Clinical Oral Investigations (2022) 26:6855–6869
https://doi.org/10.1007/s00784-022-04719-z

REVIEW

Comparison of tobacco and alcohol consumption in young and older patients with oral squamous cell carcinoma: a systematic review and meta-analysis

Elis Ângela Batistella[1] · Rogério Gondak[2] · Elena Riet Correa Rivero[2] · Saman Warnakulasuriya[3,4] · Eliete Guerra[5] · André Luís Porporatti[6] · Graziela De Luca Canto[7]

Received: 3 March 2022 / Accepted: 6 September 2022 / Published online: 21 September 2022

Abstract

Objective To compare the proportion of young (up to 45 years of age) and older (over 45 years of age) oral squamous cell carcinoma (OSCC) patients who report tobacco and alcohol consumption.

Methods Observational studies reporting tobacco and alcohol consumption among young and older OSCC patients were selected in a two-phase process. Search strategies were conducted on five main electronic databases and complemented by grey literature. The risk of bias was assessed using the Joanna Briggs Institute's Critical Appraisal Checklist for Studies Reporting Prevalence Data. Synthesis of results was calculated with the software R Statistics version 4.0.2 (The R Foundation).

Results From 6675 records identified, 38 studies met the eligibility criteria and were selected for qualitative synthesis and meta-analysis, encompassing 2439 young and 13,393 older patients. Tobacco smoking was reported by 39.5% (confidence interval (CI) = 31.7% to 47.9%, $I^2 = 78\%$) of the young patients and 48.4% (CI = 37.8% to 59.2%, $I^2 = 94\%$) of the older patients. Alcohol consumption was reported by 30.9% (CI = 22.7% to 40.5%, $I^2 = 83\%$) of the young and 45.8% (CI = 35.6% to 56.5%, $I^2 = 95\%$) of the older patients ($P < 0.05$).

Conclusion The comparison in the proportion of individuals reporting tobacco and alcohol consumption demonstrated that these habits were more prevalent in the older group (48.4% and 45.8% respectively) than in the young group (39.5% and 30.9%, respectively).

Clinical relevance As a significant proportion of patients with OSCC reported no habits, novel risk factors for OSCC need to be investigated in further research.

Keywords Oral squamous cell carcinoma · Risk factors · Young patients · Systematic review

✉ Elis Ângela Batistella
elisbatistella@hotmail.com

[1] Health Sciences Center, Federal University of Santa Catarina, Rector David Ferreira Lima Campus, Trindade, Florianopolis, SC 88037150, Brazil

[2] Department of Pathology, Health Sciences Center, Federal University of Santa Catarina, Florianopolis, SC, Brazil

[3] Department of Oral Medicine and Experimental Oral Pathology, King's College Dental Institute, Bessemer Road, London SE5 9RS, UK

[4] WHO Collaborating Centre for Oral Cancer and Precancer in the United Kingdom, Denmark Hill Campus, London SE5 9RS, UK

[5] Laboratory of Oral Histopathology, Health Sciences Faculty, University of Brasilia (UnB), Brasilia, DF, Brazil

[6] Laboratoire de Neurobiologie OroFaciale, Université de Paris, France and GHPS Assitance Publique Hopitaux de Paris, Paris, France

[7] Brazilian Centre for Evidence-Based Research, Department of Dentistry, Federal University of Santa Catarina (UFSC), Florianopolis, SC, Brazil

Introduction

The incidence of oral squamous cell carcinoma (OSCC) has increased in the past few decades in many countries. Patients are usually diagnosed between their sixth and seventh decade of life, after several years of tobacco and alcohol consumption. However, an increasing number of individuals have been diagnosed with OSCC under the age of 45 years [1, 2].

In literature, these subjects who precociously develop OSCC are referred to as "young patients." Young individuals represent about 6% of OSCC patients [2]. In a significant proportion, especially among females, the absence of traditional risk factors, smoking and drinking, has been noticed. Additionally, the period for such carcinogens to exert a detrimental effect on these individuals is relatively short [2, 3].

Molecular features and environmental factors related to the earliest establishment of OSCC remain to be unveiled. Particularly, the role of tobacco and alcohol consumption in the development of OSCC at young ages has been investigated. While some studies demonstrate a small proportion of young OSCC patients who are tobacco smokers and alcohol users compared to older OSCC individuals [4–7], other works did not find remarkable differences in these habits between the two age groups [8–10].

The elucidation of such matter is crucial to appraise the real role of tobacco and alcohol in oral carcinogenesis at early ages. It also aids to explore the identification of other possible etiological agents for OSCC. Thereby, individualized preventive measures according to the main risk factors in each group can be applied. The purpose of this systematic review (SR) and meta-analysis was to compare the proportion of tobacco and alcohol consumption between young (up to 45 years of age) and older (over 45 years of age) OSCC patients.

Methods

Eligibility criteria

Inclusion criteria Primary studies on OSCC comprising lip, anterior two-thirds of the tongue, and rest of mouth (gingiva, palate, floor of mouth, buccal mucosa, alveolar ridge) were included. To be eligible, original research papers needed reporting of data from two age groups, divided into a young OSCC group (individuals up to 45 years old), and a comparison group of older OSCC patients (over 45 years old). Due to the lack of standardization in the literature regarding the term "young," a 5-year overlap among studies was accepted; however, this 5-year overlap should not be present within individual studies. Additionally, studied needed to report alcoholic beverage consumption and use of tobacco in any forms (e.g., smoked, chewed, sniffing).

Exclusion criteria Studies were excluded when (1) it was not possible to have data separately for young and older age groups; (2) did not report tobacco and alcohol consumption in young and older patients; (3) the sample had no oral squamous cell carcinoma as a separate group; (4) reviews, case reports, protocols, personal opinions, letters, posters, conference abstracts, in vitro and in vivo animal studies.

Information sources and search strategies

Search strategies were conducted using terms for "risk factors," "tobacco," "alcohol," "young patients," and "OSCC." Appropriate word combinations were developed for each of the following bibliographic databases: PubMed. EMBASE, Scopus, LILACS, and Web of Science. A nonpeer-reviewed literature search was also performed on Google Scholar, OpenGrey, and ProQuest Dissertations & Theses Global (Appendix 1). Additionally, manuscripts were hand-searched by checking the list of references of the included studies. The references were managed using the EndNote X7 software (Thomson Reuters, New York, NY, USA). The bibliographic search was updated on July 9, 2021.

Study selection

A two-phase process was followed to select studies. In phase 1, titles and abstracts of identified records were independently screened by three reviewers (E.A.B., R.G., E.R.C.R.); studies that did not meet the inclusion criteria were excluded. In phase 2, the same investigators applied these criteria to the full text of the manuscripts. Any inconsistencies were resolved by consulting experts (E.G., S.W.) to finally decide whether the article should be included in the SR.

Data collection process

Data collection was also independently performed by the three reviewers and then cross-checked. For each included study, data regarding study design, country of first author, and year of publication; patients' age; sample size; tumor site; and prevalence of alcohol and tobacco consumption were collected. Information about the number of individuals who reported tobacco and alcohol consumption or no habits was compiled in the software Excel version 16.27.

Risk of bias assessment

Risk of bias (RoB) was independently assessed by three reviewers (E.A.B., R.G., E.R.C.R.) using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data [13]. Scoring decisions were agreed upon by all reviewers before the critical appraisal. RoB was categorized as "high" when the study reached up to 49% score "yes"; "moderate" when the study reached 50 to 69% score "yes"; and "low" when the study reached more than 70% score "yes." A weighted bar plot and a risk of bias graph were generated with software (Review Manager 5.4; the Cochrane Collaboration, 2021).

Summary measures

The comparison in the proportion of young and older OSCC patients who reported alcohol consumption and tobacco smoking was considered as the main outcome.

Synthesis of results

Data on the frequency of individuals exposed to tobacco or alcohol in both young and older patient groups collected from articles were gathered in a Microsoft® Excel (Microsoft Corporation, version 16.42) table, and then transferred to the R software Statistics version 4.0.2 (The R Foundation) ($\alpha = 0.05$) to conduct the meta-analyses. The "meta" package was applied; raw data were converted by using the "logit transformation." To estimate confidence intervals for individual studies, the Clopper-Pearson interval was applied. Regarding statistical heterogeneity analysis, the following parameters were calculated: Cochran Q (χ^2), *I*-squared (I^2), Tau-squared (τ^2), and the prediction interval. Furthermore, the τ^2 was assessed through the restricted maximum likelihood method.

The distribution of true effect sizes was expected across included studies; therefore, the random effect model was applied [14]. Studies were grouped according to the reported habits. The first meta-analysis included data from studies reporting the proportion of tobacco smokers. The second meta-analysis included data from studies informing the proportion of individuals reporting alcohol consumption. The third meta-analysis assessed the proportion of individuals who reported the concurrent habits of tobacco and alcohol consumption. Finally, a fourth meta-analysis assessed the proportion of individuals who reported no habits. These analyses were conducted for both age groups. From each of the meta-analyses, a forest plot was generated to illustrate the combined results with the software R Statistics version 4.0.2 (The R Foundation).

Certainty of evidence assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile was used to verify the overall quality of evidence using the online software version (GRADEpro GDT) [14].

Results

In phase 1 of study selection, the search across electronic databases identified 6675 studies. After removing duplicates, 4808 articles remained. In addition, 107 studies were identified from nonpeer-reviewed literature. Sixteen articles were included after searching reference lists. After a comprehensive evaluation of the titles and abstracts, the reviewers considered 97 studies for eligibility, of which 59 were excluded after full-text reading (Appendix 2). Subsequently, 38 studies [5–10, 15–45] were included for qualitative analysis and quantitative synthesis. A flow chart detailing the process of identification, inclusion, and exclusion of the studies is shown in Fig. 1.

