Kurdistan Journal of Applied Research (KJAR)
Print-ISSN: 2411-7684 | Electronic-ISSN: 2411-7706

Review Article

Smoking and Alcohol Consumption are Associated with Higher Risk of Oral Cancer Incidence: A Systematic Umbrella Review

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Submitted: 1 April 2026
Revised: 24 May 2026
Accepted: 2 June 2026

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Keywords: Smoking, Tobacco, Alcohol, Oral cancer, Systematic review, Meta-analysis.

How to cite this paper: M. k. Mahmood, B. H. Qadir, F. Q. Rash, Y. M. M. Amin, H. Tassery, D. Tardivo, R. lan " Smoking and Alcohol Con-sumption are Associated with Higher Risk of Oral Cancer In-cidence: A Systematic Umbrella Review", KJAR, vol. 11, no. 1, pp: 163-180, Jun 2026, doi: 10.24017/science.2026.1.11

Abstract: Smoking and alcohol consumption are established risk factors for oral cancer, yet the strength and consistency of their association, particularly across exposure subtypes, remain incompletely characterized in a synthesized evidence base. To assess the association of smoking and alcohol consumption with oral cancer incidence using a systematic umbrella review and meta-analysis of existing meta-analyses. MEDLINE via PubMed and Scopus/EMBASE were searched for records published up to June 2025. Association meta-analyses reporting odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI) were eligible for inclusion. Methodological quality was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2), and evidence certainty was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. A random-effects model was applied for pooling. A total of 28 meta-analyses were included, covering approximately one million participants from 561 primary studies worldwide. Smokers had four times higher odds of oral cancer (OR=4.01, 95% CI: 3.21–4.99). Smokeless/chewed tobacco conferred a significantly greater risk (OR=5.28, 95% CI: 4.32–6.46) than the smoked type (OR=2.66, 95% CI: 1.99–3.57). Secondhand smoke exposure was also associated with elevated odds (OR=1.56, 95% CI: 1.26–1.93). Any-type alcohol consumption increased oral cancer risk (RR=2.47, 95% CI: 1.91–3.19), with a clear dose-response gradient: pooled RRs were 1.37, 2.22, and 4.94 for light, moderate, and heavy drinkers, respectively. The association of smoking and alcohol with oral cancer is statistically significant, consistent across exposure subtypes, and demonstrates a dose-response gradient, underscoring the importance of tobacco and alcohol cessation in oral cancer prevention.

1. Introduction

Oral cancer is one of the top 15 most frequent malignancies worldwide, making it a serious public health concern. Its incidence keeps rising despite improvements in early detection and prevention, particularly in low- and middle-income nations [1, 2]. Of the many risk factors, alcohol and tobacco use are the most well-known and controllable causes of oral carcinogenesis [3]. The International Agency for Research on Cancer (IARC) has designated both chemicals as Group 1 carcinogens [4, 5], and several observational studies have shown their significance in causing and advancing oral cancers [6–7].

Numerous systematic reviews and meta-analyses have tried to measure the link between drinking, smoking, and oral cavity cancer within the last 20 years [8-13]. Their judgments, however, frequently

diverge in terms of the extent and, occasionally, the direction of the influence. Variations in study quality, population demographics, exposure classifications (such as smoked versus smokeless tobacco; light versus heavy drinking), and outcome classification (such as including oropharyngeal cancer) could be the cause of this discrepancy. Furthermore, there haven't been many attempts to combine the data in a way that takes into consideration biological plausibility, dose-response correlations, methodological rigor, and possible synergistic effects between the exposures.

Notably, there are still gaps in the assessment of the effects of varying alcohol consumption patterns (light, moderate, and heavy) and tobacco use (smoked versus smokeless) on the risk of oral cancer. Understudied topics with significant public health ramifications include the separate impact of secondhand smoke and the combined effect of alcohol and tobacco use. Furthermore, the GRADE framework has rarely been used in this context to evaluate the certainty of the evidence, and structured tools such as AMSTAR 2 have rarely been used to critically evaluate the methodological quality of the available reviews.

Therefore, this study's objective was to assess the relationship between alcohol use, smoking and oral cancer by means of a systematic umbrella review and meta-analysis of previous papers that included quantitative synthesis, methodological evaluation, and evidence grading.

2. Materials and Methods

2.1. Protocol Registration

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [14], and pertinent methodological criteria for umbrella reviews [15, 16] were followed in this review. This review's protocol was prospectively registered under the registration number CRD420251082562 in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251082562). No deviations were made from this protocol.

2.2. Eligibility Criteria

PECOS/T guideline was used to formulate the research questions of this review as follows: (P) Problem: what is the impact of smoking and alcohol on the incidence of oral cancer? How do practices like smoking and chewing affect the outcome? How the dose and frequency will affect the outcome? (P) Population: how exposed smokers and drinkers are affected compared to non-smokers and non-drinkers? (E) Exposure: smoking (smoked and smokeless) and alcohol intake. (C) Comparison: intergroup comparison of the exposed group over time and intragroup comparison between exposed and non-exposed groups. (O) Outcome: oral cancer. (S) Study design: including all the meta-analyses. (T): Time: all the published meta-analyses published in MEDLINE via PUBMED and Scopus/EMBASE databases before June 2025.

The data that were included did not include any experimental investigations because the only research on this association was observational. Included were all meta-analyses that reported the aforementioned association and displayed their results in OR and RR. Furthermore, the few meta-analyses that addressed oropharyngeal malignancies but had specific information about oral cancer were also included. Due to a lack of comparability, the few meta-analyses that reported their findings in percentage or prevalence were eliminated. Additionally, all pre-clinical, animal, and in vitro research was disregarded.

Only meta-analyses on oral cancer incidence were included, while studies on mortality are excluded. Those few meta-analyses that focused on the association on the usage of alcoholic mouthwashes and oral cancer without reference to actual alcohol consumption were excluded. All the meta-analyses that studied oral premalignant lesions, or cancers other than oral cancer, or oral cancers associated with human papillomavirus, or studies on the effect of cessation, or studies investigating cancer mortality as an outcome were excluded.

2.3. Search Strategy

The PubMed, MEDLINE, Scopus, and EMBASE were searched to find relevant meta-analyses assessing the association; all records published before to June 2025 were included.

A search strategy was developed using Medical Subject Headings (MeSH) terms and keywords associated with oral cancer, oral squamous cell carcinoma, review/meta-analysis, and smoking/alcohol (and its subtypes). Table S1 contains the complete list of search phrases and combinations. Only English articles that satisfied the inclusion requirements were included, however there were no limitations on publication dates.

2.4. Study Selection

Duplicate records were eliminated when all database records were put into reference management software. Two independent reviewers (M. M. and B. Q.) carried out the study selection process in two stages. Part 1 of the two-part study selection procedure involved screening titles and abstracts for possibly relevant studies based on eligibility criteria. Part 2 involved thoroughly reviewing the full-text articles of potentially eligible studies for eligibility. The umbrella review included systematic reviews and meta-analyses that satisfied all qualifying requirements. The two reviewers had a conversation to settle disagreements that arose throughout the screening process. A third reviewer (M. A.) made the final decision in cases when an agreement could not be achieved.

2.5. Data Extraction

A standardized Microsoft Excel spreadsheet designed for this comprehensive review was used for data extraction. Two reviewers (M. M. and B. Q.) separately extracted the data to minimize variability and lower the possibility of errors. When disagreements about data extraction could not be settled by conversation, a third reviewer (M. A.) was consulted.

