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Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies

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OBJECTIVE

To evaluate the association between coffee consumption and the risk of prostate cancer.

METHODS

We searched PubMed, EMBASE, and the bibliographies of relevant articles in August 2009. Two evaluators independently reviewed and selected articles based on predetermined selection criteria.

RESULTS

Twelve epidemiological studies (eight case-control studies and four cohort studies) were included in the final analysis. In a meta-analysis of all included studies, when compared with the lowest level of coffee consumption, the overall relative risk (RR) of prostate cancer for the highest level of coffee consumption was 1.16 (95% confidence interval [CI] 1.01–1.33). In subgroup meta-analyses by study design, there was a significant positive (harmful) association between coffee consumption and prostate cancer risk in seven case-control studies using both crude and adjusted data (RR 1.20, 95% CI 1.02–1.40; and RR 1.21, 95% CI 1.03–1.43, respectively), whereas there was no significant association in four cohort studies using crude or adjusted data (RR 0.97, 95% CI 0.68–1.38; and RR 1.06, 95% CI 0.83–1.35, respectively).

CONCLUSION

Given that a cohort study gives a higher level of evidence than a case-control study, there is no evidence to support a harmful effect of coffee consumption on prostate cancer risk. Further prospective cohort studies are required.

KEYWORDS

coffee consumption, prostate cancer, meta-analysis, epidemiological studies

INTRODUCTION

Prostate cancer is recognised as one of the major cancer that affects the male population worldwide. According to the National Center for Health Statistics (NCHS), prostate cancer is the most common cancer in incidence and the second most common cause of cancer death among men in the USA. Prostate cancer accounts for ≈25% of all new cancer cases and 9% of all cancer deaths among men in the USA [1].

Well-established risk factors for prostate cancer include increasing age, race/ethnicity (African-American or Jamaican), and a positive family history [1]. Additional factors, such as height, physical activity, body mass index, hormones, and diet, are thought to be associated with prostate cancer risk [2,3].

Coffee has been one of the most widely consumed beverages in the world since the 16th century and is known to be a major source of dietary antioxidants in some countries [4]. Coffee is the primary source of dietary caffeine in adults, and its various constituents have potential genotoxic, mutagenic, and anti-mutagenic activities [5]. Some animal studies have reported that coffee stimulates and suppresses tumours, depending upon the species and the phase of administration [6].

Also, in epidemiological studies, such as case-control and cohort studies, the possible relationship between coffee consumption and prostate cancer risk has been investigated since the 1960s, and the findings are inconsistent. Two case-control studies have reported that a higher consumption of coffee significantly increased the risk of prostate cancer [7,8], whereas four case-control studies showed a non-significant positive association [9–12], and two case-control studies showed a non-significant negative association between coffee consumption and prostate cancer [13,14]. In contrast, six prospective cohort studies have consistently reported that there is no significant association between coffee consumption and prostate cancer risk [15–20]. However, no meta-analysis has been published regarding the relationship between coffee consumption and prostate cancer risk.

The purpose of the present study was to estimate the quantitative association between coffee consumption and prostate cancer risk by using a meta-analysis of case-control and cohort studies. We also performed subgroup meta-analyses based on the type of study design (case-control or cohort study), type of case-control study (hospital- or population-based study), type of methodological quality (high- or low-quality), and geographical region of the study.

METHODS

We searched PubMed and EMBASE from 1966 to August 2009 using common keywords

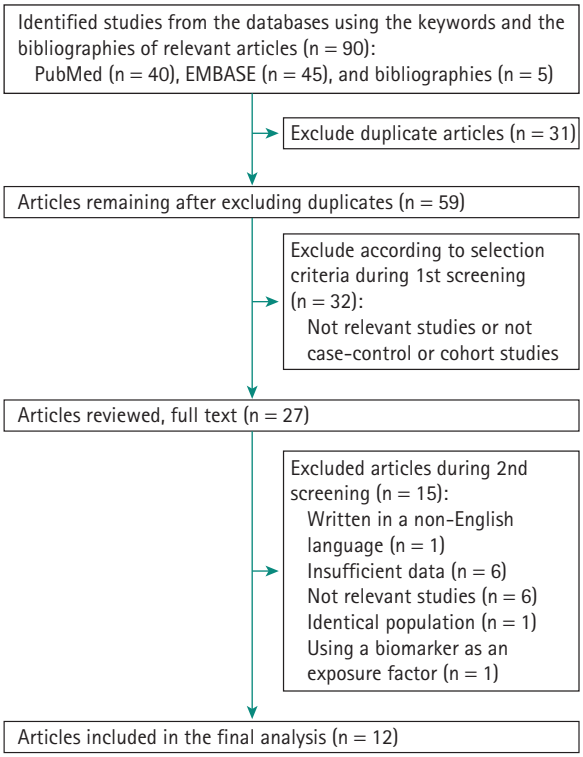


FIG. 1.
Flow diagram of identification of relevant studies.

