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

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Observational studies and animal evidence suggest an association between coffee consumption and the risk of prostate cancer. However, the results are inconsistent. We evaluated the association by conducting a meta-analysis of prospective cohort studies. PubMed and Embase were searched through June 2013 to identify studies that met predetermined inclusion criteria. A random-effects model was used to calculate the pooled risk estimates. Ten prospective cohort studies involving 8973 patients with prostate cancer and 206096 participants were included in this systematic review. Compared with individuals who seldom or never drink coffee, the pooled relative risk of prostate cancer was 0.88 (95% confidence interval: 0.82–0.95) for regular coffee drinkers. Exclusion of any single study did not materially alter the combined risk estimate. Visual inspection of a funnel plot and Beggs’s and Egger’s tests did not indicate evidence of publication bias. In summary, integrated evidence from prospective cohort studies supports the hypothesis that coffee consumption may decrease the risk of prostate cancer.

Introduction

Prostate cancer is one of the most common cancers that affect male health worldwide, especially in developed countries. Well-established risk factors for prostate cancer include age, ethnicity and family history (1). Other factors, such as physical activity, body mass index (2), hormones and diet, are also thought to be associated with prostate cancer. Coffee is one of the most widely consumed beverages in the world, and animal studies indicate that coffee can both stimulate and suppress tumors, depending on the animal species (3).

Although there have been some population-based observational epidemiological studies on the relationship between coffee consumption and prostate cancer since the 1960s, the findings have been inconsistent. In 2010, a meta-analysis of epidemiological studies (4) was conducted to evaluate the association between coffee intake and prostate cancer. It concluded that evidence from case–control studies was different from that of cohort studies and suggested that further prospective cohort studies should be required. The literature searching of that systematic review was not comprehensive. It only included four cohort studies (one is retrospective and three are prospective), but three other eligible prospective cohort studies were missing (5–7). Moreover, several additional prospective studies have been reported since then (8–11). Given that coffee is consumed very commonly all over the world (12), an improved understanding of this issue should have important public health and clinical implications.

Taking into consideration of the inconsistent conclusions of existing epidemiological studies and the higher level of evidence from prospective cohort studies, along with three missing studies in the previous meta-analysis and four additional recent literatures, we conducted an updated meta-analysis of 10 prospective cohort studies to evaluate the association between coffee consumption and the risk of prostate cancer.

Materials and methods

Ethical approval is not required for this review.

Study selection

We included studies which met the following criteria: (i) it had a prospective cohort study design, (ii) the exposure of interest was consumption of coffee, (iii) the endpoint of interest was incidence of prostate cancer, (iv) the relative risk (RR) and the corresponding 95% confidence interval (CI) of prostate cancer relating to the total or to all categories of coffee intake were reported or could be calculated from the data provided and (v) the frequency and dose of coffee consumption were provided. Studies were excluded if mixed beverages were reported in which the effect of coffee could not be desolated. If multiple published reports were from the same study cohort, we included only the one with the most detailed information for both coffee consumption and outcome.

Data extraction

The following information was extracted from the studies included in the final analysis by two investigators (S.C. and L.L.): first author, publication year, country, study period, number of cases, size of cohort, adjusted RR with 95% CI, level of coffee consumption and adjusted factors. Discrepancies were resolved by discussion with a third investigator (Z.L.).

Statistical analyses

We used RR to measure the association of interest. In any included study, when RRs were reported separately for subgroups by the different levels of coffee consumption, we combined the results of the subgroups and calculated a common RR for the main analysis using a fixed-effects model. The lowest level of coffee consumption was defined as ‘never or seldom drink coffee’, whereas other levels were identified as ‘regularly drink coffee’. We calculated an overall pooled RR using a random-effects model for the main analysis (14).

Heterogeneity was tested by Q statistic with a significance level at P < 0.10 and I² statistic (15). The I² statistic measures the percentage of total variation across studies due to heterogeneity rather than chance. It is calculated according to the following formula:

\[ I^2 = 100\% \times \frac{Q - df}{Q} \]

where Q is the heterogeneity statistic, and df is the degree of freedom. The negative value of I² is set at zero, and I² varies from 0% (no observed heterogeneity) to 100% (maximal heterogeneity). An I² value of ≥50% is considered to represent substantial heterogeneity.

