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Original Article

Alcohol Consumption and Lung Cancer Risk among Japanese : A Meta-Analysis

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Abstract It is unknown what biologic mechanism may be responsible for the harmful effects of alcohol, though several have been suggested. Alcohol consumption is an established risk factor for cancers of the oral cavity, pharynx, larynx, esophagus and liver. However, epidemiologic studies have not provided consistent evidence on the effect of alcohol consumption on the risk of lung cancer. To evaluate the role of alcohol consumption in the risk of lung cancer among Japanese, the authors performed a meta-analysis of existing epidemiological studies. The authors first examined whether current alcohol consumption could potentially increase the risk of lung cancer without considering confounding factors. The summary risk estimate based on then random effects model for current consumption was 0.65 (95% confidence interval (CI) = 0.53 - 0.77). This risk estimate might be biased due to uncontrolled confounders, especially smoking cigarettes which is highly correlated with alcohol consumption. After adjustment for cigarette smoking, the summary risk estimate based on the random effects model for current alcohol consumption was no longer statistically significant (summary risk = 1.00, 95% CI = 0.73 - 1.26). Our results do not indicate that alcohol consumption serves as a major risk factor for lung cancer among Japanese. Additional studies with detailed assessments of alcohol consumption and potential confounding factors will undoubtedly lead to a better understanding of the role of alcohol consumption in lung cancer development.

Key words : alcohol consumption, lung cancer, Japanese, meta-analysis

Introduction

Although cigarette smoking is the most important etiologic factor for lung cancer, a significant portion of lung cancer cases cannot be attributed to cigarette smoking alone. However, epidemiologic studies have not provided consistent evidence on the influence of alcohol consumption on lung cancer. The first meta-analysis[1] and a large prospective study[2] showed that alcohol consumption did not affect lung cancer risk after adjustment for cigarette smoking. On the other hand, the second meta-analysis[3] found

no clear association between total alcohol intake and lung cancer risk, except at more than five drinks per day (equivalent to ≥ 75 g of ethanol per day) among Caucasians. A pooled-analysis[4] found a significant effect of alcohol for male non-smokers. Hirayama[5)6)] reported that daily drinkers have increased risk of lung cancer compared to non-drinkers among Japanese. There might be some differences between Caucasians and Japanese in terms of the types of alcoholic beverage consumed and the alcohol metabolism rate. The third meta-analysis found that that high consumption of beer and liquors may be associated with increased lung cancer risk, whereas modest wine consumption may be inversely associated with risk[7]. Several studies examining the consumption of different types of

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alcoholic beverages suggest that the effect on lung cancer risk might be different for beer, wine, and liquors[4)8)9)]. Caucasians frequently consumed wine whereas Japanese consumed sake (Japanese rice wine)[10)]. Moreover, the appropriate volume of Japanese ($< 20g/day$)[11)] is relatively lower than that of Caucasians (15–30g/day)[12)]. Japanese may be genetically more susceptible to alcohol consumption as a risk factor for cancer compared to Caucasians due to differences in alcohol metabolism efficiency[13)]. In fact, aldehyde dehydrogenase 2 (ALDH2) Glu487Lys polymorphism is more common in Japanese than in Caucasian populations[14)]. The 487Lys allele results in lower ALDH2 activity and a higher blood concentration of acetaldehyde[14)], which is the primary metabolite of ethanol shown to be carcinogenic in animal experiments[15)].

To comprehensively evaluate the role of alcohol consumption on the risk of lung cancer among Japanese, the authors conducted a meta-analysis to summarize findings from epidemiological studies.

Materials and methods

Relevant studies were identified in the PubMed database using combinations of the search terms "Japan", "alcohol", "drinking", "lung cancer", "case-control", and "cohort" (the last search update on May 2010). Articles included in this analysis were written in either English or Japanese, published as an original article, with human subjects and had no obvious overlap of subjects with other studies. When the results of a study were published more than once, only the most complete data were included. As mortality rates for lung cancer are a very reasonable proxy for incidence because of the high fatality of lung cancer, both incidence and mortality studies were included. Under the so called "rare disease assumption" such as lung cancer the odds ratio may provide an acceptable approximation of the relative risk. Therefore, both case-control and cohort studies were eligible for this study. The