Different worksheets were developed for all-type smoking, smoked and smokeless smoking, all-type alcohol, alcohol intake frequencies (light, moderate, heavy) and combined smoking and alcohol. For smoking, the included studies were divided into two categories of smoked and smokeless.

The major statistical findings, covariate adjustments, sample size, demographic characteristics, study design of the primary studies, number of primary studies included in each meta-analysis, and subgroup/sensitivity results were all retrieved.

The meta-analytic forest plots or result tables were used to extract the effect sizes for each outcome, which were labelled as OR and 95% CI and RR with 95% CI.

2.6. Quality Assessment

The methodological quality of the included meta-analyses and systematic reviews was evaluated using the AMSTAR 2 tool [17]. This is a specialized tool for assessing the methodological quality of systematic reviews that look at randomized or non-randomized studies of healthcare interventions. Each review is given a quality grade of high, moderate, poor, or severely low using the AMSTAR 2 tool. The seven domains that AMSTAR 2 deems "critical" are given particular attention. Each evaluation was completed independently by two reviewers (M. M. and B. Q.), and disagreements were resolved by discussion or, if necessary, the participation of a third reviewer (M. A.).

2.7. Data Sysnthesis and Analysis

The DerSimonian and Laird random-effects model were used [18]. The I^2 statistical test was also used to evaluate study heterogeneity. For heterogeneity, a p-value of less than 0.10 was deemed statistically significant. According to the Cochrane guideline, values between 0% and 40% were deemed potentially unimportant, values between 30% and 60% indicated moderate heterogeneity, values between 50% and 90% indicated substantial heterogeneity, and values between 75% and 100% indicated considerable heterogeneity [19].

Additionally, statistical techniques were used to evaluate the existence of publication bias. Small-study effects were identified using Egger's regression test; a p-value of less than 0.05 indicated possible

bias [20]. Cochrane's RevMan program (RevMan Web, Cochrane Collaboration, UK) was used for all statistical analyses [21].

Moreover, GRADE framework was used to evaluate the evidence certainty of the outcomes [22]. Using the main effect sizes of this analysis, the population attributable risk (PAR) was calculated to estimate number of the global attributable oral cancer cases to smoking and alcohol [23]. Further, the corrected covered area (CCA) was measured to calculate the overlap analysis [24]. Lastly, Bradford Hill's Criteria was utilized to assess the causality degree of the association [25].

3. Results

3.1. Study Selection

A comprehensive search of PubMed, MEDLINE, Scopus, and Embase yielded 318 records. 75 records were left for screening after 243 out-of-scope and duplicate records were eliminated. We discovered that 18 papers did not fit the inclusion criteria because they lacked quantitative analysis based on our examination of titles and abstracts. 57 articles were found for full-text screening. Additionally, we eliminated thirty more articles because they were not meta-analyses (n = 5), had inadequate data (n = 2), were duplicates (n = 2), or did not contain data pertinent to the study's declared scope (n = 20). Finally, a lack of comparability or inadequate data led to the exclusion of eight meta-analyses. These excluded studies and the explanations for their exclusion are provided in table S2. In the end, the final quantitative synthesis contained 28 systematic reviews and meta-analyses that satisfied the inclusion requirements [8–13, 26–47]. Figure 1 shows the flowchart of the process of study selection.

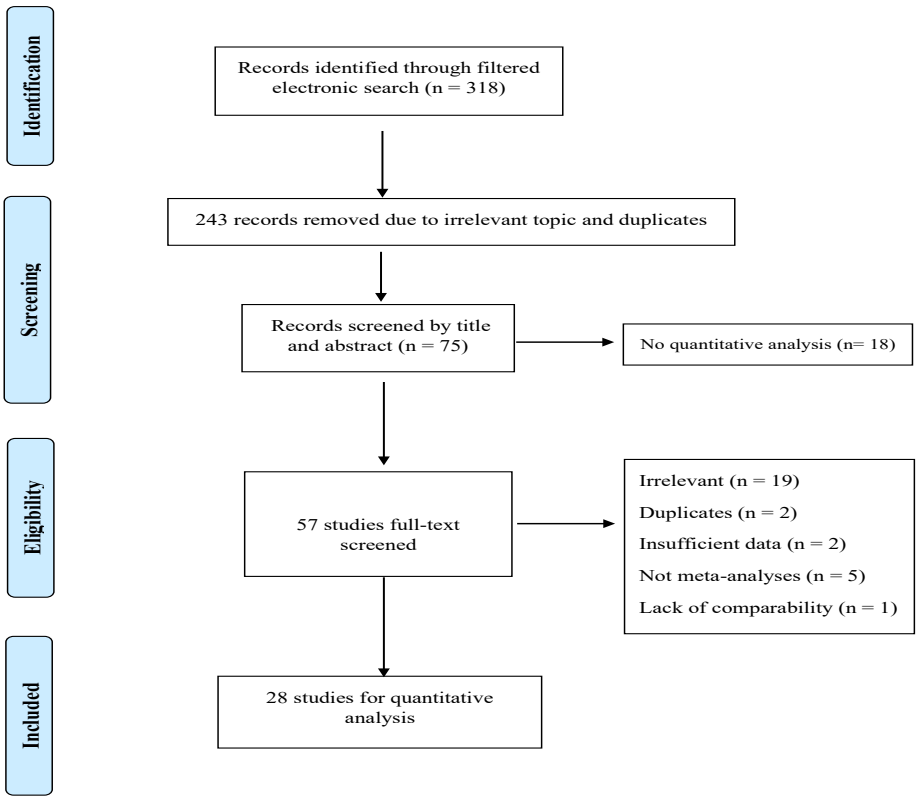

Figure 1: Flowchart of study selection process.

3.2. Characteristics of the Included Reviews

The included meta-analyses were published between 1999 and 2025. In the primary studies, information on the exposures and the outcome were commonly collected from hospital or community-based registries, while data on smoking and alcohol consumption was mainly self-reported.

The number of primary studies included in the meta-analyses ranged widely, from three to fifty-two. All of the meta-analyses contained 561 primary studies in total. Nevertheless, there were also

duplicate and overlapping records. About one million people were included in the meta-analyses. Once more, duplicating research may cause this sample size to drop to half. Seventeen studies contained research from around the world, while the rest were mainly focused on Southeast Asia where the prevalence of smoking is relatively higher. Smoking (in studies with alcohol as outcome), alcohol (in studies with smoking as outcome), age, sex, region, and various lifestyle/dietary factors were the main adjusted confounders of the association. Table 1 contains the main features of the included studies.

Table 1: Characteristics of the included reviews.

