Coffee Consumption and Risk of Prostate Cancer in Local, Advanced, and Fatal Grades: A Meta-Epidemiological Study of Prospective Cohort Studies

Jong-Myon Bae

Department of Preventive Medicine, Jeju National University School of Medicine, Jeju, Korea

There were conflict reports among the previous systematic reviews conducted to evaluate the association between coffee consumption and risk of prostate cancer. This meta-epidemiological study aimed to evaluate the reasons for conflicting findings among previous studies and then estimate a more valid summary effect size of the association between coffee consumption and prostate cancer risk in grades and all cases. The selection criteria were defined that a prospective cohort study conducted to evaluate coffee consumption and risk of prostate cancer incidence with reporting adjusted relative risk (RR) and its 95% confidence interval (95% CI). Random effect model meta-analysis and 2-stage fixed-effect dose-response meta-analysis were performed by cancer grades. From a total of 12 prospective cohort studies were selected, 11 all, 4 local, 5 advanced, and 4 fatal cohorts were organized. There was an inverse association between coffee consumption and the risk of prostate cancer in all cases with statistical significance (summary RR, 0.91; 95% CI, 0.84−0.98; I-squared=49.1%). Dose-response meta-analysis showed that the unit's decreasing risk levels were 1.0 % in all cases, 1.1% in localized cases, and 2.5% in fatal cases, respectively. There is an inverse association between coffee consumption and risk of prostate cancer in local and fatal grades, not in advanced grade. And the main reasons for conflict results among the previous studies would be due to noncomprehensive searching strategies, the interdifferent definition of selection criteria, inaccurate extraction of information, and inadequate adjustment for potential confounders. (Korean J Urol Oncol 2021;19:16-22)

Key Words: Coffee · Prostate neoplasm · Systematic review · Meta-analysis

INTRODUCTION

Prostate cancer ranks 'the second most frequent cancer and the fifth leading cause of cancer death in men' in GLOBOCAN 2018.[1] While age and genetic factors are the well-known risk factors, some modifiable risk factors as westernized diet, obesity, and physical inactivity are positively associated with prostate cancer.[2] Since Stocks[3] reported the positive correlation between coffee consumption and prostate cancer mortality through an ecological study in 1970, several epidemiological studies have been conducted to investigate the association between coffee consumption and risk of prostate cancer.[4] And experimental studies have reported that several compounds of coffee could alter cancer risk through inhibiting DNA methylation, stimulating antioxidant defense mechanisms, or increasing

insulin sensitivity, etc.[5]

Table 1 shows the results of systematic reviews (SRs) conducted to investigate the hypothesis. With the exception of Park et al.,[5] which was performed for the first time, and Xia et al.,[6] which was performed last, the other 7 SRs of population-based cohort studies[7-13] were reported to significantly reduce the risk of prostate cancer in all cases from coffee consumption. In other words, statistical significance was continuously reported in the 7 SRs published in 2011–2016, but statistical significance disappeared in Xia et al.[6] published in 2017. Especially, the selected number of cohort studies in 2 recent SR[6,13] was the same, but the results were contrary. And I-squared value indicating heterogeneity level also varied from 30.3% to 64.8%.

Therefore, this meta-epidemiological study[14] aimed to evaluate the reasons for conflicting findings among SRs and then estimate a more valid summary effect size of the association between coffee consumption and prostate cancer risk in local, advanced, fatal grade, as well as all cases.

MATERIALS AND METHODS

To estimate more valid results, the stricter selection criteria were applied such as a prospective cohort study conducted to evaluate coffee consumption and risk of prostate cancer incidence with reporting adjusted relative risk (aRR) and its 95% confidence interval (CI). Thus, 10 of 16 studies selected by SRs in Table 1 were met the selection criteria.[15-24]

Considering that the most recent publication year among them was in 2015,[24] it was necessary to secure cohort studies that met the selection criteria among the papers published until the 10 October 2020. To do this, the 'cited by' option for 10 studies[15-24] and the 'similar articles' of Xia et al.[6] were applied using the citation discovery tool provided by PubMed.[25] If the selected articles were duplicated in cohort participants, the article reporting more information for meta-analysis was selected. Cohorts from final selected studies were arranged by cancer grades such as localized,

