Estimates of alcohol-related oesophageal cancer burden in Japan: systematic review and meta-analyses
Michael Roerecke,^a Kevin D Shield,^b Susumu Higuchi,^c Atsushi Yoshimura,^d Elisabeth Larsen,^a Maximilien Rehm^c & Jürgen Rehm^a

Objective To refine estimates of the burden of alcohol-related oesophageal cancer in Japan.
Methods We searched PubMed for published reviews and original studies on alcohol intake, aldehyde dehydrogenase polymorphisms, and risk for oesophageal cancer in Japan, published before 2014. We conducted random-effects meta-analyses, including subgroup analyses by aldehyde dehydrogenase variants. We estimated deaths and loss of disability-adjusted life years (DALYs) from oesophageal cancer using exposure distributions for alcohol based on age, sex and relative risks per unit of exposure.
Findings We identified 14 relevant studies. Three cohort studies and four case-control studies had dose–response data. Evidence from cohort studies showed that people who consumed the equivalent of 100 g/day of pure alcohol had an 11.71 fold, (95% CI: 8.15–134.43) in the population at large. The difference by study design is explained by the 159 fold (95% CI: 27.2–938.2) risk among those with an inactive aldehyde dehydrogenase enzyme variant. Applying these dose–response estimates to the national profile of alcohol intake yielded 5279 oesophageal cancer deaths and 102 988 DALYs lost – almost double the estimates produced by the most recent global burden of disease exercise.
Conclusion Use of global dose–response data results in an underestimate of the burden of disease from oesophageal cancer in Japan. Where possible, national burden of disease studies should use results from the population concerned.

Introduction
Alcohol consumption is a major contributor to the global burden of disease^1,2 and is a major risk factor for cancer. Of all alcohol-related cancers, oesophageal has the highest alcohol-attributable fraction^3 – i.e. the highest proportion of these cancers would be prevented if no alcohol were consumed. The global burden of disease (GBD) study estimates that in 2010 alcohol-attributable oesophageal cancer resulted in 76 700 deaths and 1 825 000 disability adjusted life years (DALYs) lost, globally.

A large portion of oesophageal cancers attributable to alcohol consumption occur in Asian countries – 52.2% (40 000) of all alcohol-attributable oesophageal cancer deaths and 51.8% (9 450 000) of all alcohol-attributable oesophageal cancer DALYs. The alcohol-attributable portions for countries in this region have been calculated based on global meta-analyses. However, this assumes that the alcohol-attributable risk for oesophageal cancer is the same in all regions. Preliminary evidence, on the other hand, shows that the risk for this cancer is different for people of Asian origin, because of genetic polymorphisms – most importantly the aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) polymorphisms. Thus, the real risk and burden of alcohol-attributable oesophageal cancer in Asia may have been underestimated.

In Japan in 2010, oesophageal cancer was among the top 20 causes of years of life lost (11 deaths and 181 DALYs per 100 000 people per year). We did a systematic review and meta-analyses of studies conducted in the Japanese population to estimate the alcohol-attributable burden of oesophageal cancer. We then compared these estimates to the GBD 2010 estimates. We also estimated risk functions according to ALDH2 subsets and investigated potential interactions between ALDH2 and ADH1B polymorphisms.

Methods
Data search and selection
We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. We used the latest editions of the International Agency for Research on Cancer (IARC) monographs on alcohol to identify potentially eligible studies. Additionally, we searched PubMed for publications published before 2014. We did two searches using the following search terms; Search 1: “cancer or neoplasm or carcinom” and “ALDH2 or ADH1B or ADH2 or ADH3 or ADH1C or dehydrogenase” and “alcohol or ethanol”; Search 2: “alcohol or ethanol” and “cohort” and “cancer” and “Japan” and “review” and “mortality”. Inclusion criteria for analyses investigating the relationship between alcohol consumption, ALDH2, and oesophageal cancer were: (i) prospective or historical cohort or case-control study design; (ii) a measure of risk and its corresponding measure of variability was reported or there were sufficient data for us to calculate these; (iii) oesophageal cancer was reported as a separate outcome; (iv) data on total alcohol intake for at least two exposure categories among current drinkers, or estimates for ALDH2 variants by alcohol intake were reported; (v) risk estimates were at least age-adjusted; and (vi) the study was conducted in Japan after 1980. In addition, we searched reference lists of

