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Coffee consumption and liver cancer risk in Japan: a meta-analysis of six prospective cohort studies

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ABSTRACT

Previous epidemiological studies have shown that coffee consumption may reduce liver cancer risk. The present study aimed to summarize the evidence for this association in the Japanese population by performing a meta-analysis of the results of relevant cohort studies conducted in Japan. We searched studies published prior to September 1, 2018 in PubMed. Extracted data were analyzed using a random effects model. A total of six cohort studies from five publications were included in the final analysis. The pooled estimate of relative risk with 95% confidence interval (CI) for the group with highest coffee consumption was 0.50 (95% CI: 0.38–0.66, $p < 0.001$) compared with non-coffee drinkers or those who almost never drink coffee. No evidence of publication bias was observed (p for Begg's test = 0.85). This meta-analysis suggested that coffee consumption among Japanese people has a significant role in preventing liver cancer.

Keywords: Coffee, Cohort study, Liver cancer, Meta-analysis, Japan

INTRODUCTION

Liver cancer is the second leading cause of cancer-related death and the sixth most frequently diagnosed cancer worldwide. The incidence of liver cancer in Japan is the highest among developed countries.[1] There is a consensus that chronic infections with hepatitis C virus (HCV) or hepatitis B virus (HBV) are major risk factors for liver cancer.[2] High alcohol consumption, obesity, and food contaminated with aflatoxin have also been identified as risk factors; however, the evidence for other dietary factors has been inconclusive.[3] The effect of coffee on the liver is presently a topic of considerable interest, as previous studies have demonstrated that coffee consumption should be encouraged to prevent liver disease.[4] In addition, growing evidence from cohort studies has shown that coffee consumption may reduce liver cancer risk.[5] To date, several meta-analyses for this association have been carried out;[6,7] however, there have been no reports limited to the Japanese population. In Japan, approximately 80% of liver cancer incidence is caused by HCV infection, compared with other countries in which the involvement of HCV infection in liver cancer is low.[2,8] Because summarizing the evidence would yield better

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understanding of the association between coffee consumption and liver cancer risk in Japan, we aimed to evaluate this association by performing a meta-analysis of the results of relevant cohort studies conducted in Japan.

MATERIALS AND METHODS

We report this meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) guidelines.[9] Ethical approval and informed consent were not required because the study was based on published data.

Data source, search strategy, inclusion criteria, data extraction, and assessment of study quality

Two authors (T.T. and A.H.) independently conducted the literature search. Our search was limited to population-based cohort studies conducted in Japan and articles written in English. No restrictions on publication year were imposed. In this meta-analysis, PubMed was searched systematically to identify all available studies that evaluated the association between coffee consumption and liver cancer risk, using the following key words: ("coffee" OR "caffeine") AND ("hepatocellular carcinoma" OR "liver cancer") AND ("cohort study" OR "prospective study") AND ("Japanese" OR "Japan"). The search was completed on September 1, 2018. Studies were included if they fulfilled all the following criteria: (1) they had a cohort design (nested case-control studies were considered cohort studies), (2) the main exposure of interest was coffee consumption, (3) the end point of interest was incidence of liver cancer, and (4) multivariate-adjusted hazard ratios (HR) or odds ratios (OR, for nested case-control studies) and 95% confidence intervals (CI) were reported for the association of coffee consumption with liver cancer incidence or mortality. Studies that did not meet these criteria or that did not provide enough data to allow calculation of the effect estimate were excluded. If multiple reports were obtained from the same study population, the most recent or relevant article was chosen. Articles in press were added to the present analysis. References of included studies were also reviewed to identify other potential studies. Relevant study information was extracted from these publications.

The methodological quality of included studies was assessed using Newcastle-Ottawa Scale (NOS) with a maximum of nine stars for cohort studies.[10] A maximum of two stars can be assigned for the "Comparability" category; one star was awarded if the study provided risk estimates with controlling for age and sex, with an additional star awarded if it controlled for other potential confounders including alcohol intake and smoking status. A study with the follow-up of 10 years or longer was awarded one star in "Follow-up long enough for outcomes to occur" under the "Outcome" category. A study with the follow-up rate of 80% or higher was awarded one star in "Adequacy of follow-up of cohorts" under the "Outcome" category. If there was no description or statement in the articles included, no stars were awarded for each corresponding category of the NOS. Studies with scores of ≥6, 4–5, and 0–3 were considered high, moderate, and low quality studies, respectively.

