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Systematic review with meta-analysis: race-specific effects of alcohol and tobacco on the risk of oesophageal squamous cell carcinoma

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SUMMARY

Background
Oesophageal squamous cell carcinoma (OSCC) is associated with alcohol use, tobacco use and African or Asian descent. However, little is known about how racial background modifies the effects of alcohol or tobacco.

Aim
To investigate how racial and geographical background modifies the effect of alcohol and tobacco on OSCC via a systematic review and meta-analysis of published literature.

Methods
We performed a literature search in multiple online databases regardless of language. Eligible studies were population-based assessments of the effect of tobacco and/or alcohol on the risk of OSCC allowing stratification by race. The quality of studies was assessed by the Newcastle-Ottawa Scale. Meta-analyses were performed to estimate summary effects using random effect models.

Results
Systematic review identified 9668 unique citations of which 34 were eligible. The majority were of high quality. The effect of current smoking vs. never-smoking was weaker among Asians than among Europeans [European: odds ratio (OR) = 4.21, 95% confidence interval (CI) 3.13, 5.66; Asian: OR = 2.31, 95% CI 1.78, 2.99], with the 95% CIs not crossing, indicating statistical significance. Asians also trended towards weaker effects of long-duration cigarette use and of heavy daily cigarette use. There was no difference in the effect of alcohol on OSCC risk by race.

Conclusions
Contrary to our hypothesis, a weaker effect of tobacco for OSCC was observed among Asians than among Europeans. Differences in other factors must explain the higher incidence of OSCC among Asians. More studies are needed to understand the cause of the disparate incidence of OSCC between races.

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INTRODUCTION

Oesophageal carcinoma is a disease with significant worldwide impact, accounting for the fifth and ninth highest cause of mortality due to malignancy in men and women respectively.[1] The two main histological types of oesophageal cancer are oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC). Multiple studies have identified risk factors for development of OSCC, the two most notable of which are exposure to alcohol and tobacco.[2–5] These two factors, in addition to low consumption of fruits and vegetables, account for over 90% of OSCC cases.[2, 6]

For unclear reasons, the incidence of OSCC among African Americans within the United States (9.4 per 100 000) is significantly higher compared with their white counterparts (2.1 per 100 000).[7, 8] Similarly, the incidence in Asian American men (3.7 per 100 000) and in Hispanic men (2.6 per 100 000) is greater than among whites. Globally, the incidence of OSCC is highest in African and East Asian countries and lowest in European countries.[9] Social demographics such as low income may contribute to racial differences in the prevalence of OSCC.[10, 11] Furthermore, among individuals with similar exposures to risk factors, oesophageal cancer susceptibility may differ due to polymorphisms in enzymes that metabolise carcinogens.[12, 13] For instance, in 40–50% of Asians, aldehyde dehydrogenase (ALDH2) has low activity due to a single-nucleotide polymorphism that contributes to elevated blood levels of acetaldehyde (a known carcinogen) following alcohol consumption.[14–16]

We hypothesised that individuals of African or Asian descent have increased susceptibilities to the effects of tobacco and alcohol on the risk of OSCC compared with those of European descent. We aimed to synthesise the available data across multiple studies to better estimate the association between alcohol and tobacco with OSCC and how this risk is modified by race.

MATERIALS AND METHODS

Study protocol

We performed a systematic literature search in MEDLINE (1948 to February 2013), EBM reviews (ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Registry, Health Technology Assessment, NHS Economic Evaluation Database; to February 2013), EMBASE (1947 to June 2011), ISI Web of Knowledge (to February 2013) and BIOSIS preview (1926 to February 2013) to identify studies estimating the risk of OSCC in relation to the use of alcohol and tobacco without regard to language of the publication. No authors were contacted for any further study results.

Key index terms for our literature review included {esophageal carcinoma, esophageal neoplasm or [esophagus and (squamous cell carcinoma, carcinoma, cancer, neoplasms, adenosquamous carcinoma or basosquamous carcinoma)]} and (risk factors, tobacco, tobacco smokeless, tobacco use disorder, tobacco smoke pollution, smoke, smoking, marijuana smoking, cigarette, cigar, alcohols, alcohol, alcohol drinking, alcoholism, alcohol abuse, ethanol, alcoholic beverages, liquor, beer, wine, spirits, or alcoholic intoxication), also using the alternative spelling 'oesophageal' or 'oesophagus'.