data were combined using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird method) models. The authors assessed heterogeneity with I^2, which describes the percentage of total variation across studies due to heterogeneity rather than chance[16)]. High values of I^2 would show increasing heterogeneity. Publication bias was evaluated by both Begg's (regression method)[17)] and Egger's (rank correlation approach) tests[18)]. Furthermore, the newly developed Trim and Fill method was also applied to test the presence of publication bias[19)]. The presence of publication bias indicates that nonsignificant or negative findings remain unpublished. Publication bias was considered significant for P < 0.10. All the calculations were performed by the computer program Stata version 10.1.

Results

In total, 11 published studies were identified with the association between alcohol consumption and lung cancer risk among Japanese. After exclusion of duplicate studies, the authors retrieved seven epidemiological studies, five cohort[5)6)20)~23)] and two case-control studies[24)25)]. The main characteristics and results of the studies based on multivariate analysis are shown in Tables 1 and 2. The authors first examined whether current alcohol consumption could potentially increase the risk of lung cancer without considering confounding factors. Crude risk estimates or the appropriate measure of precision (95% CI, 90% CI or SE) were available in four studies[20)22)~24)]. Statistically significant heterogeneity ($I^2 = 37.2$ %, P = 0.19) was not seen in the case of all studies combined. As shown in Fig. 1, the summary risk estimate based on then random effects model for current alcohol consumption was 0.65 (95% CI = 0.53–0.77). The Begg's test was statistically significant (P = 0.04) for publication bias but not the Egger's test (P = 0.24). Although the regression method is more sensitive than the rank correlation approach, the potential presence of publication bias was further

Table 1 Summary of cohort studies of alcohol consumption and lung cancer risk among Japanese

Author, published year, (Study period)	Source of study subjects	Event followed	No. of incident cases or deaths/study subjects	Category of alcohol consumption	No. of incident cases or deaths/study subjects	HR or RR (95% or 90% CI)	Confounder
Kono et al. 1986[20] (1965-1983)	Physicians	Death	Male 74/5135	Non Past- Occasional Daily (go[a]/day) $\left\{\begin{array}{l} <2 \\ 2+ \end{array}\right.$	24/1074 5/496 12/1606 17/1034 16/925	1.0 0.6 (0.2 - 1.5) 0.4 (0.2 - 0.8) 0.8 (0.4 - 1.4) 0.9 (0.5 - 1.7)	Age and smoking
Hirayama 1990[5],1990[6] (1965-1982)	General population	Death	Male 1454/122261 Female 463/142857	None Rare Occasional Daily None Rare Occasional Daily	— — — — — — — —	1.00 0.94 (0.81 - 1.10)[b] 0.91 (0.80 - 1.03)[b] 1.27 (1.13 - 1.42)[b] 1.00 1.03 (0.79 - 1.32)[b] 1.29 (0.95 - 1.75)[b] 2.53 (1.59 - 4.03)[b]	Age
Stemmermann et al. 1990[21] (1965-1989)	Japanese Americans in Hawaii	Incidence	Male 209/7572	0 (oz/month) < 4.7 4.7-13.2 13.2-36.8 36.8 +	— — — — —	1.0 0.75 (0.48 - 1.17)[c] 0.93 (0.59 - 1.47)[c] 1.43 (0.99 - 2.06)[c] 1.09 (0.73 - 1.64)[c]	Age and smoking
Nishino et al. 2006[22] (1988-1999)	Participants in JACC study	Death	Male 377/28536	Never Ever Daily (g/day) $\left\{\begin{array}{l} < 24.9 \text{ g/day} \\ 25.0-49.9 \\ > 50.0 \\ Past \end{array}\right.$	91/5716 286/22820 113/10244 85/7511 38/3112 50/1953	1.00 0.90 (0.71 - 1.14) 0.81 (0.61 - 1.07) 0.82 (0.64 - 1.11) 0.97 (0.66 - 1.43) 1.39 (0.98 - 1.96)	Age, smoking, family history of lung cancer
Shimazu et al. 2008[23] (1990-2004)	Participants in JPHC study	Incidence	Male 651/46347	Non Occasional Weekly (g/week) $\left\{\begin{array}{l} 1-149 \\ 150-299 \\ 300-449 \\ 450+ \end{array}\right.$	211/10659 38/4218 105/10244 117/9574 99/6166 81/5486	1.47 (1.04 - 2.09) 1.00 1.10 (0.76 - 1.61) 1.07 (0.74 - 1.55) 1.34 (0.92 - 1.95) 1.31 (0.89 - 1.94)	Age, study area, smoking, passive smoking, and family history of lung cancer