Study characteristics

The included studies were conducted as retrospective analysis in which data were collected from patient's records. The 38 included studies were published in eighteen countries: Australia [23, 36–38] Brazil [19, 21, 24–26, 32, 34], Canada [7, 35], China [5, 18] [43, 45], France [16], Germany [6, 30], India [15, 27, 42], Ireland [28], Israel [20, 31], Italy [8], Japan [41], Singapore [44], South Korea [29, 40], Sri Lanka [4], Spain[17], Taiwan[22], Thailand [10], and USA [9, 32, 39] from 1977 to 2021. Table 1 summarizes the descriptive characteristics of the included studies. Most studies only reported the proportion of patients who were tobacco and alcohol consumers, without specifying the type, quantity, and frequency of the habit. Therefore, it was not possible to stratify groups according to the amount of tobacco or alcohol consumed.

Risk of bias within studies

Regarding the overall risk of bias, studies were considered at low risk, ranging an overall proportion of 88.8 to 100% yes answers to the JBI checklist [13]. The main source of bias was the small sample sizes in at least one of the study groups in sixteen studies [6, 7, 18–23,

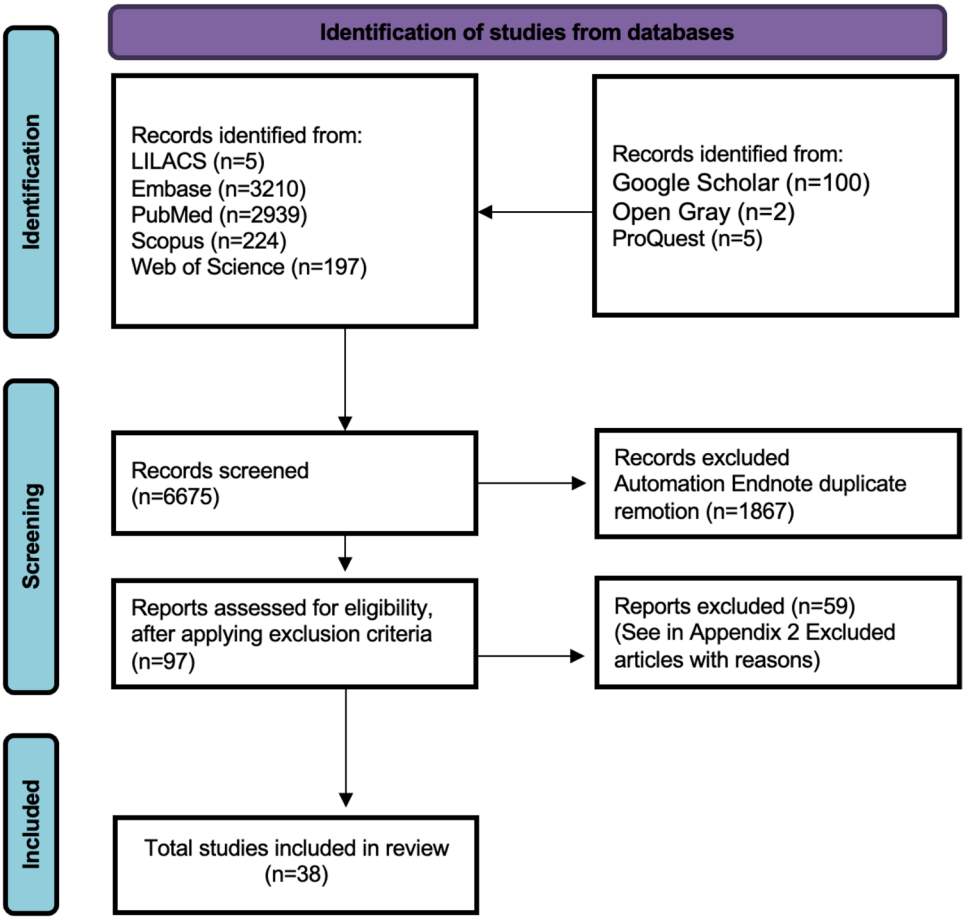


Fig. 1 PRISMA flow diagram of literature search and selection criteria

28–32, 34, 36, 40, 44] and data analysis being conducted with insufficient coverage of the identified sample [29, 31]. A weighted risk of bias bar plot and risk of bias graph is depicted in Fig. 2.

Certainty of evidence

GRADE analysis rendered a very low overall certainty of evidence due to varying proportions of (1) inconsistency, for having different methods to define quantity and frequency of consumption, and due to high methodological heterogeneity, which results from differences in the way studies were conducted; (2) indirectness, for having no healthy control groups; and (3) imprecision, due to wide confidence intervals for both outcomes. However, it is important to notice that certainty of evidence starting in a low rank is due to the observational nature of studies.

Synthesis of results

A total of 15,832 OSCC patients were included in this SR. The pooled young group comprised 2439 patients, being 861 women (35.3%) and 1578 men (64.7%). The pooled older group encompassed 13,393 patients, being 4803 women (35.8%), 8554 man (63.9%) and 36 with sex data not being reported (0.3%). The tongue was the commonest reported oral subsite of cancer onset. In the young patient's OSCC group, meta-analyses results demonstrated that 39.5% (CI = 31.7% to 47.9%, $I^2 = 78\%$) of the patients reported tobacco smoking (Fig. 3). Additionally, 30.9% (CI = 22.7% to 40.5%, $I^2 = 83\%$) reported alcohol consumption (Fig. 4). The concurrent habit of smoking and drinking alcoholic beverages was reported by 24.4% of the young patients (CI = 14.9% to 37.3%, $I^2 = 69\%$) (Fig. 5).

In the older patient's OSCC group, meta-analyses demonstrated 48.4% (CI = 37.8 to 59.2%, $I^2 = 94\%$) of the patients reported tobacco smoking (Fig. 3). Furthermore, 45.8% (CI = 35.6 to 56.5%, $I^2 = 95\%$) reported alcohol consumption (Fig. 4). The concomitant habit of smoking and drinking alcoholic beverages was informed by 47% (IC = 26% to 69.1%, $I^2 = 93\%$) of the older OSCC patients (Fig. 5).

The proportion of older individuals reporting habits of tobacco and alcohol consumption, either isolated or

Table 1 Summary of included articles' descriptive characteristics

Author/1st author country/year/study type	Number of young patients (F/M)	Site	Tobacco and alcohol users (young group)	Number of older patients (F/M)	Site	Tobacco and alcohol users (older group)
Acharya and Tayaar/India/2012/Retrospective analysis (2005–2009)	≤40 y/79 (11/68)	Buccal mucosa = 37 Gingiva and alveolar process = 19 Tongue and floor of mouth = 18 Miscellaneous (lip, central, antrum, palate tumors) = 5	Tobacco, alcohol or Both = 14 Chewed tobacco = 1 No habits = 12	> 40 y/158 (48/110)	Buccal mucosa = 59 Gingiva and alveolar process = 67 Tongue and floor of mouth = 22 Miscellaneous (lip, central, antrum, palate tumors) = 10	Tobacco, alcohol or both = 48 Chewed tobacco = 3 No habits = 37
Blanchard et al./France/2016/Retrospective analysis (1999–2012)	≤40 y/50 (11/39)	Mobile tongue = 47 Tongue and floor of mouth = 3	Tobacco = 27 Alcohol = 8	> 40 y/50 (11/39)	Mobile tongue = 29 Tongue and floor of mouth = 21	Tobacco = 46 Alcohol = 37
Cariati et al./Spain/2017/Retrospective analysis (1998–2011)	< 45 y/ 33 (15/18)	Tongue = 18 Floor of mouth = 5 Buccal mucosa = 4 Oropharynx = 3 Alveolar ridge = 1 Maxilla = 1 Gingiva = 1	Tobacco = 16 Alcohol = 4	> 45 y/100 (33/67)	Tongue = 35 Floor of mouth = 20 Retromolar = 14 Buccal mucosa = 9 Oropharynx = 8 Maxilla = 7 Palate = 5 Gingiva = 2	Tobacco = 13 Alcohol = 5 Tobacco and Alcohol = 60
Fang et al./China/2014/Retrospective analysis (2005–2011)	≤40 y/15 (9/6)	Tongue = 15	Tobacco = 5 Alcohol = 2	> 40 y/ 161 (48/113)	Tongue squamous cell carcinoma = 161	Tobacco = 109 Alcohol = 72
Farquhar et al./USA/2018/Retrospective analysis (2000–2015)	< 45 y/ 117 (59/58)	Tongue = 117	Tobacco = 56 Alcohol = 11	> 45 y/ 280 (110/170)*	Tongue = 280	Tobacco = 192 Alcohol = 22
Favia et al./Italy/2008/Retrospective analysis (1977–2004)	< 45 y/43 (11/32)	Oral cancer = 43	Tobacco = 25 Alcohol = 15	> 45 y/419 (138/281)	Oral cancer = 419	Tobacco = 180 Alcohol = 191
Fonseca et al./Brazil/2014/Retrospective analysis (1988–2008)	≤40 y/29 (9/20)	Tongue = 29	Tobacco = 5 Alcohol = 8 Tobacco and alcohol = 10 No habit = 6	> 40 y/29 (23/6)	Tongue = 29	Tobacco = 4 Tobacco and alcohol = 20 No habit = 4
Friedlander et al./USA/1998/Retrospective analysis (1984–1993)	≤40 y/36 (15/21)	Tongue = 36	Tobacco = 15 Alcohol = 21	> 60 y with tongue cancer/ 36 (proportion not available)	Tongue = 36	Tobacco = 21 Alcohol = 24
Hilly et al./Israel/2013/Retrospective analysis (1996–2012)	≤40 y/16 (7/9)	Tongue = 16	Tobacco = 2	> 60 y with tongue cancer 62 (34/28)	Tongue = 62	Tobacco = 14
Hirota et al./Brazil/2008/Retrospective analysis (1994–2004)	≤40 y/13 (5/8)	Tongue = 10 Floor of mouth = 1 Lower lip = 1 Palate = 1	Tobacco = 3 Alcohol = 1 Tobacco and alcohol = 3 No habits = 6	> 40 y/108 (26/82)	Tongue = 28 Floor of mouth = 25 Lower lip = 12 Palate = 11 Retromolar = 11 Alveolar ridge = 19 Buccal mucosa = 2	Tobacco = 24 Alcohol = 0 Tobacco and alcohol = 57 No habits = 27
Ho et al./ Taiwan/2008/Retrospective analysis (1999–2005)	≤45 y/28 (1/27)	Buccal area = 15 Tongue = 12 Palate = 1	Tobacco = 24 Alcohol = 22	> 45 y/56 (2/54)	Buccal area = 30 Tongue = 24 Palate = 2	Tobacco = 48 Alcohol = 40
Hyam et al./Australia/2003/Retrospective analysis (1979–2000)	< 40 y/15 (6/9)	Tongue cancer = 15	Tobacco = 8 Alcohol = 6	> 40 y/114 (39*/75)	Tongue cancer = 114	Tobacco = 82 Alcohol = 69