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identifying articles for additional articles. No active filters or language restrictions were applied. We excluded measures of pure drinking frequency and qualitative characteristics – such as social or problem drinker. Oesophageal cancer cases (International Classification of Diseases [ICD] version 9: 150, ICD-10: C15) were defined as newly diagnosed at the first visit to a specialized clinic, through cancer registries or cause of death on death certificates.

Most quality scores for primary studies are tailored for meta-analyses of randomized trials of interventions17–19 and many criteria for such scores do not apply to epidemiological studies examined in this study. Additionally, quality score use in meta-analyses remains controversial.19,20 As a result, we included quality components in the inclusion and exclusion criteria of the systematic search and separate meta-analyses – such as study design and alcohol measurement – and conducted subgroup analyses based on study design and genetic polymorphisms.

**Data extraction**

From all relevant articles we extracted: authors' names, year of publication, country, calendar year(s) of baseline examination, follow-up period, setting, assessment of oesophageal cancer diagnosis, range of age at baseline, sex, number of observed oesophageal cancer cases among participants by alcohol exposure category, number of total participants by alcohol exposure category, adjustment for potential confounders and effect size with its standard error. We used the most fully adjusted effect size reported and selected estimates where lifetime abstainers were used as the risk reference group when those were available. Assessment of full-text articles with uncertain eligibility and exclusion criteria of the included and exclusion criteria of the systematic search and separate meta-analyses were assessed for eligibility and used the most comprehensive data analyses based on study design and genetic polymorphisms.

**Data analyses**

We conducted several meta-analyses and used the most comprehensive data available separately for each analysis when multiple reports from the same cohort were published. For studies providing data on two or more alcohol intake categories among current drinkers, we pooled data from (i) cohort studies; (ii) case-control studies; (iii) case-control studies that provided stratified data by ALDH2 variants. We conducted sensitivity analyses on the interaction between variants of ADH1B within the genetic variants of ALDH2. In analyses investigating ALDH2 variants, studies were pooled separately for the active variant (ALDH2*1/*1) and inactive variants (ALDH2*1/*2 and ALDH2*2/*2). No cohort studies provided ALDH2 genotype data. Where possible, we avoided ALDH2*2/*2 variants because of the low number of cases. No systematic information on the distribution of ALDH2 variants by drinking level was available and we therefore used the distribution of drinking by ALDH2 variants among controls in case-control studies to estimate this distribution at the population level. Finally, studies were pooled using DerSimonian-Laird random-effect models to allow for between-study heterogeneity.24 Variation in the effect size other than chance because of heterogeneity between studies was quantified using the F statistic.24 We conducted meta-regression analyses to identify study characteristics that influenced the association between alcohol consumption and oesophageal cancer risk. Because of few available studies, we were only able to investigate study design in such meta-regression analyses. Examination of potential publication bias using Egger’s regression-based test was planned, but was not done because of the few studies included. All meta-analyses were conducted on the natural log scale in Stata statistical software, version 12.1 (StataCorp LP, College Station, United States of America) and P < 0.05 (two-sided) was considered statistically significant.

We estimated deaths and DALYs lost from oesophageal cancer attributable to alcohol consumption in Japan applying a standardized alcohol-attributable fraction method27 using the sta-
Fig. 2. Risk curves for alcohol consumption and oesophageal cancer risk based on Japanese studies or the Global Burden of Disease 2010 study

Fig. 3. Risk curves for alcohol consumption and oesophageal cancer risk based on aldehyde dehydrogenase 2 polymorphisms, Japan

GBD: Global Burden of Disease; RR: relative risk.

ALDH2: aldehyde dehydrogenase 2; RR: relative risk.

