

Association between alcohol flushing syndrome and cancer: A systematic review and meta-analysis

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ABSTRACT

Introduction: Alcohol flushing syndrome (AFS) is experienced by up to 46% of East Asians. This study aimed to review the risk of cancers in AFS patients, elucidate an exposure-response relationship, and understand risk associated with alcohol intake and cancer.

Method: An electronic database search of PubMed, Embase, Scopus and Cochrane Library was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Observational studies on AFS' effects and all cancers risk were included. Studies including patients with existing malignancy were excluded. Dichotomous variables were pooled using the Mantel-Haenszel method with a random effects model. Sensitivity and subgroup analyses were performed. PROSPERO (CRD42023392916) protocol was followed.

Results: A total of 18 articles were included in the final analysis with a total of 387,521 participants. AFS was associated with an increased risk of all cancers (odds ratio [OR] 1.19, 95% confidence interval [CI] 1.06–1.34), esophageal squamous cell carcinoma (OR 1.47, 95% CI 1.05–2.05) and gastric adenocarcinoma (OR 1.40, 95% CI 1.14–1.72). Men with AFS exhibited an increased risk of all cancers (OR 1.34, 95% CI 1.13–1.59). However, this was not observed in women. All cancers risk was associated with AFS in those who consumed drink (i.e. consumed alcohol) more than 200 g of pure ethanol/week (OR 1.68, 95% CI 1.20–2.37) but not those who consumed less than 200 g of pure ethanol/week (OR 1.27, 95% CI 0.90–1.79) or non-drinkers (OR 0.99, 95% CI 0.67–1.47).

Conclusion: AFS is associated with an increased risk of all cancers, particularly esophageal squamous cell carcinoma and gastric adenocarcinoma.

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Keywords: alcohol, alcohol dehydrogenase, alcohol flushing syndrome, aldehyde, cancer

CLINICAL IMPACT

What is New

- Alcohol flushing syndrome (AFS) is observed to be associated with an increased risk of cancer incidence.
- The risk of cancer increases with the amount of alcohol consumed by those with AFS, providing preliminary evidence of an exposure-response relationship that was not consistently observed in previous studies.

Clinical Implications

- It is important for clinicians to educate and increase public awareness of the association between AFS and increased risk of cancer.

INTRODUCTION

Alcohol flushing syndrome (AFS) is characterised by intense facial flushing, often accompanied by palpitations, headache and nausea shortly after the consumption of alcohol. This phenomenon occurs in up to 46% of East Asians and to a much lesser extent Caucasians, due to the accumulation of acetaldehyde, a metabolic byproduct of catabolism of alcohol. This results from a combination of increased production by fast metabolising alcohol dehydrogenase (ADH) enzyme and reduced clearance due to a slow metabolising or inactive aldehyde dehydrogenase (ALDH) enzyme.¹ Despite the discomfort associated with drinking (i.e. consume alcohol), many people with AFS continue to consume alcohol with societal pressures as one reason.²⁻⁴

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To date, the relationship between AFS and esophageal squamous cell carcinoma (ESCC) is the most well-studied association in previous systematic reviews. In a review of 7 studies, Andric et al. reported a positive association between AFS and ESCC.¹ This increase in risk of cancer for flushers, compared to non-flushers who consumed the same amount of alcohol, was even more pronounced at higher levels of regular alcohol consumption and indicated preliminary evidence of a dose relationship.¹ More recently in 2017, Zhang et al.⁵ found a similar positive association between AFS and cancer; however, subgroup analyses did not demonstrate a significant association for women and a dose-response relationship could not be elucidated due to lack of granularity on alcohol consumption amounts.⁵ Apart from the lack of well-defined association between AFS and non-ESCC cancers such as gastric carcinomas, 8 new studies have also emerged reporting the association of AFS with other cancers such as pancreatic cancer,⁶ bladder cancer⁷ and lung cancer.⁸

This study aimed to systematically review the risk of all cancers associated with AFS and to examine for the presence of an exposure-response relationship.

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines was used in the synthesis of this review, with the PRISMA checklist completed (Supplementary Appendix S1). An electronic database search of PubMed, Embase, Scopus and Cochrane Library was performed on 18 January 2023 using keywords and terms synonymous with “alcohol flushing syndrome” and “cancer”. An example of the search strategy has been included in Supplementary Appendix S2. The references of included articles were also assessed for suitability for inclusion. A re-run of the search was also performed across all databases on 17 August 2023 with no new relevant studies identified.

The inclusion criteria comprised observational studies, including cohort studies and case-control studies, reporting on the effect of AFS and the risk of all types of cancer. Exclusion criteria include grey literature, studies that were not in English, or studies with participants with a current or history of malignancy.

Article selection was performed by 2 authors based on the inclusion and exclusion criteria. Any discrepancy was resolved based on consensus with a third author. Data extraction was performed by the blinded pair of authors, where blinded details

include author, year of publication, title, country of origin, study design, clinical setting, patient population, comparators, number of participants, mean age, and odds ratios comparing the risk of cancer in patients who flush and those who do not.

Data analysis was performed using Revman version 5.4 (The Cochrane Collaboration, 2020) and R studio version 1.3.1093 (R Foundation for Statistical Computing, 2020) in accordance with statistical approaches laid out by the Cochrane Handbook. Dichotomous variables were pooled using the Mantel-Haenszel with a random effects model and adjusted ratios were used whenever available. Sensitivity analysis using only adjusted outcomes was performed. Next, subgroup analyses were performed based on the location of cancer, alcohol consumption status and sex. Statistical significance was considered at a P value of ≤ 0.05 . Heterogeneity was assessed with Cochran Q test and I^2 test, with a significance value at $P \leq 0.10$ or $I^2 \geq 40\%$, respectively. Publication bias was assessed by visual inspection of funnel plots when sufficient studies were available ($n > 10$).