Ref	No. of primary studies	Study designs	Total subjects (cases/controls)	Population	Adjusted confounders	Key findings	Subgroup findings
[8]	50	Case–control and cohort	NA	Indian subcontinent, Taiwan, Papua New Guinea	Tobacco use, alcohol consumption, age, sex, region	Oral/oropharyngeal cancer: BQ-T=2.56 (2.00–3.28); BQ+T=7.74 (5.38–11.13); Taiwan BQ-T=10.98 (4.86–24.84).	Half of oral cancers preventable if BQ not chewed (PAF 53.7% BQ-T Taiwan; 49.5% BQ+T India).
[9]	6	Case-control	~2,000	Pakistan	Alcohol	OR for Naswar: 11.8 (8.4–16.4).	PAF for Pakistan: 44% (35–53%). Dose-response: OR up to 28.0 for >20 pack-years.
[10]	19	Case-control (15), Cohort (4)	~30,000 (Cases: 6,593)	Global	Age, sex, smoking, alcohol, education, region, lifestyle factors	Smokeless tobacco RR: 3.95 (2.86–5.46).	Chewed SLT showed stronger sex-based differences (RRR=2.09; 1.17–3.75).
[11]	7	Case-control	NA	India	NA	Smoking (general): OR=2.0 (1.5–2.5). Chewing: OR=6.6 (5.2–8.4). Bidi smoking: OR=2.9 (1.5–5.4).	-
[12]	32	Case-control and cohort	~81,700 cases	India	Smoking, alcohol, age, region, lifestyle	OR=5.67 (3.83–8.40).	PAF: 60% of oral cancers attributable to SLT. OR=3.9 (adjusted) vs. OR=8.4 (smoking only).
[13]	5	Case-control	6,977 (1,179 cases and 5,798 controls)	Global	Smoking, alcohol, age, sex, region, lifestyle factors	Secondhand exposure OR: 1.51 (1.2–1.91).	Duration of exposure >10–15 years increased risk: OR=2.07 (1.54–2.79).
[26]	37	Case–control and cohort	NA	Global	Smoking (all), alcohol, age, BMI, region	Smokeless tobacco: OR=3.53 (2.75, 4.51). Pan tobacco/betel liquid: OR=7.18 (5.48–9.41).	Chewing: OR=4.37 (3.27–5.83) vs. non-chewing (OR=1.56, 1.04–2.36). Case-control: OR=3.66 (2.83–4.74) vs. cohort (OR=2.32, 0.91–5.94, p=0.08).
[27]	52	Case–control and cohort	18,837 (13,895/4,942)	Global	Smoking, age, sex, region, lifestyle/dietary factors	RR for light drinking: 1.13 (1.00–1.26); moderate: 1.83 (1.62–2.07); heavy: 5.13 (4.31–6.10).	Stronger association in case–control than cohort (p het=0.007). Light drinking significantly associated in Asian populations (RR=1.33).
[28]	5	Cohort	NA	Global	Smoking, age, BMI, region, lifestyle factors	Light drinking: RR=0.96 (0.84–1.11); moderate: 1.12 (1.01–1.24).	Moderate drinking for women: RR=1.18 (1.05–1.33); for men: 1.04 (0.93–1.17).

Table 1: continue

[29]	24	Case–control and cohort	7,880	Global	Smoking, age, sex, region, lifestyle/dietary factors	RR light/moderate/heavy: Men/Mediterranean 2.2, 4.2, 10.7. Women/Mediterranean: 2.3, 4.5, 12.5.	Men/Other areas: 1.9, 3.0, 5.5. Women/Other areas: 1.9, 3.2, 6.4.
[30]	30	Case–control, cross-sectional and cohort	132,390	Global	Smoking, age, region, lifestyle/dietary factors	Non-tobacco product (NTP): OR=5.0 (3.3–7.7).	Areca nut+betel quid: OR=5.9 (3.7–9.5, p<0.001). Non-specified NTP: OR=2.1 (1.6–2.7, p<0.001).
[31]	12	Case-control and cohort	NA	Global	Smoking, alcohol, age, sex, region	RR=3.43 (2.37–4.94) for current smokers.	Higher risk in current vs. former smokers. Stronger association in studies adjusted for alcohol (RR=4.03 vs. 2.03 unadjusted).
[32]	19	Case–control and cohort	Cases: 4,553; Controls: 8,632; Cohorts: 15,342	South Asia and the Pacific	Age, sex, smoking, alcohol, education, socioeconomic status	Smokeless tobacco chewing: OR=7.46 (5.86–9.50), RR=5.48 (2.56–11.71). Betel quid without tobacco: OR=2.82 (2.35–3.40).	BQ without tobacco risk varied by region (e.g., Taiwan: higher risk due to preparation differences).
[33]	5	Case–control	~12,000	Global	Smoking, age, education, lifestyle	RR=4.84 (2.51–9.32) for highest vs. lowest alcohol intake.	-
[34]	8	Case–control and cohort	~135,000	Global	Smoking, alcohol, age, sex, region	Moderate smokers and drinkers: RR=4.71 (2.37–9.38).	Heavy smokers and drinkers: RR=36.42 (24.62–53.87).
[35]	19	Case-control (16), Cohort (3)	~160,000	South Asia	Smoking, alcohol, age, sex, region	OR for chewing tobacco: 4.7 (3.1–7.1). OR for paan with tobacco: 7.1 (4.5–11.1).	Dose-response: higher frequency/duration increased risk (e.g., OR=20.0 for >10x/day chewing).
[36]	15	Case-control (31), Cohort (2)	6,897 (Cases: 2,430; Controls: 4,467)	Global	Age, sex, region, lifestyle factors	Synergistic alcohol and tobacco: OR=5.37 (3.54–8.14).	Smokeless tobacco+alcohol: OR=7.78 (2.86–21.14). Smoked tobacco+alcohol: OR=4.74 (3.51–6.40). All three: OR=16.17 (7.97–32.79).
[37]	14	Case-control (13), Cohort (1)	52,434 (Cases: 6,593; Controls: 45,841)	South-East Asia	Smoking, alcohol, betel quid chewing, age, sex	Synergistic effect of smoking-drinking-chewing: OR=40.1 (35.1–45.8).	Indian studies: OR=46.1 (38.1–55.7). Taiwanese studies: OR=55.1 (37.0–82.3). Interaction stronger in Indian studies (84.6% of excess risk).
[38]	12	Case-control	~6,000	South Asia	NA	Bidi smoking: OR=3.1 (2.0–5.0). Cigarette smoking: OR=1.1 (0.7–1.8). Combined: OR=2.2 (0.7–7.0).	Dose-response: higher risk with longer bidi smoking duration.
[39]	15	Case-control	6,839 (2,533 cases; 4,306 controls)	Global	Age, sex, alcohol, betel quid, education, ethnicity, residence	OR for tobacco smoking: 4.65 (3.19–6.77).	Americas: 7.65 (5.11–11.45). Africa: 3.62 (2.40–5.48). Europe: 3.12 (1.52–6.40). Asia: 1.88 (0.95–3.71).