Study selection and data extraction

The studies met inclusion criteria if the following were satisfied: (i) The diagnosis of OSCC was based on histology or was reported only as oesophageal cancer, but was from a region where OSCC is endemic and OAC very rare (i.e. Africa or Asia), (ii) smoking and/or alcohol status was ascertained, (iii) data were stratified by race and/or reported from a racially homogenous population, (iv) data presented as odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) or in a format from which the OR or RR could be calculated, (v) studies were either cohort or case–control population-based studies, and (vi) study subjects were unique to that publication. No studies were excluded based on sample size. Hospital-based studies were excluded unless the controls were drawn from the community and the hospital(s) was/were the only centre serving that population.

Study references and citations were collected in Endnote software application version X4 (Thomson Reuters, New York, NY, USA) with duplicate publications removed. Two investigators (A.P. and K.O.) reviewed all titles, and of those that appeared eligible, both investigators independently reviewed the abstracts to assess eligibility with conflicts resolved by the third author (J.R.). A data collection form was designed in Microsoft Access 2010 (Microsoft, Redmond, WA, USA). Abstracts, and if deemed appropriate, full articles, were translated into English as needed. For abstracts that appeared eligible on first review, both investigators independently abstracted data from the full articles. After all the data were abstracted, both investigators then compared and confirmed by consensus to account for entry error. The database collected information on study design, country of origin, sex distribution and summary measures for participants with and without OSCC based on various levels of tobacco and/or alcohol.

Strata of exposure varied among studies and needed to be harmonised across studies for meta-analysis. We reviewed eligible studies to identify those strata that were most often and consistently reported. Data were harmonised as best able based on the predominant breakdown of the studies using three sets of categories for tobacco use, and one for alcohol use, each with three strata. The classifications for tobacco use were: (i) ever-smokers (never, former and current), (ii) average daily cigarette exposure (never, <20 cigarettes per day, ≥20 cigarettes per day) and (iii) duration of cigarette use (never, <20 years, ≥20 years of smoking). Alcohol use was classified into average weekly use (0, <200 g/week, ≥200 g/week of alcohol). The mass of alcohol consumption was either directly reported or, if not, was converted based on the average alcohol content per drink based on the country of origin of the study. Reports on the duration of alcohol usage was limited to eight total studies of which four were from Asia and three were from Europe, and thus this was not assessed. Similarly, current vs. former use was only assessed in three total studies.

Where data were available for the harmonised strata, a maximally adjusted effect measure was abstracted as well as a calculated crude effect measure. When a greater number of strata were used in a study, ORs and confidence intervals were tabulated and grouped into the appropriate harmonised stratum. Additionally, when a stratum reported in a study crossed the harmonised strata defined in this study, the cases and controls were moved to either the lower or higher stratum based on the similarity of that stratum's magnitude of effect (e.g. OR) with the corresponding lower or higher stratum from that study. In both of these cases, a meta-analysis was performed of the study-reported adjusted ORs to report a single adjusted OR for our stratum to be used in the subsequent meta-analysis across studies.

Study quality criteria

Study quality was assessed by use of the Newcastle-Ottawa Scale.[17, 18] This scale measures the quality of studies on a scale of 0–9 via the assessment of three main domains: selection of study groups, comparability of groups and ascertainment of exposure. Quality was assessed in duplicate (A.P. and K.O.) and discrepancies were resolved by consensus. All studies that met the initial eligibility criteria were included in the initial meta-analysis; subgroup analysis was subsequently performed stratifying by study quality. Those studies that achieved a score of 9 were deemed 'highest quality' for the subgroup analysis.

Analysis

Meta-analyses were conducted to estimate the summary OR using MIX 2.0 Pro software (Leon Bax, Kanagawa, Japan).[19] Meta-analyses were conducted for each of the four exposure categorisations (three for tobacco and one for alcohol), separately for the abstracted crude effects and for maximally adjusted effects, using inverse variance. Heterogeneity of the pooled estimate was tested with the Cochrane's Q statistic, with a P-value <0.10 considered as indicating heterogeneity. The inconsistency index (I^2) was used to estimate the degree of heterogeneity; the low, moderate and high degrees of heterogeneity correlated with I^2 values of 25%, 50% and 75% respectively.[20] Where HR or RR was reported, we assumed that this closely approximated the OR. All summary ORs are reported from random-effect models. Heterogeneity of results can reflect differences in study design or effect modification across strata of outcomes. Resolution of heterogeneity was the primary test for difference in estimates. Heterogeneity might be resolved by performing a series of pre-determined stratified analyses, thereby identifying strata with homogeneous results with more reliable estimates of the effects of exposure within those strata than the estimates for effects in all of the studies combined. We *a priori* planned to conduct analyses stratified by continent of origin for the population studied. In all but two studies, the continent of origin was identical to the continent of residence. In one study from the United States, the data could be stratified into those of European descent (i.e. whites) and those predominantly of African descent (i.e. African Americans). We also planned analyses restricted to the highest quality studies. Given the substantial heterogeneity found in the analyses, the potential for dissemination bias was not assessed, as methods for their assessment are inaccurate in the setting of substantial heterogeneity.[21]