Risk of bias for observational studies was assessed by the 2 authors in the blinded pair using the Newcastle-Ottawa Scale, which grades studies as having a high (< 5 stars), moderate (5–7 stars) or low (≥ 8 stars) risk of bias. Studies with a high risk of bias were excluded from data synthesis. This systematic review was submitted to PROSPERO (CRD42023392916) on 18 January 2023 prior to its commencement.

RESULTS

The search strategy yielded 1853 potentially relevant articles. After the titles and abstract were screened, 111 full-text articles were reviewed, of which 18 were included in the final analysis (Fig. 1). Studies that investigated the association between AFS and cancer but contained strong confounders were excluded; for example, Harada et al.⁹ was excluded after full-text reviews due to the presence of strong confounders, as the study evaluated patients with oral and pharyngeal squamous cell carcinoma. Four studies by Yokoyama et al. have been included based on differences in recruitment methodologies, outcomes of interest, time periods and study designs leading to a low likelihood of data overlap.^{10–13} Of the 18 included articles, 14 were from Japan,^{6,7,10–21} 3 were from China^{8,22,23} and 1 was from Taiwan,²⁴ with a collective total of 387,521 participants. Eight new studies^{6–8,19–21,23,24} were included and were not previously analysed by Zhang et al.⁵ The characteristics of included studies including patient demographics, smoking percentages, alcohol consumption amounts and

quality assessment are in Table 1.

AFS was associated with an increased risk of all cancers (OR 1.19, 95% CI 1.06–1.34) (Fig. 2), with pooled adjusted OR (OR 1.43, 95% CI 1.12–1.82) (Supplementary Fig. S1). Alcohol consumption was associated with an increased incidence of ESCC (OR 1.47, 95% CI 1.05–2.05) (Fig. 3) and gastric adenocarcinoma (OR 1.40, 95% CI 1.14–1.72) (Fig. 3). There was no significant association found between drinking alcohol and oral and pharyngeal squamous cell carcinoma (OR 1.00, 95% CI 0.77–1.29) (Fig. 3).

Flushing was associated with increased risk of all cancers in men (OR 1.34, 95% CI 1.13–1.59) (Fig. 4) but this association was not seen in women (OR 1.00, 95% CI 0.88–1.14) (Fig. 4). A further subgroup analysis was supportive of an increased risk of ESCC in male flushers (OR 2.06, 95% CI 1.19–3.56) (Supplementary Fig. S2).

In the subgroup analysis based on alcohol consumption levels, flushers who consumed more alcohol than 200 g of pure ethanol/week (OR 1.68, 95% CI 1.20–2.37) (Fig. 5) had a higher risk of cancer compared to those who consumed less than 200 g of pure ethanol/week (OR 1.27, 95% CI 0.90–1.79) (Fig. 5). Flushers who were non-drinkers were not observed to have an increased risk of cancer (OR 0.99, 95% CI 0.67–1.47) (Supplementary Fig. S3).

Another subgroup analysis based on flushing status did not show a significant difference in risk of all cancers among current (OR 0.98, 95% CI 0.56–1.72) and former (OR 1.49, 95% CI 0.77–2.87) flushers (Supplementary Fig. S4).

The largely symmetrical funnel plot of the 18 studies did not indicate publication bias (Supplementary Fig. S5).

DISCUSSION

With the rising prevalence of alcohol consumption, notably in Asian countries, it is salient to inspect the health impacts of AFS, which reportedly affect 36% of East Asians²⁵ or around 610,000,000 people. Our analysis of 18 studies involving 387,521 participants supported the association between AFS and cancer, consistent with previous studies. Additionally, subgroup analyses also delineated an increased risk of ESCC and gastric adenocarcinoma while newly emerged studies on bladder⁷ and pancreatic⁶ cancers were also included in our analysis.

Acetaldehyde increases the risk of cancer through several mechanisms including the alteration of deoxyribonucleic acid (DNA) replication, formation of DNA adducts that may trigger replication errors or mutations, and impairment of DNA repair.²⁶

These mechanisms require the exposure of tissues to elevated levels of acetaldehyde, which accounts for the strong association of flushing with upper aerodigestive tract cancers.⁵ ADH is mainly expressed in the liver and gastrointestinal tract such as the esophagus and the stomach, whereas expression in the oral cavity may be lower.²⁷ While most of the alcohol ingested is processed by class I ADH in the liver, class IV ADH such as ADH7 is expressed in the esophagus and stomach²⁸ and is responsible for the first-pass metabolism of alcohol²⁹ contributing to the local aldehyde exposure.²⁸ The differential expression of ADH in various tissues may explain the different associations of AFS with various cancers. Importantly, while squamous cell carcinomas are well known to be associated with smoking and alcohol consumption, the relationship for adenocarcinomas are less defined. This study delineated the increased risk of gastric adenocarcinoma with facial flushing, and their association is also likely due to the local toxic effect of acetaldehyde that has similarly been reported by other studies.³⁰

The gut microbiome may also have a role to play in the pathogenesis of cancer by affecting the local exposure to acetaldehyde, thereby modulating the risk of cancers at different sites. For example, microbial formation of acetaldehyde can occur in the oral cavity due to the presence of certain bacteria and yeasts,³¹ while *Helicobacter pylori* in the stomach can oxidise ethanol into acetaldehyde,³² demonstrating how dysbiosis can lead to an increased risk of cancer.^{31,33–35} Additionally, genetic mutations can further contribute to the aldehyde-mediated risk of cancer by causing DNA damage and potentially triggering the carcinogenesis of BRCA2 (BRCA2) cancers.³⁶ Furthermore, it has also been shown that acetaldehyde concentrations are increased in gastric contents among those with ALDH2 deficiencies,³⁷ which may account for the strong associations in upper aerodigestive tract cancers compared to cancers of other sites, such as the breast, endometrium and bladder.³⁰

Interestingly, in a subgroup analysis of 10 studies^{6–8,10,13–16,21} using unadjusted data (Fig. 5), a consumption level of ≥ 200 g of pure ethanol/week (estimated based on US National Institute of Alcohol Abuse and Alcoholism guideline for moderate consumption of more than 14 drinks/week, which is approximately 196 g of pure ethanol/week³⁸) was associated with increased risk of all cancers in flushers, but there was no increased risk observed when consumption amounts are < 200 g of pure ethanol/week. This preliminary evidence of an exposure-response relationship was also previously reported by Oze et al. for

Table 1. Characteristics of included studies.