regarding coffee consumption and prostate cancer risk in case-control and cohort studies. Also, manual searches on the bibliographies of relevant articles were performed to identify additional studies. For the literature search, we selected 'coffee' for the exposure factor and 'prostate cancer', 'prostate carcinoma', and 'prostate neoplasm' for the outcome factors.

We included case-control and cohort studies reporting an association between coffee consumption and prostate cancer risk (*n.b.*, no randomized controlled trials have been reported). We selected articles written in English and excluded those studies with no data available.

All searches were conducted independently by two evaluators (C.-H.P. and S.-K.M.), each of whom is a co-author of the present study. Disagreements between evaluators about selected studies were resolved by discussion. In instances in which data were insufficient or missing, we attempted to contact the authors of the articles to request the relevant data. Of the articles searched from the two databases, those that did not meet selection criteria were excluded.

The following data were extracted from the studies included in the final analysis: study name (first author and year of publication), country and study design, study period (years), number of cases and controls, adjusted odds ratio (OR) or relative risk (RR) with 95% CI, level of coffee consumption, and adjustment factors.

The methodological quality of eligible case-control and cohort studies in meta-analyses was assessed by the Newcastle-Ottawa Scale (NOS) [21]. In the NOS, a star system (range, 0–9 stars) has been developed for the assessment. In the present study, we considered a case-control study awarded ≥6 stars and a cohort study awarded ≥8 stars to be a high-quality study because standard criteria have not been established. The mean values in the case-control and cohort studies were 5.8 and 7.3 stars, respectively.

We used adjusted ORs or RRs with 95% CIs for meta-analysis, whenever possible. We also performed subgroup meta-analyses by the type of study design (case-control or cohort study), type of case-control study (hospital- or population-based study), level of coffee consumption (lower, moderate, or highest), type of methodological quality (high or low), and geographical region of the study.

We estimated a pooled OR or RR with 95% CI based on fixed- and random-effects models. Heterogeneity was assessed using Higgins I^2, which measures the percentage of total variation across studies due to heterogeneity rather than chance [22]. I^2 is calculated as follows:

$$I^2 = 100\% \times (Q - \text{d.f.})/Q,$$

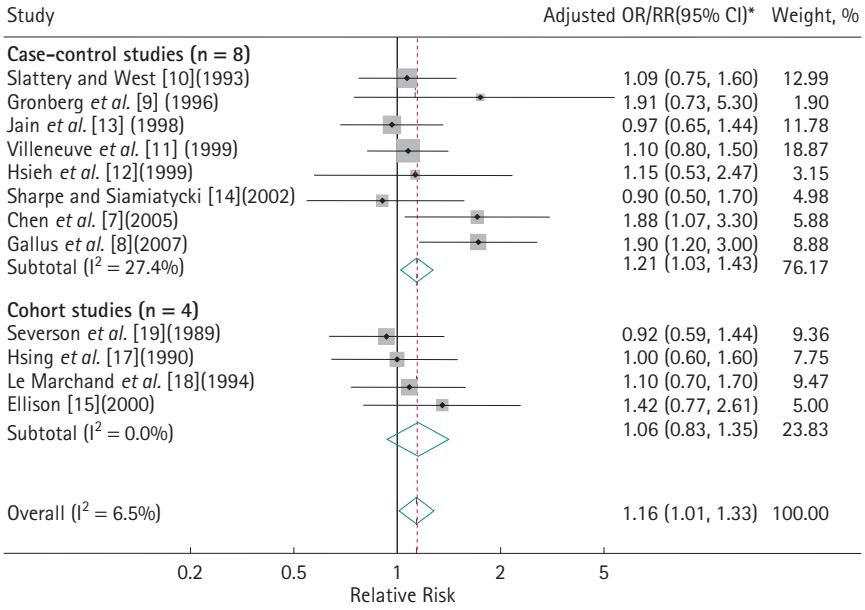
Where Q is Cochran's heterogeneity statistic, and d.f. is the degrees of freedom. Negative values of I^2 are set at zero so that I^2 lies between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). An I^2 value of >50% may be considered to represent substantial heterogeneity. We used the Mantel-Haenszel method for a fixed-effects model and the DerSimonian and Laird method for a random-effects model [23].