JPHC study, Japan Public Health Center-based prospective study ; JACC study, Japan Collaborative Cohort study ; RR, relative risk ; HR, hazard ratio : CI, confidence interval
One oz (ounce) = 28.3g ethanol
[a]Expressed as the amount of *sake* (1 *go* (180 ml) of *sake* contains 21.4g ethanol).
[b]90% CI
[c]96% CI

Table 2 Summary of case-control studies of alcohol consumption and lung cancer risk among Japanese

Author, published year, (Study period)	Study design	No. of cases/controls	Category of alcohol consumption	No. of case/controls	OR (95% CI)	Confounder
Murata et al.1996[24] (1984-1993)	Nested case-control study	Male nonsmokers 31/121	0 go[a]/day 0.1-1.0 1.1 +	13/65 10/38 8/18	1.0 1.3 2.2	Age and residential area
		Male smokers 76/93	0 go[a]/day 0.1-1.0 1.1 +	25/32 18/32 33/29	1.0 0.7 1.5	
Huang et al. 2004[25] (1988-1998)	Hospital-based case-control study	Without family history of lung cancer 1296/48443	Never Current	— —	1.00 0.90 (0.78 - 1.05)	Age and sex
		With family history of lung cancer 102/2263	Never Current	— —	1.00 0.91 (0.53 - 1.57)	

OR, odds ratio; CI, confidence interval
[a]Expressed as the amount of *sake* (1 *go* (180 ml) of *sake* contains 27 ml ethanol).
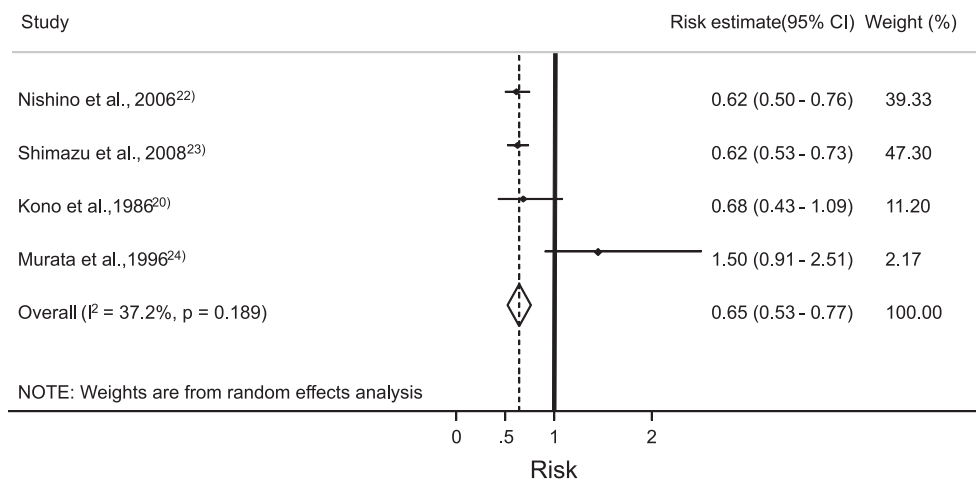
**Fig. 1** Forest plots for the association between current alcohol consumption and lung cancer risk

evaluated using the Trim and Fill analysis using random effects model. The Trim and Fill method indicated no missing study to the funnel plot in the present study and made no change in meta-analysis results and hence indicated no evidence of publication bias. The authors next combined the smoking-adjusted risk estimates for the highest drinking category from each study. Smoking-adjusted risk estimates or the appropriate measure of precision were available in three cohort studies[20]~[22]. The summary risk estimate based on then random effects model for current alcohol consumption was 1.00 (95% CI = 0.73-1.26 ; data not shown). Evidence for heterogeneity ($I^2 = 0$ %, P = 0.87) was absent. The Begg's (P = 0.60) and Egger's (P = 0.60) tests, and the Trim and Fill method for publication bias were not statistically significant. Alcohol consumption was not found to be associated with lung cancer risk among Japanese.