Note: ALDH2*1/*1 corresponds to an active enzyme and ALDH2*1/*2 corresponds to an inactive enzyme.
tistical software package R, version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). These deaths and DALYs were estimated by comparing the risk difference of oesophageal cancer under current conditions compared to the risk of oesophageal cancer under the theoretical-minimum-risk exposure scenario where no one has consumed alcohol.1,7 These calculations combine information on the prevalence of alcohol consumption adjusted for per capita consumption and RRs for oesophageal cancer. Lifetime abstainers were used as the reference group and compared to former drinkers and current drinkers – by average daily alcohol consumption. Data on alcohol drinking status were obtained from the 2010 GBD study,1 where data on drinking status were based on data from large population surveys. Data on per capita consumption were from the Global Information System on Alcohol and Health.27 Calculations for Japan were based on RRs from this study and RRs for GBD estimates for Japan were based on Corrao et al.11

Results

After removal of duplicates, we evaluated 1333 records for inclusion in our study. Based on titles and abstracts, we excluded 1174 articles and screened 159 in full-text articles (Fig. 1). After excluding duplicate reports of the same cohorts, we analysed 11 case-control studies28–38 and 3 cohort studies.39–41 Eight case-control and cohort studies28–31 reported indirect evidence for only one alcohol intake category

<table>
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<tr>
<th>Polymorphism</th>
<th>Alcohol consumption, No. of individuals (%)</th>
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<tr>
<td></td>
<td>Non-drinker</td>
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<tr>
<td>Controls</td>
<td></td>
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<tr>
<td>ALDH2*1/*2</td>
<td>145 (18)</td>
</tr>
<tr>
<td>ALDH2*1/*1</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Oesophageal cancer cases</td>
<td></td>
</tr>
<tr>
<td>ALDH2*1/*2</td>
<td>18 (12)</td>
</tr>
<tr>
<td>ALDH2*1/*1</td>
<td></td>
</tr>
</tbody>
</table>

ALDH2: aldehyde dehydrogenase 2. Note: The ALDH2*1/*1 corresponds to an active enzyme and ALDH2*1/*2 corresponds to an inactive enzyme.

Data sources: Yokoyama et al.36 Yokoyama et al.33 Oze et al.34

Table 2. Distribution of alcohol consumption and the ALDH2 polymorphism in individuals with oesophageal cancer and study controls, Japan

Fig. 4. Risk curves for alcohol consumption and oesophageal cancer risk adjusted for aldehyde dehydrogenase 2 polymorphisms, Japan

As shown in Fig. 2, the risk for oesophageal cancer identified in cohort studies from Japan39–41 was higher compared with the most recent GBD estimate (RR: 11.71; 95% confidence interval, CI: 2.67–51.32 and RR: 3.59; 95% CI: 3.34–3.87, respectively at 100 g/day of pure alcohol intake). The risk

AldH2: aldehyde dehydrogenase 2; RR: relative risk.

Notes: AldH2*1/*1 corresponds to an active enzyme and AldH2*1/*2 corresponds to an inactive enzyme. The relative risk curves by study design overlap almost completely after adjustment for drinking levels at the population level by AldH2 variants.
identified in case-control studies\(^1_2\)–\(^3_5\) (RR: 11.88; 95% CI: 4.41–31.99 at 50 g/day of pure alcohol intake; RR: 33.11; 95% CI: 8.15–134.43 at 100 g/day of pure alcohol intake) was much higher than the Japanese cohort studies or GBD estimates. In a meta-regression, the difference between case-control studies and cohort studies was significant (\(P = 0.014\)). We observed moderate heterogeneity among cohort studies (\(I^2 = 60\%, \ P = 0.082\)), and high heterogeneity among case-control studies (\(I^2 = 89\%, \ P < 0.001\)).