Table 1 (continued)

Author/1st author country/year/study type	Number of young patients (F/M)	Site	Tobacco and alcohol users (young group)	Number of older patients (F/M)	Site	Tobacco and alcohol users (older group)
Jeon et al./South Korea/2017/Retrospective analysis (2001–2011)	≤40 y/23 (8/15)	Tongue cancer = 23	Tobacco = 12 Alcohol = 11	≥40 y/94 (43/51)	Tongue cancer = 94	Tobacco = 41 Alcohol = 42
Kaminagakura et al./Brazil/2010/Retrospective analysis (1967–2004)	≤40 y/125 (32/93)	Oral cancer = 125	Tobacco = 91 Alcohol = 83	> 50 y/250 (46/204)	Oral cancer = 250	Tobacco = 195 Alcohol = 154
Kaminagakura et al. (a)/Brazil/2011/Retrospective analysis (1970–2004)	≤40 y/90 (25/65)	Oral cancer = 90	Tobacco = 68 Alcohol = 61	> 50 y/125 (26/99)	Oral cancer = 125	Tobacco = 100 Alcohol = 76
Kaminagakura et al. (b)/Brazil/2011/Retrospective analysis (1970–2006)	≤40 y/47 (17/30)	Tongue = 23 Floor of mouth = 14 Retromolar area = 3 Buccal mucosa = 1 Other = 6	Tobacco = 36 Alcohol = 28	> 50 y/67 (16/51)	Tongue = 37 Floor of mouth = 11 Retromolar area = 9 Buccal mucosa = 2 Other = 8	Tobacco = 48 Alcohol = 34
Komolmalai et al./Thailand/2015/Retrospective analysis (1988–1990)	≤40 y/36 (13/23)	Lip = 1 Tongue = 27 Floor of mouth = 2 Palate = 2 Buccal mucosa = 2 Retromolar area = 1 MNOS = 1	Tobacco = 18 Alcohol = 18; Tobacco and alcohol = 12	≥40/838 (344/494)	Lip = 63 Tongue = 309 Gingiva = 156 Floor of mouth = 69 Palate = 91 Buccal mucosa = 119 Retromolar = 12 MNOS = 16 Multiple sites = 3	Tobacco = 527 Alcohol = 469 Tobacco and alcohol = 282
Kuriakose et al./India/1992/Retrospective analysis (2001–2010)	≤35 y/32 (16/16)	Tongue = 25 Gingivae = 4 Buccal mucosa = 7 Palate = 1	Alcohol = 6 Tobacco = 4	> 60 y/37 (10/27)	Tongue = 12 Gingivae = 6 Buccal mucosa = 14 Palate = 2 Lip = 3	Alcohol = 21 Tobacco = 5
Mizuno et al./Japan/2020/Retrospective analysis (2008–2019)	< 35 y/276 (108/168)	Tongue = 276	Tobacco = 129	≥45 y/2039 (641/1398)	Tongue = 2039	Tobacco = 976
Oh et al./Australia/2021/Retrospective analysis (1990/2015)	< 45 y/478 (165/313)	Oral cancer = 478	Tobacco = 239	≥45 y/2901 (1008/1893)	Oral cancer = 2901	Tobacco = 1574
O'Regan et al./Ireland/2006/DNA analysis	≤40 y/10 (4/6)	Mouth = 10	Tobacco = 4	> 40 y/10 (2/8)	Mouth = 10	Tobacco = 6
Park et al./South Korea/2010/Retrospective analysis (1994–2008)	≤45 y/23 (12/11)	Tongue = 23	Tobacco = 5 Alcohol = 6	> 45 y/ 62 (22/40)	Tongue = 62	Tobacco = 27 Alcohol = 25
Pfeiffer et al./Germany/2011/Retrospective analysis (2004–2008)	≤45 y/3 (all male)	Tongue = 1 Floor of mouth = 2	Tobacco and alcohol = 3	> 45/1 (female)	Tongue = 1	Alcohol = 1
Popovtzer et al./Israel/2004/Retrospective analysis (1983–2001)	≤45 y/32 (16/16)	Tongue = 32	Tobacco = 12 Alcohol = 1	> 45 y with tongue cancer/16 (4/12)	Tongue = 16	Tobacco = 5
Santos-Silva et al./Brazil/2010/Retrospective analysis (1988–2008)	≤40 y/37 (14/23)	Tongue = 37	Tobacco = 19 Alcohol = 22	> 50 y/28 (5/23)	Tongue = 28	Tobacco = 25 Alcohol = 25

Table 1 (continued)

Author/1st author country/year/study type	Number of young patients (F/M)	Site	Tobacco and alcohol users (young group)	Number of older patients (F/M)	Site	Tobacco and alcohol users (older group)
Siegelmann-Danielli et al./USA/1998/Retrospective analysis (1985–1996)	≤45 y/30 (8/22)	Tongue = 30	Tobacco and/or alcohol = 12	> 45 y with tongue cancer/57 (24/33)	Tongue = 57	Tobacco and/or alcohol = 47
Siriwardena et al./Sri Lanka/2006/Retrospective analysis (1996–2001)	≤40 y/56 (11/45)	Buccal mucosa = 12 Palate = 3 Alveolar ridge = 5 Tongue = 23 Floor of mouth = 4 Commissure = 1 Retromolar = 6 Lip = 2	Alcohol = 3 Tobacco only = 3 Tobacco and alcohol = 4 Alcohol only = 6	> 50 y/56 (12/44)	Buccal mucosa = 21 Palate = 2 Alveolar ridge = 14 Tongue = 7 Floor of mouth = 3 Commissure = 5 Retromolar region = 4	Alcohol = 9 Tobacco only = 3 Tobacco and alcohol = 9 Alcohol only = 0
Stagunaseelan et al./Australia/2020/Retrospective analysis (1982–2014)	< 45 y/215 (99/116)	Floor of mouth = 18 Buccal = 7 Alveolar/ Retromolar = 9 Lip = 10 Hard palate = 1 Oral non-specified = 170*	Tobacco = 82	> 45 y/ 1599 (615/984)	Floor of mouth = 289 Buccal mucosa = 126 Alveolar/Retromolar = 247 Lip = 28 Hard palate = 34 Oral non-specified = 1128*	Tobacco = 783
Subramaniam et al./India/2020/ Retrospective analysis (2004–2015)	< 45 y/114 (26/88)	Tongue = 114	Tobacco = 58	≥45 y/311 (94/217)	Tongue = 311	Tobacco = 144
Sun et al./China/2015/ Retrospective analysis (2005–2012)	≥40 y/31 (12/19)	Gingiva = 8 Tongue = 15 Floor of mouth = 7 Buccal = 1	Tobacco = 14 Alcohol = 8	< 40 y/399 (122/277)	Gingiva = 83 Tongue = 161 Floor of mouth = 89 Buccal = 66	Tobacco = 252 Alcohol = 168
Teixeira et al./Brazil/2019/ Retrospective analysis (unknown time range)	< 40 y/17 (3/14)	Tongue = 10 Floor of mouth = 4 Palate = 2 Buccal mucosa = 1	Tobacco = 14 Alcohol = 12	> 40 y / 40 (5/35)	Tongue = 14 Floor of mouth = 11 Palate = 2 Buccal mucosa = 2 Retromolar trigone = 10 Alveolar ridge = 1	Tobacco = 36 Alcohol = 31
Tremblay et al./Canada/2006/ Retrospective analysis (1995–2004)	≤40 y/42 (13/29)	Tongue = 31 Floor of mouth = 3 Buccal mucosa = 3 Alveolus = 2 Tongue/floor of mouth = 1 Tongue base = 1 Palate = 1	Alcohol = 10 Tobacco = 21	≥60 y/62 (28/34)	Tongue = 13 Floor of mouth = 19 Buccal mucosa = 10 Alveolus = 8 Tongue = 5 Tongue base = 3 Palate = 2 Retromolar = 2	Alcohol = 25 Tobacco = 30
Troeltzsch et al./Germany/2014/Retrospective analysis (2001–2012)	≤40 y/11 (5/6)	Floor of mouth = 1 Tongue = 7 Alveolar process mandible = 1 Buccal mucosa = 1 Palate = 1	Tobacco = 1 Alcohol = 0 Tobacco and alcohol = 0	40–80 y; > 80 y 17 (5/12); 17 (6/11)	Floor of mouth = 9; 2 Tongue = 1; 3 Alveolar process = 3; 10 Buccal mucosa = 1; 2 Palate = 3; 0	Tobacco = 6; 5 Alcohol = 0; 2 Tobacco and alcohol = 11; 1
Veness et al./Australia/2003/ Retrospective analysis (1980–2000)	≤40 y/22 (9/13)	Tongue = 22	Tobacco = 9 Ex-smokers = 5 Alcohol = 13	> 40 y/142 (49/93)	Anterior tongue = 142	Tobacco = 72 Ex-smokers = 25 Alcohol = 87