Table 1. Results of previous meta-analysis of population-based cohort studies

Study	Searching	Cancer grade	Selected cohort studies	sRR (95% CI)	I-squared (%)
Park et al.[5] (2010)	Aug 2009	All	4	1.06 (0.83–1.35)	0.0
Yu et al.[7] (2011)	Mar 2010	All	5	0.79 (0.61–0.98)	57.1
Lu et al.[8] (2014)	Jun 2013	All	9	0.89 (0.84–0.95)	8.0
		Localized		0.89 (0.83–0.96)	0.0
		Advanced		0.85 (0.58–1.12)	68.9
		Fatal		0.64 (0.47–0.80)	47.8
Cao et al.[9] (2014)	Jun 2013	All	10	0.88 (0.82–0.95)	31.9
Zhong et al.[10] (2014)	Jul 2013	All	12	0.83 (0.72–0.96)	66.5
		Local		0.74 (0.47–1.17)	79.4
		Advanced		0.71 (0.47–1.08)	75.8
		Fatal		0.61 (0.42–0.90)	61.4
Huang et al.[11] (2014)	Aug 2013	All	8	0.86 (0.79–0.95)	25.0
		Local		0.90 (0.83–0.97)	0.0
		Advanced		0.73 (0.50–1.07)	72.8
		Fatal		0.70 (0.46–1.05)	57.5
Liu et al.[12] (2015)	Aug 2013	All	13	0.90 (0.85–0.95)	17.5
		Local	5	0.89 (0.83–0.96)	0.0
		Advanced	6	0.82 (0.61–1.10)	64.1
		Fatal	4	0.76 (0.55–1.06)	49.1
Wang et al.[13] (2016)	Jul 2015	All	14	0.89 (0.84–0.93)	30.3
Xia et al.[6] (2017)	Jul 2016	All	14	0.97 (0.84–1.12)	64.8
		Local	4	0.90 (0.83–0.97)	0.0
		Advanced	4	0.84 (0.58–1.21)	72.0

sRR: summary relative risk, CI: confidence intervals.

advanced, and fatal. Based on the tumor-node-metastasis staging score suggested by 3 studies,[19,21,22] the localized group was defined as 'T1-2 and NX-0 and MX-0.' And the advanced group was defined as 'T3-4, N1 or M1.'

As the lowest level was defined as 'never or seldom' categories,[9] aRR and its 95% CI of the highest category in each study were extracted. To evaluate potential effects of confounders, the author checked whether alcohol habits, body mass index, or physical activity were adjusted in estimating RR in each study and appraised the level of smoking status adjustment. The high level was defined as adjusting for the intensity as well as the status, while the low level was defined as adjusting for the only status or none.

The heterogeneity level of the cohorts was evaluated by I-squared value (%). In the case of over 50%, the random effect model meta-analysis of highest versus lowest method (HLMA) was performed. Egger test as well as funnel plot were performed to evaluate the publication bias. Subgroup analyses by adjustment of 4 potential confounders—alcohol habit, body mass index, physical activity, and level of smoking status—were conducted.

A 2-stage fixed-effect dose-response meta-analysis (DRMA) after checking p-value of Goodness-of-fit over 0.10 was performed to calculate the risk of prostate cancer per unit dose of coffee consumption (cup per day).[26] The author defined 250 g of coffee equal to 1 cup.[10] Using a restricted cubic spline model with 4 knots at fixed percentiles (5%, 35%, 65%, and 95%) of the distribution, the linear relationship was confirmed based on the coefficients of the second and third spline. The level of statistical significance was set at 0.05.

RESULTS

As of 10 October 2020, a total of 247 papers cited 10 articles[15-24] and 104 papers were similar to Xia et al.[6] through the citation discovery tool provided by PubMed. The author secured newly 3 studies that met the selection criteria from them.[27-29] While Wilson et al.[19] and Russnes et al.[27] have the same cohort participants, the author selected Wilson et al.[19] because it had more information for HLMA and DRMA. Thus, a total of 12 prospective cohort studies were selected for HLMA, finally (Fig. 1).[15-24,28,29] A total of 920,547 persons participated and 53,943 cases oc-

curred during the follow-up periods. There were 5 in North America, 5 in Europe, and 2 in Asia according to regional distribution. And 11 all, 4 local, 5 advanced, and 4 fatal cohorts from 12 studies were organized.