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Yokoyama ¹²	2003a	Japan	271 (71/200)	All males	ESCC	Case: 56.7 (7.1) Control: 54.9 (8.9)	Smoking, % Case: 93.8 Control: 92.1	Cases/control, mean (SD) 10.2 (0.8)/10.4 (0.4) drinks per day		7
Yokoyama ¹³	2003b	Japan	843 (469/374)	All males	ESCC	Case: 61.7 (7.9) Control: 58.9 (7.1)	Smoking, % Case: 91 Control: 71.9	Drinking <196 g/week, % Case: 12.5 Control: 58.1 ≥196 g/week, % Case: 82 Control: 40.2 Ex-drinker, % Case: 5.6 Control: 1.7	Vegetable intake, % (1–2 days/week) Case: 90.5 Control: 96.7	7
Yokoyama ¹⁰	2006a	Japan	655 (120/535)	All males	Upper aerodigestive tract and ESCC	Age group: no. 40–49: 221 50–59: 250 60–69: 153 70–79: 31	No. (%) of drinkers based on age groups <20: 246 (37.6) 20–29: 234 (35.7) ≥30: 175 (26.7)	Drinking ≤99 g/day, % Case: 46.6 Control: 52.3 ≥100 g/day Case: 53.4 Control: 47.7		8
Yokoyama ¹¹	2006b	Japan	457 (199/258)	All females	ESCC	Case: 63.0 (8.8) Control: 58.7 (7.6)	Drinking, % Case: 42.3 Control: 17.5	Drinking <196 g/week, % Case: 67.3 Control: 88.8 ≥196 g/week, % Case: 25 Control: 8.5 Ex-drinker, % Case: 7.7 Control: 2.7	Vegetable intake, % (1–2 days/week) Case: 88.5 Control: 98 Hot tea consumption, % (likes very much or likes somewhat) Case: 48.1 Control: 31.2	7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Asakage ¹⁴	2007	Japan	738 (352/386)	All males	Oral cavity and pharynx	Overall: 59.1 (7.3)	Drinking, % Case: 95.1 Control: 72.1	Drinking, % ≤196 g/week Case: 18.8 Control: 54.2 >196 g/week Case: 69.8 Control: 43.4 Ex-drinkers Case: 11.5 Control: 2.5	Vegetable intake, % (1–2 days/week) Case: 88.5 Control: 96.1 Hot tea consumption, % (likes very much or likes somewhat) Case: 27.1 Control: 25.4	6
Hosono ¹⁷	2008	Japan	1527 (800/727)	All females	Endometrial	Median (min–max) Case: 56.0 (26–79) Control: 56.0 (23–80)	Drinking, % Case: 16.2 Control: 16.5 Regular exercise, % Case: 68.2 Control: 71.6 Age and reproductive details, cases/control Age and menarche, median (min–max), years 14.0 (10–20)/ 14.0 (10–21) Duration of menstruation, years (quartiles) 37.0 (0–49)/ 36.0 (11–43)			7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
							Parity, median (min–max) 2 (0–4)/ 2 (0–6)			
							Contraceptive usage, % 5.4/5.0			
							Hormone replacement usage: 10.1% / 6.8%			
Ishiguro ¹⁵	2009	Japan	44994 (23360/21634)	All males	ESCC	Overall: 51.4 (7.9)	Drinking, % Case: 52.1 Control: 53.2	Regular drinkers, % (>3 days/month) Flushing: 59.7 Non-flushing: 69.1	Vegetable intake, % (≥3 days/week) Case: 57.8 Control: 56.4 Hot tea consumption, % Case: 25.3 Control: 23.3	6
Oze ¹⁶	2010	Japan	1721 (842/879)	1755 (1461/294)	Upper aerodigestive tract cancers: oral cavity and oropharynx, hypopharynx, oral cavity-oropharynx-hypopharynx not otherwise specified, larynx, and esophagus (C15)	Age group: no. (%) <40: Case: 20 (3.42) Control: 42 (3.59) 40–49: Case: 46 (7.86) Control: 101 (8.63) 50–59: Case: 186 (31.79) Control: 355 (30.34) 60–69: Case: 217 (37.09) Control: 460 (39.32) ≥70 Case: 116 (19.83) Control: 212 (18.12)	Drinking, no. (%) Never Case: 94 (16.07) Control: 361 (30.85) Moderate Case: 89 (15.21) Control: 332 (28.38) High-moderate Case: 134 (22.91) Control: 287 (24.53) Heavy Case: 253 (43.25) Control: 170 (14.53)		Vegetable intake, no. (%) Lowest tertile Case: 243 (41.54) Control: 372 (31.79) Middle tertile Case: 189 (32.31) Control: 370 (31.62) Highest tertile Case: 138 (23.59) Control: 411 (35.13)	7

