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ORIGINAL ARTICLE

Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies

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BACKGROUND/OBJECTIVES: Coffee is one of the most popularly consumed beverages worldwide. Many epidemiological studies have investigated the association between coffee consumption and lung cancer risk, but the results are inconsistent. Hence, we conducted a systematic analysis of relevant population-based studies to examine this association and derive a more precise estimation.

SUBJECTS/METHODS: The Cochrane library, PubMed and Embase databases were searched to identify studies published through Mar 2015 that met the predetermined inclusion criterion. Seventeen studies (5 cohort and 12 case–control studies) involving 12 276 cases and 102 516 controls were included.

RESULTS: The summary odds ratio (OR) of lung cancer was 1.17 (95% confidence interval (CI): 1.03–1.33) for coffee drinkers compared with nondrinkers and 1.31 (95% CI: 1.11–1.55) for the highest category of coffee consumption compared with the lowest category. Compared with nondrinkers, the pooled ORs for lung cancer were 1.10 (95% CI: 0.92–1.31) for ⩽1 cup per day, 1.10 (95% CI: 0.93–1.30) for 2–3 cups per day and 1.20 (95% CI: 1.02–1.39) for ⩾3 cups per day. Further analysis showed that the ORs for hospital-based case–control studies, population-based case–control studies and prospective cohort studies were 1.36 (95% CI: 1.10–1.69), 0.99 (95% CI: 0.77–1.28) and 1.59 (95% CI: 1.26–2.00), respectively. Significant associations for high coffee intake with increased risk of lung cancer were observed in men (OR = 1.41 95% CI: 1.21–1.63), but not in women (OR = 1.16, 95% CI: 0.86–1.56), in American (OR = 1.34 95% CI: 1.08–1.65) and Asian populations (OR = 1.49 95% CI: 1.28–1.74), but not in European populations (OR = 1.12, 95% CI: 0.74–1.67), and in smokers (OR = 1.24, 95% CI: 1.00–1.54), but not in nonsmokers (OR = 0.85, 95% CI: 0.64–1.11). Particularly over the last 5 years, studies have consistently indicated that lung cancer risk is significantly increased by 47% in the population with the highest category intake of coffee compared with that with the lowest category intake (OR = 1.47, 95% CI: 1.21–1.79).

CONCLUSION: The present study suggested that coffee intake was associated with an increased risk of lung cancer.

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INTRODUCTION

Lung cancer is one of the most prevalent malignancies and is the leading cause of cancer death in the United States, in both men and women.[1] The incidence and mortality rate of lung cancer are continuing to increase worldwide, particularly in developing countries. As reported by World Health Organization, the steadily increasing proportion of elderly people in the world will result in ~50% increase in new cancer cases over the next 20 years. If the current smoking levels and the adoption of unhealthy lifestyles persist, the increase will be even greater. Epidemiological studies and systematic analyses have showed the intimate association between dietary factors and the risk of lung cancer. The high consumption of saturated fat may increase the risk of lung cancer, whereas the consumption of vegetables, fruit and carotene may decrease the risk of lung cancer.[2–5] Therefore, the identification of modifiable risk factors, particularly in the diet, for lung cancer is of importance because it may lead to potential prevention opportunities.

Coffee is one of the most widely consumed beverages in the world. Because of its popularity, even small potentially unhealthy or beneficial properties could have important public health consequences. In addition to caffeine, coffee has been reported to contain more than a thousand different chemical compounds with many bioactivities, such as anti-oxidative,[6] anti-inflammatory[7] and insulin-sensitizing[8] effects. Coffee contains complex mixtures of biochemically active components that have been hypothesized to impact the etiology of certain diseases ranging from carcinogenesis and cancer progression to cellular apoptosis, oxidative stress and inflammatory diseases.[9–12] Thus, it is important to elucidate the association between coffee consumption and the risk of cancers. In fact, extensive epidemiological studies have been performed to estimate the relationship between coffee consumption and various types of cancer, including lung cancer. However, these studies have reported inconsistent findings for coffee consumption and lung cancer risk. To derive a more precise estimation of this relationship, we performed a meta-analysis to summarize the available evidence from prospective and case–control studies.