Fig. 2 shows the extraction values from each study and their HLMA results by cancer grades. The risk of prostate cancer in localized, advanced, and fatal grade according to coffee consumption did not show the statistical significance. But there was an inverse association between coffee consumption and the risk prostate cancer in all cases with statistical significance (summary RR [sRR], 0.91; 95% CI, 0.84–0.98; I-squared=49.1%). The p-value of Egger test (p=0.435) and funnel plot (Fig. 3) did not show a publication bias.

Table 2 illustrates the results of subgroup analysis to find out the influence of 4 potential confounders in cohorts of all cases showing statistical significance in Fig. 2. Statistical significance maintained when the level of adjusting smoking status was high, and alcohol habits, obesity, or physical activity were adjusted.

Two of 12 studies had not the information needed to conduct a DRMA.[16,28] Table 3 summarizes the results of DRMA by cancer grades as well as of previous DRMA studies. Except for advanced cases, the risk of prostate cancer had the linearly inverse association by a cup of coffee consumed daily with statistical significance (Fig. 4). The unit's decreasing risk levels were 1.0% in all cases, 1.1% in localized cases, and 2.5% in fatal cases, respectively.
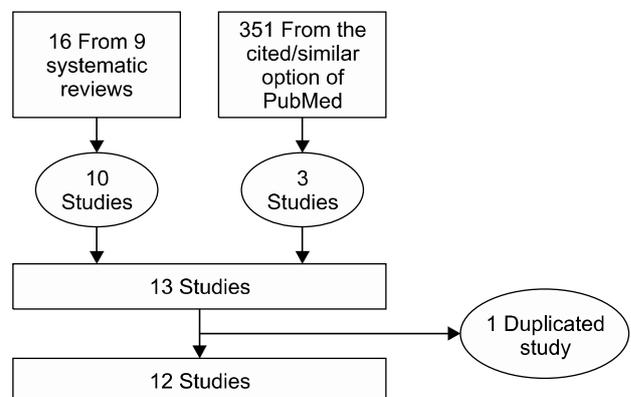

Fig. 1. Flow chart of the final selection of prospective cohort studies.

Year	First author	Adjusting level of smoking status	Adjusting for alcohol habit	Adjusting for body mass index	Adjusting for physical activity		Relative risk (95% CI)	Weight (%)
All								
1989	Severson	N	N	N	N		0.92 (0.59, 1.44)	2.56
1994	Le Marchand	N	N	N	N		1.10 (0.71, 1.71)	2.58
2004	Allen	N	N	N	N		1.02 (0.71, 1.46)	3.71
2010	Nilsson	L	N	Y	Y		1.03 (0.77, 1.38)	5.26
2011	Wilsson	H	Y	Y	Y		0.82 (0.68, 0.98)	10.09
2012	Shafique	L	Y	Y	N		0.93 (0.66, 1.31)	4.04
2013	Bosire	H	N	Y	Y		0.94 (0.87, 1.02)	19.45
2013	Li	H	Y	Y	Y		0.63 (0.39, 1.01)	2.32
2015	Tverdal	L	Y	Y	Y		0.78 (0.69, 0.89)	14.53
2018	Park	H	Y	Y	Y		0.89 (0.79, 1.00)	15.44
2019	Sen	L	Y	Y	Y		1.02 (0.95, 1.10)	20.03
Subtotal (I-squared=49.1%, p=0.033)							0.91 (0.84, 0.98)	100.00
Localized								
2011	Wilsson	H	Y	Y	Y		0.93 (0.74, 1.16)	12.58
2013	Bosire	H	N	Y	Y		0.92 (0.84, 1.01)	39.02
2013	Discacciati	L	Y	Y	Y		0.81 (0.69, 0.96)	20.13
2019	Sen	L	Y	Y	Y		1.02 (0.90, 1.16)	28.27
Subtotal (I-squared=37.1%, p=0.189)							0.92 (0.85, 1.01)	100.00
Advanced								
2011	Wilsson	H	Y	Y	Y		0.47 (0.28, 0.78)	9.60
2013	Bosire	H	N	Y	Y		1.15 (0.92, 1.43)	21.93
2013	Discacciati	L	Y	Y	Y		0.87 (0.66, 1.15)	18.41
2018	Park	H	Y	Y	Y		0.92 (0.78, 1.09)	25.03
2019	Sen	L	Y	Y	Y		1.09 (0.92, 1.29)	25.04
Subtotal (I-squared=68.9%, p=0.012)							0.94 (0.77, 1.13)	100.00
Fatal								
2011	Wilsson	H	Y	Y	Y		0.40 (0.22, 0.74)	15.36
2013	Bosire	H	N	Y	Y		0.80 (0.54, 1.19)	24.54
2013	Discacciati	L	Y	Y	Y		0.88 (0.59, 1.32)	24.15
2019	Sen	L	Y	Y	Y		0.97 (0.78, 1.20)	35.96
Subtotal (I-squared=59.1%, p=0.062)							0.79 (0.59, 1.06)	100.00

