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Facial flushing response to alcohol and the risk of esophageal squamous cell carcinoma: A comprehensive systematic review and meta-analysis

Juliana Andrici, Sharon X.H. Hu, Guy D. Eslick*

The Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney, Nepean Hospital, Level 5, South Block, Penrith, NSW 2751, Australia

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ABSTRACT

Objective: The alcohol flushing response is common among ethnic East Asian populations, and has been associated with an increased risk in developing esophageal cancer, especially squamous cell esophageal cancer (ESCC). We aimed to quantify the relationship between the facial flushing response to alcohol consumption and ESCC.

Methods: We conducted a meta-analysis of studies reporting on the association between the facial flushing response to alcohol consumption and ESCC. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random effects model for the risk of ESCC associated with the facial flushing response in general, as well for different levels of alcohol consumption. Four databases, Medline, PubMed, Embase, and Current Contents Connect, were searched to 31August 2015.

Results: Seven studies, with 1014 ESCC cases, met the inclusion criteria. There was a positive relationship between the flushing response and ESCC (OR 1.97; 95% CI 1.25–3.13). Heterogeneity was observed (I^2 = 80%, $P < 0.001$). Publication bias was not present. An increased risk of ESCC was present in the moderate and heavy drinkers who experienced flushing, compared with moderate and heavy drinkers who did not (OR 2.54; 95% CI 1.64–3.91, and OR 2.90; 95% CI 1.82–4.82, respectively).

Conclusion: Individuals who experience a facial flushing response to alcohol intake may be at increased risk of developing ESCC, particularly if they are moderate to heavy drinkers.

1. Introduction

The alcohol flushing response is common among ethnic East Asian populations, including Japanese, Chinese and Koreans [1–3]. Affected subjects experience facial flushing, drowsiness, and tachycardia, as a physiological response to alcohol consumption [4]. The response is associated with an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2) which is involved in the metabolism of ethanol, specifically the rapid degradation of acetylaldehyde [5]. This mutation is present in approximately 36% of ethnic Japanese, Chinese, and Koreans [5] (Fig. 1). As a result of the deficiency in ALDH2, acetaldehyde accumulates, thereby causing the symptomatology associated with the flushing response [5]. Acetaldehyde associated with consumption of alcoholic beverages has been classified as a Group 1 human carcinogen by the International Agency for Research on Cancer of the World Health Organization [6], and a link between ALDH2 deficiency and an increased risk in the development of esophageal cancer, especially squamous cell esophageal cancer (ESCC), has been studied and reported by various investigators [7–9].

ESCC is one of two main histologic subtypes of esophageal cancer, the other one being esophageal adenocarcinoma. It has a well-established association with smoking and alcohol consumption [10,11], and studies out of Iran, China and South America have suggested an association of ESCC with poor nutrition, low socioeconomic status, opiate use [11], the consumption of maté [12,13], and the consumption of excessively hot drinks [14]. A number of studies have linked ESCC to ALDH2 deficiency and the polymorphisms associated with this deficiency [7–9]. Given the poor prognosis of esophageal cancer [10], which has reported 5-year survival rates between 12% and 21% in Europe and the US [15,16], the importance of identifying modifiable risk factors is obvious.

A number of studies have examined the relationship between the flushing response and ESCC [7–9,17–20]. To date, no meta-analysis has been performed on this subject. Our aim was to perform a systematic review and meta-analysis combining the results of studies which reported on the relationship between the flushing response to alcohol and ESCC, thus quantifying the strength of the association.

* Corresponding author. Fax: +61 2 47 343 432.
E-mail address: eslickg@med.usyd.edu.au (G.D. Eslick).

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2. Materials and methods

2.1. Study protocol

We followed the PRISMA Statement for Systematic Reviews and Meta-Analyses in performing our systematic review [21]. A systematic search was performed independently by two investigators (J.A. and S.H.) through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949) and Current Contents Connect (from 1998) through to 31 August 2015, to identify relevant articles. The search used the terms 'flushing' AND 'alcohol' AND 'oesophageal cancer' OR 'oesophageal neoplasms' OR 'esophageal cancer' OR 'esophageal neoplasms', which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

2.2. Study selection

Studies were included if they met the following inclusion criteria: (1) the study used a cohort or case control study design (2) the study reported on the facial flushing response to alcohol intake among ESCC cases and cancer-free controls; (3) the risk point estimate was reported as an odds ratio (OR), or the data was presented such that an OR could be calculated; (4) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; (5) an internal comparison was used when calculating the risk estimate. We excluded studies that did not meet the inclusion criteria. Studies were included or excluded following consensus between three authors (J.A., S.H. and G.E.).