MATERIALS AND METHODS

Search strategy

We conducted a systematic search of the literature published on 1 March 2015 using the Cochrane, PubMed and Embase databases. The following search terms were used: 'coffee', 'beverages', 'diet', 'lifestyle' and 'lung cancer'. We also performed a manual search via reference lists.

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Only full-length journal articles with a prospective cohort or case–control study design were considered.

Study selection

Articles were eligible for the present meta-analysis if they conformed to the following criteria: (i) the study design was a population-based study, including cohort or case–control study; (ii) a relatively complete assessment of coffee intake was performed; (iii) the association of coffee intake with lung cancer risk was specifically evaluated; and (iv) the relative risk (RR), hazard ratio or odds ratio (OR) and the corresponding 95% confidence interval (95% CI) values were available. In cases in which duplicate reports from the same study were identified, we chose the most recent one.

Data extraction

The data from each paper fulfilling the inclusion criteria were extracted carefully by two independent reviewers. The following information from each study was recorded: (i) the first author's name, publication year and country or city of origin; (ii) the study design (prospective cohort study, population-based case–control study or hospital-based case–control study); (iii) the mean follow-up time used in the study; (iv) the population (numbers of cases and controls); (v) coffee consumption; (vi) the relative risk, hazard ratio or OR values from the most fully adjusted model and their 95% CI values; and (vii) the listed confounders adjusted for in the multivariate analysis. In addition, because of the low incidence of lung cancer, the OR was assumed to be the same as the hazard ratio and relative risk, and the summary results were reported as OR for simplicity.[13]

Statistical analysis

The summary ORs and corresponding 95% CIs of the included studies were used as a measure to assess the association of coffee consumption with lung cancer risk. The statistical heterogeneity among studies was assessed using the Q test and I^2 statistics. If a statistical difference in heterogeneity existed ($P < 0.10$ or $I^2 > 50\%$), a random-effects model was selected to pool the data; otherwise, a fixed-effects model was used. When statistical heterogeneity was detected, a sensitivity analysis was performed to explore potential sources of heterogeneity, both in the overall pooled estimate and within the subgroups. The potential publication bias was examined by the funnel plot and Egger's test ($P < 0.10$). All of the analyses were performed using STATA version 11.0 (Stata Corp, College Station, TX, USA). A *P*-value < 0.05 was considered to be statistically significant unless otherwise specified.

RESULTS

Characteristics of the included studies

As shown in Figure 1, the systematic search of the literature identified a total of 2658 studies. After excluding 2625 irrelevant titles and/or abstracts, the remaining 33 full-text articles were subjected to a more detailed evaluation. Among those articles, 16 were excluded as irrelevant or because they did not meet the inclusion criteria. In the end, 17 studies relevant to the role of coffee intake in the risk of lung cancer were included in the present meta-analysis.[14–30]

The characteristics of these studies are presented in Table 1. The studies included in the final analysis included 12 276 cases and 1 02 516 controls. The selected studies were published between 1986 and 2014, which is a period that spans 28 years. One of the studies was published in Japanese, and the others were published in English. Among these 17 studies, five were prospective cohort studies, four were population-based case–control studies and eight were hospital-based case–control studies. In addition, five were conducted in America (two in USA, one in Canada and one in Uruguay), five were conducted in Europe (two in Sweden, one in Norway, one in France and one in Czech) and seven were conducted in Asia (three in Japan, one in Hong Kong, one in Korea, one in India and one in Pakistani). Two studies did not have any adjustments, two studies only adjusted for age and smoking, and the other 13 studies adjusted for a wide range of potential confounders of lung cancer, such as age, smoking, occupation, radon index, alcohol, education, residence, socioeconomic status, and intake of fruit and vegetables.