Table 1 (continued)

Author/1st author country/year/study type	Number of young patients (F/M)	Site	Tobacco and alcohol users (young group)	Number of older patients (F/M)	Site	Tobacco and alcohol users (older group)
Wang et al./Canada/2001/Retrospective analysis (1995–1999)	≤44 y/19 (9/10)	Tongue = 15; Floor of mouth = 3 MNOS = 1	Tobacco = 8 Alcohol = 5	> 45 y/19 (6/13)	Tongue = 9 Floor of mouth = 6 Buccal = 1 Palate = 1 Oral cavity = 2	Tobacco = 16 Alcohol = 12
Xu et al./China/2018/Retrospective analysis (1998–2014)	≤40 y/143 (49/94)	Tongue = 102 Lower gingival = 12 Buccal mucosa = 6 Floor of mouth = 13 Upper gingival = 8 Hard palate = 2	Tobacco = 58 Alcohol = 48	41–75 y; > 75 y 2300 (1016/1284)	Tongue = 920 Lower gingival = 428 Buccal mucosa = 409 Floor of mouth = 238 Upper gingival = 236 Hard palate = 69	Tobacco = 930 Alcohol = 693
Yip et al./Singapore/2010/Retrospective analysis (1998–2006)	≤40 y/17(9/8)	Tongue = 17	Tobacco = 4 Alcohol = 4	> 40 y/106 (31/75)	Tongue = 106	Tobacco = 48 Alcohol = 35
Zhang et al./China/2017/Retrospective analysis (2001–2014)	≤30 y/36 (19/17)	Tongue = 36	Tobacco = 3 Alcohol = 2	46–59 y; ≥ 70 y/227 (110/117)	Tongue = 227	Tobacco = 85 Alcohol = 69

F female, *M* male, *MNOS* mouth not otherwise specified, *y* years

*Estimated by authors

concurrently, was higher than in young patients. However, in the proportion meta-analysis of patients reporting no habits, a higher rate was observed in the young patients' group (28.1%, IC = 8.9 to 61%, $I^2 = 80\%$) than in the older patients' group (24%, IC = 19.3% to 29.5%, $I^2 = 0\%$) (Fig. 6).

Discussion

This SR and meta-analysis included 38 studies in which tobacco and alcohol consumption were investigated in young and older OSCC patients. In the current study, the number of male patients in both samples outweighed the number of female individuals, which is in accordance with the previous literature [1, 2, 46]. The tongue was the most common site of occurrence of OSCC, conforming to other studies [1, 47].

Despite some studies in this SR demonstrating a small proportion of smokers in the young group [4–7], tobacco was still the most frequently reported risk factor attributed to OSCC in both young and older patients. Overall, the meta-analysis of studies reporting tobacco smoking demonstrated that 39.5% of the young OSCC patients reported smoking habits, and almost half of the older patients were tobacco smokers.

Tobacco smoke has over 70 carcinogens which have been evaluated by the International Agency for Research on Cancer (IARC) as having sufficient evidence for carcinogenicity in either laboratory animals or humans, acting both as a tumor initiator and promoter [48]. Tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and volatile aldehydes present in several forms of tobacco derivates have been attributed to mutations in oncogenes, loss of cell cycle control, and decrease of apoptosis, contributing to carcinogenesis [49, 50].

Some studies included in this SR highlighted that those individuals reaching the age of 40 years who started smoking early in adolescence might have been exposed to tobacco carcinogens for over 20 years [51, 52]. Therefore, the exposure time would be long enough to induce oral carcinogenesis in these young individuals [51, 52].

However, a noteworthy proportion of patients in both groups did not report any recognized risk factors for OSCC and should be closely evaluated in future studies [15, 21]. Specific risk factors for OSCC not addressed in the present study, which are more common in certain global areas, could potentially contribute to the development of OSCC at younger ages [1, 53]. For instance, exposure to secondhand smoke (SHS) from childhood should be investigated in further studies as SHS has recently been implicated as a significant risk factor for OSCC [54].

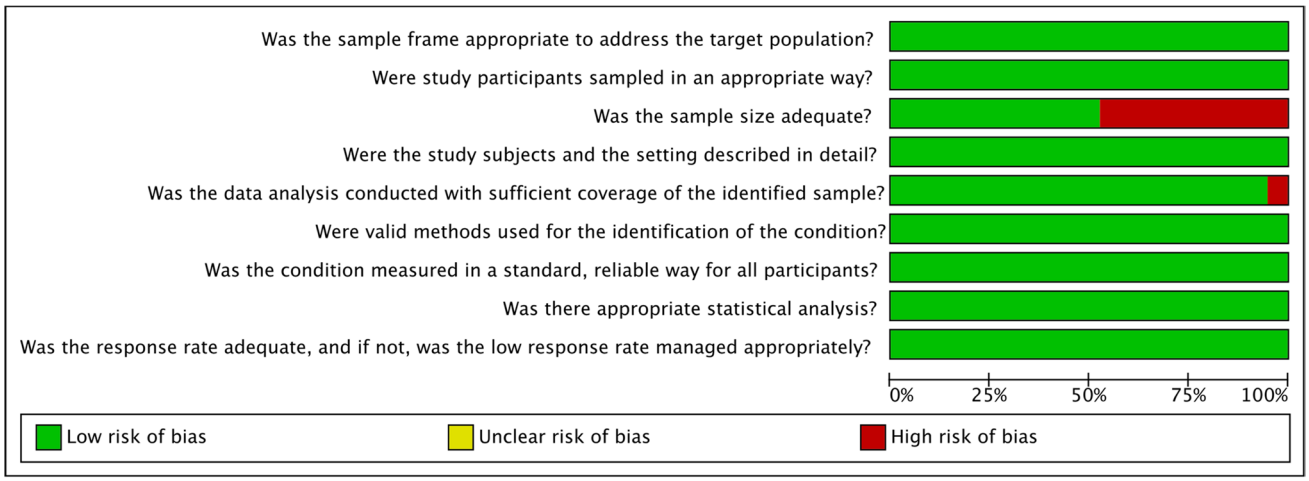


Fig. 2 Risk of bias graph: authors' judgments about each risk of bias item presented as percentage across all included studies

Additionally, in Southeast Asia, where OSCC ranks among the most frequent cancer types, there is a traditional habit of chewing areca nut derivates (in forms of pan/paan, gutka, betel quid, etc., with or without tobacco), which is reported as a risk factor for OSCC [2, 53]. These habits could reflect on the high incidence of OSCC not only in the elderly but also in the young individuals as observed in studies included in this SR. These studies involved patients from countries such as India, Bangladesh, Pakistan, and Sri Lanka [2, 4, 22, 27], in which a high frequency of betel quid consumption has been reported [2, 56].

Environmental smoke exposure [54], polymorphism in genes relating to the detoxification of carcinogens [55], anemia, chronic mechanical irritation [56], periodontal pathogens and microbial dysbiosis [57], and other possible risk factors need to be investigated to unveil etiological agents for OSCC in this young group of patients [3].