Begg's funnel plot and Egger's test were used to identify publication bias [24,25]. Funnel plots are scatter plots of the log ORs of individual studies on the *x*-axis against the 1/standard error (SE) (or SEs or sample size; a measure of precision) of each study on the *y*-axis. If there is no publication bias, the log ORs of small studies are scattered widely at the bottom of the graph, with the spread narrowing among large studies. Such a plot resembles a symmetric inverted funnel. In the presence of a publication bias, however, the plot will be asymmetric because some small studies showing no statistical significance tend to go unpublished. Egger's test is a test for a linear regression of a normalized effect estimate (log OR/SE) against its precision (1/SE). If the *P* value for Egger's test is <0.05, we assume that there is publication bias. All statistical analyses were conducted using Stata statistical software version 10.0. (College Station, TX, USA).

RESULTS

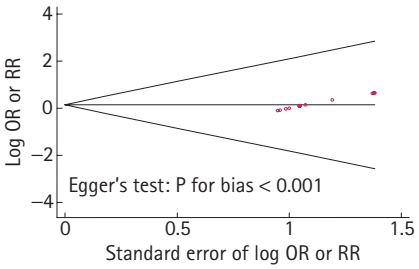
The present study included 12 epidemiological studies (eight case-control [7–14] and four cohort studies [15,17–19]) published between 1989 and 2007. Figure 1 is a flow diagram of the procedure used to identify the relevant studies. Searches of the two databases and the bibliographies of relevant articles yielded 90 articles. After excluding duplicates ($n = 31$), we reviewed 59 articles and excluded 32 articles in the first screening according to predetermined selection criteria described in the methods section. During the second

FIG. 2. Coffee consumption and prostate cancer risk by the type of study design in a meta-analysis of epidemiological studies (n = 12).



* CI, confidence interval. Fixed-Effect Model.

FIG. 3. Begg's funnel plots and Egger's test for identifying publication bias in a meta-analysis of epidemiological studies (n = 12).



screening, we reviewed the full text of the remaining 27 articles and included 12 studies in the final analysis. During the final selection process, we excluded 15 studies for the following reasons: written in a language other than English (one) [26], insufficient data (six) [16,20,27–30], studies not relevant (six) [31–36], identical populations (one) [37], and use of a biomarker as an exposure factor (one) [38]. For the identical population studies, we selected a recent study [19].

The general characteristics of the 12 studies included in the final analysis are presented in Table 1 [7–15,17–19]. Of the eight case-control studies, three were conducted in Canada, and the remaining five were conducted in the USA, Sweden, Italy, Greece, and Taiwan. Of the four cohort studies, three were conducted in the USA, and one was conducted in Canada. Three of the four cohort studies were published between the late 1980s and the 1990s, while five of the eight case-control studies were published between the late 1990s and 2000s. The study periods of the cohort studies ranged from 5 to 23 years.

Figure 2 [7–15,17–19] shows the association between coffee consumption and prostate cancer risk by using a meta-analysis of all 12 studies. Compared with the lowest consumption of coffee, the pooled RR of the highest coffee consumption and prostate cancer risk was 1.16 (95% CI 1.00–1.33) in a fixed-effects model. There was no significant heterogeneity across studies in the analyses (I^2 6.5%). In funnel plots, publication bias existed: an inverted asymmetric funnel plot was shown, and the *P* value was <0.001 based on the Egger's test (Fig. 3).

Figure 2 [7–15,17–19] also shows the results from the subgroup meta-analysis by type of study design. In case-control studies, there was a significant positive (i.e. harmful) relationship between coffee consumption and prostate cancer risk (RR 1.21, 95% CI 1.03–1.43, I^2 27.4%). Further, in subgroup meta-analyses by type of case-control study, a significant positive association existed in hospital-based case-control studies (RR 1.61, 95% CI 1.20–2.15, I^2 0%), whereas no association existed in population-based case-control studies (RR 1.05, 95% CI 0.86–1.28, I^2 11.9%; Table 2). In cohort studies, there was no significant association (RR 1.06, 95% CI 0.83–1.35, I^2 0%; Fig. 2).

In subgroup meta-analyses by geographical region of study, there was a positive association between coffee consumption and prostate cancer risk in the studies conducted in Europe and Taiwan; the pooled RRs were 1.70 (95% CI 1.18–2.45, I^2 0%) and 1.88 (95% CI 1.07–3.30), respectively. On the contrary, there was no significant association in the studies conducted in the USA and Canada (Table 2).