Table 1: continue

[40]	10	Case-control	2,123 cases	South-East Asia	Age, sex, alcohol, betel quid chewing, education, ethnicity, residence	Betel quid+smoking: OR=3.5 (2.16–5.65). BQ without tobacco: OR=2.14 (1.06–4.32).	-
[41]	45	Case-control and cohort	17,085 cases	Global	Age, sex, smoking, education, region, lifestyle/dietary factors	RR for light drinking (≤1 drink/day): 1.21 (1.10–1.33). Heavy (>4 drinks/day): 5.24 (4.36–6.30).	Dose-response: RR=1.29 for 10 g ethanol/day, 3.24 for 50 g/day, 8.61 for 100 g/day.
[42]	22	Case-control	7,419 cases	Global	Age, sex, smoking, education, region, lifestyle/dietary factors	Light drinking (≤1 drink/day): RR=1.17 (1.01–1.35). Heavy (>4 drinks/day): RR=4.64 (3.78–5.70).	Dose-response: RR=1.28 (10 g/day), 3.00 (50 g/day), 6.65 (100 g/day).
[43]	49	Case-control and cohort	18,387 cases	Global	Age, sex, region, smoking, lifestyle/dietary factors	Any drinking: RR=2.55 (2.15–3.02). Heavy (≥4 drinks/day): RR=5.40 (4.49–6.50). Moderate (1–2 drinks/day): RR=1.36 (1.20–1.54).	Never/non-current smokers: RR=1.32 (1.05–1.67). Smokers: RR=2.92 (2.31–3.70).
[44]	3	Cross-sectional	~1,000 cases	Global	Age, sex, smoking status, other tobacco use	Waterpipe tobacco smoke: OR=4.17 (2.53–6.89).	-
[45]	32	Case-control (29), Cohort (3)	16,540 cases	Global	Smoking, alcohol, age, social status	Smokeless tobacco: OR=1.87 (1.40–2.48).	No significant risk after adjustment for smoking and alcohol: OR=1.02 (0.82–1.28).
[46]	7	Case-control and cohort	NA	Global	Smoking, alcohol, age, sex, region, betel quid use	Passive smoking: OR=1.85 (1.07–3.17).	-
[47]	7	Case-control	NA	Global	Age, sex, region, smoking, alcohol, lifestyle/dietary factors	OR for light/moderate/heavy smoking: 1.51 (1.19–1.93), 2.79 (1.93–4.04), 4.00 (2.57–6.22).	OR for light/moderate/heavy alcohol: 1.30 (1.14–1.49), 2.28 (1.68–3.10), 3.93 (2.78–5.57).

OR: odds ratio; RR: risk ratio (relative risk); BQ: betel quid; T: tobacco; PAF: population attributable fraction; SLT: smokeless tobacco; NA: not available.

3.3. Quality of the Included Reviews

The methodological quality of the included systematic reviews and meta-analyses was assessed using the AMSTAR 2 tool. Twelve of the 28 included meta-analyses were rated as "low," five as "critically low," eight as "moderate," and only three as "high."

The funding sources of the included research were not disclosed by any of the meta-analyses (Q10). Only two meta-analyses justified the exclusions and offered a list of the studies that were eliminated (Q7). Just five of the studies had previously recorded their methodology in databases (Q2). When evaluating and explaining the review's findings, several research either ignored or only partially took the risk of bias in individual studies into account (Q13). Once more, a large number of review authors either failed to conduct a sufficient examination into publication bias or just partially did so (Q15). A complete itemized AMSTAR 2 rating for every included meta-analysis is provided in table S3.

3.4. Meta-analyses Results

Table 2 shows the detailed findings.

Table 2: Meta-analysis results of the association between smoking, alcohol, and oral cancer incidence.

Exposure	No. of included estimates	Effect size (95% CI)	p-value	I^2 (%), p-value heterogeneity	Egger's test p-value	GRADE
Smoking						Moderate
Cross-sectional studies (OR)	25	4.01 (3.21- 4.99)	<0.0001	93%, <0.0001	0.15	
Smoked	11	2.66 (1.99- 3.57)	Intergroup diff: p=0.0001	81%, <0.0001		
Smokeless	14	5.28 (4.32-6.46)		93%, <0.0001		
Subgroup analysis by region (OR)	25		<0.0001	94%, <0.0001		
Global	9	3.47 (2.38-5.06)	Intergroup diff: p=0.48	92%, <0.0001		
Southeast Asia	16	4.09 (3.13-5.36)		93%, <0.0001		
Sensitivity analysis by study quality (OR)	25					
Low quality	20	3.75 (2.79-5.05)	Intergroup diff: p=0.24	93%, <0.0001		
Moderate quality	5	4.97 (3.43- 7.22)		92%, <0.0001		
Sample size (OR)	18					
<10,000	8	3.38 (1.93-5.92)	Intergroup diff: p=0.29	90%, <0.0001		
>10,000	10	4.74 (3.52-6.37)		93%, <0.0001		
Passive smoking (OR)	2	1.56 (1.26-1.93)	<0.0001	0%, 0.51		
Cohort studies (RR)	7	4.00 (2.70-5.93)	<0.0001	87%, <0.0001	0.12	
Smoked	3	2.98 (1.82-4.91)	Intergroup diff: p=0.18	80%, 0.007		
Smokeless	4	5.07 (2.80-9.20)		90%, <0.0001		
Alcohol (RR)	21	2.47 (1.91-3.19)	<0.0001	97%, <0.0001	0.01	Low
Trim and fill analysis	30	1.41 (1.07-1.87)	0.01	98%		
Subgroup analysis by dose	21		Intergroup diff: <0.0001			
Light	7	1.37 (1.11-1.68)	<0.0001	94%, <0.0001	0.33	
Moderate	6	2.22 (1.49-3.31)	0.001	95%, <0.0001	0.12	
Heavy	8	4.94 (4.35-5.60)	<0.0001	20%, 0.27	0.71	
Sensitivity analysis by study quality	21					
Low quality	13	2.11 (1.54-2.89)	Intergroup diff: p=0.06	98%, <0.0001		
Moderate quality	8	3.24 (2.32-4.53)		80%, <0.0001		
Sample size	16					
<15,000	9	3.54 (2.30-5.45)	Intergroup diff: p=0.18			
>15,000	7	2.27 (1.38-3.75)				
Alcohol + Smoking (RR)	6	8.83 (4.05-19.24)	<0.0001	90%, <0.0001	0.33	Moderate

CI: confidence interval; OR: odds ratio; RR: relative risk; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.

3.4.1. *Effect of Smoking on Oral Cancer*

Twenty-five effect sizes were included for the association between overall smoking and oral cancer in the cross-sectional studies. The pooled analysis demonstrated a statistically significant association, i.e. smokers were more likely to have (OR = 4.01, 95% CI: 3.21, 4.99, p <0.0001). The meta-analyses showed a high degree of statistically significant heterogeneity (I^2 = 93%, p < 0.0001). Nevertheless, there was no indication of publication bias (p = 0.25). The GRADE framework assigned a moderate level of assurance to the evidence supporting this link (Table 2, Figures 2 and 3).