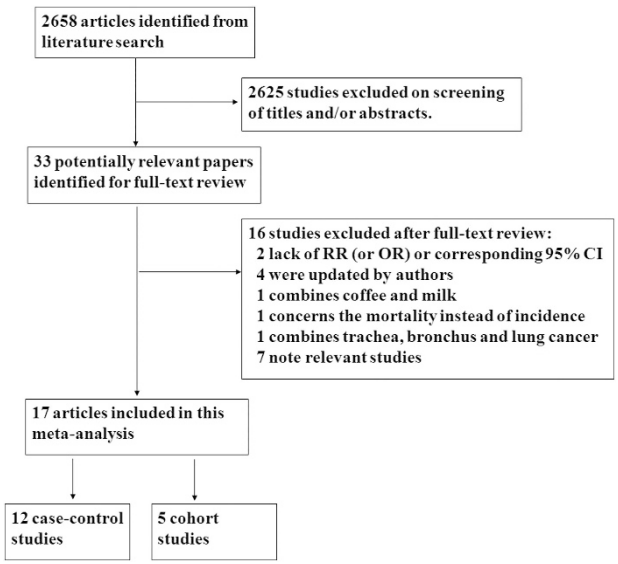

Figure 1. Flow chart showing study selection procedure.

Coffee consumption and lung cancer risk

The summary OR values of lung cancer included in the studies were calculated using fixed- or random-effects models depending on the heterogeneities. As shown in Figure 2a, the pooled OR of lung cancer from the combination of the included studies was 1.17 (95% CI: 1.03–1.33) for coffee drinkers compared with nondrinkers, indicating that the risk of lung cancer is significantly increased in coffee drinkers. In addition, the pooled OR is higher in magnitude when it is estimated as the highest category intake of coffee versus the lowest category (OR = 1.31, 95% CI: 1.11–1.55; Figure 2b). Nevertheless, substantial heterogeneities existed across these studies. Hence, we estimated ORs for different contrasts for coffee consumption. As shown in Figures 2c, d and e, the pooled OR of lung cancer for the population with $\leqslant 1$ cup per day, 2–3 cups per day and $\geqslant 3$ cups per day coffee consumption compared with nondrinkers were 1.10 (95% CI: 0.92–1.31), 1.10 (95% CI: 0.93–1.30) and 1.20 (95% CI: 1.02–1.39), respectively. No significant heterogeneities were observed in these studies. The data suggested that an increase in coffee consumption was associated with an increased risk of lung cancer and that the consumption of more than three cups of coffee per day might significantly increase lung cancer risk.

We then stratified the included studies by design, sex, population, smoking and publication time. As shown in Table 2, the pooled ORs for hospital-based case–control studies, population-based case–control studies and prospective cohort studies were 1.36 (95% CI: 1.10–1.69), 0.99 (95% CI: 0.77–1.28) and 1.59 (95% CI: 1.26–2.00), respectively. The prospective cohort studies revealed a significant positive association for lung cancer risk with coffee intake, and no substantial heterogeneity existed across these studies. Next, a significant association for high coffee intake with increased risk of lung cancer was observed in men (OR = 1.41 95% CI: 1.21–1.63) but not in women (OR = 1.16, 95% CI: 0.86–1.56). Statistical heterogeneity existed across the studies conducted in women but not in those conducted in men. Furthermore, statistically significant associations between high coffee consumption and lung cancer risk were observed among studies conducted in American (OR = 1.34 95% CI: 1.08–1.65) and Asian populations (OR = 1.49 95% CI: 1.28–1.74) but not in European populations (OR = 1.12, 95% CI: 0.74–1.67). In addition,