The risk curves by ALDH2 variants in Japan are displayed in Fig. 3. Three case-control studies\(^3_{33}\)–\(^3_5\) provided dose–response data for an investigation of ALDH2 polymorphisms in reference to non-drinkers: ALDH2*1/*2 (372 cases) and ALDH2*1/*1 (151 cases). Inactive variants of ALDH2 enzyme showed markedly higher risks with increasing alcohol consumption. The RR compared to non-drinkers was 36.15 (95% CI: 10.34–126.40) at 50 g/day of pure alcohol and 159 (95% CI: 27.2–938.2) at 100 g/day of pure alcohol intake among people carrying the ALDH2*1/*2 variant. In comparison, the RR among those carrying the ALDH2*1/*1 variant was 2.99 (95% CI: 1.75–5.12) at 50 g/day of pure alcohol intake and 8.94 (95% CI: 3.05–26.23) at 100 g/day of pure alcohol. Based on two studies that included people with alcohol dependence (median 120 g/day of pure alcohol intake), people with the inactive variant of ALDH2 had an RR of 13.00 (95% CI: 8.99–18.80) compared to non-drinkers:28,29 We interpolated this difference in risk in the curve for ALDH2*1/*2 in Fig. 3, and held the risk increase among people with this ALDH2 variant constant beyond 100 g/day of pure alcohol intake because there were insufficient data to reliably estimate this risk function. Once case-control studies were stratified by ALDH2 variant, there was little or no heterogeneity (ALDH2*1/*1, \(I^2 = 0\%, \ P = 0.78\); ALDH2*1/*2, \(I^2 = 44\%, \ P = 0.17\)). Another two studies,\(^6_{31}\) although they did not provide data in reference to non-drinkers, were in close agreement with our reported risk functions.

With regard to differences in risk curves by study design, Table 2 shows that among case-control studies with multiple alcohol intake categories, 72% (350/483) of oesophageal cancer cases among drinkers occurred in 32% (313/980) of the drinking population, namely individuals with the genetic variant ALDH2*1/*2. When the risk curves from case-control studies (Fig. 3) were combined (weighted by their distribution of alcohol consumption by ALDH2 variants at the population level) the risk functions from case-control and cohort studies almost entirely overlapped (Fig. 4). Combining adjusted case-control and cohort studies, at 100 g/day pure alcohol intake, the risk in Japan was markedly elevated (RR: 11.65, 95% CI: 4.16–32.62) compared to GBD estimates (RR: 3.55, 95% CI: 3.30–3.82) (Fig. 5).

To investigate the interaction between ALDH2 and ADH1B gene variants, we performed a sensitivity analysis using five of the 11 identified case-control studies.\(^29_{31,36–38}\) Regardless of ALDH2 variant, the pooled RRs were higher for Japanese with the slow-acting ADH1B*1/*1 variant than for Japanese with the fast-acting ADH1B*1/*2 or *2/*2 variants. The RR was 3.99 (95% CI: 2.41–6.61; \(I^2 = 81\%, \ P < 0.001\)) and 2.40 (95% CI: 1.92–3.16; \(I^2 = 1\%, \ P = 0.40\)) for individuals with an inactive and active ALDH2, respectively (Fig. 6 and Fig. 7).

Using our calculated risk relations for alcohol-attributable oesophageal cancer results in almost twofold higher estimates for deaths (5279) and DALYs lost (102 988) compared with the current GBD estimates (2749 and 53 826, respectively; Table 3). These results are irrespective of whether the estimates were based on cohort studies or on case-control studies, in each case.
Table 3. Estimated mortality and burden of disease for alcohol-attributable oesophageal cancer in Japan 2010

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>No. of DALYs</td>
<td>No. of deaths</td>
</tr>
<tr>
<td>GBD 2010</td>
<td>202</td>
<td>3 089</td>
<td>2 547</td>
</tr>
<tr>
<td>Japanese cohort studies</td>
<td>346</td>
<td>5 498</td>
<td>4 925</td>
</tr>
<tr>
<td>Japanese adjusted case-control studies</td>
<td>346</td>
<td>5 514</td>
<td>4 933</td>
</tr>
</tbody>
</table>

DALYs: disability-adjusted life-years; GBD: Global Burden of Disease.
well, where a considerable proportion of the population also carry the inactive ALDH2 allele, (34% and 29%, respectively). In populations with a high proportion of these polymorphisms, studies based on global dose response data are likely to underestimate many alcohol-attributable cancers. Efforts should be made to estimate country-specific risks for diseases affected by genetic polymorphisms, especially in countries with higher proportions of such polymorphisms. The current standard of applying global risk functions to local exposure data should be replaced by country-specific risk functions whenever possible. Country-specific risk functions should also be applied for other risk factors than alcohol. This will allow for better estimation of the burdens caused by risk factors and consequently better informed policy measures.