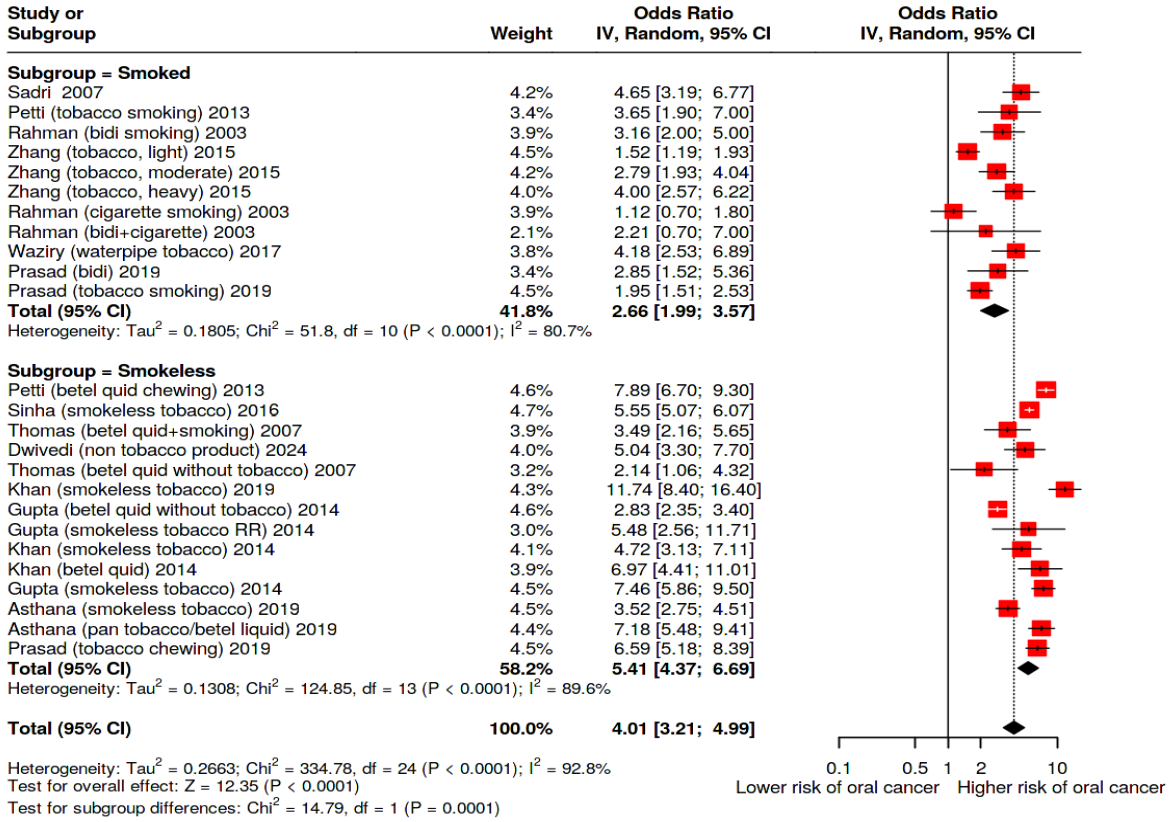

Figure 2: Forest plot of of the association between smoking and oral cancer in the cross-sectional studies.

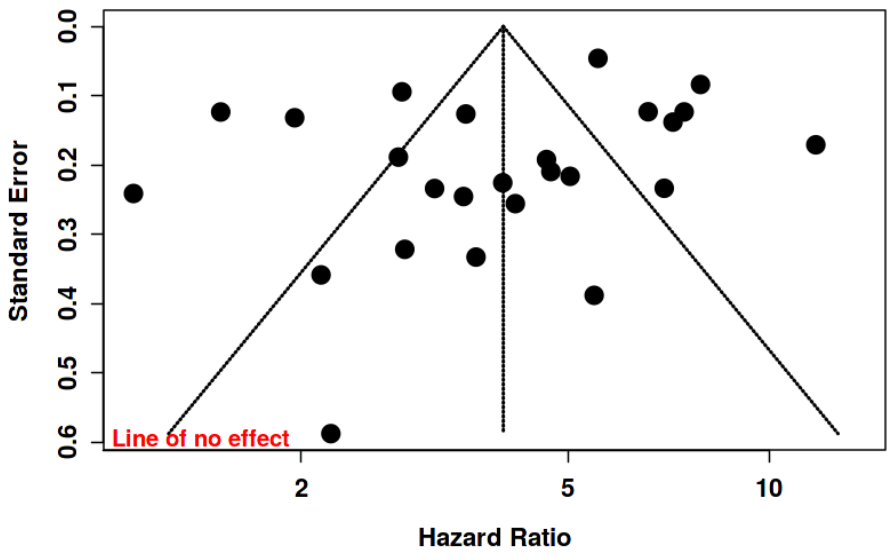

Figure 3: Funnel plot of the association between smoking and oral cancer in cross-sectional studies showing no significant publication bias.

Concerning the smoking type, the difference between smokeless (OR = 5.24, 95% CI: 4.32, 6.46) and smoked tobacco (OR = 2.66, 95% CI: 1.99, 3.57) was statistically significant. (Table 2, Figure 2)

Passive smokers were having higher odds of oral cancer compared to those who were not exposed to secondhand smoke (OR = 1.56, 95% CI: 1.26-1.93) (Table 2).

We compared meta-analyses with global focus with meta-analyses principally on Southeast Asia. Even though the Southeast Asia showed a higher risk (OR = 4.09 vs. OR = 3.47), the difference was not statistically significant (p = 0.48) (Table 2, Figure S1)

To see whether the result changes by quality of the studies, we conducted a sensitivity analysis comparing moderate quality papers with low quality papers. No statistically significant difference was observed (p = 0.24), indicating the consistency of the finding (Table 2, Figure S2). Moreover, the small and large sample studies showed no significant difference also (Table 2, Figure S3).

Concerning the cohort studies, seven estimates contributed to a significant RR of 4.00 (95% CI: 2.70, 5.93), however the difference between smoked vs. smokeless was not significant (Table 2, Figure 4).

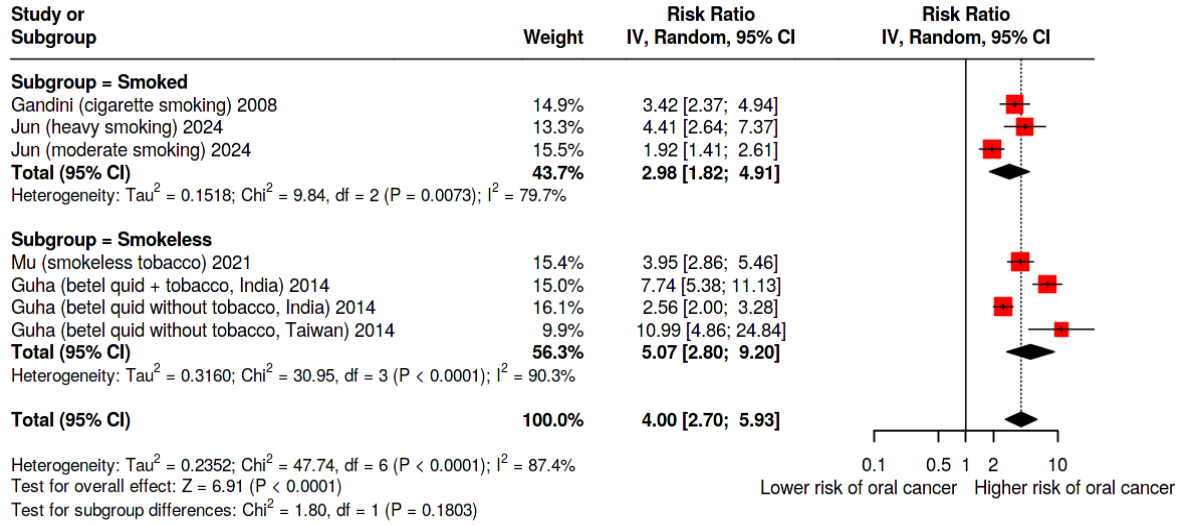

Figure 4: Forest plot of the association between smoking and oral cancer in cohort studies.

3.4.2. Effect of Alcohol on Oral Cancer

Pooled analysis from 21 estimates for the association between alcohol consumption and oral cancer was significant in cohort studies (RR = 2.47, 95% CI: 1.91, 3.19) with significant publication bias (Table 2, Figure 5). The trim and fill analysis to compensate for the publication bias showed the consistency and significance of the findings (RR = 1.41, 95% CI: 1.07, 1.87) (Table 2, Figure S4).