Table 1. Characteristics of studies included in the meta-analysis

Author, year and region	*Study design*	*Population confirm*	*Mean follow-up (year)*	*Cases/ controls*	*Coffee consumption*	*RR/OR (95% CI)*	*Adjustments*
Luqman M, 2014, Pakistani	Hospital-based case–control	Histological	2010–2013	400/800	Nondrinker	1.00	None
					Drinker	1.80 (1.10–2.80)	
Ganesh B, 2011, Mumbai, India	Hospital-based case–control	Male microscopically	1997–1999	408/1383	Nondrinker	1.00	Smoking, alcohol, milk, red meat, chicken, fish, pesticide
					Drinker	1.90 (1.30–2.70)	
Kubik A, 2008, Czech	Hospital-based case–control	Microscopically	1998–2006	1096/2996		Men Nonsmokers / Smokers	Age, residence, education and pack years of smoking
					Nondrinkers	1.00 / 1.00	
					Drinkers	0.91 (0.43–1.92) / 1.07 (0.61–1.86)	
						Women Nonsmokers / Smokers	
					Nondrinkers	1.00 / 1.00	
					Drinkers	0.86 (0.59–1.26) / 0.76 (0.48–1.20)	
Baker JA, 2005, United States	Hospital-based case–control	Smokers histological	1982–1998	993/986	Nondrinkers	1.00	Age, sex, smoking status, occupational exposure, number of cigarettes smoked per day
					⩽1 cup per day	1.03 (0.73–1.45)	
					2–3 cups per day	1.34 (0.99–1.82)	
					⩾4 cups per day	1.51 (1.11–2.05)	
Takezaki T, 2001, Japan	Hospital-based case–control	Histological	1988–1997	1045/4153		Men Adenocarcinomas / SCSCC	Age, senson and year of visit, occupation, prior lung disease, smoking, vegetables and meat
					<1 cup per day	1.00 / 1.00	
					1 cup per day	0.85 (0.61–1.19) / 0.98 (0.70–1.37)	
					2 cups per day	0.87 (0.60–1.25) / 1.15 (0.80–1.64)	
					⩾3 cups per day	1.18 (0.80–1.74) / 1.61 (1.09–2.39)	
						Women Adenocarcinomas / SCSCC	
					<1 cup per day	1.00 / 1.00	
					1 cup per day	0.76 (0.51–1.13) / 0.96 (0.43–2.18)	
					2 cups per day	0.82 (0.49–1.35) / 0.61 (0.21–1.78)	
					⩾3 cups per day	1.28 (0.65–2.54) / 0.28 (0.05–1.58)	
Mendilaharsu M, 1998, Uruguay	Hospital-based case–control	Male smokers	1994–1996	427/428	Nondrinkers	1.00	Age, residence, urban/rural status, smoking, total energy intake, dairy foods, desserts, vegetables and fruits
					<1 cup per week	1.11 (0.72–1.73)	
					1 cup per week	1.32 (0.75–2.33)	
					2–3 cups per week	0.88 (0.49–1.55)	
					1 cup per day	1.20 (0.60–2.41)	
					⩾2 cups per day	1.22 (0.53–2.80)	
Axelsson G, 1996, Sweden	Hospital-based case–control	Male histological	1989–1993	308/504	<2 times per week	1.00	Age, cigarettes per day, marital status, job classification, smoking-years, socioeconomic
					Daily	0.94 (0.38–2.29)	
					7–25 times per week	1.16 (0.53–2.52)	
					>25 times per week	1.60 (0.72–3.54)	
Mettlin C, 1989, United States	Hospital-based case–control		1982–1987	569/569	Nondrinkers	1.00	Sex, smoking history, β-carotene intake index and education
					<1 cup per day	1.01 (0.67–1.51)	
					2–3 cups per day	0.94 (0.65–1.37)	
					⩾4 cups per day	1.26 (0.86–1.84)	
Sanikini H, 2014, France	Population-based case–control		2001–2007	5926/4673	Never	Men / Women	Age, gender, area of residence, a comprehensive smoking index
					<2 cups per day	1.00 / 1.00	
					2–3 cups per day	1.30 (0.83–2.04) / 1.61 (0.97–2.67)	
					3–5 cups per day	1.07 (0.69–1.67) / 1.08 (0.64–1.83)	
					⩾5 cups per day	0.95 (0.61–1.46) / 1.13 (0.68–1.88)	
						1.11 (0.72–1.72) / 1.15 (0.69–1.94)	

Table 1. (Continued)

