Alcohol drinking and bladder cancer risk from a pooled analysis of ten cohort studies in Japan

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Abstract

Background: The association of alcohol drinking with bladder cancer risk remains unclear in East Asian populations. Aldehyde dehydrogenase 2 (ALDH2) enzyme oxidizes alcohol-metabolized carcinogenic acetaldehyde into acetate. It is well known that the inactive ALDH2 carriers, specific to East Asian populations, have an increased risk of several cancer types because of increased exposure to acetaldehyde after alcohol consumption. The aim of this study was to examine the association between alcohol drinking and bladder cancer risk using data from ten population-based prospective cohort studies in Japan, where approximately 40% of the population has inactive ALDH2 enzyme.

Methods: We analyzed 340,497 Japanese participants with average follow-up of 13.4 years. The association between alcohol drinking and bladder cancer risk was evaluated using Cox regression models within each study, and random-effects models were used to estimate pooled hazard ratios (HR) with corresponding 95% confidence intervals (CI).

Results: During 4,729,071 person-years, 936 men and 325 women were newly
diagnosed with bladder cancer. Our results showed no evidence of significant
association between alcohol drinking and bladder cancer risk even among men who
consumed alcohol of $\geq 69$ g/week, with HR of 1.02 (95% CI, 0.79-1.33). The null result
was observed consistently among women.

**Conclusions:** Our findings do not support an association between alcohol drinking and
bladder cancer risk in the Japanese, at least without consideration of the polymorphisms
of alcohol-metabolizing enzymes.

**Key words:** alcohol drinking, bladder cancer, cohort study, Japan, pooled analysis
According to the GLOBOCAN 2018 database, bladder cancer is the 10th most common cancer worldwide, responsible for an estimated 549,000 new cases and 200,000 deaths in 2018. Cigarette smoking is a leading risk factor for bladder cancer, accounting for about 50% of all cases. Smoking cessation has been therefore recommended to prevent bladder cancer. Despite the efforts to promote smoking cessation, the age-standardized incidence of bladder cancer among Japanese men has been increasing from 10.6 in 2005 to 14.7 per 100,000 in 2010. Further primary prevention by identifying a modifiable risk factor other than smoking cigarette and avoiding its exposure is essential to decrease bladder cancer incidence.

Alcohol consumption is recognized as a risk factor for several types of cancer, including oral cavity, head and neck, esophagus, breast, liver and colorectum cancer. A previous meta-analysis showed no significant association between alcohol drinking and bladder cancer, although the analysis included only two East Asian studies. Thus, the impact of alcohol consumption on bladder cancer risk remains unclear in East Asian populations.
Approximately 540 million people in the world, mainly in East Asian countries, have been estimated to carry an inactive aldehyde dehydrogenase 2 (ALDH2) enzyme, which oxidizes alcohol-metabolized acetaldehyde into acetate. The ALDH2 enzyme activity is dependent on the polymorphism of the ALDH2 gene (rs671). Those with inactive ALDH2 alleles (inactive ALDH2 carriers) have been shown to be exposed to higher concentration of acetaldehyde after alcohol consumption, and alcohol-related acetaldehyde is classified by the International Agency for Research on Cancer (IARC) as group 1 carcinogen.

Our previous case-control study suggested that those with inactive ALDH2 alleles showed increased risk of bladder cancer among drinkers. Furthermore, moderate drinkers with flushing response, most of whom were considered to carry inactive ALDH2 alleles, had a higher risk of bladder cancer than those without flushing response in the Japanese cohort study. These two epidemiological studies consistently indicate that drinkers with inactive ALDH2 alleles may have an increased risk of bladder cancer. Given that the inactive ALDH2 alleles are specific to East Asian populations, alcohol drinking may have a strong effect of bladder cancer risk in East Asian populations.
compared with Western populations, implying carcinogenic effects of alcohol-related
acetaldehyde on the bladder.

To address this hypothesis, we examined the association of alcohol drinking
with bladder cancer from a pooled analysis of ten population-based cohort studies in
Japan, where approximately 40% of the population has inactive ALDH2 enzyme despite
some variation across areas.10, 11

Methods

Participants

Participants were collected from population-based prospective cohort studies in Japan.
Inclusion criteria for this pooled analysis have been described elsewhere.12 Ten
following studies met the criteria: the Japan Public Health Center-based Prospective
study (JPHC-I and -II),13 the Japan Collaborative Cohort Study (JACC),14 the Miyagi
Cohort Study (MIYAGI-I),15 the Three-Prefecture Cohort Study in Miyagi
(MIYAGI-II),16 the Three-Prefecture Cohort Study in Aichi (AICHI),16
Three-Prefecture Cohort Study in Osaka (Osaka),16 the Takayama Study
The selected characteristics of each study are shown in eTable 1. Participants with a past history of any cancer at baseline, with missing information on alcohol consumption or smoking, and with exposure to radiation of atomic bomb of equal to or more than 100 mGy (for LSS) were excluded. Data on 340,497 participants were finally analyzed. The study protocols were approved by the institutional review boards of respective study centers.