Note: weights are from random effects analysis
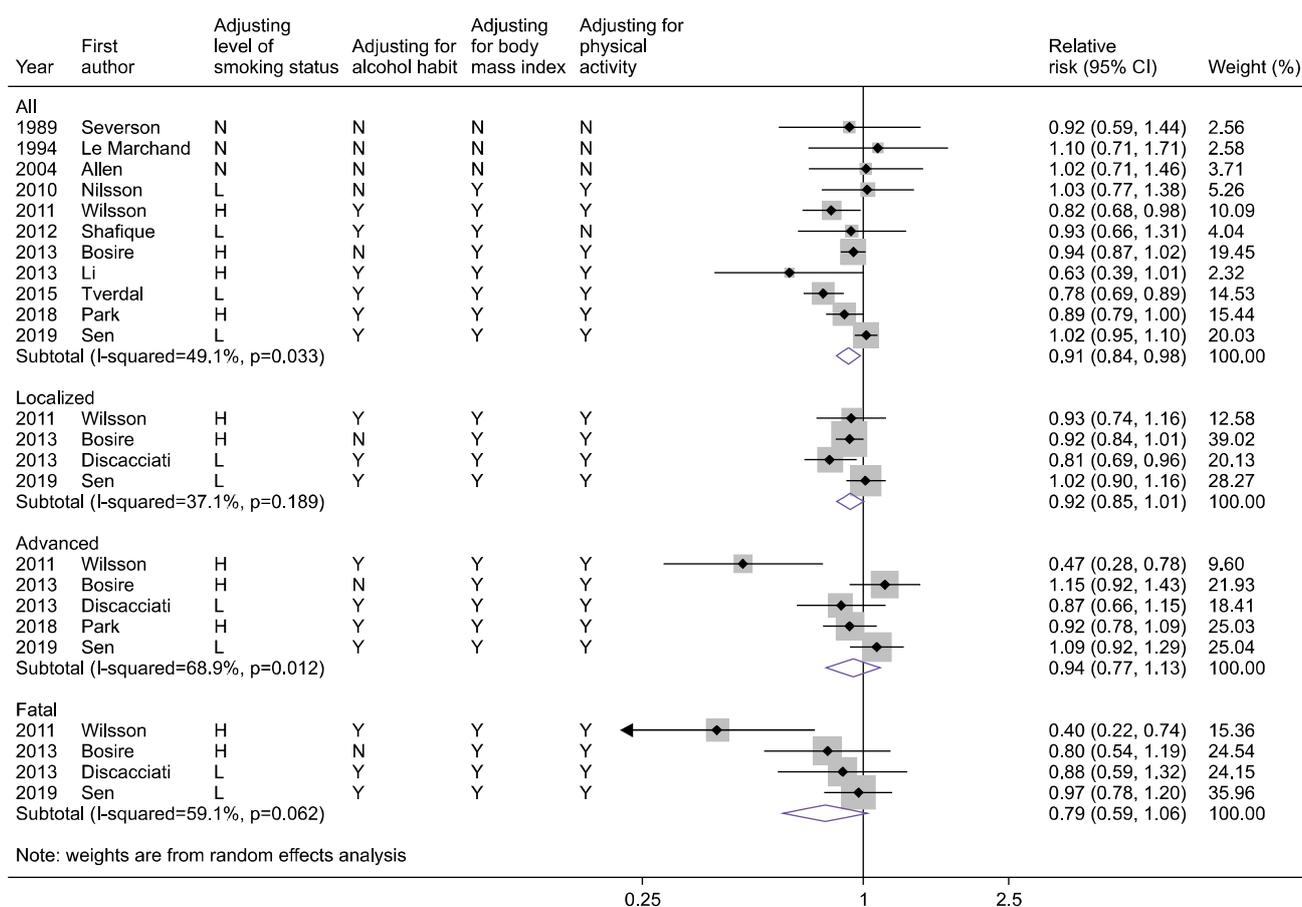
0.25   1   2.5