Author, year and region	*Study design*	*Population confirm*	*Mean follow-up (year)*	*Cases/ controls*	*Coffee consumption*	*RR/OR (95% CI)*		*Adjustments*
						Overall	Nonsmokers	
					Never	1.00	1.00	Age, smoking, employment, education, radon index, family cancer history, dish-years.
Chiu YL, 2010, Hong Kong, China	Population-based case–control	Female histological	2002–2004	279/322	1–10 cup-years	0.41 (0.21–0.78)	0.37 (0.18–0.78)	
					10 cup-years	1.36 (0.77–2.43)	1.62 (0.54–3.26)	
Hu J, 2002, Canada	Population-based case–control	Female nonsmokers histological	1994–1997	161/483	⩽1 cups per week	1.00		Age, province, education and social class
					2–7 cups per week	0.90 (0.50–1.60)		
					8-17.5 cups per week	0.90 (0.50–1.60)		
					⩾17.5 cups per week	0.80 (0.40–1.80)		
Nyberg F, 1998, Sweden	Population-based case–control	Nonsmokers histological	1989–1995	124/235	Less than daily	1.00		Age, gender, catchment area, smoking, residence, exposure to risk occupations, ever-exposure status, environmental tobacco smoke, carrot, fruits
					Daily	0.57 (0.27–1.22)		
					⩾3 cups per day	0.50 (0.24–1.06)		
Bae JM, 2013, Korea	Prospective cohort	Male smokers	1993–2008	93/7009	Nondrinkers	1.00		None
					1–6 times per week	1.27 (0.49–3.41)		
					⩾7 times per week	1.89 (0.94–4.30)		
						Men	Women	
Khan MMH, 2004, Japan	Prospective cohort		1984–2002	51/3158	Nondrinkers	1.00	1.00	Age and smoking
					Drinkers	0.70 (0.40–1.40)	2.10 (0.50–8.00)	
						Men	Women	
Fu 1997, Japan	Prospective cohort		1985–1995	161/24489	Nondrinkers	1.00	1.00	Smoking, tea, vegetables, fruits, alcohol
					Drinkers	2.02 (1.34–3.05)	0.92 (0.44–1.93)	
Stensvold I, 1994, Norway	Prospective cohort	Histological	1977–1990	125/42973	⩽4 cups per day	1.00		Age, sex, cigarettes per day, county of residence
					5–6 cups per day	1.54 (0.87–2.72)		
					⩾7 cups per day	2.29 (1.38–3.80)		
Nomura A, 1986, Japanese in Hawaiian	Prospective cohort	Male	1965–1983	110/7355	0 cup per day	1.00		Age, smoking
					1–2 cups per day	1.05 (0.60–2.59)		
					3–4 cups per day	1.05 (0.65–2.90)		
					⩾5 cups per day	1.44 (1.15–4.63)		

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk; SCSCCs, squamous cell and small cell carcinomas. 1 cup-year means drinking one cup of coffee per day for 1 year.