**Exposure data**

Information on alcohol consumption and smoking was collected using self-administered questionnaires in each study at baseline. According to frequency and amount of alcohol consumption, alcohol drinking was categorized as follows: non-drinkers (never and former drinkers), occasional drinkers (<1/week) and regular drinkers (≥1/week: 0.1-22.9, 23.0-45.9, 46.0-68.9, ≥69 g/day of ethanol) for men. For women, regular drinkers were summarized into one category because a preliminary analysis showed only about 2% of the women consumed more than 23 g/day of alcohol in the JPHC-I and –II (data not shown). Correlation coefficients between self-reported alcohol consumption and diet
records were 0.79 in men and 0.44 in women for the JPHC-I,\textsuperscript{20} 0.59 in men and 0.40 in women for the JPHC-II,\textsuperscript{21} 0.77 in men and 0.71 in women for the MIYAGI,\textsuperscript{22} 0.72 in men and 0.64 in women for the TAKAYAMA,\textsuperscript{23} 0.70 in men for the OHSAKI.\textsuperscript{24} The questionnaires similar to these studies were used in the other cohort studies although validation was not conducted.

**Statistical analysis**

Cancer cases were identified through population-based cancer registries and active patient notification from major local hospitals. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) or the International Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10).

Person-years of follow-up were counted from the date of baseline survey in each study until the date of bladder cancer diagnosis, migration from the study area, death or the end of follow up, whichever came first. Cox regression models were used to estimate hazard ratios (HR) with corresponding 95% confidence intervals (CI) in the following three models within each study. Model 1 was adjusted for age, area (for JPHC,
JACC and LSS), and smoking (pack-year category for men [0, 0.1-20, 20.1-40, 40<], smoking status category for women [never, former, current]). In model 2, cases diagnosed within 3 years from baseline were excluded. In model 3, the analysis was restricted to never smokers to minimize confounding by smoking. Furthermore, in model 4, the analysis was restricted to ever smokers to examine interaction between smoking and drinking. Trend associations were estimated by calculating the regression coefficient per 10g of ethanol increase and its standard error among current drinkers. Random-effects models were used to calculate pooled estimates. Heterogeneity among studies was assessed using Q-statistics and I² statistics. Statistical analyses were conducted using STATA statistical software version 13.1 (StataCorp LP, College Station, Texas, USA). All two-sided \( P \) values <0.05 were considered statistically significant.

**Results**

During the average follow-up of 13.4 years (4,729,071 person-years), 936 men and 325 women were diagnosed with bladder cancer. The frequencies of regular drinking were 71% among men and 14% among women. When adjusted for age, area and smoking
(model 1), no evidence of increased bladder cancer risk was observed for regular drinking (Table 1). Even among men who consumed alcohol of ≥69 g/week, HR was 1.02 (95% CI, 0.79-1.33). No significant linear trend between bladder cancer risk and alcohol consumption was also seen (HR 1.01; 95% CI, 0.99-1.03). These results were consistent with the analysis restricted to never smokers and ever smokers (model 3 and model 4), suggesting no significant interaction between smoking and drinking regarding bladder cancer risk. Furthermore, for women, regular drinkers showed no increased risk of bladder cancer compared with non-drinkers, as shown in Table 2.

Discussion

Our large-scale pooled analysis showed alcohol consumption was not associated with bladder cancer risk among Japanese populations. This finding was consistent with a previous meta-analysis, mainly consisting of Western population studies. A mechanistic role of alcohol drinking in the development of bladder cancer is plausible, given carcinogenic effects of alcohol-derived acetaldehyde. Acetaldehyde forms protein and DNA with adducts, leading to genotoxic and mutagenic effects.
Carcinogenic effects of alcohol-derived acetaldehyde have been also shown in epidemiological studies of esophagus, head and neck, and gastric cancer. Alcohol consumption caused increased concentration of urinary acetaldehyde among alcohol drinkers, suggesting increased carcinogenic effects on the bladder among drinkers.

On the contrary, the association between alcohol consumption and bladder cancer risk was not observed in the present study despite the high prevalence of inactive ALDH2 alleles in Japan. This may be explained by our previous finding that those with active ALDH2 alleles showed no increased risk of bladder even though they drank heavily. Moderate to heavy drinkers have more frequently active ALDH2 alleles than never to light drinkers. Thus, the frequent active ALDH2 alleles of moderate to heavy drinkers may lead to no significant association between alcohol consumption and bladder cancer. In addition, those with inactive ALDH2 alleles were shown to consume less amount of alcohol because of acetaldehyde-related adverse effect such as flushing, palpitations, nausea and headache. The carcinogenetic effect of the inactive ALDH2 alleles on the bladder may be therefore attenuated by decreased amount of alcohol consumption in inactive ALDH2 carriers. Another explanation for the null association
was the involvement of alcohol dehydrogenase 1B (ADH1B). The ADH1B enzyme metabolizes alcohol to acetaldehyde. Our previous study suggested that the fast alcohol-metabolizing ADH1B alleles, more prevalent in East Asian countries than Western countries, had a decreased risk of bladder cancer possibly due to reduced amount of alcohol consumption. This protective effect of fast alcohol-metabolizing ADH1B alleles may play some role in the null association. Because the present analysis did not examine either ALDH2 or ADH1B polymorphisms, these explanations remain just hypotheses. Nevertheless, the analysis without consideration of the genetic polymorphisms of alcohol-metabolizing enzymes may obscure true association between alcohol consumption and bladder cancer given the carcinogenetic effects of these polymorphisms. The present null result may therefore emphasize on future studies that investigated bladder cancer risk associated with alcohol consumption stratified by the ALDH2 and ADH1B polymorphisms in East Asians.