Discussion

Alcoholic beverage consumption has been established as a human carcinogen for several cancers, including cancers of the oral cavity, pharynx, larynx, esophagus, and liver[26]. The mechanisms by which alcoholic beverages cause cancer are yet-to -be defined and probably differ by target organ. Based on a review of Boffetta and Hashibe[27], the authors diagrammed the known and suspected carcinogenic mechanisms of alcohol (Fig. 2). Ethanol and its primary metabolite acetaldehyde are biologically plausible carcinogens. Without adjustment, current alcohol consumption was significantly associated with an decreased risk of lung cancer. The association between alcohol consumption and lung cancer risk is fully due to the confounding effect of cigarette smoking. After adjustment for cigarette smoking, alcohol drinking was not associated with lung cancer risk among Japanese in this study. The presence of heterogeneity and/or publication bias may compromise the interpretation of meta-analyses and result in an erroneous and potentially misleading conclusion[28][29]. The presence of publication bias indicates that nonsignificant or negative findings remain unpublished. The Trim and Fill method indicated no evidence of publication bias as well as commonly used Begg's and Egger's tests. The possibility of publication bias cannot be denied because the performance of the Trim and Fill method may not be ideal for this study. Although publication bias is always a possible limitation of combining data from various sources as in a meta-analysis, Sutton et al. concluded that publication or related biases did not affect the conclusions in most meta-analyses[30].

Many studies have evaluated an association between alcohol consumption and lung cancer
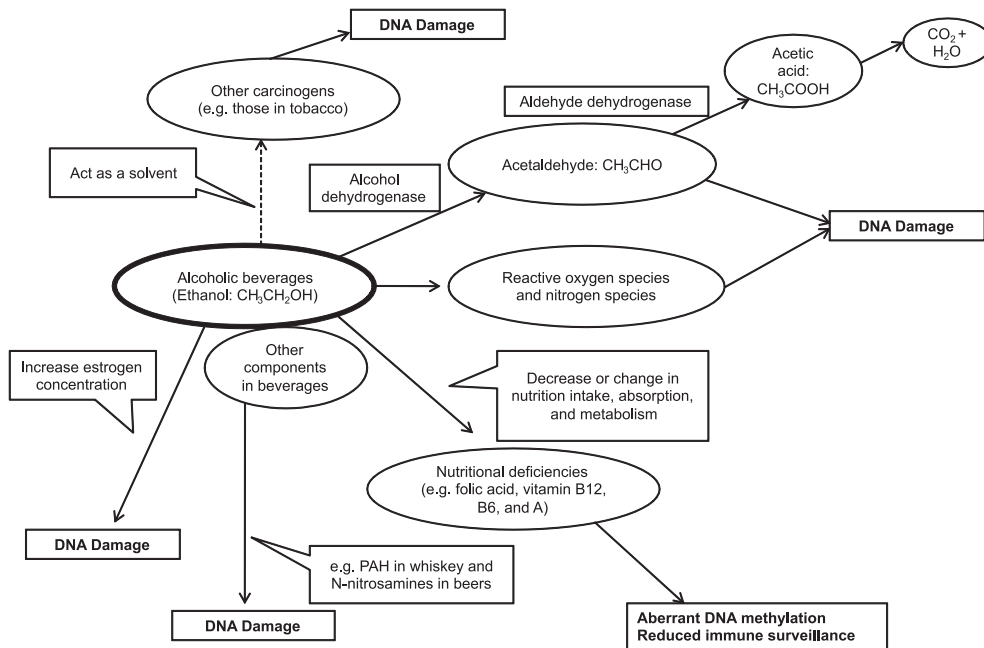
Fig. 2 The possible mechanisms of alcohol-related carcinogenesis