RESULTS

Our initial database search identified 9668 citations (Figure 1). Following removal of duplicates, 7629 abstracts were assessed and 411 articles appeared to be appropriate for review. The full-text papers of these 411 citations were reviewed and 34 studies met eligibility requirements for inclusion (Table 1).[6, 22–54]

Study characteristics

Of the 34 eligible citations, 13 studies provided data on individuals of European (including 1 from Australia), 14 of Asian, 5 of South American and 2 of African descent. One of the studies[6] contained data on both Caucasians

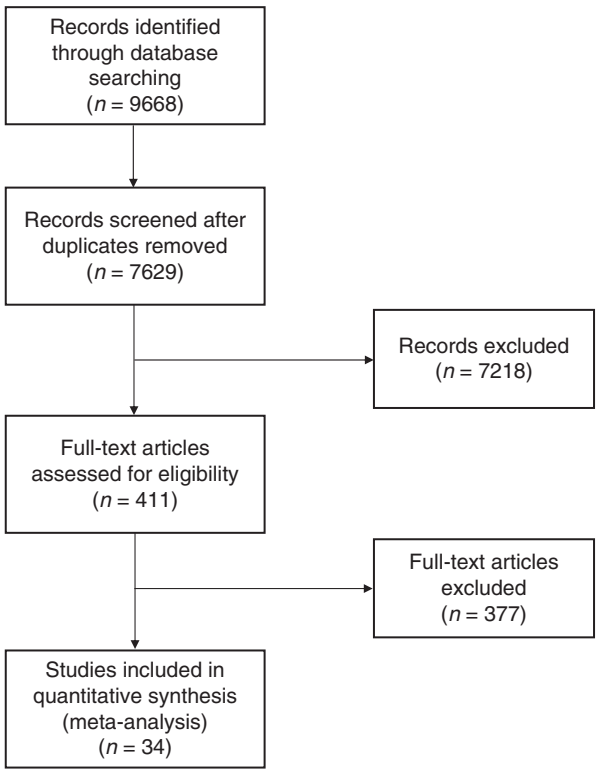

Figure 1 | Flow chart of literature search, selection, and analysis.

and African Americans, so the study was included twice. Twenty-five were case–control and 9 were cohort studies; 28 studies included data on smoking status (never, former or current), 22 included data on daily cigarette use and 13 included data on smoking duration. Alcohol consumption was reported in 18 of the studies.

The forest plots for the maximally adjusted effects of tobacco and alcohol on the risk of OSCC are shown in Figures S1–S4, comparing maximal exposure vs. no exposure. The maximally adjusted OR for alcohol consumption of greater than 200 g/week was 4.65 [95% confidence interval (CI) = 3.61, 5.99], but the results were heterogeneous (Q = 15.75, P = 0.03, I^2 = 56%). The maximally adjusted OR for exposure to tobacco by current smokers vs. never smokers was 3.13 (95% CI = 2.53, 3.86). For greater than 20 cigarettes per day vs. nonsmokers, the maximally adjusted OR was 3.66 (95% CI = 2.73, 4.90). The maximally adjusted OR for a smoking duration of greater than 20 years vs. nonsmokers was 2.81 (95% CI = 2.06, 3.83). The results for tobacco exposure were each very heterogeneous with I^2 values between 86% and 87% as demonstrated in Table S1. Dose–response relationships were found for each classification of alcohol and tobacco use (Table S2).