Fig. 2. Forest plot of meta-analysis using highest versus lowest method by prostate cancer grades. H: high, L: low, N: none, Y: yes, CI: confidence interval.
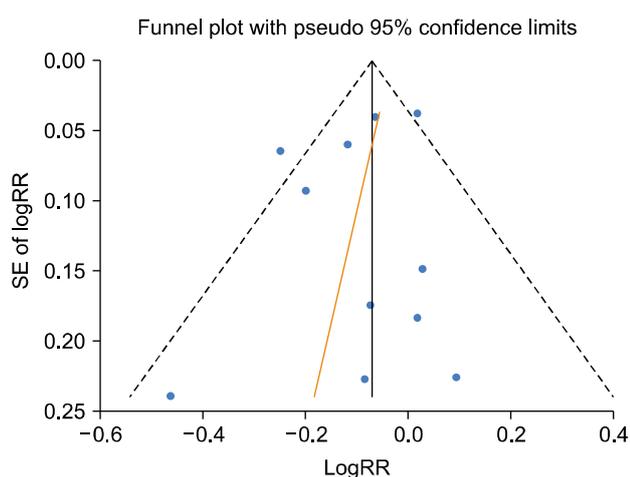
Fig. 3. Funnel plot. SE: standard error.

DISCUSSION

The HLMA showed that habitual coffee consumption would decrease prostate cancer risk in all cases (sRR, 0.91; 95% CI, 0.84–0.98). Also, the DRMA suggested that habitual coffee consumption of a cup daily would decrease the risk in all cases of prostate cancer at 1.0%. These findings suggested that the conflict reports among the previous SRs would be due to 3 main factors, such as noncomprehensive searching strategies, the interdifferent definition of selection criteria, and inaccurate extraction of information.

The reasons were as follows. Firstly, this meta-epidemiological study could secure 3 new cohort studies[27-29] not included in the previous SRs introduced in Table 1. Considering that the most recent searching year in SRs was in 2016,[6] Russnes et al.[27] published in 2014 had to be evaluated. It is highly recommended to appraise and select the list of articles selected by the SRs published previously under the same research hypothesis. Secondly, there were 16 cohort studies selected by the previous 9 SRs, but 6 did not meet this study's selection criteria. It needs to apply stricter selection criteria to estimate a more valid effect size.

Lastly, the author found some different RRs and their 95% CI between forest plots in SRs and original articles. It is necessary to check the sameness of extracted values between the original article and the forest plot in order to prevent an error in the process of calcul ating logRR and SElogRR.

The subgroup analysis results in Table 2 could be interpreted that statistical significance disappeared when the level of adjusting smoking status was low, and alcohol hab-

its, obesity, or physical activity were not adjusted. These results are interesting because aRR moves toward a null, and statistical significance disappears as the intensity of adjustment increases in general. Based on these findings, it could be inferred that the interdifferent intensity of adjustment in selected studies could also cause conflicting results of SRs.

In contrast to HLMA in all cases, sRRs by cancer grades showed that habitual coffee consumption did not associate with prostate cancer risk in localized, advanced, and fatal
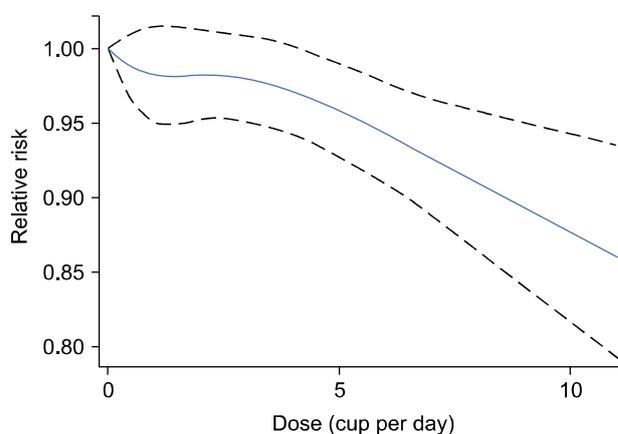
Table 2. Subgroup analyses by potential confounders