Competing interests: SH has received grants from Lundbeck Japan during the conduct of the study; grants from the Japanese government, Lundbeck Japan, Santory, grants and personal fees from Nippon Shinyaku, outside the submitted work. JR has received an unrestricted grant from Lundbeck pharmaceuticals for the study. The other authors declare no competing interests.
Estimaciones de la carga del cáncer esofágico relacionado con el consumo de alcohol en Japón: una revisión sistemática y metaanálisis

Objetivo Refinar las estimaciones de la carga del cáncer esofágico relacionado con el consumo de alcohol en Japón.

Métodos Se buscaron revisiones y estudios originales publicados antes de 2014 sobre la ingesta de alcohol, polimorfismos del aldehído deshidrogenasa y el riesgo de cáncer de esófago en Japón en la base de datos PubMed. Se efectuaron metaanálisis de efectos aleatorios, que incluían análisis de subgrupos de variantes del aldehído deshidrogenasa y se estimaron las muertes y la pérdida de años de vida ajustados por discapacidad (AVAD) por cáncer de esófago mediante distribuciones de exposición para el alcohol basadas en la edad, el sexo y los riesgos relativos por unidad de exposición.

Resultados Se identificaron 14 estudios pertinentes. Tres estudios de cohorte y cuatro estudios de casos y controles contenían datos sobre la respuesta en relación con la dosis. Las pruebas de los estudios de cohorte demostraron que el riesgo de cáncer esofágico de que quienes consumen 100 g/día de alcohol puro era 11,71 veces mayor (intervalo de confianza del 95% [IC]: 2,67–51,32) que el de quienes nunca consumieron alcohol. Las pruebas de los estudios de casos y controles demostraron que el riesgo de desarrollar un cáncer de esófago por consumo de alcohol es de 33,11 veces superior (IC a 95%: 8,15–134,43) entre personas con un variant de aldehído deshidrogenasa. En aplicando estas estimaciones de dose-réponse al perfil nacional de consumo de alcohol, las personas que consumen el equivalente de 100 g/día de alcohol puro tienen un riesgo de 11,71 veces superior de desarrollar un cáncer de esófago en comparación con aquellos que nunca consumieron alcohol.

Conclusion L’application de ces estimations de dose-réponse au profil national de consommation d’alcool, nous sommes arrivés à 5279 décès et 102 988 EVCI dus au cancer de l’œsophage – soit presque le double des estimations produites par la plus récente charge globale de la maladie.

Resumen

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Conclusion L’utilisation de données globales de dose-réponse se traduit par une sous-estimation de la charge de morbidité pour le cancer de l’œsophage au Japon. Dans la mesure du possible, la charge nationale des études portant sur les maladies devrait utiliser les résultats obtenus sur la population concernée.
inactiva de la enzima aldehído deshidrogenasa. La aplicación de estas estimaciones de la respuesta en relación con la dosis al perfil nacional del consumo de alcohol dio lugar a la notificación de 5279 muertes de cáncer esofágico y 102 988 AVAD perdidos, lo equivale a casi el doble de las estimaciones producidas por la carga mundial más reciente de la actividad de la enfermedad.

### References


Conclusión El uso de datos mundiales sobre la respuesta en relación con la dosis da lugar a una subestimación de la carga de enfermedad de cáncer esofágico en Japón. Siempre que sea posible, los estudios sobre la carga nacional de la enfermedad deben utilizar los resultados de la población afectada.