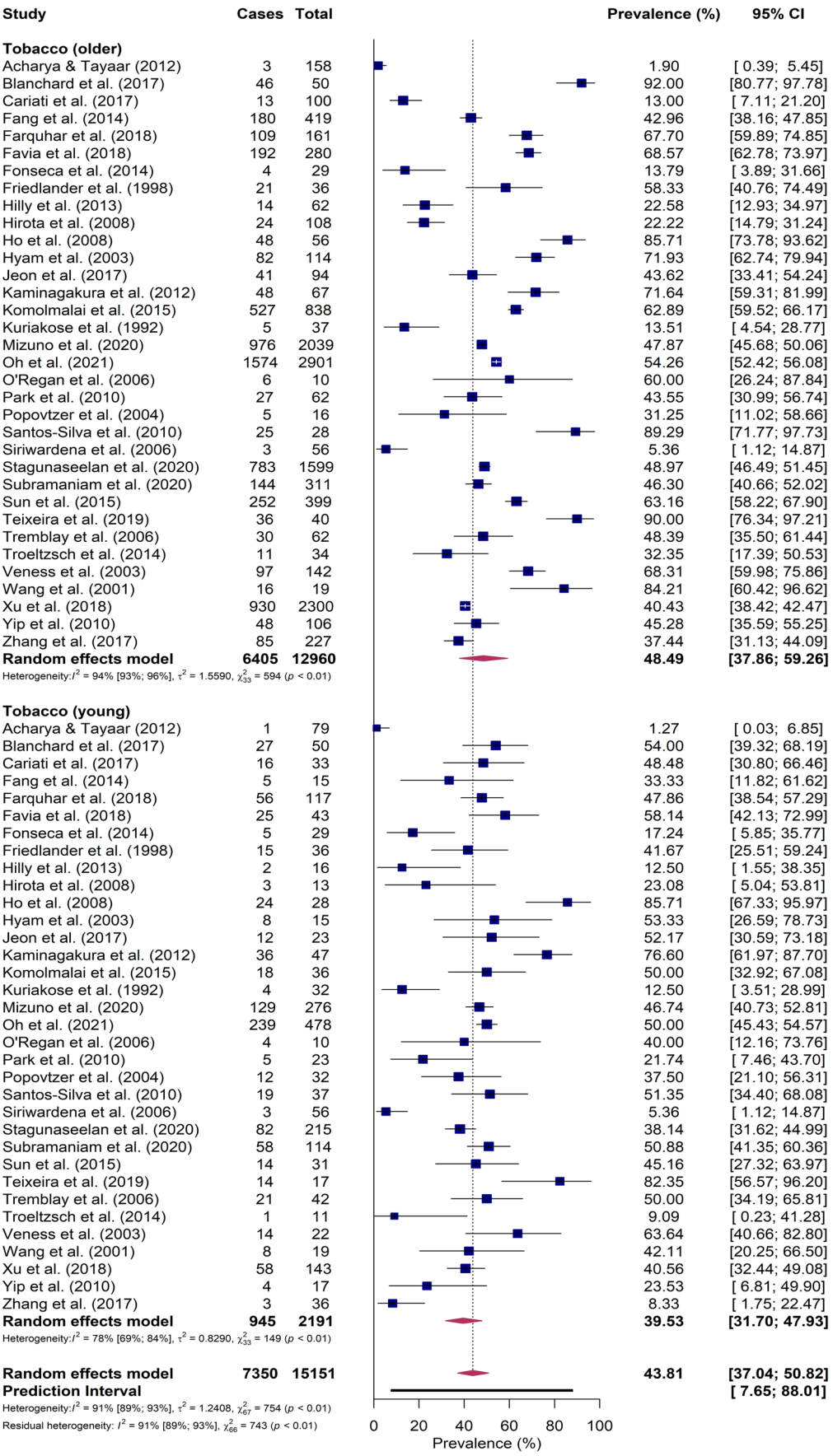
Some articles included in this SR have shown a high rate of young patients reporting alcohol consumption, with an increased intake among women [10, 22, 24–26, 28], as well as early and heavy alcohol consumption habits [43]. However, the overall proportion of older patients who reported drinking habits was markedly higher than the proportion of young patients reporting alcohol consumption. The evaluation by the IARC Working Group (Monograph 100E-2012), based on a significant number of analytical epidemiological studies with different designs (both cohort and case–control) from several geographical regions, provide sufficient evidence that alcohol consumption is a carcinogenic agent especially to oral and pharyngeal cancer [58].

The independent effect of alcohol consumption on the risk of oral and pharyngeal cancer is demonstrated in studies including non-smokers [59]. The risk increases with added amounts of alcohol drinking in most of these studies [60, 61]. However, it should be observed that intrinsic susceptibility to metabolize carcinogens derived from alcohol, particularly acetaldehyde, may vary among individuals [62]. This could partially explain why some patients may develop cancer at younger ages.

This SR revealed that in six studies [4, 10, 15, 19, 21, 33], about a quarter of the young patients and 47% of older individuals with OSCC reported the concurrent habit of alcohol consumption and tobacco smoking. According to the results of a recent meta-analysis including fifteen primary studies, the synergistic consumption of alcohol and tobacco both smoked and smoke-less significantly increased the odds for the occurrence of oral squamous cell carcinoma, and its concurrent consumption was more harmful than the sole consumption of alcohol or tobacco in most included studies [63].

In a review, Poschl and Seitz [64] discuss some possible mechanisms of alcohol as a cocarcinogen. Locally, alcohol acts as a solvent that increases the absorption of carcinogens into the mucosa. Ethanol facilitates the uptake of environmental carcinogens, especially from tobacco smoke, through the cell membrane of oral keratinocytes made more permeable by its direct effect [40]. Therefore, alcohol may contribute to oral carcinogenesis solely or as an adjuvant factor [65].

The main risk of bias in the included studies of this SR was related to small sample sizes and data analysis being conducted with insufficient coverage of the identified


Study
Cases
Total
Prevalence (%)
95% CI
Tobacco (older)
Acharya & Tayaar (2012) 3 158 1.90 [0.39; 5.45]
Blanchard et al. (2017) 46 50 92.00 [80.77; 97.78]
Cariati et al. (2017) 13 100 13.00 [7.11; 21.20]
Fang et al. (2014) 180 419 42.96 [38.16; 47.85]
Farquhar et al. (2018) 109 161 67.70 [59.89; 74.85]
Favia et al. (2018) 192 280 68.57 [62.78; 73.97]
Fonseca et al. (2014) 4 29 13.79 [3.89; 31.66]
Friedlander et al. (1998) 21 36 58.33 [40.76; 74.49]
Hilly et al. (2013) 14 62 22.58 [12.93; 34.97]
Hirota et al. (2008) 24 108 22.22 [14.79; 31.24]
Ho et al. (2008) 48 56 85.71 [73.78; 93.62]
Hyam et al. (2003) 82 114 71.93 [62.74; 79.94]
Jeon et al. (2017) 41 94 43.62 [33.41; 54.24]
Kaminagakura et al. (2012) 48 67 71.64 [59.31; 81.99]
Komolmalai et al. (2015) 527 838 62.89 [59.52; 66.17]
Kuriakose et al. (1992) 5 37 13.51 [4.54; 28.77]
Mizuno et al. (2020) 976 2039 47.87 [45.68; 50.06]
Oh et al. (2021) 1574 2901 54.26 [52.42; 56.08]
O'Regan et al. (2006) 6 10 60.00 [26.24; 87.84]
Park et al. (2010) 27 62 43.55 [30.99; 56.74]
Popovtzer et al. (2004) 5 16 31.25 [11.02; 58.66]
Santos-Silva et al. (2010) 25 28 89.29 [71.77; 97.73]
Siriwardena et al. (2006) 3 56 5.36 [1.12; 14.87]
Stagunaseelan et al. (2020) 783 1599 48.97 [46.49; 51.45]
Subramaniam et al. (2020) 144 311 46.30 [40.66; 52.02]
Sun et al. (2015) 252 399 63.16 [58.22; 67.90]
Teixeira et al. (2019) 36 40 90.00 [76.34; 97.21]
Tremblay et al. (2006) 30 62 48.39 [35.50; 61.44]
Troeltzsch et al. (2014) 11 34 32.35 [17.39; 50.53]
Veness et al. (2003) 97 142 68.31 [59.98; 75.86]
Wang et al. (2001) 16 19 84.21 [60.42; 96.62]
Xu et al. (2018) 930 2300 40.43 [38.42; 42.47]
Yip et al. (2010) 48 106 45.28 [35.59; 55.25]
Zhang et al. (2017) 85 227 37.44 [31.13; 44.09]
Random effects model 6405 12960 48.49 [37.86; 59.26]
Heterogeneity: I^2 = 94% [93%; 96%], τ^2 = 1.5590, χ^2_{33} = 594 (p < 0.01)
Tobacco (young)
Acharya & Tayaar (2012) 1 79 1.27 [0.03; 6.85]
Blanchard et al. (2017) 27 50 54.00 [39.32; 68.19]
Cariati et al. (2017) 16 33 48.48 [30.80; 66.46]
Fang et al. (2014) 5 15 33.33 [11.82; 61.62]
Farquhar et al. (2018) 56 117 47.86 [38.54; 57.29]
Favia et al. (2018) 25 43 58.14 [42.13; 72.99]
Fonseca et al. (2014) 5 29 17.24 [5.85; 35.77]
Friedlander et al. (1998) 15 36 41.67 [25.51; 59.24]
Hilly et al. (2013) 2 16 12.50 [1.55; 38.35]
Hirota et al. (2008) 3 13 23.08 [5.04; 53.81]
Ho et al. (2008) 24 28 85.71 [67.33; 95.97]
Hyam et al. (2003) 8 15 53.33 [26.59; 78.73]
Jeon et al. (2017) 12 23 52.17 [30.59; 73.18]
Kaminagakura et al. (2012) 36 47 76.60 [61.97; 87.70]
Komolmalai et al. (2015) 18 36 50.00 [32.92; 67.08]
Kuriakose et al. (1992) 4 32 12.50 [3.51; 28.99]
Mizuno et al. (2020) 129 276 46.74 [40.73; 52.81]
Oh et al. (2021) 239 478 50.00 [45.43; 54.57]
O'Regan et al. (2006) 4 10 40.00 [12.16; 73.76]
Park et al. (2010) 5 23 21.74 [7.46; 43.70]
Popovtzer et al. (2004) 12 32 37.50 [21.10; 56.31]
Santos-Silva et al. (2010) 19 37 51.35 [34.40; 68.08]
Siriwardena et al. (2006) 3 56 5.36 [1.12; 14.87]
Stagunaseelan et al. (2020) 82 215 38.14 [31.62; 44.99]
Subramaniam et al. (2020) 58 114 50.88 [41.35; 60.36]
Sun et al. (2015) 14 31 45.16 [27.32; 63.97]
Teixeira et al. (2019) 14 17 82.35 [56.57; 96.20]
Tremblay et al. (2006) 21 42 50.00 [34.19; 65.81]
Troeltzsch et al. (2014) 1 11 9.09 [0.23; 41.28]
Veness et al. (2003) 14 22 63.64 [40.66; 82.80]
Wang et al. (2001) 8 19 42.11 [20.25; 66.50]
Xu et al. (2018) 58 143 40.56 [32.44; 49.08]
Yip et al. (2010) 4 17 23.53 [6.81; 49.90]
Zhang et al. (2017) 3 36 8.33 [1.75; 22.47]
Random effects model 945 2191 39.53 [31.70; 47.93]
Heterogeneity: I^2 = 78% [69%; 84%], τ^2 = 0.8290, χ^2_{33} = 149 (p < 0.01)
Random effects model 7350 15151 43.81 [37.04; 50.82]
Prediction Interval [7.65; 88.01]
Heterogeneity: I^2 = 91% [89%; 93%], τ^2 = 1.2408, χ^2_{67} = 754 (p < 0.01)
Residual heterogeneity: I^2 = 91% [89%; 93%], χ^2_{66} = 743 (p < 0.01)
0
20
40
60
80
100
Prevalence (%)

◂**Fig. 3** Forest plot depicting the overall proportion of tobacco smokers among young and older cancer patients. Squares represent sample sizes; horizontal lines regard to confidence intervals, and the diamond represents the pooled prevalence from all studies included in meta-analysis. Figure generated with the software R Statistics version 4.0.2 (The R Foundation)

sample. When primary studies rely upon collected data from patients' records, the quality of evidence could be compromised, as data are often improperly completed and important information about patients' lifestyles might be missing. Cohort studies would be appropriate to aid the identification of risk factors for OSCC at young ages.