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
							Smoking, no. (%) Pack-years (PY)<5: Case: 103 (17.61) Control: 448 (38.29) 5<PY<20: Case: 67 (11.45) Control: 164 (14.02) 20<PY<40: Case: 161 (27.52) Control: 258 (22.05) 40≤PY: Case: 249 (42.56) Control: 288 (24.62)		Hot tea consumption, no. (%) ≥3/day Case: 250 (42.74) Control: 472 (40.34) <3/day Case: 317 (54.19) Control: 671 (57.35)	
Suzuki ¹⁸	2010	Japan	47681 (13803/23878)	All females	Breast cancer	Overall mean: 52 Non-drinkers: 52.8 (8.1) Occasional: 48.7 (6.7) ≤150 g/week: 49.2 (7.4) 151–299 g/week: 48.8 (7.1) 300 g/week: 48.2 (6.2)	Overall drinking, % Non-drinkers: 5.7 Occasional: 11.5 1≤150 g/week: 5.8 151–299 g/week: 37.9 300 g/week: 46.1	Mean alcohol consumption g/week (SD) ≤150 g/week: 57.0 (38) 151–299 g/week: 212.8 (45) ≥300 g/week: 496.4 (183)		8
Song ²²	2014	China	397 (186/211)	All males	Gastric adenocarcinoma and ESCC	Overall: 61.7 (8.4)	Smoking, PY, mean (SD) Gastric cardia adenocarcinoma: 23.1 (25.9) ESCC: 26.4 (22.0) Control: 11.0 (17.9)	Overall: 1740.9 (2397.3) g-year		8

Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Hirata ¹⁹	2017	Japan	1776 (341/1435)	All males	Upper aerodigestive tract squamous cell carcinoma	Overall: 56.7 (10.1)	Overall drinking, %: 89.8	Overall: 121.9 (80) g/day		7
Masaoka ⁷	2017	Japan	41,422 (23,454/17,968)	All males	Bladder cancer	Overall: 51.9 (7.8)	Overall drinking, %: 83.3	Overall: 292.0 (313.6)		8
Lu ²⁰	2018	Japan	Total: 71,038 (41,000/30,308)	Males: 40,696 (23,092/17,604) Females: 30,342 (17,908/12,434)	Oral and Pharyngeal	Flushing: 53.6 (8.1) Non-flushing: 52.1 (7.9)	Drinking, % Flushing: 6.4 Non-flushing: 8.8	Heavy consumption ≥300 g/week, % Flushing: 4 Non-flushing 8.3	Hot tea consumption, % Flushing 33.3 Non-flushing: 34	7
Yu ²³	2018	China	28,756 (15,989/12,767)	All males	ESCC	Overall: 50.9 (10.6)	Smoking, % Flushing: 24.9 Non-flushing: 25.7 Drinking, % Flushing: 86.4 Non-flushing: 87.6 Physical activity, %: Flushing: 24.3 Metabolic equivalent of task (MET)-hour/day Non-flushing: 23.8 MET-hour/day	Flushing: 69.6 g/day Non-flushing: 71.2 g/day	Vegetable intake, mean Flushing: 6.8 days/week Non-flushing: 6.8 days/week Hot tea consumption, % Flushing: 35.3% daily Non-flushing 33.9% daily	7

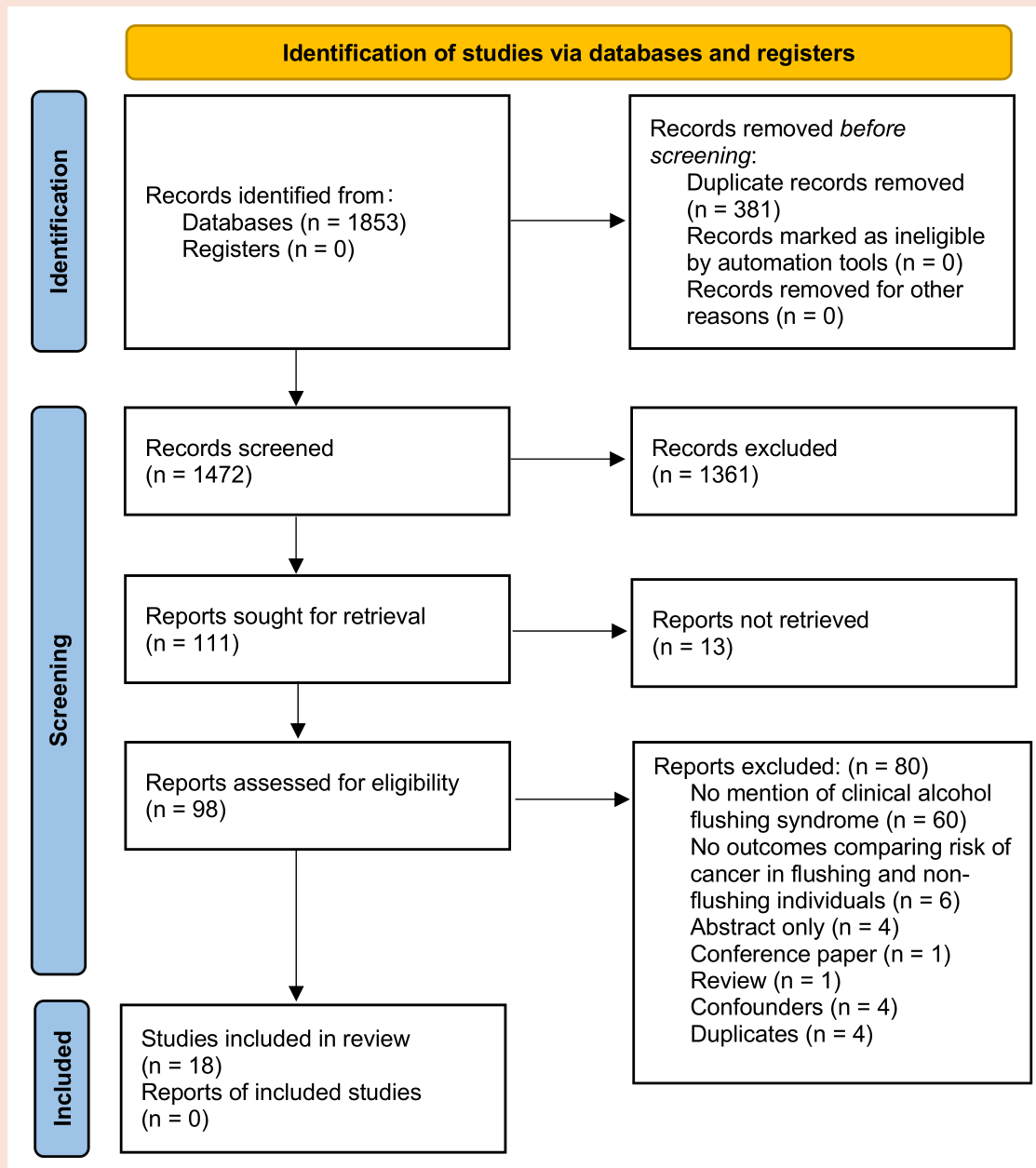
Table 1. Characteristics of included studies. (Cont'd)