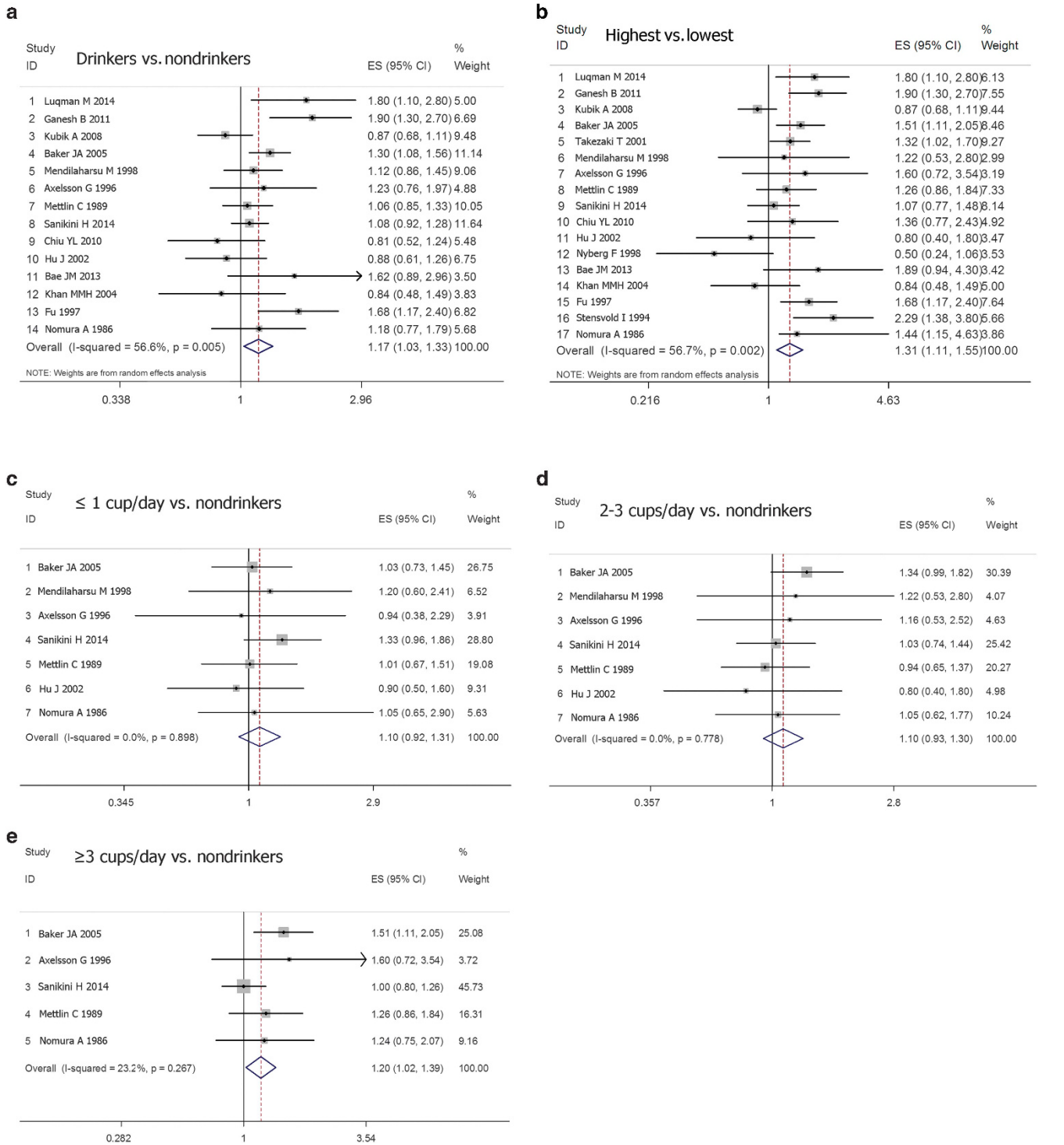

Figure 2. Forest plots of investigating association for various categories of coffee consumption with lung cancer risk. (**a**) Coffee drinkers versus nondrinkers. Coffee consumption < 2 times per week or $\leqslant 1$ cups per week was also defined as nondrinkers. (**b**) The highest level of coffee consumption in each included study versus the lowest level of intake. We also estimated ORs for different contrasts for coffee consumption. (**c**) Less than or equal to 1 cups per day coffee consumption versus nondrinkers. (**d**) Two to 3 cups per day coffee consumption versus nondrinkers. (**e**) More than or equal to 3 cups per day coffee consumption versus nondrinkers.

a positive association was observed in smokers (OR = 1.24, 95% CI: 1.00–1.54) but not in nonsmokers (OR = 0.85, 95% CI: 0.64–1.11). Last, when the various studies were stratified by publication time, a positive association between coffee intake and lung cancer risk was shown among the studies published before 2000 (OR = 1.45, 95% CI: 1.19–1.76) and after 2010 (OR = 1.47, 95% CI: 1.21–1.79), but not in those published in the period from 2000 to 2009 (OR = 1.09, 95% CI: 0.84–1.43). In particular, the studies published over the last 5 years consistently revealed that the risk of lung cancer was significantly increased by 47% in the population with the highest category intake of coffee versus the lowest category.