Analyses restricted to highest study quality or stratified by design

Table S1 shows the summary ORs for alcohol and tobacco when maximally adjusted estimates and estimates from only the highest quality studies (scoring 9 out of 9 possible points on the Newcastle-Ottawa Index) were used. The summary maximally adjusted estimate for consuming >200 g/week of alcohol was lower when the analysis was restricted to the highest quality studies (OR = 3.49; 95% CI = 2.82, 4.32), and heterogeneity was resolved (Q = 7.94, P = 0.16, I^2 = 37%). Those studies included four from East Asia, one from India and one from Europe. The estimated effects of tobacco use in the highest quality studies were comparable to the estimates from the entire set of studies, and the results remained heterogeneous (I^2 range: 86–89%). When the studies were stratified by design (case–control vs. cohort), there were greater effect estimates for each exposure in the case–control studies than in the cohort studies, but still with substantial heterogeneity (Table S3).

Stratifying by race

Table 2 shows the results for analyses stratified by continent of origin, which was the primary objective of this study. For current tobacco use, the summary OR for the risk of OSCC vs. never use in Europeans was 4.21 (95% CI = 3.13, 5.66), compared to lower values in Asians and South Americans [2.31 (95% CI = 1.78, 2.99) and 3.29 (95% CI = 1.75, 6.18) respectively]. Of particular note, the effect of current tobacco vs. never use was nearly twice as strong among Europeans than among Asians, with the 95% CIs not overlapping, indicating a statistically significant difference. For daily use of more than 20 cigarettes vs. never smokers, the summary ORs were 4.42 (95% CI = 3.23, 6.06) for Europeans and 2.52 (95% CI = 1.78, 3.57) for Asians. For duration of smoking more than 20 years vs. never smokers, the summary ORs were 3.31 (95% CI = 2.15, 5.10) for Europeans and 2.34 (95% CI = 1.57, 3.50) for Asians. Notably, for all three categories of tobacco quantification (ever usage, daily exposure, and duration of usage), the summary OR for developing OSCC was higher for Europeans than for Asians. However, there was still substantial heterogeneity in each stratum for all effect estimates. When we further categorised our analysis by sub-continent to compare Southern Europe (including Iran) to Eastern Asia, there was an overall trend for a higher adjusted OR amongst the Southern European countries (Table S4). However, again, the results were heterogeneous.

For weekly consumption of more than 200 g of alcohol vs. never drinkers, the summary ORs were 5.05 (95% CI = 3.40, 7.49) for Asians and 3.42 (95% CI = 2.29, 5.09) for Europeans. There was no difference in the effects of alcohol on the risk of OSCC across continents of origin. Due to the small number of studies of African populations (n = 2), meta-analyses could not be performed for that stratum.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis estimating the effects of alcohol and tobacco on the risk of OSCC among different populations based on race and geographical location. As African Americans and Asian Americans are at greater risk of OSCC than white Americans, we had hypothesised that the effects of alcohol and tobacco on the risk of OSCC would be greater among individuals of Asian or African descent than among those of European descent due to genetic factors. A recent Italian study evaluated 30 single-nucleotide polymorphisms involved in metabolising alcohol, acetaldehyde and tobacco-related carcinogens. Four were significantly associated with risk of upper aerodigestive tract cancer: cytochrome P450 (CYP) enzymes CYP1A1 and CYP2A6, gluthathione 6-transferase (GSTA2) and alcohol dehydrogenase (ADH1C). CYP enzymes are involved in tobacco metabolism, and efficiency in the conversion of ethanol to acetaldehyde, and subsequent oxidation to acetate, is mainly driven by the alcohol dehydrogenase (ADH) and ALDH gene families.[13] A polymorphism of ADH1C has been associated with an increased risk of upper aerodigestive tract cancers.[13] In 40–50% of Asians, ALDH2 has low activity due to a single-nucleotide polymorphism that contributes to elevated blood levels of acetaldehyde following alcohol consumption.[12, 16]