<table>
<thead>
<tr>
<th>Study and year</th>
<th>Study design (follow-up)</th>
<th>Setting</th>
<th>Study period, age and sex</th>
<th>No. of cases and controls</th>
<th>Case and control identification</th>
<th>Alcohol assessment</th>
<th>Adjustment</th>
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<tbody>
<tr>
<td>Yokoyama et al., 1998</td>
<td>Case-control</td>
<td>National Institute on Alcoholism, Kurihama National Hospital</td>
<td>1987–1997, ≥ 40 years, men</td>
<td>Cases: 87, whereof ALDH2*1/<em>1: 41, ALDH2</em>1/<em>2: 46 and ALDH2</em>2/*2: 46 Controls: 487</td>
<td>Cases: SCC histologically diagnosed at alcohol treatment entry or before onset of alcoholism Controls: cancer-free алкоголics</td>
<td>Alcohol dependence (DSM-III), mean alcohol intake 123 g/day</td>
<td>Age at admission to alcohol treatment, daily alcohol consumption, number of cigarettes</td>
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<td>Takezaki et al., 2000</td>
<td>Case-control</td>
<td>Aichi Cancer Centre</td>
<td>1988–1997, 40–79 years, men</td>
<td>Cases: 284 Controls: 11 384 (former alcohol drinkers were excluded in the analysis)</td>
<td>Cases: first-out-visit outpatients diagnosed with primary cancer of the oesophagus (ICD-9: 150, ICD-10: C15) Controls: first-out-visit outpatients confirmed to be cancer-free (including no history of cancer assessed by questionnaire)</td>
<td>Drinking levels never or occasionally, former drinkers, current drinkers &lt; 1.5 drinks/day, ≥ 1.5 drinks/day. One drink = 1 go (Japanese sake with 27 mL ethanol)</td>
<td>Age, year, and season of visit, smoking (never, former, current, &lt; 30 and ≥ 30 pack-years), consumption of raw vegetables</td>
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<tr>
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<td>Case-control</td>
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<td>1993–2000, ≥ 40 years, men</td>
<td>Cases: 112, whereof ALDH2*1/<em>1: 50, ALDH2</em>1/<em>2: 62 and ALDH2</em>2/*2: 56 Controls: 526</td>
<td>Cases: SCC histologically diagnosed at alcohol treatment entry or before onset of alcoholism Controls: cancer-free алкоголics</td>
<td>Alcohol dependence (DSM-III), mean alcohol intake 123 g/day</td>
<td>Age at admission to alcohol treatment, daily alcohol consumption, number of cigarettes</td>
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<td>Matsuo et al., 2001</td>
<td>Case-control</td>
<td>Aichi Cancer Centre</td>
<td>1984–2000, 40–76 years, women and men</td>
<td>Cases: 102, whereof ALDH2*1/<em>1: 35, ALDH2</em>1/<em>2: 66, ALDH2</em>2/*2: 1 Controls: 241</td>
<td>Cases: first diagnosis for oesophageal cancer Controls: first-out-visit outpatients confirmed to have no oesophagus or stomach cancer</td>
<td>Drinking status (2 categories): &gt; 3 go (Japanese sake with 75 mL pure alcohol/day ≥ 5 times per week, and all others (non-drinkers and drinkers with ≤ 3 go per day and &lt; 5 times per week)</td>
<td>Age, smoking (never, former, current, &lt; 30 and ≥ 30 pack-years), consumption of raw vegetables</td>
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<td>Yokoyama et al., 2002</td>
<td>Case-control</td>
<td>National Cancer Centre Hospital, National cancer Centre Hospital East, Kawasaki Municipal Hospital, National Osaka Hospital</td>
<td>2000–2001, 40–79 years, men</td>
<td>Cases: 220 SCC, whereof ALDH2*1/<em>1: 60, ALDH2</em>1/*2: 160 Controls: 590</td>
<td>Cases: SCC newly diagnosed by histology within 3 years before registration in study Controls: cancer-free men who visited two Tokyo clinics for annual health check-up</td>