Table 2. Summary risk estimates for coffee intake (highest versus lowest) and lung cancer risk.

Study	*No.of studies*	*RR (95% CI)*	*Heterogeneity test*	
			P	I^2(%)
Design				
Hospital-based case–control	8	1.36 (1.10–1.69)	0.014	60.1
Population-based case–control	4	0.99 (0.77–1.28)	0.176	39.4
Prospective cohort	5	1.59 (1.26–2.00)	0.124	44.7
Gender				
Men	10	1.41 (1.21–1.63)	0.108	37.6
Women	8	1.16 (0.86–1.56)	0.046	51.0
Population				
American	5	1.34 (1.08–1.65)	0.630	0.0
European	5	1.12 (0.74–1.67)	0.003	75.4
Asian	7	1.49 (1.28–1.74)	0.236	25.3
Smoking				
Smokers	4	1.24 (1.00–1.54)	0.086	54.6
Nonsmokers	4	0.85 (0.64–1.11)	0.264	24.6
Publication time				
2010–2014	5	1.47 (1.21–1.79)	0.151	40.6
2000–2009	5	1.09 (0.84–1.43)	0.026	63.9
Before 2000	7	1.45 (1.19–1.76)	0.053	51.7

Abbreviations: CI, confidence interval; RR, relative risk.

Sensitivity analysis

Statistical heterogeneities existed across studies in the overall pooled estimate. We performed sensitivity analysis to evaluate the stability of the results, in which individual studies were sequentially dropped. The analysis excluded any single study in turn and pooled the OR of the remaining included studies. The overall summary OR did not substantially change, with a range from 1.14 (95% CI: 1.01–1.30) to 1.21 (95% CI: 1.06–1.37) for coffee drinkers compared with nondrinkers, and 1.27 (95% CI: 1.08–1.50) to 1.38 (95% CI: 1.18–1.61) for the highest category compared with the lowest. To exclude the residual confounding by smoking, we also omitted three studies with no adjustment for smoking and pooled the OR of the remaining included studies. The ORs were reduced but did not apparently change, which were 1.15 (95% CI: 1.01–1.32) for coffee drinkers versus nondrinkers and 1.29 (95% CI: 1.08–1.54) for the highest category versus the lowest category.

Publication bias

We performed Begg's funnel plots and Egger's tests to assess the publication bias in the included studies. As shown in Figure 3, the shape of the funnel plot did not reveal any evidence of obvious asymmetry. Egger's test, which provides statistical evidence of the funnel plot symmetry, indicated little evidence of publication bias. Therefore, no significant publication bias was observed in these studies.

DISCUSSION

Cigarette smoking has been well established as a major risk factor in the carcinogenesis and progression of lung cancer. In addition to smoking, some other potential risk factors also have been considered, including occupational and non-occupational pollutants. The major occupational exposures occur in workers

