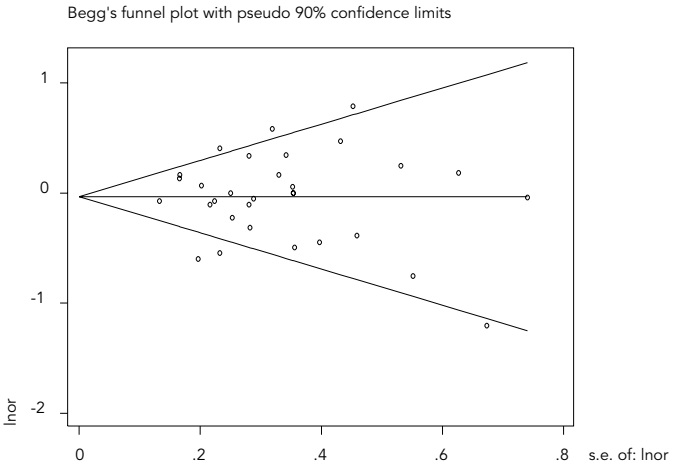
Coffee consumption tends to be associated with tobacco smoking [54,60], but many studies did not account for this potential confounding in the data analysis. Moreover, adding to residual confounding by tobacco smoking, other factors may be influencing the estimates for the association between coffee and gastric cancer, since non-coffee drinkers may differ from the general population of coffee drinkers concerning other exposures such as tea, alcohol, or fruit and vegetable intake [61,62]. The studies included in our review rarely considered confounding or interaction from these variables.

We observed differences in risk estimates according to the geographical origin of the study. Methodological options in study design did not explain such differences, but none of the reviewed studies considered in detail the characteristics of the coffee consumed. It is known that the type of coffee beans [63,64,65], roasting procedure [66,67], and specific method of preparing the coffee can influence composition [68,69,70]. We can speculate on any potential adverse effect of specific constituents present in coffee consumed in North America. The underlying risk of gastric cancer in each population, international differences in the typical amount of coffee consumed, coffee type, or brewing method [70] may contribute to these differences. Studies presenting different risk estimates across strata of gender [48,51,58], ethnicity [41], or generation of Japanese migrants to Hawaii [40] favor this hypothesis of various exposures under the label coffee, but the alternate explanation of confounding seems sounder.

The complexity of coffee composition and the multiple social contexts underlying consumption make the evaluation of the effect of coffee on gastric cancer very difficult. Human experimental studies on such associations are unlikely, making observational studies the best available source of evidence on risk. Overall, it is reassuring that this meta-analysis showed no adverse effect of coffee associated with gastric cancer. Knowledge on the level of exposure to different coffee constituents may provide a deeper understanding of the real role of coffee on cancer risk and ultimately allow the design of safer beverages.

Figure 2

Funnel plot of studies evaluating the association between gastric cancer and coffee consumption*.



* Begg adjusted rank correlation test (p = 0.68), Egger's regression asymmetry test (p = 0.92).

Resumo

Efetuamos uma revisão sistemática dos estudos publicados avaliando a associação entre café e câncer de estômago. Identificamos estudos de coorte e caso-controle na PubMed e nas listas de referências. Foram obtidas estimativas conjuntas do risco por meta-análise de 23 estudos (método de efeitos aleatórios). A heterogeneidade foi explorada por estratificação e meta-regressão. O odds ratio *(OR) conjunto para a associação entre café e câncer gástrico (categoria de exposição mais elevada vs. mais baixa) foi de 0,97 (IC95%: 0,86-1,09), semelhante para estudos de coorte (OR = 1,02; IC95%: 0,76-1,37) e caso-controle (populacional: OR = 0,90; IC95%: 0,70-1,15; hospitalar: OR = 0,97; IC95%: 0,83-1,13). O OR foi de 1,26 (IC95%: 1,02-1,57) para cinco estudos efetuados nos Estados Unidos, 0,97 (IC95%: 0,82-1,14) para cinco estudos japoneses, 0,98 (IC95%: 0,81-1,17) para cinco estudos europeus, e 0,64 (IC95%: 0,47-0,86) para dois estudos sul-americanos. Nesta meta-análise não observamos efeito significativo do consumo de café na ocorrência de câncer gástrico. Contudo, o conhecimento dos níveis de exposição a diferentes constituintes do café poderá permitir uma melhor compreensão deste resultado e o verdadeiro contributo do café para a ocorrência de câncer.*

Café; Neoplasias Gástricas; Meta-análise

Contributors

F. Botelho was responsible for the searches in PubMed and the lists of references, extracted data from the articles, and wrote the first draft of the manuscript. N. Lunet extracted data from the articles, performed the statistical analysis of data, and contributed to drafting of the final manuscript. H. Barros extracted data from the articles and contributed to the drafting of the final manuscript. All authors approved the final version of the manuscript.

Acknowledgements

Nuno Lunet received a grant from Fundação para a Ciência e a Tecnologia (SFRH/BD/3293/2000).

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Submitted on 28/Mar/2005
Final version resubmitted on 31/Aug/2005
Approved on 27/Sep/2005