2.3. Data extraction

Relevant data was extracted via a standardised data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction, whether the study examined incident or prevalent ESCC cases, population type, country, continent, case control matching, mean age, number of adjusted variables, the level of alcohol consumption, the risk estimates or data used to calculate the risk estimates, and CIs or data used to calculate CIs. Quality of the studies was not assessed and authors were not contacted for missing data. Adjusted ratios were extracted in preference to non-adjusted ratios, however, where ratios were not provided, unadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, the ratio with the highest number of adjusted variables was selected. Where studies provided multiple risk estimates, such as risk estimates for different levels of alcohol consumption, they were included as separate risk estimates.

2.4. Statistical analysis

Pooled ORs and 95% CIs were calculated for the risk of ESCC associated with the flushing response to alcohol using a random effects model [22]. A subgroup analysis grouping studies by either cohort or case control design assessed the impact of study design on our results. A subgroup analysis by level of alcohol consumption was also performed to examine for a possible dose response. If the level of alcohol consumption was reported by the individual studies, it was usually categorized into three groupings, namely "light", "moderate" and "heavy" alcohol drinkers. Light drinking generally indicated a consumption of less than 200 g of ethanol per week, moderate drinking indicated a consumption of between 200 g and 390 g, while heavy drinking indicated a consumption of over 390 g of alcohol per week. These categories were kept and used in our analysis. Where studies provided risk estimates for different levels of alcohol intake, but not an overall risk estimate for ESCC in flushing versus non-flushing subjects, the risk estimates for the various levels of alcohol intake were combined to arrive at an overall risk estimate for the flushing response. Some of the studies reported risk estimates for ESCC using the non-drinking participants as the reference group. That is, the risk estimates for both flushing and non-flushing subjects in the "light", "moderate" and "heavy" alcohol intake categories were calculated using non-drinkers as the reference group. We recognize that there were two variables with the potential to impact the risk estimates for these groups, namely the flushing response, and the different levels of alcohol consumption. Since increased alcohol intake is an established risk factor for development of ESCC [10,11], we wanted to isolate the effect of the flushing response on the risk of ESCC. For these studies, ORs were thus calculated from available data

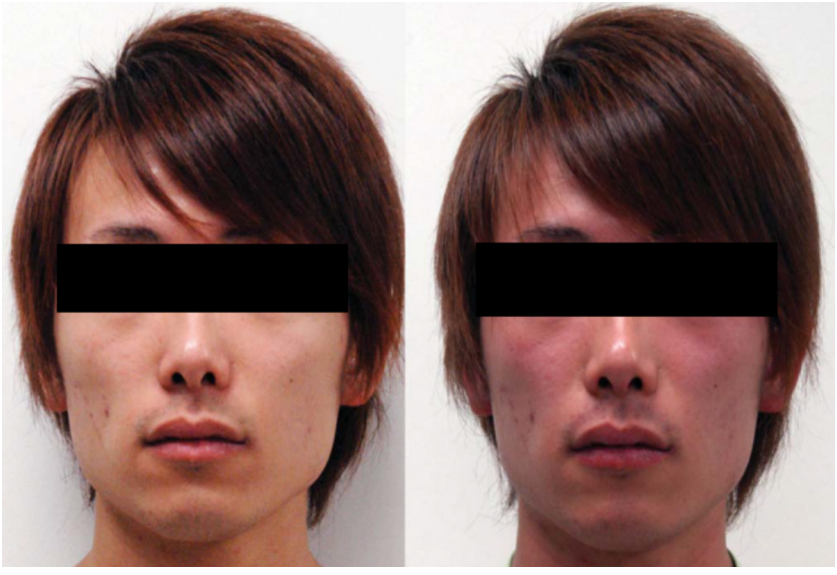

Fig. 1. The facial flushing response to alcohol consumption.