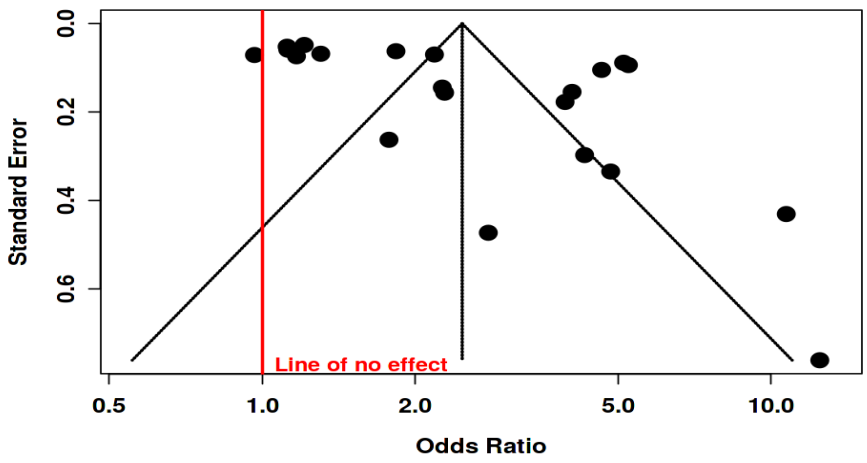

Figure 5: Funnel plot of the association between alcohol and oral cancer showing significant publication bias (0.01).

Concerning the alcohol consumption frequencies, all the light, moderate and heavy drinkers had greater chances of oral cancer incidence compared to their non-drinker or occasionally drinker counterparts. The pooled analyses showed a dose-response relation, i.e. lowest for light and highest for heavy drinkers (Table 2, Figure 6).

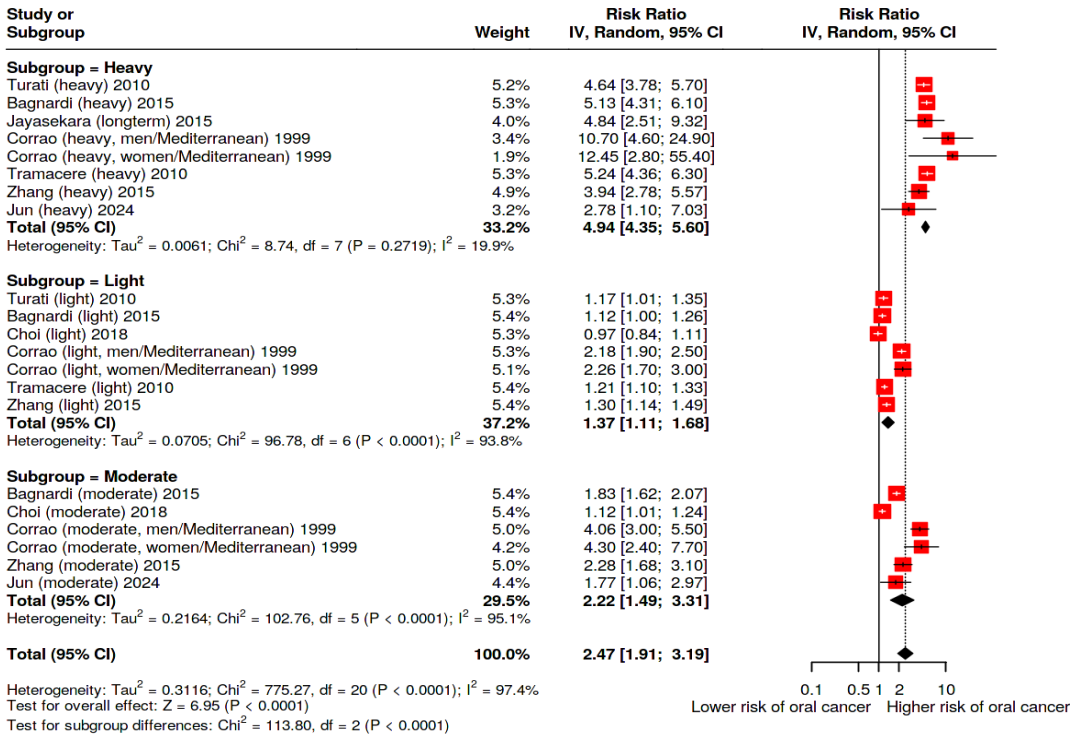

Figure 6: Forest plot of the association between alcohol intake and oral cancer in cohort studies comparing light, moderate and heavy drinking patterns.

In the sensitivity analyses comparing low vs. moderate and small vs. large sample size studies, the association remained significant and consistent (Table 2, Figures S5 and S6). Nevertheless, significant heterogeneity and publication bias downgraded the evidence quality to "low" as measured by GRADE.

3.4.3. Synergetic Effect of Smoking and Alcohol on Oral Cancer

Two meta-analyses with 6 effect sizes contributed to the pooled analysis on the combined effect of smoking and alcohol on oral cancer, making combined smokers and drinkers 8 times more at higher risk compared to non-smokers and non-drinkers (RR = 8.83, 95% CI: 4.05, 19.24). Despite the large effect size, the wide confidence intervals and presence of significant heterogeneity among the studies led only to a "moderate" certainty of evidence measured by GRADE (Table 2, Figure S7).

3.4.4. Population Attributable Fraction Analysis

We conducted a population attributable risk (PAR) analysis to determine the number of oral cancer cases attributable to drinking and smoking in order to convert the review's findings into the language of public health interventions. Our pooled RR for all-type smoking was 3.80 (3.11-4.64). According to the Global Burden of Disease (GBD) 2019 smoking prevalence among adults (15+ years) was approximately 22.3% [48]. Hence, we took 20% for smoking. The latest estimates from GLOBOCAN 2022 (by IARC), the number of new oral cancer cases worldwide is approximately 377,713 annually [49]. From here we took an approximate of 300,000 for the global prevalence of oral cancer. We used the following equation calculating PAR in which Pe is the prevalence of the exposure in the population:

$$PAR\% = \frac{\text{Pe (RR}-1)}{\text{Pe (RR}-1)+1} \text{ x } 100$$

According on the PAR results, with the current estimation 20% prevalence of smoking, approximately 37.5% (~113 thousand cases) can be attributed to smoking.

WHO Global Alcohol Report (2018 and 2022) reports a global prevalence of 43% for any drinker, 20% for heavy drinkers [50]. Here, again we took only 20% which is a modest estimate for all-type drinking. The PAR result revealed that with the current 20% prevalence of alcohol consumption, 22.7% corresponding to nearly 70 thousand cases of oral cancer can be attributed to alcohol. Table 3 shows the estimated calculation of PAR analysis.

Table 3: Estimated number of oral cancer cases attributable to smoking and alcohol globally.

	Relative risk (95% CI)	Population attributable risk, % (95% CI)	Number of attributable oral cancer cases, thousands (95% CI)
Global prevalence of smoking			
20% (current estimation)	4.00 (2.70–5.93)	38% (25%–50%)	113 (76–149)
If reduced to 10%	4.00 (2.70–5.93)	23% (15%–33%)	69 (44–99)
If reduced to 5%	4.00 (2.70–5.93)	13% (8%–20%)	39 (24–59)
Global prevalence of alcohol intake			
20% (current estimation)	2.47 (1.91–3.19)	23% (15%–30%)	68 (46–91)
If reduced to 10%	2.47 (1.91–3.19)	13% (8%–18%)	38 (25–54)
If reduced to 5%	2.47 (1.91–3.19)	7% (4%–10%)	21 (13–30)

PAR: Population Attributable Risk; 95% CI: 95% Confidence Interval. Estimated based on GLOBOCAN 2022 global oral cancer incidence of approximately 300,000 new cases annually.