Study	Year of study	Country	N (flushers/non-flushers)	N (male/female) ^a	Type of cancer (e.g. esophageal squamous cell carcinoma [ESCC], lung etc.)	Mean age (SD), years ^a	Smoking/drinking alcohol/physical activity/reproductive details	Mean alcohol consumption ^b	Green leafy vegetable intake/daily consumption of hot or burning hot tea	Newcastle-Ottawa score
Chuang ²⁴	2019	Taiwan	2920/5215	4050/4085	ESCC	Age group: no. 20–49: 3122 50–69: 3872 70–97: 1141	Drinking, % Case: 70.5 Control: 32.8	Any type of alcohol ≥1 per week		7
			2920/5215	4050/4085	Gastric adenocarcinoma	Age group: no. 20–49: 3122 50–69: 3872 70–97: 1141	Drinking, % Case: 30 Control: 34.2	Any type of alcohol ≥1 per week		
Ono ²¹	2020	Japan	24,133/32,757 All males: 13,153/13,152 All females: 10,980/19,605	Males + females: 56,890 All males: 26,305 All females: 30,585	All cancers: mouth, pharynx and larynx, ESCC, stomach cancer, colorectal cancer, liver cancer, and breast cancer	Overall: 53.0 (8.9) All males: 52.7 (8.8) All females: 53.3 (8.9)	Overall smoking %: 28.1 Smoking, % All males: 52.4 All females: 7.2 Overall physical activity, %: 20.4 Physical activity, % All males: 20.2 All females: 20.5	Overall: 244.2 (286.5) All males: 277.2 (297.8) g/week All females: 109.2 (179.9) g/week	Overall vegetable intake, %: 22.6 Vegetable intake ≥5 times/week, % All males: 18.8 All females: 25.9	8
Im ⁸	2021	China	12,492/57,252	69,734 (all males)	All cancers	Overall: 51.2 (10.8)	Overall drinking, %: 71.8			7
Okita ⁶	2022	Japan	6900/1536 (non-drinker <1 day/month)	8436 (all males)	Pancreatic	Overall: 51.9 (7.9)	Overall drinking, %: 75.7 Overall physical activity, %: 19.5	Overall: 291.5 (300.8) g/week		7

Superscript numbers: refer to REFERENCES

^a Unless otherwise specified.^b In grams of pure ethanol.

Fig. 1. PRISMA flow diagram of included studies.



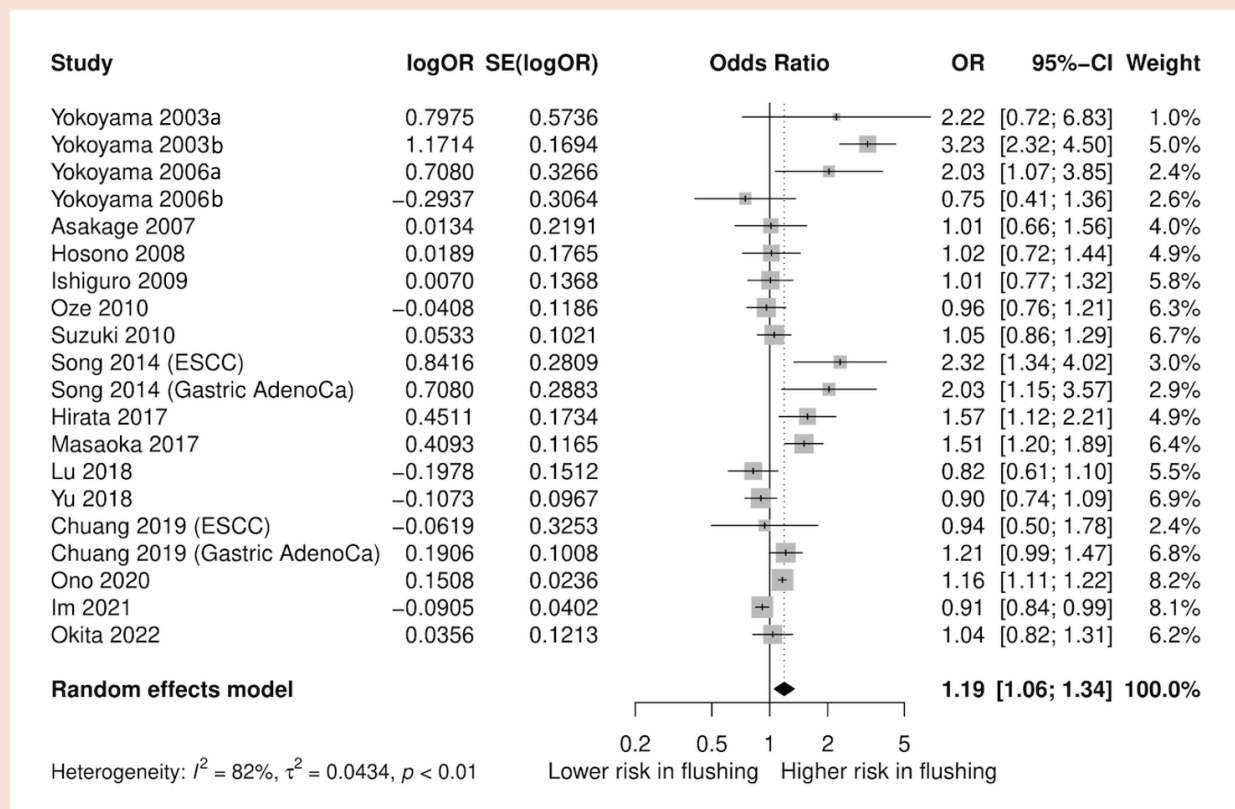
Adapted from: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n271.