Table 3 [7–15,17–19] shows the methodological quality of studies included in the final analysis. The range of quality scores was 5–8; the average score was 5.8 in case-control studies and 7.3 in cohort studies. In case-control studies, there was no significant association in the six high- (RR 1.17, 95% CI 0.94–1.46, I^2 42.4%) or the four low-quality studies (RR 1.25, 95% CI 0.98–1.60, I^2 38.3%) when categorizing those studies with a threshold of 5. Similarly, there was no significant association in the two high- (RR 1.01, 95% CI 0.74–1.38, I^2 0%) or the two low-quality studies (RR 1.15, 95% CI 0.78–1.68, I^2 0%) among the cohort studies (a threshold of 7).

DISCUSSION

The findings of the present study indicate that there was no significant association between coffee consumption and prostate cancer risk from the meta-analysis of cohort studies, although coffee consumption increased the risk of prostate cancer in the meta-analysis of case-control studies. In subgroup meta-analyses by type of case-control study, there was an increased risk of prostate cancer in hospital-based case-control studies, but not in population-based control studies. Although there was a positive association in three case-control studies from Europe, two were hospital-based case-control studies.

We do not have a clear explanation for the discrepancy in findings between case-control and cohort studies. One of the possible

TABLE 1 Characteristics of the studies included in the final analysis (n = 12)

Reference (year)	Country, design	Follow-up period	No. of cases	No. of controls or size of cohort, n	Adjusted OR or RR (95% CI)	Coffee consumption ('low' vs 'high')	Adjustment
Case–control studies (*n* = 8)							
Slattery and West [10] (1993)	USA, P-B	1983–86	362	685	0.99 (0.68–1.47) 1.09 (0.75–1.60)	1–20 cups/week vs none >20 cups/week vs none	Age
Gronberg *et al.* [9] (1996)	Sweden, P-B	1959–89	406	1 218	1.77 (0.65–5.09) 1.99 (0.78–5.46) 1.91 (0.73–5.30)	1–2 cups/day vs none 3–5 cups/day vs none 6–9 cups/day vs none	Specific food items, smoking habits, and alcohol consumption
Jain *et al.* [13] (1998)	Canada, P-B	ON: 1990–92 QC: 1989–93 BC: 1989–91	617	637	All centres: 0.84 (0.58–1.22) 0.97 (0.65–1.44) BC: 1.00 (0.48–2.09) 1.40 (0.66–2.98) ON: 0.53 (0.28–0.98) 0.57 (0.30–1.11) QC: 1.16 (0.63–2.12) 1.15 (0.58–2.28)	0–500 g/day vs none >500 g/day vs none	Age and total energy intake
Villeneuve *et al.* [11] (1999)	Canada, P-B	1994–97	1623	1 623	0.8 (0.6–1.1) 1.0 (0.7–1.3) 1.1 (0.8–1.5)	<1 cup/day vs none 1–3 cups/day vs none ≥4 cups/day vs none	Age, province of residence, race, years since quitting smoking, cigarette pack-years, grains and cereals, alcohol, fruit and fruit juices, tofu, meat, income, and family history of cancer
Hsieh *et al.* [12] (1999)	Greece, H-B	1994–97	246	320	1.15 (0.53–2.47)	≥3 cups/day vs none	Age, height, BMI, and years of schooling.
Sharpe and Siemiatycki [14] (2002)	Canada, P-B	1979–85	399	476	1.1 (0.6–1.9) 1.1 (0.6–1.9) 0.9 (0.5–1.7)	1–2 drank/day vs none 3–4 drank/day vs none ≥5 drank/day vs none	Age, ethnicity, respondent status, family income, BMI, cumulative cigarette smoking, and cumulative alcohol consumption.
Chen *et al.* [7] (2005)	Taiwan, H-B	1996–98	237	481	1.88 (1.07–3.30)	Drinkers vs non-drinkers	Age and BMI.
Gallus *et al.* [8] (2007)	Italy H-B	1991–2002	219	431	1.9 (1.2–3.0)	3rd vs 1st tertile	Age, study entry, education, occupational physical activity at 30–39, BMI, and family history, and total energy intake.
Cohort studies (*n* = 4)							
Hsing *et al.* [17] (1990)	USA	1966–86	149	17 633	0.8 (0.6–1.2) 1.0 (0.6–1.6)	3–4 vs <3 cups/day ≥5 vs <3 cups/day	Age
Ellison [15] (2000)	Canada	1969–93	145	3 400	1.14 (0.66–1.97) 1.42 (0.80–2.52) 1.35 (0.75–2.43) 1.42 (0.77–2.61)	>0–250 mL/day vs none >250–500 mL/day vs none >500–750 mL/day vs none >750 mL/day vs none	5-year age group and wine consumption
Severson *et al.* [19] (1989)	USA	1965–86	174	7 999	0.96 (0.39–2.37) 0.92 (0.59–1.44)	2–4 vs ≤1 cup/week ≥5 vs ≤1 cup/week	Age
Le Marchand *et al.* [18] (1994)	USA	1975–80	198	20 316	1Q; 1.0 2Q; 0.9 (0.6–1.4) 3Q; 1.2 (0.8–1.8) 4Q; 1.1 (0.7–1.7)	2Q and 3Q ranges for the variables were as follows; coffee 0–2.5 cups/day	Age, ethnicity, and income