Statistical analysis

We derived a combined relative risk (RR) and 95% CI for the highest level of consumption versus the lowest consumption using a random effects model, as the results from this model are more conservative in measuring the impact of coffee consumption on liver cancer risk than a fixed effects model.[11] The heterogeneity across studies was evaluated using the I^2 statistic, and we applied the following interpretation: $I^2 < 25\%$ = low heterogeneity; $25\% \leq I^2 < 75\%$ = moderate heterogeneity; and $I^2 \geq 75\%$ = high heterogeneity.[12] Publication bias was tested using the Begg's

test.[13] We additionally performed stratified analysis according to adjustment for hepatitis virus infection, to consider the effect of this adjustment on the association with liver cancer risk. The p value < 0.05 was considered statistically significant. All statistical analysis was performed using Stata 12.1 software (StataCorp LLC, College Station, TX, USA).

RESULTS

In the initial search, 20 records were identified in PubMed according to our primary search key words. At the time of the search, there was a relevant article in press. We first excluded 14 records in a review of their abstracts, as they were not population-based cohort studies among Japanese or the main exposure or outcome did not meet the inclusion criteria. Among the remaining seven records, two was excluded because these had been superseded by a more recent report in the same study population. Finally, five articles were included in the present meta-analysis as shown in Figure 1. The characteristics of the included studies are presented in Table 1. Liver cancer cases in all included studies were identified using cancer registries or death certificates. All included studies defined cancer incidence as the end point, with the exception of a study conducted by Kurozawa et al in which the end point was liver cancer death. Table 2 shows the methodological quality of the included cohort studies according to the NOS. One study had a score of 8, three scored 6, and two scored 5; all the studies included in the present meta-analysis were generally of high quality.

The pooled RR and study-specific RRs with 95% CIs for the group with the highest coffee consumption versus that with the lowest consumption are shown in Figure 2. The pooled result showed a significant inverse association between coffee consumption and liver cancer risk; the summary RR was 0.50 (95% CI: 0.38–0.66, p < 0.001) with no heterogeneity observed (I^2 = 0%,

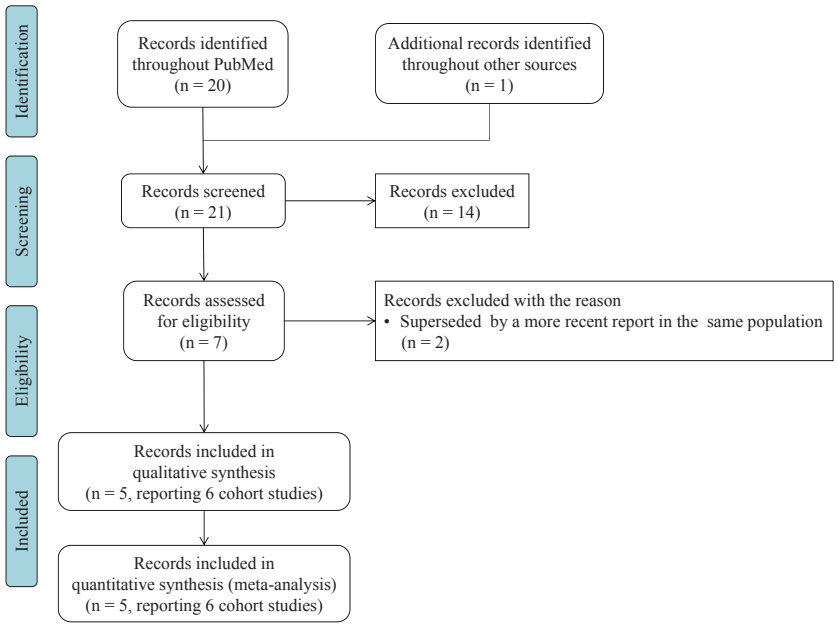

Fig. 1 Flow diagram of the selection of studies included in the meta-analysis

Table 1 Characteristics of included prospective cohort studies conducted in Japan for the association between coffee consumption and liver cancer risk