Subgroup analyses were conducted to determine the possible influence of some factors such as publication years, countries, obesity and smoking. A sensitivity analysis was conducted to explore potential sources of heterogeneity and to investigate the influence of various exclusion criteria on the pooled risk estimate. Potential publication bias was assessed by both the Beggs’s rank correlation and the Egger’s linear regression tests (16,17). All analyses were conducted using STATA statistical software (version 12.0: College Station, TX). P < 0.05 was considered statistically significant, except where otherwise specified. All statistical tests were two sided.
Results

Literature search
The process of study identification and inclusion was shown in Figure 1. Initially, we retrieved 61 citations from the PubMed database and 89 citations from Embase. After 49 duplicates were excluded, 101 citations were screened through titles and abstracts, of which 88 were excluded mainly because they were case–control studies, cross-sectional studies, reviews or irrelevant studies. After full-text review of the remaining 11 articles, three articles (18–20) were excluded because one was a retrospective cohort study and the other two did not report RRs and the corresponding 95% CI of interest or provide sufficient data to calculate them. Finally, 10 studies (5–11,21–23) were included.

Characteristics of the included studies
The main characteristics of the 10 studies were summarized in Table I. These studies were published between 1986 and 2013. Of them, five were conducted in America, two in Norway and one each in England, Sweden and Japan. The sizes of the cohorts ranged from 6017 to 47,911 (total 206,096). Two studies were adjusted for age only, and the others controlled for a group of conventional risk factors for prostate cancer, including age, ethnicity, body mass index and so on.

Results of meta-analysis
Figure 2 showed the results from the random-effects model combining the risk estimates. Of the 10 studies, six showed a significantly inverse relationship between coffee consumption and the risk of prostate cancer, and four suggested no statistically significant association of interest. Overall, compared with individuals who seldom or never drink coffee, the pooled RR of prostate cancer was 0.88 (95% CI: 0.82–0.95) for regular coffee drinkers. No significant heterogeneity was observed ($P = 0.153, I^2 = 31.9\%$).

Results of subgroup analyses and sensitivity analyses
Subgroup analysis by countries (European countries versus USA versus Japan) and publication years (before 2000 versus after 2000) showed no statistically significant difference in results (Table II).

Given the possible influence of obesity and smoking on the association between coffee and prostate cancer risk, we also conducted subgroup analyses by whether they were controlled. In the results, whether body mass index was adjusted or not, the association did not change. But the pooled result from studies in which smoking was not adjusted showed no statistically significant risk of coffee drinking on prostate cancer (RR = 0.88, 95% CI: 0.74–1.04) (Table II). We excluded any single study in turn and pooled the results of the remaining included studies. The overall combined RR did not materially change, with a range from 0.89 (95% CI: 0.81–0.97) to 0.91 (95% CI: 0.83–0.99).

Publication bias
Visual inspection of a funnel plot failed to identify substantial asymmetry (Figure 3). The Begg’s rank correlation test and Egger’s linear regression test also indicated no evidence of publication bias among the studies (Begg’s test $Z = 0.54, P = 0.592$; Egger’s test $t = -1.67, P = 0.133$)

![Fig. 1. Flowchart of identification of relevant prospective cohort studies of coffee consumption in relation to prostate cancer.](https://academic.oup.com/carcin/article-abstract/35/2/256/2463094)
S. Cao et al.

Discination

Coffee is a widely consumed beverage around the world and previous studies have suggested that coffee intake may affect the etiology of cancer of various sites along multiple pathways, ranging from carcinogenesis to cellular apoptosis (24). Roasted coffee is a complex mixture of >1000 chemicals, in which many constituents could potentially alter cancer risk through several biological mechanisms. Firstly, caffeine has been reported to stimulate or suppress different tumors (3). Secondly, two specific diterpenes in coffee, cafestol and kahweol, produce biological effects compatible with anticarcinogenic properties, including specific inhibition of the activity of phase 1 enzyme responsible for carcinogen activation and stimulation of intracellular antioxidant defense mechanisms (25), and the induction of phase 2 enzymes involved in carcinogen detoxification (26). Thirdly, coffee is also a major source of the chlorogenic acid that contributes to its antioxidant effect. Intake of chlorogenic acid has been shown to reduce glucose concentrations in the chlorogenic acid that contributes to its antioxidant effect. Intake of chlorogenic acid that contributes to its antioxidant effect. Intake of chlorogenic acid that contributes to its antioxidant effect.