P-B, population-based; H-B, hospital-based; BC, British Columbia; ON, Ontario; QC, Quebec; BMI, body mass index.

reasons for the discrepancy between the two types of studies, however, would be potential biases of case-control studies, such as selection bias and recall bias. As for selection bias, only one-half of 10 case-controls studies included in the final analysis showed there was no significant difference in response rate for the case and control groups in each study. That is, the remaining five studies had a large difference in response rate between the case and control groups, indicating that some subjects in the target population were less likely to be included than others, resulting in selection bias. Given that coffee is generally considered not to be good for health, patients with prostate cancer might recall their past coffee consumption habits differently from healthy controls and might tend to overestimate the past coffee consumption at the time of the interview. Healthy controls tend to underestimate their past coffee consumption. This recall bias also could affect the findings toward a positive association between coffee consumption and prostate cancer risk.

*TABLE 2 Subgroup analyses by the type of case-control study, geographical region of study, and methodological quality of studies**

Variable	No. of studies	No. of cases	Adjusted OR or RR (95% CI)	Heterogeneity, I^2 (%)
Type of case-control study:				
Hospital-based	4	1005	1.61 (1.20–2.15)	0.0
Population-based	6	3178	1.05 (0.86–1.28)	11.9
Geographic region of study:				
USA	4	883	1.03 (0.83–1.28)	0.0
Canada	4	2784	1.07 (0.86–1.32)	0.0
Europe	3	945	1.70 (1.18–2.45)	0.0
Taiwan	1	237	1.88 (1.07–3.30)	
Methodological quality of study:				
Case-control study:				
High quality	6	2883	1.17 (0.94–1.46)	42.4
Low quality	4	1300	1.25 (0.98–1.60)	38.3
Cohort study:				
High quality	2	372	1.01 (0.74–1.38)	0.0
Low quality	2	294	1.15 (0.78–1.68)	0.0

**All the subgroup meta-analyses were performed based on a fixed-effects model.*

We also found that there was a distinct difference in findings between hospital- and population-based case-control studies. In general, both hospital- and population-based case-control studies have biases, such as selection and recall bias. However, we consider population-based control studies as more reliable because the cases and controls of population-based case-control studies are more representative than those of hospital-based case-control studies.

Regarding the differences in findings by the geographical region of the study, it could be considered that those differences may be attributable to the underlying risks of prostate cancer in each population, national differences in the typical amount of coffee consumed, the type of coffee beans [39–41] or roasting procedure [42,43], and the brewing method [33–35]. However, the main reason why the studies from Europe and Taiwan showed a positive association between coffee consumption and prostate cancer risk is thought to be the type of studies, that is, two of three studies from Europe and one study from Taiwan were hospital-based case-control studies.

In an overall meta-analysis of case-control and cohort studies, there was publication bias. Based on the funnel plot, studies having a negative or null association between coffee consumption and prostate cancer risk were not included (or published) in our meta-analysis. Thus, this publication bias might cause the overall overestimated positive association between coffee consumption and prostate cancer.