Several limitations should be noted. First, occupational information was unavailable although occupational chemical exposure was an established risk factor for bladder cancer. Second, limited number of women drinkers did not allow for
Despite these limitations, the data of this study were derived from large-scale population-based cohort studies in Japan, where those with inactive ALDH2 alleles are frequent unlike Western countries. The analysis restricted to never smokers allowed our results to remove confounding by smoking. Furthermore, prospective data collection can reduce information bias, inherent in retrospective study design. In conclusion, our results do not support an association between alcohol consumption and bladder cancer risk in the Japanese, without consideration of polymorphisms in alcohol-metabolizing enzymes.

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Conflicts of interest: None declared.
Appendix

Research group members are listed at the following site (as of August 2018):

http://epi.ncc.go.jp/en/can_prev/796/7955.html
References


Table 1. HRs and 95% CIs of bladder cancer risk according to drinking status and amount of alcohol drinking among current drinkers in men.

<table>
<thead>
<tr>
<th>Drinking status and amount of alcohol drinking among regular drinkers (g/week of ethanol)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-drinker</td>
</tr>
<tr>
<td></td>
<td>(&lt;1/week)</td>
</tr>
<tr>
<td></td>
<td>0.1-22.9</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>37,719</td>
</tr>
<tr>
<td>Person-years</td>
<td>486,764</td>
</tr>
<tr>
<td>Number of cases</td>
<td>247</td>
</tr>
<tr>
<td>HR1 (model 1)a</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td></td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>HR2 (model 2)b</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td></td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>HR3 (model 3)c</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.94-1.06)</td>
</tr>
<tr>
<td>HR4 (model 4)d</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td></td>
<td>1.02 (0.99-1.04)</td>
</tr>
</tbody>
</table>

*Model 1: adjusted for age (continuous), public health center area (JPHC, JACC and LSS only) and smoking (pack-year category; 0, 0-20, 20-40, 40+). |
*Model 2: model 1 excluding early cases (within the first 3 years). |
*Model 3: model 1 restricted to never smokers. |
*Model 4: model 1 restricted to ever smokers. |
*HRs are pooled from JPHC I/II, MIYAGI I/II, OSAKA and TAKAYAMA. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I/II, TAKAYAMA, OHSAMI and LSS. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I/II, TAKAYAMA and OHSAMI. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I, AICHI, TAKAYAMA and OHSAMI. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I, AICHI, OSAKA, TAKAYAMA, OHSAMI and LSS. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I, AICHI, OSAKA, TAKAYAMA, OHSAMI and LSS. |
*HRs are pooled from JPHC I/II, JACC, MIYAGI I, AICHI, OSAKA, TAKAYAMA, OHSAMI and LSS. |
HR, hazard ratio; CI, confidence interval.
Table 2. HRs and 95% CIs of bladder cancer risk according to drinking status in women.

<table>
<thead>
<tr>
<th>Drinking status</th>
<th>Non-drinker (&lt;1/week)</th>
<th>Occasional drinker (≥1/week)</th>
<th>Regular drinker (≥1/week)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>130,609</td>
<td>26,498</td>
<td>26,095</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>1,854,786</td>
<td>364,524</td>
<td>364,679</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>246</td>
<td>41</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>CR (per 100,000)</td>
<td>13.3</td>
<td>11.2</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>HR1 (model 1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00 (Ref)</td>
<td>1.31 (0.91-1.88)</td>
<td>0.96 (0.66-1.40)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.810 0</td>
</tr>
<tr>
<td>HR2 (model 2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (Ref)</td>
<td>1.51 (1.02-2.24)</td>
<td>1.10 (0.74-1.62)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.563 0</td>
</tr>
<tr>
<td>HR3 (model 3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00 (Ref)</td>
<td>1.48 (1.00-2.19)</td>
<td>1.11 (0.70-1.75)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.700 0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Model 1: adjusted for age (continuous), public health center area (JPHC, JACC and LSS only) and smoking (status category; never, former, current).

<sup>b</sup>Model 2: model 1 excluding early cases (within the first 3 years).

<sup>c</sup>Model 3: model 1 restricted to never smokers.

<sup>d</sup>HRs are pooled from JPHC I/II, JACC, MIYAGI I, AICHI, OSAKA, TAKAYAMA, OHSAKI and LSS.

<sup>e</sup>HRs are pooled from JPHC I/II, JACC, MIYAGI I, OSAKA, TAKAYAMA, OHSAKI and LSS.

<sup>f</sup>HRs are pooled from JPHC I/II, JACC, OSAKA, TAKAYAMA and LSS.

HR, hazard ratio; CI, confidence interval.