ESCC¹⁶ and by Asakage et al.¹⁴ for oral cavity and pharyngeal cancers, although both studies did not demonstrate an association between AFS and cancer. Importantly, this study did not observe an increased risk of cancers in flushers who do not consume alcohol, thus alleviating concerns of elevated cancer risk due to environmental sources of aldehyde such as in the air, foods and beverages we consume.

The effect sizes in this study may have been underestimated due to several reasons. First, the heterogeneity in the definition of facial flushing

resulted in participants who flush quickly, after some time, currently flush or used to flush being analysed as a single entity. The accumulation of acetaldehyde in the body depends on the combination of alcohol and ALDH polymorphisms. A fast-metabolising ADH paired with an inactive ALDH will lead to the fastest accumulation of acetaldehyde and the soonest flushing response, which has been reported by Yu et al.²³ to increase the risk of cancer by up to 48 times compared to non-flushers. With further granularity on the speed of flushing after drinking, risks of cancer can be

Fig. 2. Forest plot of risk of all cancers.



CI: confidence interval; ESCC: esophageal squamous cell carcinoma; Gastric AdenoCa: gastric adenocarcinoma; OR: odds ratio; SE: standard error

sharply delineated especially for those who are most susceptible. Additionally, as heterozygotes for ALDH polymorphisms may retain some function of the enzyme and may experience reduced flushing with prolonged alcohol consumption,³⁹ there is value to categorise participants based on current or past flushing to investigate the risks of cancer in all subgroups. Second, the definition of flushing that quizzes only on the presence of facial redness could include patients with rosacea as flushers though they do not possess defective ALDH polymorphisms responsible for increased cancer risk, potentially leading to underestimated effect sizes. Third, while the jury is still out on the net effect of wine on our health, some studies have shown reduction in cancer risk,⁴⁰ and therefore, it could be interesting to analyse subgroups based on the type of alcohol consumed.

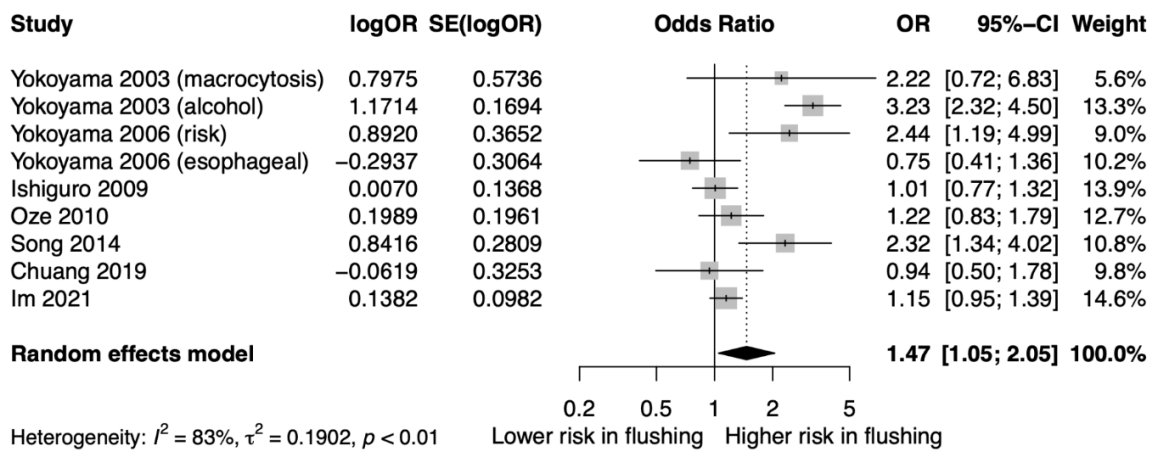
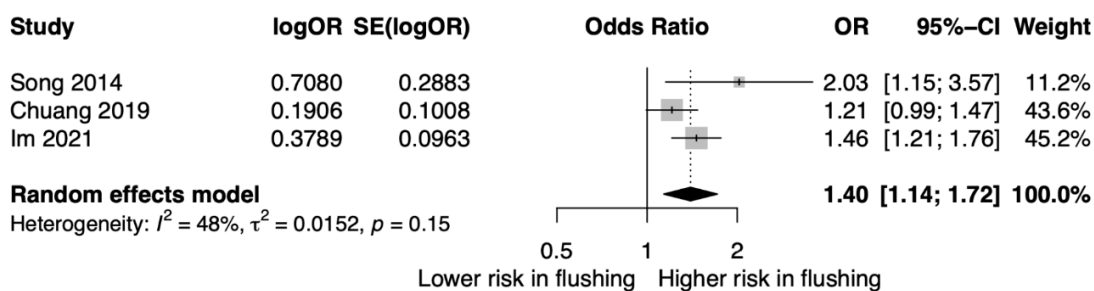
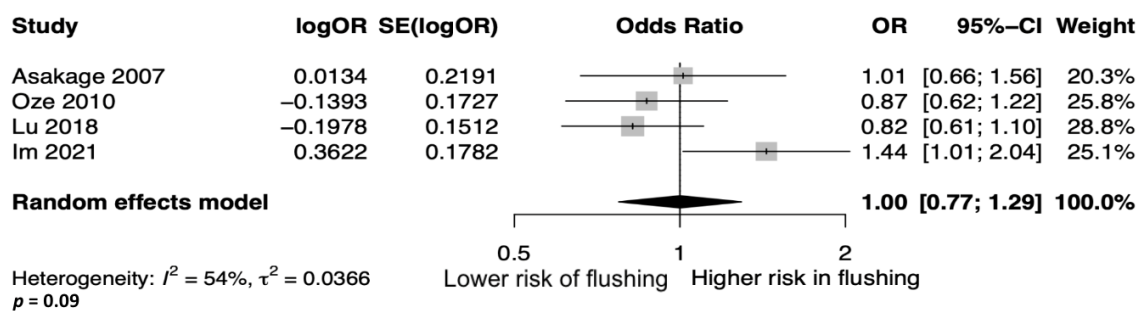
Globally, there is growing interest in products that reduce facial flushing, such as the use of topical alpha-adrenergic brimonidine gel,⁴¹ patches, antihistamines and traditional remedies. While such products may mask the flushing response, they have not been evidenced to reduce the adverse relations of flushing to cancer and instead, can lead to higher levels of alcohol