This study confirmed the expected dose-dependent relationship between both alcohol and tobacco with the risk of OSCC. Strong associations were found regardless of study quality and in all races, but the results of nearly all analyses were very heterogeneous. Contrary to our hypothesis, we did not find any substantial differences in the effect of alcohol on the risk of OSCC based on race. We were also surprised to discover a statistically significant *weaker* effect of tobacco for OSCC among Asians than among Europeans, as the 95% confidence intervals for current smokers vs. never smokers did not overlap. As there is relatively less regulation of carcinogen content in tobacco in Asian countries than in European countries, this finding is even more striking.[55] In addition to a true finding, there are a few possible other explanations for this finding. First, there may have been residual misclassification of smoking status by the duration and intensity of tobacco use. Although the effects of smoking duration and smoking intensity appeared stronger among Europeans than among Asians, the 95% confidence intervals overlapped, and the heterogeneity of those effect estimates were not resolved by stratifying by race. If European smokers, on average, smoke a greater quantity and for a longer duration than Asians, the effect of current smoking might appear stronger among Europeans than among Asians. The finding could also reflect a time-lag between commencement of smoking and disease onset; for instance, in countries such as China where smoking did not reach its peak popularity until the mid-1990s, the full impact of tobacco may not yet have been realised in published studies.[56, 57] In addition, there may be differences in smoking behaviours across cultures, including depth and frequency of inhalation. Finally, given the substantial heterogeneity in results across studies, even within strata of races, the differences between races may reflect differences in study designs.

If differences in the effects of alcohol and tobacco do not explain the greater incidences of OSCC among Asian American and African Americans than white Americans, then what does? The differences might still be explained by a higher prevalence of heavy use in those populations compared with whites. Although our study attempted to harmonise similar quantities of alcohol and tobacco use across different population-based studies, amounts used were generally presented in broad categories and specific types of alcohol were not taken into account. Studies have also indicated an increased risk of OSCC with specific types of alcohol including home-brewed, moonshine whiskey and hard liquor, use of both of which is found to be more common in African Americans.[5] Lower socioeconomic status and less education have also been identified as factors that might explain the racial disparity within the United States.[11] Differences in consumption of fruits and vegetables may also play a role. Engel *et al.* demonstrated in a population-based study that almost 90% of the cases of OSCC could be accounted for by smoking, alcohol consumption or low consumption of fruits and vegetables among the American population studied; low fruit and vegetable consumption alone accounted for 20% of OSCC.[2] Additional studies are needed to confirm those findings.

Furthermore, it is well understood that OSCC has a geographical prevalence that may not limit itself to continents as we have defined in our study. There is indeed an oesophageal cancer belt that extends from Iran to central China.[58, 59] When we further categorised our analysis by sub-continent to compare Southern Europe

Table 1 | Studies included in the meta-analysis (to be read in conjunction with the following three pages)

Author	Year	Reference #	Country/ region	Continent of origin	Study type	% cases male	% controls male
Allen	2009	22	United Kingdom	Europe	Prospective cohort	0	0
Bahmanyar	2006	23	Sweden	Europe	Case–control	72	83
Brown	1994	6	USA	Europe, Africa	Case–control	100	100
De Stefani	1990	24	Uruguay	South America	Case–control	76	76
De Stefani	2008	25	Uruguay	South America	Case–control	79	79
Fan	2008	26	China	Asia	Prospective cohort	100	100
Gallus	2003	27	Italy, Switzerland	Europe	Case–control	82	82
Gallus	2001	28	Italy, Switzerland	Europe	Case–control	0	0
Ganesh	2009	29	India	Asia	Case–control	64	53
Garidou	1996	30	Greece	Europe	Case–control	65	72
Gledovic	2007	31	Serbia	Europe	Case–control	85	85
Hanaoka	1994	32	Japan	Asia	Case–control	100	100
Ishiguro	2009	33	Japan	Asia	Prospective cohort	100	100
Kimm	2010	34	Korea	Asia	Prospective cohort	100	100
Lagergren	2000	35	Sweden	Europe	Case–control	72	83
Menezes	2002	36	Brazil	South America	Case–control	81	81
Nasrollahzadeh	2008	37	Iran	Asia	Case–control	50	49
Pandeya	2008	39	Australia	Australia	Case–control		
Sharp	2001	38	UK	Europe	Case–control	0	0
Steevens	2010	40	Netherlands	Europe	Prospective cohort	55	49
Sun	2004	41	Korea	Asia	Prospective cohort	100	100
Szymanska	2011	42	Brazil, Argentina, Cuba	South America	Case–control	81	79
Tai	2010	43	Taiwan	Asia	Case–control	0	0