Adjustment	Summary RR (95% CI) in cohorts of all cases
Level of smoking status	
Low	0.994 (0.830–1.075)
High	0.911 (0.845–0.982)
Alcohol habit	
No	0.952 (0.885–1.024)
Yes	0.870 (0.768–0.984)
Body mass index	
No	1.012 (0.799–1.283)
Yes	0.899 (0.826–0.980)
Physical activity	
No	0.985 (0.810–1.197)
Yes	0.897 (0.819–0.982)

RR: relative risk, CI: confidence interval.

Fig. 4. Dose-response meta-analysis in 9 all cohorts per unit (cup daily).

Table 3. Results of dose-response meta-analysis

Study	Unit (cup/day)	Cancer grade	Selected cohort studies	p-value of nonlinearity	RR (95% CI)
This study	1	All	9	0.32	0.990 (0.985–0.996)
		Localized	4	0.32	0.989 (0.981–0.997)
		Advanced	4	0.08	0.988 (0.956–1.022)
		Fatal	4	0.68	0.975 (0.951–0.999)
Xia et al.[6] (2017)	1	All	10	-	0.990 (0.980–1.000)
		Localized	4	-	0.990 (0.980–0.990)
		Advanced	4	-	0.970 (0.910–1.020)
Wang et al.[13] (2016)	2	All	10	0.15	0.970 (0.960–0.980)
Liu et al.[12] (2015)	2	All	9	-	0.975 (0.957–0.995)
Zhong et al.[10] (2014)	2	All	10	0.07	0.930 (0.880–0.990)
Huang et al.[11] (2014)	2	All	8	0.36	0.980 (0.930–1.030)
		Localized	4	0.47	0.980 (0.920–1.040)
		Advanced	5	0.74	0.980 (0.860–1.120)
		Fatal	3	0.62	0.950 (0.770–1.160)
Discacciati et al.[30] (2014)	3	Localized	4	0.12	0.970 (0.950–0.990)
		Advanced	4	0.18	0.910 (0.800–1.050)
		Fatal	3	0.36	0.890 (0.820–0.970)

RR: relative risk, CI: confidence interval.

cases (Fig. 2). Compared with the results presented by 3 grades in previous SRs in Table 1, there was no consistency. These results might be attributed to the decrease in the number of cohorts selected for meta-analysis as studies were divided by grades.

In contrast to HLMA in 3 grades, DRMA shows a linearly inverse association between habitual consumption of coffee and risk of prostate cancer in localized and fatal, except advanced grade. And the unit's decreasing risk level was higher in fatal grade rather than local grade. These results of this study were also confirmed in Xia et al.[6] and Discacciati et al.[30] in Table 3. The different results between HLMA and DRMA might be caused by that DRMA uses the presented information relatively more than HLMA. If so, we could suggest that coffee consumption lowers the risk of prostate cancer in local and fatal grades based on DRMA results. On the other hand, the advanced grade had no statistical significance in DRMA compared to local and fatal grade. This could be interpreted as the fact that local and fatal showed a linear relationship (p>0.10), but advanced showed a nonlinear (p<0.10).

The advantages of this study are as follows. First, 3 additional cohort studies that were not selected in the existing SRs were additionally evaluated. Second, stricter selection criteria were applied, and then HLMA and DRMA were performed for 3 kinds of grade. Last, accordingly, the reasons for the conflict results among the existing SRs could be identified. On the other hand, the main limitation was that the effect on low and moderate dosage could not be analyzed as the category of coffee dosage was different for each study. Accordingly, DRMA was performed to confirm the level of risk reduction per unit consumption.

CONCLUSIONS

There is an inverse association between coffee consumption and risk of prostate cancer in local and fatal grades as well as all cases. And the main reasons of conflict results among the previous SRs would be due to non-comprehensive searching strategies, the interdifferent definition of selection criteria, inaccurate extraction of information, and inadequate adjustment for potential confounders.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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