3.4.5. Overlap Analysis

The overall CCA was 6.2% indicating moderate overlapping between the included reviews. The result was 6.6% and 39.3 for smoking and alcohol respectively. Among the smoking category, The CCA was only 3.7% for smoked and 11.2% for smokeless. Details of the overlap analysis is presented in table S4.

3.4.6. Causality Analysis

Additionally, we utilized Bradford Hill's Criteria to evaluate the whether the studies association qualifies to be called causality or not. The evidence supports a causal relationship between smoking, alcohol, and oral cancer, particularly for smokeless tobacco, heavy alcohol use and synergistic effects. Table S5 provides a thorough evaluation of every domain.

4. Discussion

This umbrella meta-analysis supports both individual and synergistic effects and offers strong and thorough data about the relationship between alcohol use, smoking, and the risk of oral cancer. A clear, persistent, and statistically significant connection across various exposure types and intensities was demonstrated by the pooled estimates derived from the included meta-analyses.

All-type smoking was linked to a significantly higher risk of oral cancer (OR = 4.04), with smokeless tobacco having a much higher risk (OR = 5.28) than smoked tobacco (OR = 2.66). Overall, this outcome was rated as "moderate" certainty.

Due to regional variations in exposure types (such as a higher incidence of smokeless tobacco use), Southeast Asian populations displayed risk estimations that were higher than the world average. However, the findings' generalizability was supported by the fact that these differences were not statistically significant. In addition, the findings were robust independent of methodological quality and sample size of the included studies.

With a pooled OR of 1.56 (95% CI: 1.26–1.93), the results further emphasize the risks of passive smoking, indicating that even nonsmokers who are exposed to secondhand smoke have a markedly

elevated risk of having oral cancer. This finding supports public health initiatives to establish and enforce smoke-free environments, albeit being based on fewer studies.

Additionally, drinking alcohol was linked independently to a markedly higher risk of developing oral cancer (RR = 2.47; 95% CI: 1.91–3.19). Light (RR = 1.37), moderate (RR = 2.22), and heavy drinkers (RR = 4.94) all displayed rising levels of risk, demonstrating a pronounced dose-response relationship. The strength of this link was highlighted by the high certainty of the evidence for heavy alcohol intake, its low heterogeneity (I^2= 20%), and the absence of publication bias. However, because of significant between-study variability and less consistent results across groups, the overall alcohol outcome received a "low" GRADE of confidence.

The overlap analysis showed varied degrees. The overall result was 6%, indicating moderate overlap. However, this reached 39% and 11% for alcohol and smokeless categories respectively. This indicates that the same pool of original studies has been used in the analyses of multiple included meta-analyses of this review and some categories have reached the state of saturation in this regard. In summary, this field needs new primary studies that study the association from novel perspectives instead of repeating meta-analyses with the same pool of included studies.

AMSTAR 2 was used to assess the methodological quality of the included studies. Five studies scored "critically low", 11 received a "low" quality, 8 had "moderate" quality, while only 3 studies gained a "high" quality assessment. Although AMSTAR 2 has been proven to be a successful tool in this regard, it is a relatively recent tool which was published in 2017 [17]. This umbrella review included some relatively older studies that had no chance to apply this tool or another comparable one while conducting their analysis. For example, nowadays it is widely accepted that record screening and data extraction should be done by two authors, and this information should be explicitly stated in the systematic review. However, it is rare to find these kinds of statements in the older articles. Therefore, on the one hand we tried not to be unfair and not to downgrade the quality of some well-structured older studies. On the other hand, objectivity pushed us to evaluate all the studies equally and the best tool we had in hand was AMSTAR 2. Therefore, we focused more on the seven critical domains of the tool which are mainly about handling bias and heterogeneity. Despite this, our sensitivity analysis of smoking comparing the high-medium and low-quality studies showed no statistically significant difference between the groups.

Funding is a sensitive issue when the topic is smoking and alcohol. While there is no problem in smoking and alcohol related companies or anti- smoking/alcohol pressure groups to fund research; however, this should be clearly stated. Unfortunately, many included studies failed to declare a proper funding statement. Eight studies received funds from academic institutions. Only two studies clearly reported that they have received no funding. The Foundation for Alcohol Research and Education (FARE), which defines itself as a non-profit organization with a vision for an Australia free from alcohol harms funded one meta-analysis [33]. Another review [45] was funded by Philip Morris International, which is a major tobacco company. According to both studies, the financial sources had no control on their results and interpretations. The rest of the included meta-analyses (n=16) didn't report whether they have reported funding or not.

There are several documented molecular pathways including carcinogenic, genetic, and epigenetic factors that may contribute to the development of oral cancer. Some chemicals found in smoked substances and alcohol can harm oral epithelial cells and encourage carcinogenesis either singly or in combination.

At least 70 of the more than 7,000 compounds included in tobacco smoke, whether smoked or smokeless, are recognized carcinogens [51]. The primary mechanisms consist of: First, mutagenesis and DNA damage: in epithelial cells, carcinogens like polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs) create DNA adducts [52, 53]. Point mutations are brought on by these DNA adducts, particularly in oncogenes like RAS and tumor suppressor genes like TP53 [54, 55]. Second, oxidative stress: smoking produces reactive nitrogen species (RNS) and reactive oxygen species (ROS), which lead to protein modification, DNA strand breakage, and lipid peroxidation [56]. Further, cellular transformation and chronic inflammation are exacerbated by this oxidative stress [57]. Third, immunosuppression and chronic inflammation: Tobacco irritants stimulate pro-inflammatory

cytokines (such as TNF-α and IL-6), which create an environment that is favorable to cancer [58]. Smoking also weakens mucosal immunity by lowering the function of natural killer cells and Langerhans cells [59].

Regarding alcohol, even though it is not directly mutagenic, its metabolic byproducts and biological consequences make it carcinogenic: First, acetaldehyde production: alcohol dehydrogenase (ADH) converts ethanol to acetaldehyde, which the IARC classifies as a group 1 carcinogen [5, 60]. Acetaldehyde then promotes mutagenesis by inhibiting DNA repair enzymes and forming DNA adducts and formation of reactive oxygen species through oxidative stress [60]. Second, solvent effect: alcohol makes mucosal permeability higher, which makes it easier for ambient pollutants and tobacco carcinogens to enter oral tissues [61]. Third, deficits in nutrition: Long-term alcohol consumption is linked to deficiencies in vitamins A, C, E, folate, and zinc, all of which are critical for antioxidant defense and DNA repair [62]. This could result in a compromised mucosal barrier and increased vulnerability to carcinogens [63]. Figure 7 depicts the major pathways of this interaction.