Table 1. Main characteristics of the included cohort studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Follow-up year</th>
<th>Number of cases</th>
<th>Size of cohort</th>
<th>RR</th>
<th>Coffee consumption</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discacciati</td>
<td>2013</td>
<td>Sweden</td>
<td>1998 to 2010</td>
<td>2368</td>
<td>44 613</td>
<td>0.93 (0.83–1.03)</td>
<td>4–5 cups/day versus 1–3 cups/day ≥6 cups/day versus 1–3 cups/day</td>
<td>Tea, alcohol, body mass index, personal history of diabetes, family history of prostate cancer, smoking status, physical activity, education and total energy intake</td>
</tr>
<tr>
<td>Hsing</td>
<td>1990</td>
<td>USA</td>
<td>1966 to 1986</td>
<td>149</td>
<td>17 633</td>
<td>0.8 (0.6–1.2)</td>
<td>3–4 cups/day versus &lt;3 cups/day ≥5 cups/day versus &lt;3 cups/day ≥7 cups/day versus ≤2 cups/day</td>
<td>Age</td>
</tr>
<tr>
<td>Jacobsen</td>
<td>1986</td>
<td>Norway</td>
<td>1968 to 1989</td>
<td>205</td>
<td>13 664</td>
<td>0.72 (0.55–0.90)</td>
<td>Age, residence and cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Le Marchand</td>
<td>1994</td>
<td>USA</td>
<td>1975 to 1980</td>
<td>198</td>
<td>20 316</td>
<td>1Q: 1.0 2Q: 0.9 (0.6–1.4) 3Q: 1.2 (0.8–1.8) 4Q: 1.1 (0.7–1.7)</td>
<td>2Q and 3Q ranges for the variables were as follows: coffee 0–2.5 cups/day</td>
<td>Age, ethnicity and income</td>
</tr>
<tr>
<td>Li</td>
<td>2013</td>
<td>Japan</td>
<td>1995 to 2005</td>
<td>318</td>
<td>18 853</td>
<td>0.81 (0.61–1.07)</td>
<td>Occasionally versus none</td>
<td></td>
</tr>
<tr>
<td>Nomura</td>
<td>1986</td>
<td>USA</td>
<td>1965 to 1983</td>
<td>108</td>
<td>7355</td>
<td>0.69 (0.44–0.94)</td>
<td>Age, year of smoking, smoking status at exam, past smoking status, number of cigarettes smoked per day</td>
<td></td>
</tr>
<tr>
<td>Severson</td>
<td>1989</td>
<td>USA</td>
<td>1965 to 1986</td>
<td>174</td>
<td>7999</td>
<td>0.96 (0.39–2.37)</td>
<td>2–4 cups/week versus ≤1 cups/week ≥5 cups/week versus ≤1 cups/week ≥1–2 cups/day versus none ≥3 cups/day versus none ≥1 cup/day versus &lt;1 cup/day</td>
<td>Age</td>
</tr>
<tr>
<td>Shafique</td>
<td>2012</td>
<td>UK</td>
<td>(1970–73) to 2007</td>
<td>380</td>
<td>6017</td>
<td>0.95 (0.72–1.24)</td>
<td>Age, cholesterol, systolic blood pressure, body mass index, alcohol intake, tea consumption, smoking status, social class</td>
<td></td>
</tr>
<tr>
<td>Stensvold</td>
<td>1994</td>
<td>Norway</td>
<td>(1977–82) to 1990</td>
<td>38</td>
<td>21 735</td>
<td>0.96 (0.81–1.13)</td>
<td>Age, cigarettes per day and county of residence</td>
<td></td>
</tr>
<tr>
<td>Wilson</td>
<td>2011</td>
<td>USA</td>
<td>1986 to 2006</td>
<td>5035</td>
<td>47 911</td>
<td>0.94 (0.85–1.05)</td>
<td>Race, height, body mass index at different ages, current body mass index, vigorous physical activity, smoking, diabetes, family history of prostate cancer in father or brother, multivitamin sue, intakes of processed meat, tomato sauce, calcium, alpha linolenic acid, supplemental vitamins, alcohol intake, energy intake and history of PSA testing</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Coffee is a widely consumed beverage around the world and previous studies have suggested that coffee intake may affect the etiology of cancer of various sites along multiple pathways, ranging from carcinogenesis to cellular apoptosis (24). Roasted coffee is a complex mixture of >1000 chemicals, in which many constituents could potentially alter cancer risk through several biological mechanisms. Firstly, caffeine has been reported to stimulate or suppress different tumors (3). Secondly, two specific diterpenes in coffee, cafestol and kahweol, produce biological effects compatible with anticarcinogenic properties, including specific inhibition of the activity of phase 1 enzyme responsible for carcinogen activation and stimulation of intracellular antioxidant defense mechanisms (25), and the induction of phase 2 enzymes involved in carcinogen detoxification (26). Thirdly, coffee is also a major source of the chlorogenic acid that contributes to its antioxidant effect. Intake of chlorogenic acid has been shown to reduce glucose concentrations in rats and intake of quinides, degradation products of chlorogenic acid, increases insulin sensitivity (27). In addition, many others components we do not list also can affect the incidence of cancer.