consumption among those with AFS. With growing evidence supporting the association between AFS and cancers, the flushing response can be potentially used as part of a predictive tool to identify at-risk patients to screen for alcohol-related cancers in a cost-effective manner. It is salient for clinicians and the public to be cognisant of the ramifications of alcohol consumption for individuals who flush.⁴

Limitations

This study is limited by heterogeneity across studies attributable to differences in study design, method of assessment and definition of flushing, and differences in patient baseline characteristics such as alcohol consumption amounts and smoking status which were not always reported. To account for such heterogeneity, a random effects model was utilised in analysis and sensitivity analyses were further performed using only adjusted ratios. Subgroup analyses were also performed based on sites of cancer, alcohol consumption amounts and sex leading to reductions in heterogeneity in several subgroups. While no association was observed in the female subgroup, the subgroup analysis of studies on women was dominated by

Fig. 3. Forest plot of risk of cancers by site: esophageal squamous cell carcinoma, gastric adenocarcinoma and oral cavity and pharyngeal squamous cell carcinoma.

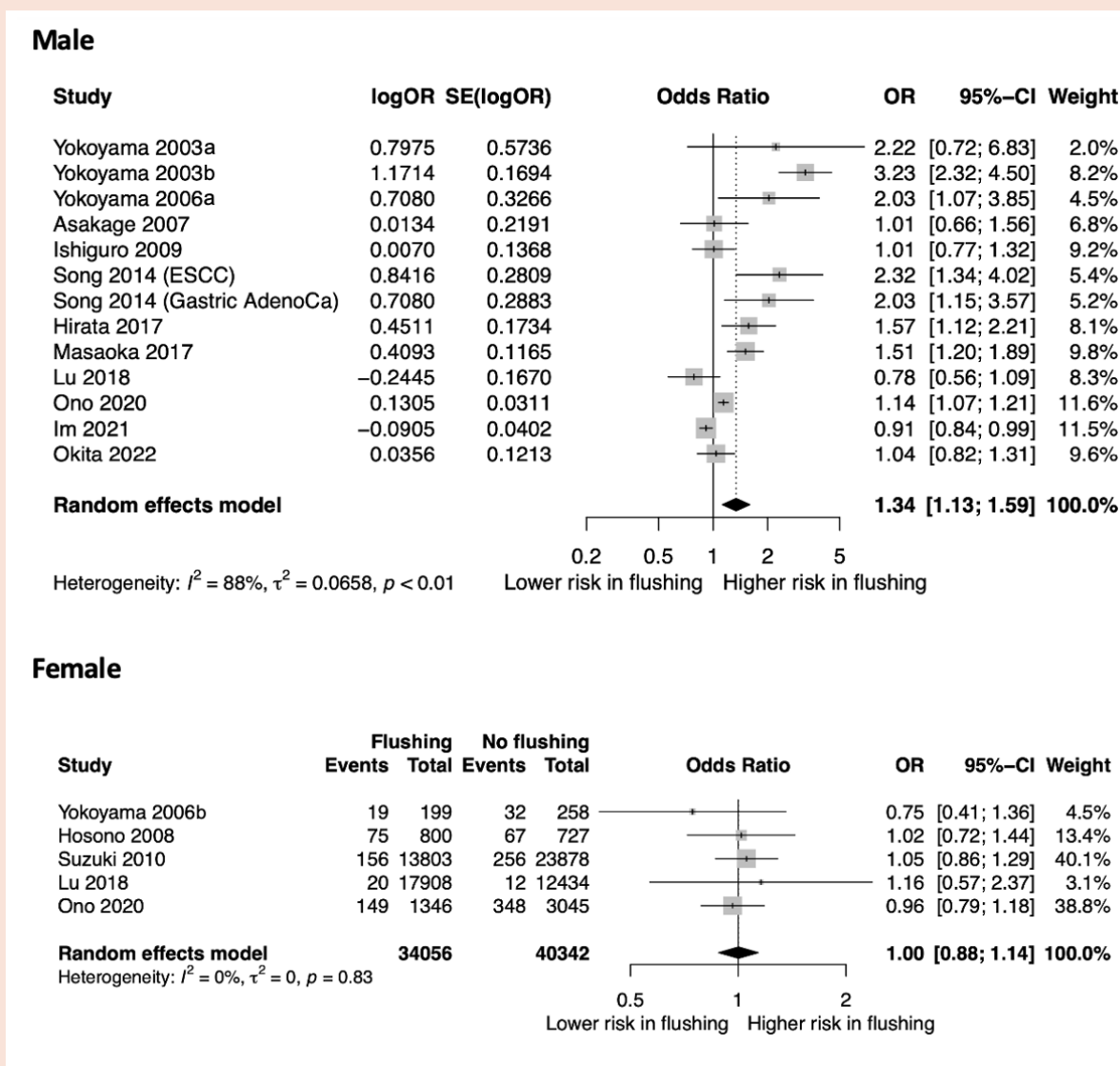
Esophageal squamous cell carcinoma**Gastric adenocarcinoma****Oral cavity and pharyngeal squamous cell carcinoma**

CI: confidence interval; OR: odds ratio; SE: standard error

1 study showing a negative association between flushing and cancer and that a low level of alcohol consumption in women who flush may mask the association between flushing and cancer.²¹ This has similarly been reported for patients with rs671 ALDH2 mutations in whom esophageal cancers are less common as patients avoid alcohol due to the intense flushing response.⁴² The study may also be limited by the presence of confounders, as adjusted

effect sizes were not always available and raw numbers were used for analysis (female subgroup, Fig. 5 and Supplementary Fig. S3). Additionally, the lack of uniformity in the stratification of alcohol consumption amounts resulted in difficulty analysing all the studies in an all-inclusive manner. There is a need for more high-quality prospective studies with control of major confounders such as smoking status, alcohol consumption amounts

Fig. 4. Forest plot of risk of all cancers in male and female patients.