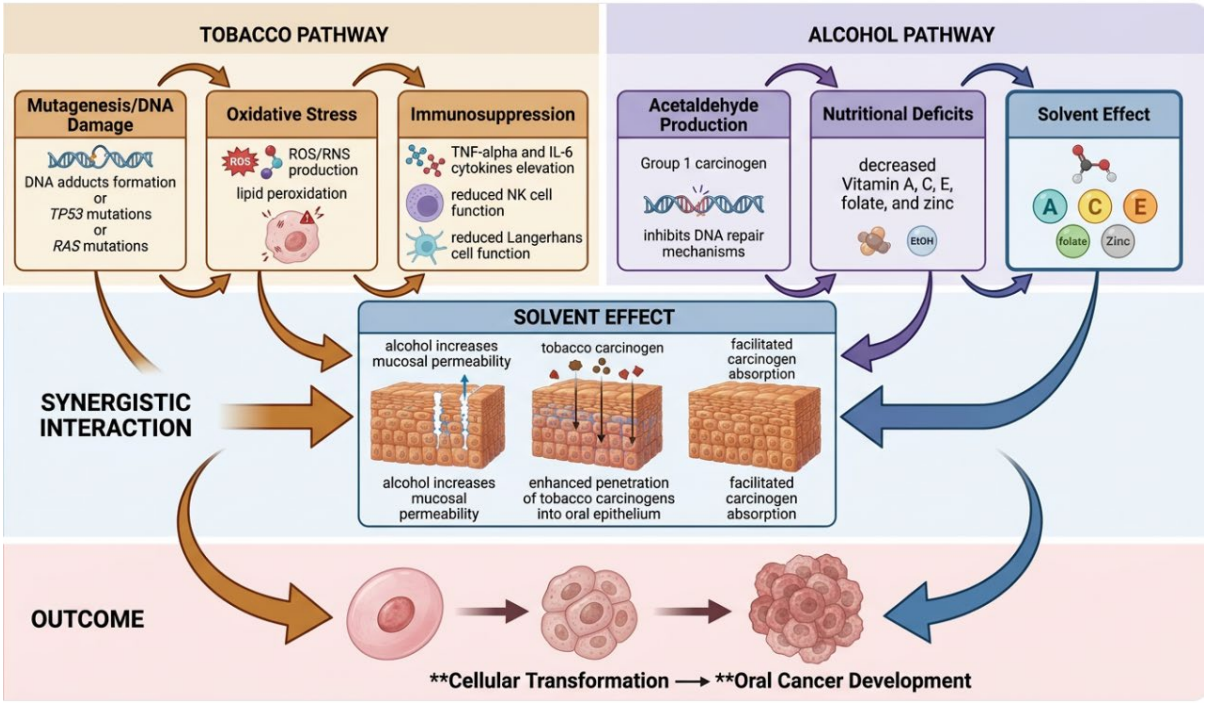

Figure 7: Diagram of the biological pathway interactions by which smoking and alcohol may induce oral cancer.

The effect of smoking and alcohol consumption is not confined only to oral cancer. The same increased odds are reported for other cancers as well. However, it appears that head and neck, respiratory and digestive tract are at greater risk compared to the other body parts. For instance, cigarette smoking was linked to a higher risk of head and neck cancer in never drinkers (OR of ever versus never smoking = 2.13, 95% CI = 1.52-2.98), while frequency, duration, and pack-years showed dose-response correlations. In nonsmokers, head and neck cancer was only linked to high frequency alcohol use [64]. According to another meta-analysis, among never drinkers and those with all ethanol intake levels, the risk of head and neck cancer increased significantly with smoking intensity, beginning at one cigarette per day. Smokers had a threshold effect at 50 g/day, and their chance of using ethanol rose with exposure. Compared to those who abstained from both alcohol and tobacco, those who consumed 10 cigarettes per day and 84 grams of ethanol per day had a 35-fold increased chance of developing cancer (95% CI 27.30–43.61). High levels of alcohol and tobacco use were associated with the highest risk [65].

Another argument for the link between smoking and/or alcohol with oral cancer is the cessation studies. In a cohort study, the 3- and 5-year survival rates were 46% and 40%, respectively. Mortality at 3 and 5 years was significantly reduced by reducing tobacco use and quitting smoking. At 3 and 5

years, mortality was significantly lower in alcohol reduction or total cessation [66]. Alcohol-induced higher risk for pharyngeal and laryngeal malignancies was reversible; it took 36 and 39 years, respectively, before the risks were comparable to those of never drinking. Additionally, a 15% decrease in the alcohol-related higher risk of laryngeal and pharyngeal malignancies was linked to quitting drinking for five years [67]. Compared to current users (RR 7.89), former betel quid users had a 28.9% risk reversal for betel quid without tobacco and oral cancer (RR 5.61) [68].

The PAR results showed that with the current estimation of 20% prevalence of smoking, approximately 38% (more than 100 thousand cases) can be attributed to smoking. Rahman et al, reported a 24% PAR for bidi smoking and oral cancer in South Asia [38]. The PAR result for alcohol revealed that with the current 20% prevalence of alcohol consumption, 23% corresponding to nearly 70 thousand cases of oral cancer can be attributed to alcohol. Table 2 shows the estimated calculation of PAR analysis. Lastly, when the association was evaluated using Bradford Hill's criteria for causality, the evidence strongly fulfilled nearly all the criteria, especially strength, consistency, dose-response, plausibility, and temporality. The evidence supports a causal relationship between smoking, alcohol, and oral cancer, particularly for smokeless tobacco, heavy alcohol use and synergistic effects. However, the observational nature of the included studies prevents drawing a definite causality.

The major strength of this review lies in its comprehensive design, large dataset, rigorous quality appraisal, inclusion of both cross-sectional/case-control and cohort studies and, exploration of dose-response and synergistic effects. However, limitations were the observational nature of included studies, which limits causal inference, and the high heterogeneity in some outcomes. The lack of standardization in exposure measurement (e.g., variation in defining "moderate" or "heavy" drinking) also adds variability. Publication bias was detected in some outcomes, which may overestimate the true effect sizes. Furthermore, the high overlap analysis of some categories may have led to overrepresentation of certain datasets and reduce the independence of the synthesized evidence. Finally, some included studies covered oropharyngeal cancers, and this might have obscured a more precise estimate for oral cancer.

Based on these limitations, future research should prioritize prospective cohort studies with standardized definitions of exposure levels (e.g., consistent thresholds for light, moderate, and heavy drinking) to reduce heterogeneity across studies. There is an urgent need for high-quality meta-analyses that explicitly distinguish oral cancer from oropharyngeal cancer, as their etiologies and HPV involvement differ significantly. Studies should also investigate region-specific risk profiles, particularly in high-burden areas.

5. Conclusions

The association of smoking and alcohol with oral cancer is statistically significant, consistent and has a dose-response gradient. The risk is especially higher for chewing tobacco, heavy drinking and combined smoking and alcohol habits. However, for most of the pooled analyses the quality of the evidence was rated moderate to low due to observational nature of the included primary studies, heterogeneity and publication bias. Moreover, due to high overlap of the included primary studies, the findings should be interpreted with caution, as there is some potential risk of pooled analyses overestimation. Still, the findings underscore the importance of tobacco and alcohol cessation in oral cancer prevention.

Author contributions: Author Contributions: Mohammed Khalid Mahmood: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Balen Hamid Qadir:** Conceptualization, Data curation, Investigation, Methodology, Project administration. **Faraidun Qadir Hama Rash:** Writing – original draft, Writing – review & editing. **Yad Mariwan Mohammed Ali:** Conceptualization, Data curation, Formal Analysis. **Herve Tassery:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing. **Delphine Tardivo:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing. **Romain Lan:** Supervision, Validation, Project administration, Writing – original draft, Writing – review & editing.

Data availability: Data supporting this article is presented in the supplementary material.

Conflicts of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: The authors did not receive support from any organization for the conducting of the study.

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