<td>Drinking levels non- or rare drinkers, former drinkers, current drinkers 1–8.9 U/week, 9–17 9 U/week, ≥ 18 U/week U = unit of alcohol (1 serving of sake, 22 g pure alcohol/U)</td>
<td>Age, frequency of drinking strong alcoholic beverages, smoking (pack-years), intake frequency of green-yellow vegetables, intake frequency of fruits</td>
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<tr>
<th>Study and year</th>
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<td>2000–2001, 40–79 years, men</td>
<td>Cases: 220 SCC Controls: 598 (former alcohol drinkers were excluded in the analysis)</td>
<td>Cases: SCC newly diagnosed by histology within 3 years before registration in study Controls: cancer-free men who visited two Tokyo clinics for annual health check-ups</td>
<td>Drinking levels non- or rare drinkers, former drinkers, current drinkers 1–8.9 U/week, 9–17.9 U/week, ≥ 18 U/week. U = unit of alcohol (1 serving of sake, 22 g pure alcohol/U)</td>
<td>Age, frequency of drinking strong alcoholic beverages, smoking (pack years), intake frequency of green-yellow vegetables, intake frequency of fruits</td>
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<td>Nakaya et al., 2005</td>
<td>Cohort (7 years follow-up)</td>
<td>Miyagi II</td>
<td>1990–1997, 40–64 years, men</td>
<td>Cases: 48 among 19607 participants (former alcohol drinkers were excluded in the analysis)</td>
<td>Cases were identified via record linkage to cancer registry</td>
<td>Drinking levels five categories based on drinking frequency and amount per occasion: never, former-drinkers, current drinkers &lt; 22.8 g pure alcohol/day, 22.8–45.5 g/day, and ≥ 45.6 g/day</td>
<td>Age, smoking (never, former, current 1–19 cigarettes per day, 20–29 per day, 30 or more per day), education, daily consumption of orange and other fruit juice, spinach, carrot or pumpkin, and tomato</td>
</tr>
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<td>Yokoyama et al., 2006</td>
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<td>National Cancer Centre Hospital, National cancer centre Hospital East, Kawasaki Municipal Hospital, National Osaka Hospital</td>
<td>2000–2004, 40–79 years, women</td>
<td>Cases: 43 SCC, whereof ALDH2*1/<em>1: 25, ALDH2</em>1/*2: 18 Controls: 365</td>
<td>Cases: SCC newly diagnosed by histology within 3 years before registration in study Controls: cancer-free women who visited two Tokyo clinics for annual health check-up</td>
<td>Drinking levels non- or rare drinkers, former drinkers, current drinkers &lt; 54 mL pure alcohol/day, 54–80 mL/day, ≥ 81 mL/day</td>
<td>Age, smoking (pack years), intake frequency of green-yellow vegetables, intake frequency of fruits, preference for hot food or drinks</td>
</tr>
<tr>
<td>Ozasa et al., 2007</td>
<td>Cohort (not reported)</td>
<td>JACC</td>
<td>1988–1990, 40–79 years, men</td>
<td>Cases: 117 among 42,578 participants (former alcohol drinkers were excluded)</td>
<td>Death certificates (ICD-10: C15)</td>
<td>Drinking levels non- or rare drinkers, former drinkers, current drinkers &lt; 54 mL pure alcohol/day, 54–80 mL/day, ≥ 81 mL/day</td>
<td>Age, study area</td>
</tr>
<tr>
<td>Cui et al., 2009</td>
<td>Case-control</td>
<td>Biobank Japan</td>
<td>2003–2008, 35–85 years, men and women</td>
<td>Cases: 1066, whereof ALDH2*1/<em>2: 735, ALDH2</em>1/<em>1 and ALDH2</em>2/*2: 331 Controls: 2761</td>
<td>Cases: histologically diagnosed SCC Controls: volunteers or registered in Biobank for diseases other than cancer</td>
<td>Drinking status: none/rare (0–96.5 g pure alcohol/week), and other drinkers (≥ 96.5 g/week)</td>
<td>Age, gender (analyses among heavy alcohol consumers, &gt; 96.5 g/week)</td>
</tr>
<tr>
<td>Ishiguro et al., 2009</td>
<td>Cohort (14 years follow-up)</td>