The main limitation of this SR concerns the overall low certainty of evidence in primary studies. Other limitations include

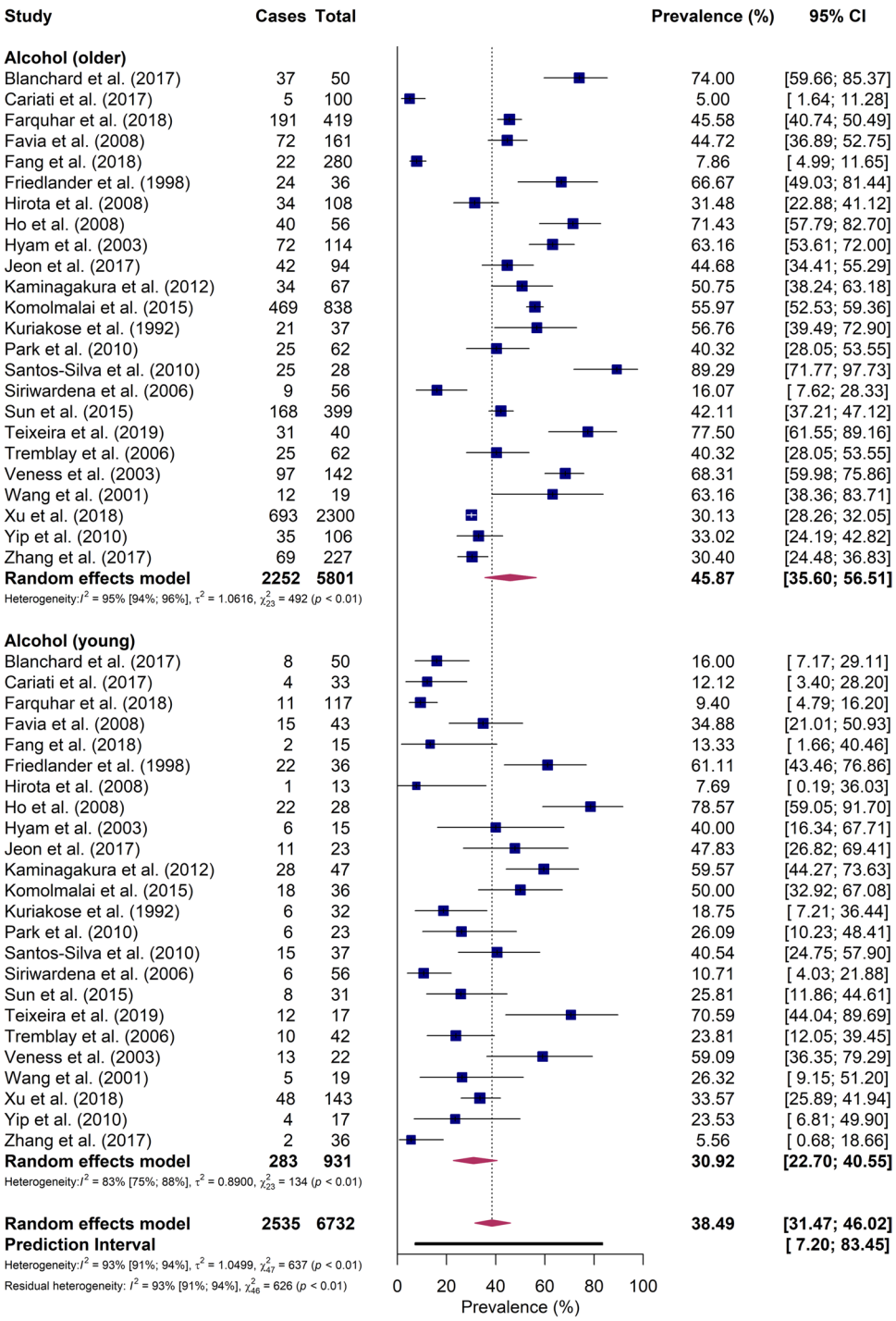


Fig. 4 Forest plot depicting the overall proportion of alcohol consumption within young and older oral cancer patients. Squares represent sample sizes; horizontal lines regard to confidence intervals, and the diamond represents the pooled prevalence from all studies included in meta-analysis. Figure generated with the software R Statistics version 4.0.2 (The R Foundation)

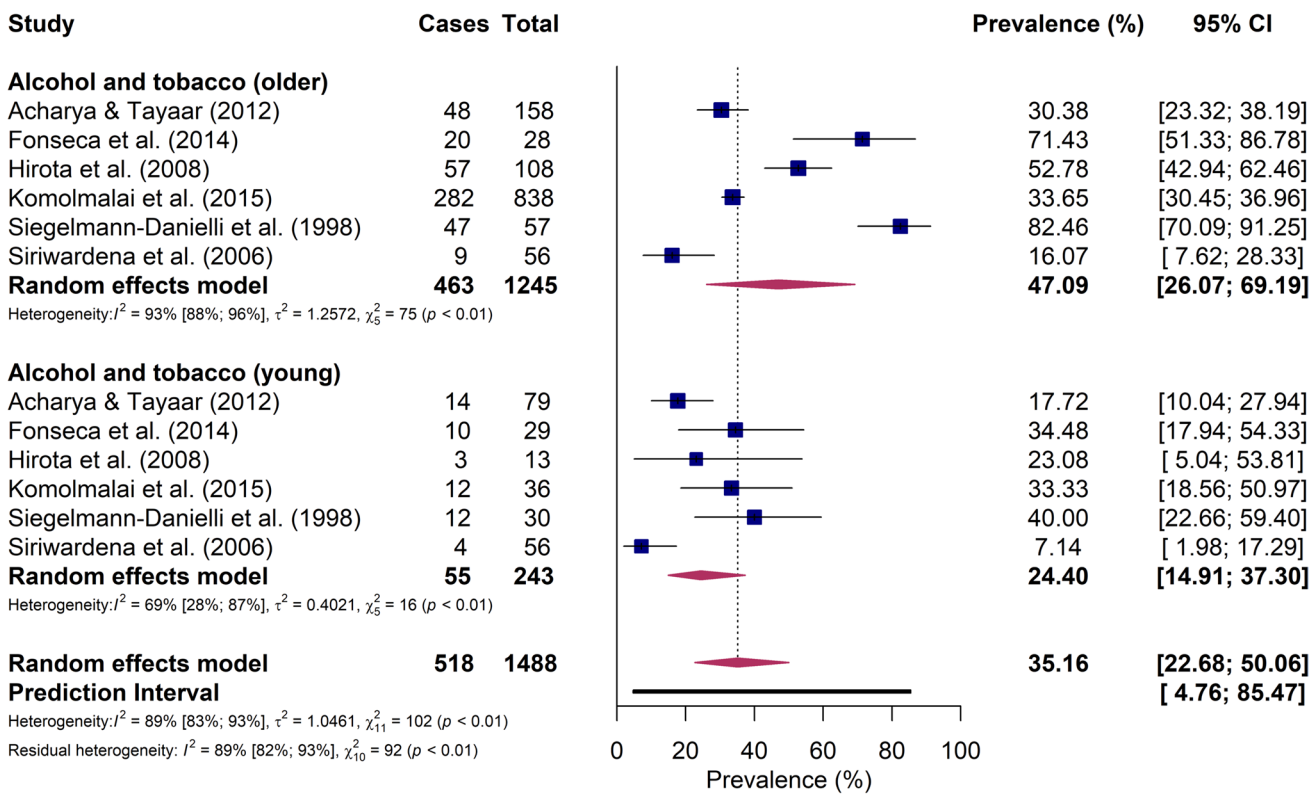


Fig. 5 Forest plot depicting the overall proportion of concurrent tobacco and alcohol consumption within young and older oral cancer patients. Squares represent sample sizes; horizontal lines regard to confidence intervals, and the diamond represents the pooled prevalence from all studies included in meta-analysis. Figure generated with the software R Statistics version 4.0.2 (The R Foundation)