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Tobacco use quantification			Alcohol quantified by weekly use	Factors controlled for	Newcastle-Ottawa Scale for Quality
Ever use	Daily quantity used	Duration of use			
–	–	–	+	Age, tobacco use, obesity, physical activity, region of residence, socioeconomic status, use of oral contraceptives, and hormone replacement therapy	8
+	–	–	–	–	8
+	+	–	–	Age, tobacco use, alcohol use, geography, income	9
–	–	–	+	Age, tobacco use, alcohol use, residence	8
+	–	–	–	Age, sex, tobacco use, obesity, total energy intake, residence (urban/rural), birthplace, education, family history of oesophageal cancer	8
+	+	–	+	Alcohol use, obesity, summed intakes of preserved foods, fresh fruits and vegetables, education	9
+	+	+	–	Age, sex, alcohol use, study centre, education	8
+	+	–	+	Education, obesity, non-alcohol use energy intake, tobacco use, alcohol use	8
–	–	+	–	Age, sex, residence, occupation	7
–	+	–	+	–	8
+	–	–	–	–	8
+	–	–	+	–	7
+	+	–	+	Age, alcohol use, obesity, preference for hot foods and drinks, region of residence, flushing response	9
+	+	–	+	Age, alcohol use, obesity, exercise, aspartate aminotransferase levels	9
+	+	+	+	Age, sex, tobacco use, obesity, energy intake and physical activity, intake of fruit and vegetables, educational level, reflux symptoms	8
+	–	–	–	Alcohol use, race, vitamin consumption, region of residence, education, household pollution, lung cancer, profession	7
+	+	+	–	Education, ethnicity	8
+	+	+	–	Age, sex, alcohol use, obesity, education, aspirin use, frequency of GERD	7
+	–	+	+	Diet, tobacco use, regular use of aspirin, temperature of tea/coffee	7
+	+	–	+	Age, sex, tobacco use, alcohol use, obesity, energy intake, food consumption, education	9
+	–	–	–	Age	9
+	+	+	+	Age, sex, tobacco use, alcohol use, fruit and cruciferous consumption, enrolment centre, education	7
+	–	–	+	Age, tobacco use, alcohol use, tea consumption, areca chewing, education	9

Table 1 | (Continued)

Author	Year	Reference #	Country/ region	Continent of origin	Study type	% cases male	% controls male
Tran	2005	44	China	Asia	Prospective cohort	49	45
Van Rensburg	1985	45	South Africa	Africa	Case–control	100	100
Vassallo	1985	46	Uruguay	South America	Case–control	100	100
Vioque	2008	47	Spain	Europe	Case–control	93	63
Wang	2007	48	China	Asia	Case–control	100	100
Wu	2006	49	Taiwan	Asia	Case–control	100	100
Yang	2005	50	China	Asia	Case–control	64	64
Yun	2004	51	Korea	Asia	Prospective cohort	100	100
Zambon	2000	52	Italy	Europe	Case–control	100	100
Zendehdel	2008	53	Sweden	Europe	Prospective cohort	100	100
Znaor	2003	54	India	Asia	Case–control	100	100

(including Iran) with Eastern Asia, our results were similar showing a greater effect of tobacco among East Asians than among Southern Europeans.

There are some important limitations to this study. First is the relative paucity of studies regarding African populations. The majority of the studies identified in African populations were either not methodologically specific enough or did not classify exposures in the appropriate strata. We had hoped to compare the effects of exposure in Africans vs. African Americans. However, many of the US-based studies, although containing a significant number of African American subjects, did not provide data stratified by race and thus most of those studies were not included. The one study from Africa confirmed an overall increased trend towards OSCC in African men who were exposed to tobacco as well as those who consumed a diet low in micronutrients such as zinc, magnesium and riboflavin.[45] Similarly, the study assessing racial trends in African Americans found a higher incidence of OSCC in African American men for the same level of alcohol and tobacco use, with a 14.9 per 100 000 more cases of OSCC in African American men compared with white men for the same exposure of alcohol and tobacco.

Similarly, sex-specific analyses could not be reported, as most studies did not separate out the incidence based on sex, instead reporting overall prevalence of each sex in the population. Furthermore, the pooled alcohol- and tobacco-related risk for OSCC was calculated using studies that met the pre-defined criteria, notably ones that were stratified by race. As such, the summary estimates for all races with regard to alcohol and tobacco may not reflect estimates from the entire set of publications on this topic. Importantly, heterogeneity was not explained by stratifying by race, so it is possible that the finding of weaker effects of smoking in Asians than Europeans is not true. We chose our protocol for harmonising strata of exposures to improve the precision of effect estimates, but it could have introduced bias in those estimates. Additionally, as not all studies reported data on each outcome of interest, our estimates of the effects might be biased in an unpredictable direction. Finally, recall bias may have affected the results of case–control studies as patients and or family members were asked to estimate alcohol or tobacco use after development of OSCC.