Some experimental studies have reported the biological effects of coffee constituents on cancer risk. Coffee contains a large number of compounds, such as caffeine [37], diterpenes (cafestol and kahweol) [38], and chlorogenic acid [44]. The previous *in vivo* animal models and *in vitro* cell culture studies have suggested that those compounds could potentially alter cancer risk through several biological mechanisms. Among those compounds, caffeine is a major component in coffee, and some animal studies have reported that caffeine stimulates and suppresses tumours, according to the species and the phase of administration [6]. For example, caffeine inhibits DNA methylation (hypermethylation of DNA is a common characteristic in tumour cells) in cultured MCF-7 and MAD-MB-231 human cancer cells [45]. In addition, coffee contains two specific diterpenes (cafestol and kahweal) that produce biological effects compatible with anti-carcinogenic properties, including the induction of phase II enzymes involved in carcinogen detoxification [38,39], specific inhibition of the activity of phase I enzyme responsible for carcinogen activation, and stimulation of intracellular antioxidant defence mechanisms [40]. Coffee is also a major source of chlorogenic acid, which contributes to its antioxidant effect [41]. Intake of chlorogenic acid has been shown to reduce glucose concentrations in rats and intake of quinides, which are degradation products of chlorogenic acid, increases insulin sensitivity [42]. Chronic hyperinsulinaemia and insulin resistance are confirmed markers of high risk for some cancer sites [43]. Therefore, coffee may possess both carcinogenic and anti-carcinogenic properties.

There are potential limitations in the present study as follows. First, the exclusion of non-English language articles might distort the findings. However, there have been few studies on this topic written in other languages other than English; therefore this exclusion criterion would not have substantially altered our results. Second, there are no standardized assessments or measurements for the amounts of coffee consumption. In the included studies, coffee consumption was mostly assessed as cups per day or weekly. However, there were differences in the brewing method and container size for coffee in each study.

TABLE 3 Methodological quality of the studies included in the final analysis, based on the NOS for assessing the quality of epidemiological studies (n = 14)

A. Case-control studies (n = 10)

Reference (year)	Selection Adequate definition of cases	Represent of cases	Selection of controls	Definition of controls	Comparability Control for import. factor or additional factor	Ascertain. of exposure (blinding)	Exposure Same method of ascertain. for subjects	Non-response rate*	Total score†
Slattery and West [10] (1993)	1	1	1	0	1	0	0	1	5
Gronberg *et al.* [9] (1996)	0	1	1	1	2	0	1	1	7
Jain *et al.*[13] (1998):									
Ontario	1	1	1	0	2	0	1	0	6
Quebec	1	1	1	0	2	0	1	0	6
British Columbia	1	1	1	0	2	0	1	1	7
Villeneuve *et al.* [11] (1999)	1	0	1	0	2	0	1	1	6
Hsieh *et al.* [12] (1999)	1	0	0	1	2	0	1	0	5
Sharpe and Siemiatycki [14] (2002)	1	0	1	1	2	0	0	0	5
Chen *et al.* [7] (2005)	1	0	0	1	2	0	1	1	6
Gallus *et al.* [8] (2007)	1	0	0	1	2	0	1	0	5

B. Cohort studies (n = 4)

Reference (year)	Selection Repres. of the exposed cohort	Selection of non-exposed cohort	Ascert. of exposure	Comparability Demonstrat. that outcome of interest was not present at start	Comparability of cohorts based on design/analysis	Assess. of outcome	Exposure Follow-up long enough for outcomes to occur	Adequacy of follow-up	Total score‡
Hsing *et al.* [17] (1990)	1	1	0	0	2	1	1	0	6
Ellison [15] (2000)	1	1	0	0	2	1	1	1	7
Severson *et al.* [19] (1989)	1	1	1	1	1	1	1	0	8
Le Marchand *et al.* [18] (1994)	1	1	1	1	2	1	1	0	8

**When there was no significant difference in the response rate between both groups by using the chi-squared test (P < 0.05), 1 point was awarded. †Total score could range from 0 to 9 points. Represent., Representativeness; Ascertain., Ascertainment. ‡Total score could range from 0 to 9 points. Represent., Representativeness; Ascertain., Ascertainment; Demonstrat., Demonstration; Assess., Assessment.*

In conclusion, our meta-analysis indicates that there is no association between coffee consumption and prostate cancer based on the findings of cohort studies, which generally give a higher level of evidence than case-control studies. The present findings should be evaluated from further additional prospective cohort studies.

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S.-K.M. was responsible for the initial plan, study design, and statistical analysis and for conducting the study. C.-H.P. and S.-K.M. contributed to data collection, data extraction, data interpretation, and manuscript drafting. T.-Y.K., H.-G.S., Y.-J.J. and Y.K. contributed to data interpretation and manuscript drafting. S.-K.M. was the guarantor for this paper and has full responsibility for this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Abbreviations: **RR**, relative risk; **OR**, odds ratio; **NOS**, Newcastle-Ottawa Scale.