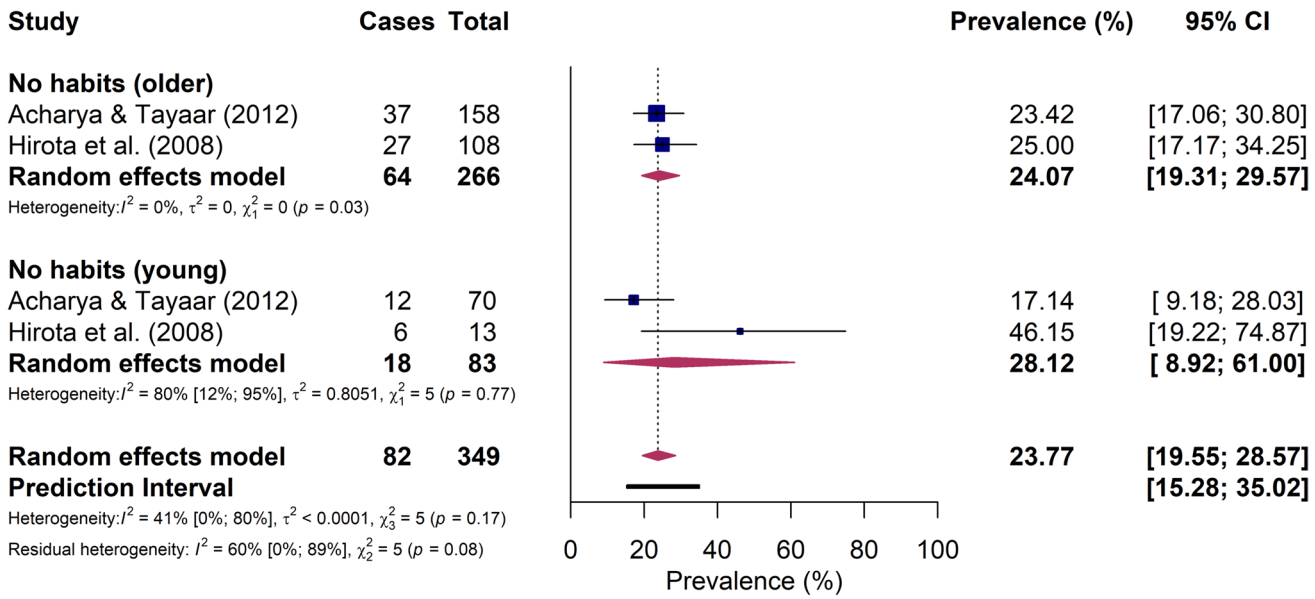


Fig. 6 Forest plot depicting the overall proportion of young and older oral cancer patients reporting no habits. Squares represent sample sizes; horizontal lines regard to confidence intervals, and the diamond represents the pooled prevalence from all studies included in meta-analysis. Figure generated with the software R Statistics version 4.0.2 (The R Foundation)

the retrospective nature of primary studies, lack of healthy control groups, differences in reporting quantity and frequency of tobacco and alcohol consumption, having not the same age cutoffs for young and older patients, and lack of reporting confounding factors. Tobacco and alcohol consumption were usually reported as a general term without specifying the types, frequency, or duration of use. Additionally, the relation between alcohol consumption and smoking history and demographic variables such as gender and ethnicity were not approached in the current SR and should be in-depth addressed in further research.

For future studies, it is highly recommended for researchers to specify the frequency of consumption as well as the type of beverages, for the alcoholic percentual may vary significantly between fermented beverages and distilled spirits. The same applied to tobacco use, i.e., future studies should specify the form of tobacco use (smoking, chewing, snuffing, etc.), the daily frequency and quantity of years that the patient has smoked, and the exposure to passive smoking. Moreover, a meta-analysis of association, including studies addressing both patients with OSCC and healthy individuals who have alcohol intake or smoking history, is recommended for future research. This was not feasible in the current study due to the lack of a healthy control group.

Conclusions

According to this systematic review, tobacco smoking and alcohol consumption had an elevated prevalence in both young and older groups of patients. However, the comparison in the proportion of individuals reporting tobacco and alcohol consumption demonstrated that these habits were more prevalent in the older group (48.4% and 45.8% respectively) than in the young group (39.5% and 30.9%, respectively). Nontraditional risk factors for OSCC in young patients need to be investigated in future research, and individualized preventive measures according to the main risk factors in either group should be readily addressed in clinical practice.

Registration and protocol

This systematic review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Checklist (PRISMA) [11]. The study protocol was registered at the Prospective Register of Systematic Reviews (PROSPERO; Centre for Reviews and Dissemination, University of York; and the National Institute for Health Research) [12] under the registry code CRD42017065583.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-022-04719-z.

Acknowledgements The authors would like to thank Gilberto Mello for helping with figures generation.

Author contribution EAB, RG, and GDLC conceived the study.
SW, AP, EG helped in study design.
EAB, RG and ERCR collected the data.
EAB, RG and ERCR analyzed the data.
EAB led the writing.
EAB, RG, SW, ALP, EG, ERCR, and GDLC reviewed the manuscript.

Funding Elis Angela Batistella was supported in part by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil* (CAPES) – Finance Code 001.

Declarations

Ethics approval Not applicable.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Hussein AA, Helder MN, de Visscher JG et al (2017) Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. Eur J Cancer 82:115–127. https://doi.org/10.1016/j.ejca.2017.05.026
2. Llewellyn CD, Johnson NW, Warnakulasuriya KAAS (2001) Risk factors for squamous cell carcinoma of the oral cavity in young people — a comprehensive literature review. Oral Oncol 37:401–418. https://doi.org/10.1016/S1368-8375(00)00135-4
3. Toner M, O'Regan EM (2009) Head and neck squamous cell carcinoma in the young: a spectrum or a distinct group? Part 1. Head Neck Pathol 3:246–248. https://doi.org/10.1007/s12105-009-0135-0
4. Siriwardena BSMS, Tilakaratne A, Amaratunga EAPD, Tilakaratne WM (2006) Demographic, aetiological and survival differences of oral squamous cell carcinoma in the young and the old in Sri Lanka. Oral Oncol 42:831–836. https://doi.org/10.1016/j.oraloncology.2005.12.001
5. Sun Q, Fang Q, Guo S (2015) A comparison of oral squamous cell carcinoma between young and old patients in a single medical center in China. Int J Clin Exp Med 8:12418–12423
6. Troeltzsch M, Knösel T, Eichinger C et al (2014) Clinicopathologic features of oral squamous cell carcinoma: do they vary in different age groups? J Oral Maxillofac Surg 72:1291–1300. https://doi.org/10.1016/j.joms.2014.01.009
7. Wang Y, Irish J, MacMillan C et al (2001) High frequency of microsatellite instability in young patients with head-and-neck squamous-cell carcinoma: Lack of involvement of the mismatch repair geneshMLH1 ANDhMSH2. Int J Cancer 93:353–360. https://doi.org/10.1002/ijc.1337
8. Favia G, Maiorano E, Capodiferro S et al (2008) Oral squamous cell carcinoma: a mono-institutional epidemiological study on 462 cases highlighting differences among young and adult patients. Minerva Stomatol 57:413–421
9. Friedlander PL, Schantz SP, Shaha AR et al (1998) Squamous cell carcinoma of the tongue in young patients: a matched-pair