Strengths of the study include the exhaustive literature search including for articles in non-English languages, the overall high quality of the studies included, and the pre-specified plan for stratified analyses.

In summary, the effect of tobacco on the risk of OSCC appears to be weaker among Asians than among Europeans, without a difference in the effect of alcohol, but the results from different studies are very hetero-

Tobacco use quantification			Alcohol quantified by weekly use	Factors controlled for	Newcastle-Ottawa Scale for Quality
Ever use	Daily quantity used	Duration of use			
+	+	+	–	Age, sex, tobacco use, first-degree relatives with OSCC	9
+	–	–	–	Age, tobacco use, diet	7
–	+	–	–	Age	6
+	+	+	+	Age, sex, tobacco use, alcohol use, energy-adjusted intake of fruit and vegetables, province inhabited, education	7
+	+	–	–	Age, tobacco use, alcohol use, dietary habits, green tea drinking history, marital status, education	8
+	+	+	+	Age, alcohol use, tobacco use, betel-quid chewing, level of education, occupation.	7
–	+	–	+	Tobacco use, alcohol use, diet, family history of oesophageal cancer, occupation	7
+	+	+	–	Age, alcohol use, obesity, physical activity, diet, place of residence	9
+	+	+	+	Age, tobacco use, alcohol use, area of residence, education	7
+	–	–	–	Age, obesity	9
+	–	+	+	Age, tobacco use, alcohol use, enrolment centre, education level	9

Table 2 | Racial differences in the summary associations of alcohol and tobacco use with oesophageal squamous cell carcinoma

Exposure	Race/continent	Number of studies	Summary adjusted OR	Confidence interval		Q	*P*-value	I^2 (%)
				Lower limit	Upper limit			
Current tobacco use vs. never	All	29	3.13	2.53	3.86	213.38	<0.001	87
	Asia	12	2.31	1.78	2.99	79.02	<0.001	86
	Europe	12	4.21	3.13	5.66	37.91	<0.001	71
	South America	3	3.29	1.75	6.18	4.57	0.10	56
>20 cigarettes daily vs. never	All	21	3.66	2.73	4.90	144.97	<0.001	86
	Asia	9	2.52	1.78	3.57	42.72	<0.001	81
	Europe	9	4.42	3.23	6.06	20.26	<0.002	61
>20 years of smoking vs. never	All	13	2.81	2.06	3.83	90.65	<0.001	87
	Asia	6	2.34	1.57	3.50	48.85	<0.001	90
	Europe	6	3.31	2.15	5.10	11.45	<0.05	56
>200 g of alcohol per week vs. never	All	18	4.65	3.61	5.99	57.99	<0.001	71
	Asia	8	5.80	3.64	9.24	51.83	<0.001	77
	Europe	8	3.87	2.57	5.82	15.75	<0.003	56

OR, odds ratio; *Q, Cochrane's Q*; I^2, inconsistency index.

geneous. As such, it appears that Asian race may modify the risk of tobacco for the development of OSCC. However, given the heterogeneity of the estimates, future studies are needed both to explain this finding and to examine for differential effects in individuals of African descent.

AUTHORSHIP

Guarantor of the article: The guarantor of this work and its integrity is Joel Rubenstein, MD, MSc.

Author contributions: All authors listed contributed equally to the study design, data collection, review, analysis and manuscript preparation and submission.

All authors have approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Forest plot of the maximally adjusted odds ratio of OSCC with drinking >200 g of alcohol per week vs. not drinking.

Figure S2. Forest plot of the maximally adjusted odds ratio of OSCC with current tobacco use vs. never use.

Figure S3. Forest plot of the maximally adjusted odds ratio of OSCC with smoking >20 cigarettes per day vs. nonsmoking.

Figure S4. Forest plot of the maximally adjusted odds ratio of OSCC with >20 years of smoking vs. nonsmoking.

Table S1. Summary estimates of associations between tobacco and alcohol use with oesophageal squamous cell carcinoma.

Table S2. Maximally adjusted summary odds ratio for the dose-dependent association of OSCC with alcohol and tobacco.

Table S3. Summary estimates of associations between tobacco and alcohol use with oesophageal squamous cell carcinoma based on study design.

Table S4. Summary estimates of associations between tobacco and alcohol use with oesophageal squamous cell carcinoma based on sub-continent of study origin.

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