Author	Cohort name	Population	Age	No. of cases	Cohort size	Duration of follow-up (years)	Coffee consumption	No. of cases/N		Relative risk (95% CI)	Adjusted covariates
								The highest consumption group	The lowest consumption group		
Tamura et al (2018) [18]	Takayama Study	Japan	≥35	172	30,824	16	≥Twice/d vs. nondrinkers	11/4,985	74/7,497	0.40 (0.20–0.79)	Age, sex, alcohol intake, smoking, BMI, education, total energy intake, physical activity, and medical history of diabetes mellitus.
Inoue et al (2009) [17]	JPHC Study II	Japan	40–69	110	18,815	12	≥3 cups/d vs. almost never	6/1,646	51/6,324	0.54 (0.21–1.39)	Age, sex, study areas, alcohol intake, smoking, BMI, green tea consumption, medical history of diabetes mellitus, serum ALT level, HCV infection, and HBV infection.
Ohishi et al (2008) [16]	Adult Health Study[a]	Japan	NA	224	644	44	Daily vs. never	N/A	N/A	0.40 (0.16–1.02)	Age, sex, alcohol intake, smoking, BMI, medical history of diabetes mellitus, radiation dose to the liver, HCV infection, and HBV infection.
Kurozawa et al (2005) [15]	JACC Study	Japan	40–79	258	83,966	12	≥1 cup/d vs. nondrinkers	98/44,151	103/24,556	0.50 (0.31–0.79)	Age, sex, alcohol intake, smoking, medical history of diabetes mellitus and liver diseases, and education.
Shimazu et al (2005) [14]	Japan Miyagi Prefecture, Cohort 1	Japan	>40	70	22,404	9	≥1 cup/d vs. almost never	16/7,959	29/4,938	0.53 (0.28–1.00)	Age, sex, alcohol intake, smoking, and medical history of liver disease.
	Japan Miyagi Prefecture, Cohort 2	Japan	40–64	47	38,703	8	≥1 cup/d vs. almost never	14/17,619	12/6,954	0.68 (0.31–1.51)	Age, sex, alcohol intake, smoking, and medical history of liver disease.

Abbreviation: JACC, the Japan Collaborative Cohort; JPHC, the Japan Public Health Center-based Prospective.
[a]Nested case-control study.

Table 2 Quality scores of included six cohort studies using Newcastle-Ottawa Scale

Author	Cohort name	Selection				Comparability[b]		Outcome			Overall score
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts on the basis of the design or analysis		Assessment of outcome	Follow-up long enough for outcomes to occur[c]	Adequacy of follow-up of cohorts[d]	
Tamura et al (2018) [18]	Takayama Study	*	*	–	*	*	*	*	*	*	8
Inoue et al (2009) [17]	JPHC Study II	–	–	–	*	*	*	*	*	*	6
Ohishi et al (2008) [16]	Adult Health Study[a]	–	–	–	*	*	*	*	*	–	5
Kurozawa et al (2005) [15]	JACC Study	–	–	–	*	*	*	*	*	–	5
Shimazu et al (2005) [14]	Japan Miyagi Prefecture, Cohort 1	*	*	–	*	*	*	*	–	–	6
	Japan Miyagi Prefecture, Cohort 2	*	*	–	*	*	*	*	–	–	6

Abbreviation: JACC, the Japan Collaborative Cohort; JPHC, the Japan Public Health Center-based Prospective.
[a]Nested case-control study.
[b]A maximum of two stars can be assigned for the "Comparability" category. One star was awarded if the study provided risk estimates with controlling for age and sex, with an additional star awarded if it controlled for other potential confounders including alcohol intake and smoking status.
[c]A study with the follow-up of 10 years or longer was awarded one star.
[d]A study with the follow-up rate of 80% or higher was awarded one star.

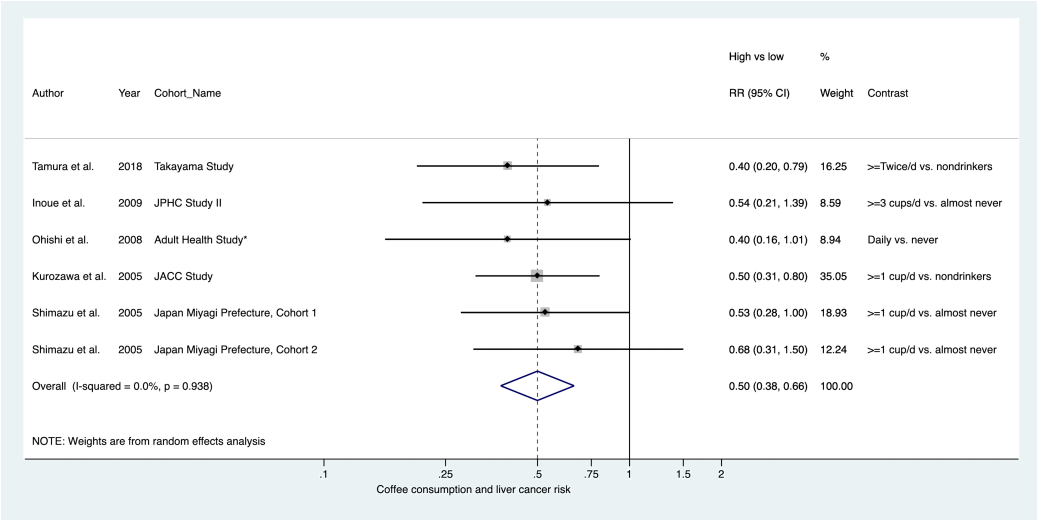

Fig. 2 Forest plot of study-specific and pooled relative risks (RR) and 95% confidence intervals (CI) of liver cancer risk for the highest coffee consumption group compared with the lowest
Abbreviation: JACC, the Japan Collaborative Cohort; JPHC, the Japan Public Health Center-based Prospective. *Nested case-control study.