The association between coffee consumption and the risk of prostate cancer has been of increasing interest to the general public recently. Though the potential mechanisms that how coffee impacts prostate cancer risk have not been studied thoroughly, some epidemiological studies investigated the association between them. Our meta-analysis of 10 cohort studies involving 8973 patients with prostate cancer and 206 096 participants showed an inverse association between coffee consumption and prostate cancer. Compared with individuals who seldom or never drink coffee, regular coffee drinkers experienced a significantly decreased risk of 12% for prostate cancer. There was no evidence of substantial heterogeneity among studies on the association between coffee consumption and prostate cancer.

Our result was different from the result of a previous meta-analysis (4). The previous meta-analysis including case–control and cohort studies suggested there was no statistically significant association between coffee consumption and the risk of prostate cancer. Its
Coffee consumption and prostate cancer risk

Subgroup analysis showed a positive association in a case–control study subgroup and no statistically significant association in a cohort study subgroup (RR = 1.06; 95% CI: 0.83–1.35). The different results between our meta-analysis and the previous meta-analysis may be due to the different types and numbers of original studies included. A cohort study gives stronger evidence than a case–control study, and a retrospective cohort design may suffer more confounding factors and biases than a prospective one. In the previous meta-analysis, eight case–control and four cohort (one retrospective and three prospective) studies were included, whereas in our meta-analysis, we included prospective cohort studies only and the number increased to 10. There are three prospective cohort studies included both in our meta-analysis and the previous one, but we excluded a retrospective study that was included in the previous meta-analysis. In addition, we included seven additional studies, of which three were missing in the previous meta-analysis possibly because of incomprehensive literature searching, and four were reported after the previous meta-analysis.

Taking into consideration the potential differences in coffee bean roasting and brewing methods and prostate cancer risk profiles among men in the USA versus Europe, subgroup analysis by country was conducted but no significant difference was found. For diagnosis of prostate cancer, prostate-specific antigen (PSA) screening was mainly used in the 1980s and 1990s, whereas the widespread use of PSA testing emerged in the later years. Compared with PSA testing, PSA screening mainly identified serious patients with prostate cancer. Therefore, prostate cancers in the early studies were likely to be more lethal or advanced than those included in the latest papers. We conducted a subgroup analysis by publication years but found the pooled result of studies before 2000 was not significantly different from that after 2000. Subgroup analyses by adjusted variables such as obesity and smoking were also conducted to explore the possible influence of them on the association between coffee and prostate cancer risk. We found that the pooled result from studies in which smoking was not adjusted showed no statistically significant risk of coffee on prostate cancer (RR = 0.88, 95% CI: 0.74–1.04). The reduced number of included studies or the influence of smoking may be the reason.