<td>JPHC I+II</td>
<td>1990 and 1993, 40–59 years, men</td>
<td>Cases: 215 SCC among 60,876 participants</td>
<td>Active patient notification from hospital and linkage to Cancer Registry (ICD-0–3: C15.0–15.9)</td>
<td>Drinking levels non-drinkers, less than weekly drinking (frequency only), 1–149 g pure alcohol/week, 150–299 g/week, ≥ 300 g/week</td>
<td>Age, study area, body mass index, preference for spicy food and drinks, smoking status (never, past, current), flushing response</td>
</tr>
</tbody>
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(continues . . .)
<table>
<thead>
<tr>
<th>Study and year</th>
<th>Study design</th>
<th>Setting</th>
<th>Study period, age and sex</th>
<th>No. of cases and controls</th>
<th>Case and control identification</th>
<th>Alcohol assessment</th>
<th>Adjustment</th>
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<tr>
<td>Oze et al., 2010</td>
<td>Case-control</td>
<td>Aichi Cancer Centre</td>
<td>2001–2005, ≥ 18 years, men and women</td>
<td>Cases: 260, whereof ALDH2*1/<em>1: 67, ALDH2</em>1/<em>2 and ALDH2</em>2/*2: 198 Controls: 487</td>
<td>Cases: first out-visit outpatients diagnosed with primary cancer of the oesophagus (ICD-10: C15) Controls: First-visit outpatients confirmed to be cancer-free (including no history of cancer assessed by questionnaire)</td>
<td>Drinking levels: never, moderate (≤ 4 days/week), high-moderate (≥ 5 days/week and &lt; 46 g pure alcohol/occasion), heavy (≥ 5 days/week and ≥ 46 g/occasion)</td>
<td>Frequency matched by age group (&lt; 40, 40–49, 50–59, 60–69, ≥ 70 years) and sex. Adjustment for cumulative smoking, facial flushing, fruit and vegetable intake, frequent intake of hot beverages and body mass index</td>
</tr>
<tr>
<td>Yang et al., 2005</td>
<td>Case-control</td>
<td>Aichi Cancer Centre</td>
<td>2000–2004, 18–79 years, men and women</td>
<td>Cases: 165, whereof ALDH2*1/<em>1: 38, ALDH2</em>1/<em>2 and ALDH2</em>2/*2: 127 Controls: 495</td>
<td>Cases: histologically diagnosed with primary cancer of the oesophagus (159 SCC, 6 adenocarcinomas) Controls: first-visit outpatients confirmed to be cancer-free (including no history of cancer assessed by questionnaire)</td>
<td>Drinking levels: non-drinker, non-heavy drinkers (&lt; 5 drinking days/week and &lt; 50 g pure alcohol/occasion) and heavy drinkers (drinking ≥ 5 days/week and ≥ 50 g pure alcohol/occasion) were adjusted for in regression model as reported</td>
<td>Age, sex, smoking, drinking</td>
</tr>
<tr>
<td>Tanaka et al., 2010</td>
<td>Case-control</td>
<td>Juntendo University Hospital, National Cancer Center Hospital, Kurume University Hospital, Saitama Cancer Center, Kagoshima University Hospital, Kyushu University Hospital</td>
<td>2000–2008, 35–85 years, men and women</td>
<td>Cases: 742, whereof ALDH2*1/<em>1: 194, ALDH2</em>1/<em>2 and ALDH2</em>2/*2: 548 Controls: 820</td>
<td>Cases: pathologically newly diagnosed SCC Controls: healthy controls without cancer history recruited from Kyushu University and Hospital and related hospitals</td>
<td>Drinking levels: non-drinker and ever drinkers</td>
<td>Sex, age, study area</td>
</tr>
</tbody>
</table>

ADH1B: alcohol dehydrogenase 1B; ALDH2: aldehyde dehydrogenase 2; DSM: diagnostic statistical manual; ICD: International Classification of Diseases; JACC: Japan collaborative cohort study; JPHC: Japan public health centre-based prospective study; SCC: squamous cell carcinoma of the oesophagus.

* Included in the sensitivity analysis on interaction between ALDH2 and ADH1B on oesophageal cancer risk in Japan.

Note: ALDH2*2/*2 was excluded in our analyses wherever possible because of the low number of cases.