CI: confidence interval; ESCC: esophageal squamous cell carcinoma; Gastric AdenoCa: gastric adenocarcinoma; OR: odds ratio; SE: standard error

(based on recommended alcohol guidelines such as 14 and 7 drinks per week for men and women, respectively³⁸) and speed of flushing after drinking.

CONCLUSION

In summary, our findings support the association between AFS and increased risk of cancer. Significant associations were similarly observed in our ESCC and gastric adenocarcinoma but not in the oral cavity and pharyngeal cancers subgroup. Preliminary evidence is supportive of a dose response relationship between alcohol consumption and risk of cancer in flushers. However, high-quality prospective studies comparing cancer risk between flushers and non-flushers at different alcohol consumption levels will provide value in confirming this association.

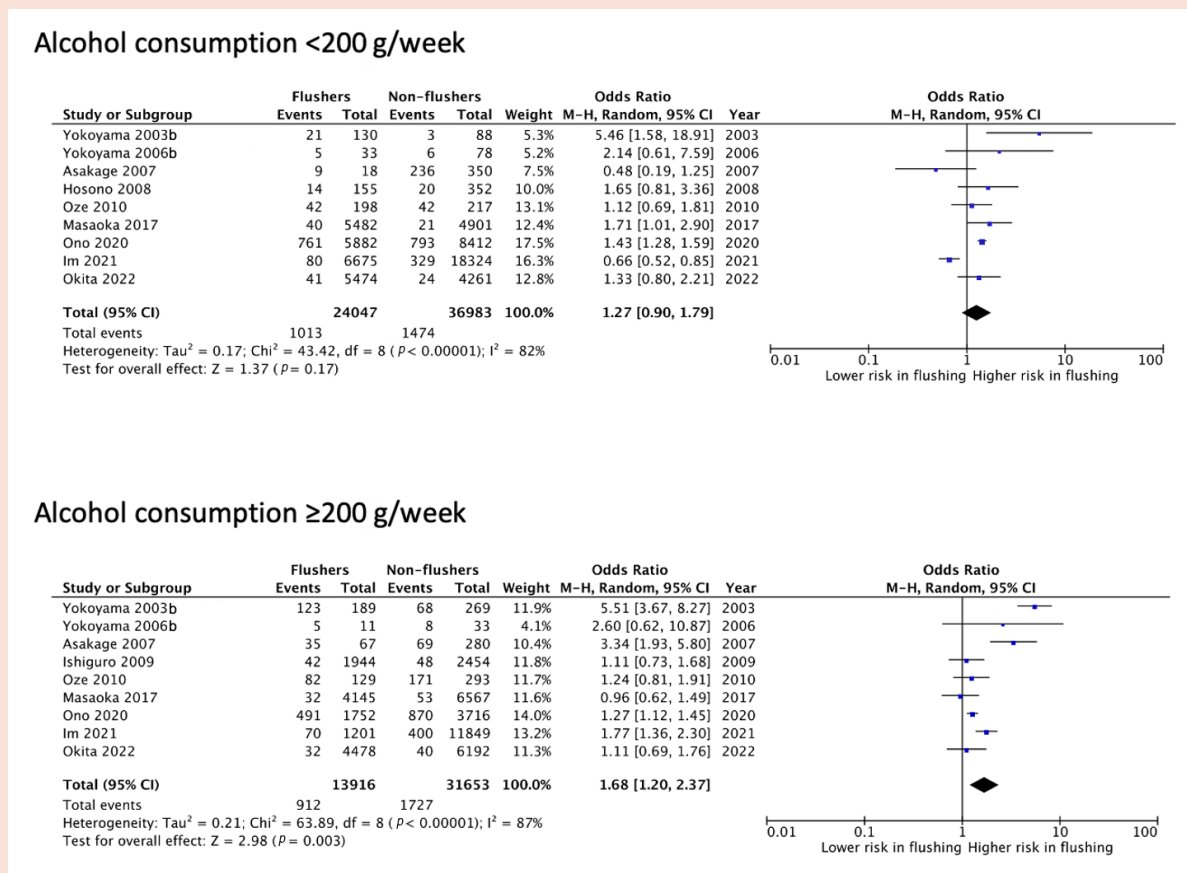
Supplementary materials

- Fig. S1. Forest plot of pooled adjusted odds ratios for all cancers.
- Fig. S2. Forest plot of risk of ESCC in males.
- Fig. S3. Forest plot of risk of all cancers in non-drinkers.
- Fig. S4. Risk of all cancers in current and former flushers.
- Fig. S5. Funnel plot of included studies.
- Appendix S1. PRISMA checklist.
- Appendix S2. PubMed search strategy.

Declaration

Hazel H Oon is a speaker, advisory board member and researcher for AbbVie, Galderma, Janssen and Novartis. She has also been a clinical investigator for Pfizer, advisory board member

Fig. 5. Forest plot of risk of all cancers at an alcohol consumption level below and above 200 g of pure ethanol/week.



for Amgen, speaker and advisory board member for Boehringer Ingelheim and Eli Lilly. The remaining authors disclose no conflicts. No financial support was received for this work.

Data transparency statement

The data that support the findings of this study are available from the corresponding author, Hazel H Oon, upon reasonable request.

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