analysis. Head Neck 20:363–368. https://doi.org/10.1002/(SICI)1097-0347(199808)20:5%3c363::AID-HED1%3e3.0.CO;2-W
10. Komolmalai N, Chuachamsai S, Tantiwipawin S et al (2015) Ten-year analysis of OSCC focusing on young people in northern Thailand. J Oral Sci 57:327–334. https://doi.org/10.2334/josnusd.57.327
11. Page MJ, Moher D, Bossuyt PM, et al. (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ n160. https://doi.org/10.1136/bmj.n160
12. Booth A, Clarke M, Ghersi D et al (2011) An international registry of systematic-review protocols. The Lancet 377:108–109. https://doi.org/10.1016/S0140-6736(10)60903-8
13. Munn Z, Moola S, Riitano D, Lisy K (2014) The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag 3:123–128
14. Manheimer E (2012) Summary of findings tables: presenting the main findings of Cochrane Complementary and alternative medicine-related reviews in a transparent and simple tabular format. Glob Adv Health Med 1:90–91. https://doi.org/10.7453/gahmj.2012.1.1.015
15. Acharya S, Tayaar AS (2012) Analysis of clinical and histopathological profiles of oral squamous cell carcinoma in young Indian adults: a retrospective study. J Dent Sci 7:224–230. https://doi.org/10.1016/j.jds.2012.05.005
16. Blanchard P, Belkhir F, Temam S et al (2017) Outcomes and prognostic factors for squamous cell carcinoma of the oral tongue in young adults: a single-institution case-matched analysis. Eur Arch Otorhinolaryngol 274:1683–1690. https://doi.org/10.1007/s00405-016-4419-1
17. Cariati P, Cabello-Serrano A, Perez-de Perceval-Tara M, Monsalve-Iglesias F (2017) Oral and oropharyngeal squamous cell carcinoma in young adults: a retrospective study in Granada University Hospital. Medicina Oral Patología Oral y Cirugia Bucal 0–0. https://doi.org/10.4317/medoral.21755
18. Fang Q-G, Shi S, Liu F-Y, Sun C-F (2014) Tongue squamous cell carcinoma as a possible distinct entity in patients under 40 years old. Oncol Lett 7:2099–2102. https://doi.org/10.3892/ol.2014.2054
19. Fonseca FP, Coletta R, della, Azevedo MB, et al (2014) Stromal myofibroblasts in squamous cell carcinoma of the tongue in young patients – a multicenter collaborative study. Oral Surg Oral Med Oral Pathol Oral Radiol 118:483–489. https://doi.org/10.1016/j.oooo.2014.07.012
20. Hilly O, Shkedy Y, Hod R et al (2013) Carcinoma of the oral tongue in patients younger than 30 years: comparison with patients older than 60 years. Oral Oncol 49:987–990. https://doi.org/10.1016/j.oraloncology.2013.07.005
21. Hirota SK, Braga FPF, Penha SS et al (2008) Risk factors for oral squamous cell carcinoma in young and older Brazilian patients: a comparative analysis. Medicina oral, patologia oral y cirugia bucal 13:E227–E231
22. Ho H-C, Lee M-S, Hsiao S-H et al (2008) Squamous cell carcinoma of the oral cavity in young patients: a matched-pair analysis. Eur Arch Otorhinolaryngol 265:57–61. https://doi.org/10.1007/s00405-007-0496-5
23. Hyam D, Conway R, Sathiyaseelan Y et al (2003) Tongue cancer: do patients younger than 40 do worse? Aust Dent J 48:50–54. https://doi.org/10.1111/j.1834-7819.2003.tb00009.x
24. Kaminagakura E, Vartanian JG, da Silva SD et al (2010) Case-control study on prognostic factors in oral squamous cell carcinoma in young patients. Head Neck 32:1460–1466. https://doi.org/10.1002/hed.21347
25. Kaminagakura E, Werneck da Cunha I, Soares FA et al (2011) CCND1 amplification and protein overexpression in oral squamous cell carcinoma of young patients. Head Neck 33:1413–1419. https://doi.org/10.1002/hed.21618
26. Kaminagakura E, Villa LL, Andreoli MA et al (2012) High-risk human papillomavirus in oral squamous cell carcinoma of young patients. Int J Cancer 130:1726–1732. https://doi.org/10.1002/ijc.26185
27. Kuriakose M, Sankaranarayanan M, Nair MK et al (1992) Comparison of oral squamous cell carcinoma in younger and older patients in India. Eur J Cancer B Oral Oncol 28:113–120. https://doi.org/10.1016/0964-1955(92)90038-3
28. O'Regan EM, Toner ME, Smyth PC et al (2006) Distinct array comparative genomic hybridization profiles in oral squamous cell carcinoma occurring in young patients. Head Neck 28:330–338. https://doi.org/10.1002/hed.20354
29. Park J-O, Sun D-I, Cho K-J et al (2010) Clinical outcome of squamous cell carcinoma of the tongue in young patients: a stage-matched comparative analysis. Clin Exp Otorhinolaryngol 3:161. https://doi.org/10.3342/ceo.2010.3.3.161
30. Pfeiffer J, Wiech T, Maier W et al (2011) Head and neck cancer in young adults and nonsmokers: study of cancer susceptibility by genome-wide high-density SNP microarray mapping. Acta Otolaryngol 131:1091–1098. https://doi.org/10.3109/00016489.2011.590151
31. Popovtzer A, Shpitzer T, Bahar G et al (2004) Squamous cell carcinoma of the oral tongue in young patients. Laryngoscope 114:915–917. https://doi.org/10.1097/00005537-200405000-00025
32. Santos-Silva AR, Ribeiro ACP, Soubhia AMP et al (2011) High incidences of DNA ploidy abnormalities in tongue squamous cell carcinoma of young patients: an international collaborative study. Histopathology 58:1127–1135. https://doi.org/10.1111/j.1365-2559.2011.03863.x
33. Siegelmann-Danieli N, Hanlon A, Ridge JA et al (1998) Oral tongue cancer in patients less than 45 years old: institutional experience and comparison with older patients. J Clin Oncol 16:745–753. https://doi.org/10.1200/JCO.1998.16.2.745
34. Teixeira LR, Almeida LY, Silva RN et al (2019) Young and elderly oral squamous cell carcinoma patients present similar angiogenic profile and predominance of M2 macrophages: comparative immunohistochemical study. Head Neck 41:4111–4120. https://doi.org/10.1002/hed.25954
35. Tremblay S, Pintor dos Reis P, Bradley G et al (2006) Young patients with oral squamous cell carcinoma. Arch Otolaryngol-Head Neck Surg 132:958. https://doi.org/10.1001/archotol.132.9.958
36. Veness MJ, Morgan GJ, Sathiyaseelan Y, Gebski V (2003) Anterior tongue cancer: age is not a predictor of outcome and should not alter treatment. ANZ J Surg 73:899–904. https://doi.org/10.1046/j.1445-2197.2003.02818.x
37. Satgunaseelan L, Allanson BM, Asher R et al (2020) The incidence of squamous cell carcinoma of the oral tongue is rising in young non-smoking women: an international multi-institutional analysis. Oral Oncol 110:104875. https://doi.org/10.1016/j.oraloncology.2020.104875
38. Oh LJ, Satgunaseelan L, Asher R et al (2021) Young age is not a predictor of disease specific survival in OSCC: a multi-institutional study. Oral Oncol 115:105162. https://doi.org/10.1016/j.oraloncology.2020.105162
39. Farquhar DR, Tanner AM, Masood MM et al (2018) Oral tongue carcinoma among young patients: an analysis of risk factors and survival. Oral Oncol 84:7–11. https://doi.org/10.1016/j.oraloncology.2018.06.014
40. Jeon J-H, Kim MG, Park JY et al (2017) Analysis of the outcome of young age tongue squamous cell carcinoma. Maxillofac Plast Reconstr Surg 39:41. https://doi.org/10.1186/s40902-017-0139-8
41. Mizuno K, Takeuchi M, Kikuchi M et al (2020) Outcomes in patients diagnosed with tongue cancer before and after the age of 45 years. Oral Oncol 110:105010. https://doi.org/10.1016/j.oraloncology.2020.105010

42. Subramaniam N, Balasubramanian D, Low T-HH et al (2020) Squamous cell carcinoma of the oral tongue in young patients: outcomes and implications for treatment. Indian J Surg Oncol 11:274–280. https://doi.org/10.1007/s13193-020-01049-y
43. Xu Q, Wang C, Li B et al (2019) The impact of age on oral squamous cell carcinoma: a longitudinal cohort study of 2,782 patients. Oral Dis 25:730–741. https://doi.org/10.1111/odi.13015
44. Yip CSP, Charn TC, Wee JTS et al (2010) Outcomes of oral tongue cancer: does age matter? Ann Acad Med Singapore 39:897–907
45. Zhang Y-Y, Wang D-C, Su J-Z et al (2017) Clinicopathological characteristics and outcomes of squamous cell carcinoma of the tongue in different age groups. Head Neck 39:2276–2282. https://doi.org/10.1002/hed.24898
46. Santos H, dos Santos T, Paz A, et al. (2016) Clinical findings and risk factors to oral squamous cell carcinoma in young patients: a 12-year retrospective analysis. Medicina Oral Patología Oral y Cirugia Bucal e151–e156. https://doi.org/10.4317/medoral.20770
47. Warnakulasuriya S (2009) Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 45:309–316. https://doi.org/10.1016/j.oraloncology.2008.06.002
48. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2004) Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 83:1–1438
49. Khariwala SS, Hatsukami D, Hecht SS (2012) Tobacco carcinogen metabolites and DNA adducts as biomarkers in head and neck cancer: potential screening tools and prognostic indicators. Head Neck 34:441–447. https://doi.org/10.1002/hed.21705
50. Peterson LA, Oram MK, Flavin M et al (2021) Coexposure to inhaled aldehydes or carbon dioxide enhances the carcinogenic properties of the tobacco-specific nitrosamine 4-methylnitrosamino-1-(3-pyridyl)-1-butanone in the A/J mouse lung. Chem Res Toxicol 34:723–732. https://doi.org/10.1021/acs.chemrestox.0c00350
51. Byers RM (1975) Squamous cell carcinoma of the oral tongue in patients less than thirty years of age. Am J Surg 130:475–478. https://doi.org/10.1016/0002-9610(75)90487-0
52. Jones J, Lampe H, Cheung H (1989) Carcinoma of the tongue in young patients. J Otolaryngol 18:105–108
53. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2004) Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum 85:1–334
54. Mariano LC, Warnakulasuriya S, Straif K, Monteiro L (2021) Secondhand smoke exposure and OSCC risk: a systematic review and meta-analysis. Tobacco Control tobaccocontrol-2020–056393. https://doi.org/10.1136/tobaccocontrol-2020-056393
55. Taniyama Y, Takeuchi S, Kuroda Y (2010) Genetic polymorphisms and OSCC. J UOEH 32:221–236. https://doi.org/10.7888/juoeh.32.221
56. Piemonte ED, Lazos JP, Gilligan GM et al (2022) Chronic mechanical irritation enhances the effect of tobacco and alcohol on the risk of oral squamous cell carcinoma: a case-control study in Argentina. Clin Oral Invest. https://doi.org/10.1007/s00784-022-04584-w
57. Gallimidi AB, Fischman S, Revach B et al (2015) Periodontal pathogens *Porphyromonasgingivalis* and *Fusobacteriumnucleatum* promote tumor progression in an oral-specific chemical carcinogenesis model. Oncotarget 6:22613–22623. https://doi.org/10.18632/oncotarget.4209
58. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2012) Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum 100:1–538
59. Goldstein BY, Chang S-C, Hashibe M et al (2010) Alcohol consumption and cancers of the oral cavity and pharynx from 1988 to 2009: an update. Eur J Cancer Prev 19:431–465. https://doi.org/10.1097/CEJ.0b013e32833d936d
60. Purdue MP, Hashibe M, Berthiller J et al (2009) Type of alcoholic beverage and risk of head and neck cancer—a pooled analysis within the INHANCE Consortium. Am J Epidemiol 169:132–142. https://doi.org/10.1093/aje/kwn306
61. di Credico G, Polesel J, Dal Maso L et al (2020) Alcohol drinking and head and neck cancer risk: the joint effect of intensity and duration. Br J Cancer 123:1456–1463. https://doi.org/10.1038/s41416-020-01031-z
62. Ogden GR (2005) Alcohol and OSCC. Alcohol 35:169–173. https://doi.org/10.1016/j.alcohol.2005.04.002
63. Mello FW, Melo G, Pasetto JJ et al (2019) The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. Clin Oral Invest 23:2849–2859. https://doi.org/10.1007/s00784-019-02958-1
64. Poschl G (2004) Alcohol and cancer. Alcohol Alcohol 39:155–165. https://doi.org/10.1093/alcalc/agh057
65. Prabhu A, Obi KO, Rubenstein JH (2014) The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. Am J Gastroenterol 109:822–827. https://doi.org/10.1038/ajg.2014.71