$p = 0.94$). No publication bias was found in the Begg's test ($p = 0.85$). When the analysis was stratified by the presence of adjustment for hepatitis virus infection, the summary RRs appeared not to be modified; the summary RR with and without adjustment was 0.46 (95% CI: 0.24–0.90, $p = 0.023$) and 0.51 (95% CI: 0.37–0.69, $p < 0.001$), respectively.

DISCUSSION

In the present study, we summarized the evidence for an association between coffee consumption and liver cancer risk among Japanese people by performing a meta-analysis of the results from six prospective cohort studies conducted in Japan, with the high or moderate methodological quality according to the NOS. Our results suggested that coffee consumption significantly reduces liver cancer risk in the Japanese population.

The summary RR estimated in the present meta-analysis is consistent with the result from a recent worldwide study in which the RR was 0.54 (95% CI: 0.44–0.67, $I^2 = 38.0\%$) for those with the highest coffee consumption compared with non-coffee drinkers or those who almost never consumed coffee.[7] In that study, the RRs in Europe, Asia, and North America were reported to be 0.37 (95% CI: 0.25–0.54, $I^2 = 22.6\%$), 0.50 (95% CI: 0.38–0.66, $I^2 = 0.0\%$), and 0.75 (95% CI: 0.59–0.95, $I^2 = 0.0\%$), respectively.[7] In comparing these results, the impact of coffee consumption on liver cancer risk may differ among different races or regions. Possible points to consider include the following. Differences in the consumption pattern or preparation method for brewing coffee may account for the difference in the association, as the original components of coffee, such as cafestol, kahweol, or chlorogenic acid, might be responsible for this inverse association.[19] For example, one study has shown that the amount of cafestol and kahweol in drip-filtered or instant coffee is much lower than that in French press or boiled coffee.[20] Coffee consumers in Japan mostly drink drip-filtered and/or instant coffee; therefore, the effect of coffee

consumption on liver cancer risk may be somewhat smaller in Japan than that in Europe. It is also notable that coffee is a primary source of caffeine, which inhibits carcinogenesis.[21] Interestingly, a previous cohort study conducted in Japan demonstrated that caffeine intake from coffee, green tea, black tea, and other sources was unrelated to liver cancer risk whereas decaffeinated coffee appeared to be associated with reduced liver cancer risk;[18] this is in accordance with the results from a multiethnic cohort study in the United States.[22] Other studies have also shown no association between caffeine-containing beverages other than coffee, such as green tea, and liver cancer risk.[14,17] Further studies are needed to reveal the association between caffeine intake and liver cancer risk.

Some limitations of this study should be mentioned. We did not evaluate the associations according to whether coffee was caffeinated or decaffeinated, as all included studies did not report the results separately by the type of coffee, with the exception of one study.[18] The presence of unmeasured confounders in the original studies may be a matter of concern; even so, all included studies provided multivariate-adjusted HRs, as shown in Table 1. HBV and HCV infections are well known as major risk factors for liver cancer; nevertheless, only two included studies reported the association with liver cancer risk after controlling for these infections.[16,17] When the analysis was stratified by the presence of this adjustment, however, no clear difference was observed in the association with liver cancer risk between the two strata. One study reported a similar inverse association, even among those with hepatitis virus infections,[17] suggesting that coffee consumption may reduce liver cancer risk independently of these infections. Some studies have demonstrated an inverse association in the analysis, after excluding early diagnosis of liver cancer within 2–3 years of a baseline survey.[14,18] Another study also showed an inverse association, even among those with a history of liver disease.[15] However, reverse causation cannot be ruled out, even in prospective cohort studies, because there is a possibility that coffee consumption might have changed owing to preclinical symptoms in people with hepatitis or hepatic cirrhosis at baseline. A recent genome-wide association study conducted by Nakagawa-Senda et al identified specific loci associated with coffee consumption;[23] therefore, a Mendelian randomization approach, a method of using the measured variation in genes to examine the causal effect of modifiable exposures on diseases, would be useful in the evaluation of the association between coffee consumption and liver cancer risk.[24]

In conclusion, the findings of the present study suggested that coffee consumption among Japanese people has a significant role in preventing liver cancer.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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