All the studies included in this paper were conducted in affluent countries in Western Europe, North America or Japan, so the results should not be extended to developing countries. Of note, although our founding suggested that coffee should have a protective role in prostate cancer risk, prostate cancer incidence is still higher in the

Table II. Results of subgroup analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of studies</th>
<th>RR</th>
<th>95% CI</th>
<th>I²</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European countries</td>
<td>4</td>
<td>0.87</td>
<td>0.77–0.98</td>
<td>35.8%</td>
<td>0.197</td>
</tr>
<tr>
<td>USA</td>
<td>5</td>
<td>0.93</td>
<td>0.88–0.98</td>
<td>0.0%</td>
<td>0.442</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
<td>0.75</td>
<td>0.62–0.91</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Publication years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 2000</td>
<td>6</td>
<td>0.84</td>
<td>0.71–0.99</td>
<td>29.2%</td>
<td>0.216</td>
</tr>
<tr>
<td>After 2000</td>
<td>4</td>
<td>0.90</td>
<td>0.84–0.97</td>
<td>40.6%</td>
<td>0.168</td>
</tr>
<tr>
<td>Controlling for body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0.92</td>
<td>0.88–0.97</td>
<td>0.0%</td>
<td>0.635</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>0.82</td>
<td>0.72–0.93</td>
<td>25.9%</td>
<td>0.231</td>
</tr>
<tr>
<td>Controlling for smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>0.89</td>
<td>0.82–0.96</td>
<td>36.0%</td>
<td>0.167</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>0.88</td>
<td>0.74–1.04</td>
<td>38.2%</td>
<td>0.183</td>
</tr>
</tbody>
</table>

Fig. 2. Association between coffee consumption and the risk of prostate cancer in a meta-analysis of prospective cohort studies.
affluent American and European countries, where coffee drinking is very popular. The high incidence of prostate cancer in affluent countries should be partly attributable to obesity, bad dietary habit and so on. As is known to all, obesity and bad dietary habit are more common in developed countries than developing countries. Therefore, the protective role of coffee intake in prostate cancer risk should be unlikely to offset the increased risk of prostate cancer caused by these factors. Our subgroup analysis suggested that, whether body mass index was controlled or not, the association between coffee intake and prostate cancer risk did not changed. That is, even obese people with high risk of prostate cancer can benefit from coffee consumption.

There are several strengths in our study. Firstly, when several RRs were reported separately in terms of the different levels of coffee consumption for a single study, we combined the results of subgroups and calculated a common RR by a fixed-effects model. Therefore, we could pool the outcomes of the prostate cancer risk of regular coffee drinkers compared with those who seldom or never drink coffee. Secondly, consistent results from sensitivity analysis and the absence of heterogeneity among included studies indicated that our findings were reliable and robust. In addition, publication bias was unlikely to account for our findings, as identified by visual inspection of a funnel plot, the Begg’s rank correlation test and the Egger’s linear regression test.

Some limitations in the present meta-analysis should be of concern. Firstly, adjusted confounders varied among the included studies. Some possibly important residual confounders such as obesity, smoking, age and race were not adjusted in some studies. For instance, two cohort studies (21,23) only controlled for age. Secondly, due to the limited information provided by the included studies, a dose–response analysis was not performed to provide further evidence in support of an association between coffee consumption and the risk of prostate cancer. Thirdly, different data collection instruments for coffee consumption, such as diet habit questionnaire (5), dietary recall history (23) and food frequency questionnaire (21), were used in different studies. The veracity of these devices was different, and lack of unity in the type of them might contribute to heterogeneity among studies. There were also no standardized assessments or measurements for the amounts of coffee consumption. In the included studies, coffee consumption was mostly assessed by the number of cups per day or per week. However, there were differences in coffee bean roasting and brewing methods, and coffee cup size among the included studies.

Fourthly, since there was no sufficient pertinent information in the included studies, our study did not address the distinction between caffeinated and decaffeinated coffee.

In summary, our meta-analysis of prospective cohort studies with the most up-to-date evidence suggests that regular coffee consumption is associated with a significantly decreased risk of prostate cancer in developed countries. Coffee intake may have benefits on the prevention of prostate cancer.

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**References**


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