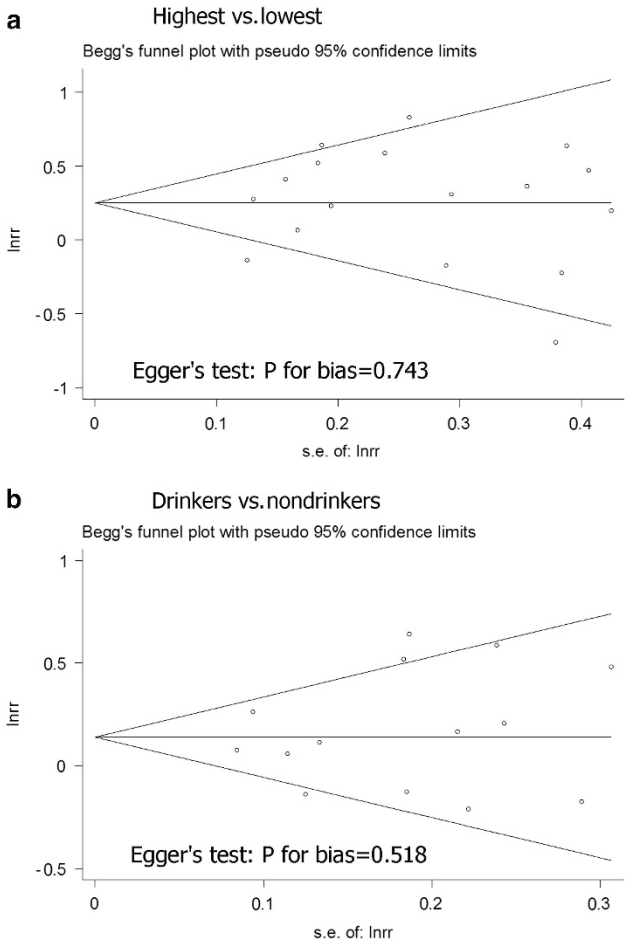

Figure 3. Funnel plot of coffee consumption and the risk of lung cancer.

who are engaged in the smelting and refining of metals or in the production of pesticides, pigments, dyes, glass, semi-conductors, wood/cotton products and various pharmaceutical substances.[31–33] Non-occupational exposures mainly include outdoor and indoor air pollution, arsenic and chlorinated by-products in drinking water, asbestos, dioxins and electromagnetic fields.[34–36] Some dietary components may also exert significant effects on the carcinogenesis and development of lung cancer. The identification of these modifiable risk factors in the diet is important for cancer prevention.

Coffee is a popular beverage worldwide, and its potentially unhealthy and beneficial bioactivities have been extensively investigated in epidemiological and experimental studies. However, the role of coffee consumption in the development of various types of cancer remains unclear. A previous meta-analysis conducted in 2010 indicated a significant positive association between the highest coffee intake category and lung cancer (OR = 1.27, 95% CI: 1.04–1.54),[37] but substantial heterogeneities and controversy existed across the studies included in the analysis. Importantly, the previous study only included 13 studies involving 5347 lung cancer cases. In fact, the association between lung cancer with coffee consumption, either the data were too inconsistent or the number of studies and cases were too few to allow conclusions to be reached.[30] Thus, in recent years, several population-based studies were conducted to further examine the association between coffee consumption and lung cancer risk. Notably, a large French population-based case–control study, the ICARE study (investigation of occupational and environmental causes of respiratory cancers), including a total of 5926

lung cancer cases, suggested that coffee consumption is not associated to the risk of lung cancer. Therefore, it is necessary and important to provide an updated meta-analysis and derive a more precise estimation. The present study included 17 studies involving 12 276 cases, which was more than twice the number of cases in the previous meta-analysis. Although the large French study recently showed that coffee consumption is not associated to the risk of lung cancer (OR = 1.11, 95% CI: 0.72–1.72; for $\geqslant 5$ cups per day versus never). The present meta-analysis still indicated that an increase in coffee consumption was associated with an increased risk of lung cancer, and that consumption of more than three cups of coffee per day might significantly increase lung cancer risk. Furthermore, the positive association between coffee consumption and lung cancer is particularly notable and consistent in prospective cohort studies. In case–control studies, it is difficult to ascertain the 'typical' coffee consumption patterns among the cases, who likely changed their habits near the time of their diagnosis, which would contribute to differential recall bias. Therefore, data from prospective cohort studies should exhibit more reliability and consistency. Given this, more carefully designed cohort studies would be performed to assess the association of coffee consumption with lung cancer.

Although the present study indicated the association of coffee intake with an increased risk of lung cancer, it should be noted that several recently updated meta-analysis have reported that coffee consumption is associated with a reduction in the risk of various types of cancers, including prostate cancer, bladder cancer, colorectal cancer and liver cancer.[38–41] A recent meta-analysis showed that coffee consumption was not statistically significantly associated with total cancer mortality.[42] Certainly, residual confounding by smoking is always a great concern in studies of lung cancer. The association between coffee consumption and lung cancer risk is strongly confounded by smoking. Because the residual confounding influences of smoking or other risk factors may still exist, the result of the present study should be interpreted with caution.

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