after attempting to control for cigarette smoking. Despite of the effort of a large prospective study and meta-analyses, epidemiological studies have not provided consistent evidence for an association between alcohol consumption and lung cancer risk. A pooled analysis found a slightly greater risk for the consumption of 30 g alcohol/day than for that of 0 g alcohol/day in men (relative risk (RR)= 1.21 ; 95% CI = 0.91–1.61) and in women (RR = 1.16, 95% CI = 0.94–1.43)[4]. However, the results may be biased due to residual confounding by cigarette smoking because there is a strong relation between cigarette smoking and alcohol consumption and between cigarette smoking and lung cancer risk. Men who had never smoked who reported drinking at least one drink per day had a 6-fold higher lung cancer incidence (RR = 6.38, 95% CI = 2.74–14.9) than non-drinking men who had never smoked[4]. The interpretation of this was not clear, however, because the reference category in men included only 10 lung cancer cases among those who reported neither smoking nor drinking, increasing the potential for bias or chance. Furthermore, wine drinking has been associated with lower cigarette consumption, lower fat intake, higher socioeconomic status and higher consumption of fruits and vegetables[31]. These observations suggested that alcoholic beverage consumption may be part of a health related lifestyle pattern that may affect lung cancer risk, including socioeconomic status and occupation. As not only cigarette smoking but other lifestyle factors may deserve attention, our results also should be interpreted carefully in light of the limitation of potential residual confounding.

Epidemiological studies have suggested that the effect on lung cancer risk may be different for different types of alcoholic beverage. Among the articles reviewed, only Hirayama[5)6)] evaluated the risk of lung cancer stratified by alcoholic beverage type. In Japan, sake (Japanese rice wine) was one of the major alcoholic beverages and it has not been popular in other countries. The meta-analysis of Chao[7] showed a positive association between beer drinking and lung cancer risk when the estimates of the highest beer-drinking category (RR = 1.23, 95% CI = 1.06–1.41). Similarly, a recent study reported that heavy drinkers of beer faced a 1.46-fold (95% CI = 1.07–1.98) increased risk of lung cance[32]. Currently, according to the 132st National Tax Agency

Annual Statistics Report in 2006[33)34)], beer, including low-malt beer (sparkling liquor) is the most popular alcoholic beverage in Japan. Beer has much higher levels of nitrosamines than any other alcoholic beverage[35)]. These chemicals are formed during the process of production of the different alcoholic beverages. Because production techniques vary over time, different levels of these chemicals over time and in different geographical areas can be anticipated. The lifestyle in the studies included in our meta-analysis did not represent current Japanese lifestyle. Association between alcohol drinking and lung cancer may vary with change in tastes of type of alcoholic beverage. Well-designed epidemiologic studies are needed to determine the risk for beer intake and to establish the dose-response relationship.

In conclusion, our results do not indicate that alcohol consumption serves as a major risk factor for lung cancer among Japanese. Additional studies with detailed assessments of alcohol drinking and potential confounding factors are will undoubtedly lead to a more thorough understanding of the role of alcohol use in lung cancer development.

Acknowledgments

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（和文抄録）

日本人における飲酒と肺がんとの関連性：メタ分析

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　アルコールの生体に及ぼす害についての生物学的メカニズムは，いくつか示されているが明らかにされてはいない．アルコール飲用は口腔がん，咽頭がん，喉頭がん，食道がんおよび肝臓がんにおいては確立した危険因子である．しかし，アルコール飲用と肺がん発症との関連性を検討した疫学研究は一致した結果を示していない．そこで，日本人におけるアルコール飲用と肺がんとの関連性を明確にするために，著者らはメタアナリシスを行った．まず，交絡因子を調整しない粗統合リスクを算出した．粗統合リスクは0.65（95%信頼区間=0.53-0.77）であった．この推定された統合リスクは交絡因子，特にアルコール飲用と強く相関している喫煙を調整していないので，正しく統合リスクが評価されていないと考えられる．そこで，次に喫煙を調整した統合リスクを算出したところ，アルコール飲用と肺がんとの間の有意な負の関連性は消失した（調整統合リスク=1.00，95%信頼区間=0.73-1.26）．我々の結果は日本においてはアルコール飲用は肺がんの重要な危険因子ではないこを示唆している．今後，アルコール飲用や交絡要因についての詳細な評価を行うことにより，アルコール飲用による肺がん発症におけるアルコール飲用の役割についてのよりよい理解が得られると考えられる．