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Systematic Review

The Relationship Between Smokeless Tobacco and the Incidence of Oral Cancer: A Systematic Review Study

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Abstract

Background: Many studies have examined the association between smokeless tobacco and the risk of oral cancer. In South and Southeastern Asia, the use of smokeless tobacco, which increases the risk of oral cancer, is very common. The aim of this study is to provide a comprehensive review of studies conducted and published in a period of ten years to provide a more accurate assessment of the association between smokeless tobacco and oral cancer.

Methods: An electronic search in six databases (PubMed, Scopus, Embase, Web of Science, ProQuest, and Cochrane Library) was conducted using keywords equivalent to oral cancer and smokeless tobacco. After selecting the articles according to the inclusion and exclusion criteria, a total of 30 prospective cohort and case-control studies from 2010 to 2020, which investigated the association of smokeless tobacco with oral cancer, were examined. The articles were qualitatively assessed using the Newcastle Ottawa Quality Assessment scale checklist. Then, study design (study type, setting, and duration of data collection), sample population (number, gender, and age), cancer type, smokeless tobacco type, effect size, and confounder adjustment were extracted from the studies.

Results: Five studies examined smokeless tobacco and chewing tobacco, and 25 studies reported and evaluated the type of smokeless tobacco, most of which were related to betel quid and supari. While the results of 21 studies revealed a positive and significant relationship between oral cancer and smokeless tobacco use (OR: 0.67–149.5), seven studies did not find a significant correlation.

Conclusion: This systematic review confirms the positive and significant association between non-smoking tobacco use and the risk of oral cancer.

Keywords: Tobacco, Smokeless, Carcinoma, Squamous cell, Cancer, Risk factor, Systematic review

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Introduction

Oral cancer ranks as the sixth most prevalent cancer globally, with an estimated 377 000 new diagnoses and over 130 000 deaths each year.[1-5]

Oral and pharyngeal cancers have an overall five-year survival rate of 66%, which is higher in white people than black people.[6]

Some major risk factors for oral cancer include alcohol consumption, tobacco smoking, age over 40 years, and male sex. In addition, several dietary factors, nutritional deficiencies, viral infections, sexually transmitted diseases, chronic trauma, and genetic predisposition have been associated with oral cancer.[7,8] Squamous cell carcinomas (SCCs) account for more than 90% of oral neoplasms in the upper digestive tract, while the remaining 10% comprises salivary gland tumors, verrucous carcinomas, lymphomas, sarcomas, and melanomas.[9,10] In South Asia, SCCs are the second and sixth most common neoplasm among males and females, respectively.[11]

The term "smokeless tobacco" (such as naswar, betel quid, snuff, gutkha, etc.[12-15]) refers to a variety of tobacco products that are not consumed by combustion, but are chewed, spitted, dipped, or snuffed.[16, 17]

It is estimated that 365 million people around the world use smokeless tobacco, with 90% of all consumers living in Southeast Asia, but its consumption is increasing in many countries.[18-20]

Smokeless tobacco products contain more than 30 carcinogens, including volatile and tobacco-specific nitrosamines, nitrosamine acids, arsenic, nickel, cadmium, beryllium, nitrate, and nitrite, making them a leading cause of oropharyngeal cancers.[21-24]

Previous studies from Southeast Asia have described smokeless tobacco as a risk factor for oral cancer.[25,26] However, research in other regions has not shown an association between oral cancer and some smokeless tobacco products.[27]

Due to the relatively high prevalence of smokeless tobacco in Iran, especially in the eastern regions, as well as the contradictory results of various studies, we conducted a systematic review of studies published in the last 11 years to provide a clear picture of the possible association between oral cancer and smokeless tobacco. We hope our findings in this study can be helpful in determining tobacco control policies and raise the awareness of health professionals and the general public.

Methods

Reporting format

This systematic review was performed in the Faculty of Dentistry at Mashhad University of Medical Sciences, Iran, in 2021. The PRISMA checklist was used. The outline of the screening process is shown in Figure 1 based on the PRISMA guidelines. The five important steps of these guidelines are as follows:

1. The main research question has been developed and formulated.
2. An extensive search was done by choosing suitable keywords from reliable Iranian and non-Iranian databases.
3. The quality of studies has been evaluated using the Newcastle-Ottawa Quality Assessment Scale checklist.
4. The evidence from the reviewed studies has been summarized using tables, and various topics have been scientifically categorized.
5. After sorting the selected studies, the findings have been interpreted in line with the main research question.

Objective of the review

The purpose of this study is to determine the association of smokeless tobacco with the risk of oral cancer.

Population

In the case-control studies, the case population was those with oral cancer. Some studies surveyed head and neck cancer, but they provided separate statistics for oral cancer, so these studies were also included in the study. In addition, the control population included healthy people or people with other types of lesions.

Prospective cohort studies were included, if their case groups consisted of those who consumed one of the smokeless tobacco products, and the control groups consisted of those who did not use them.

Exposure

Smokeless tobacco was evaluated in various studies based

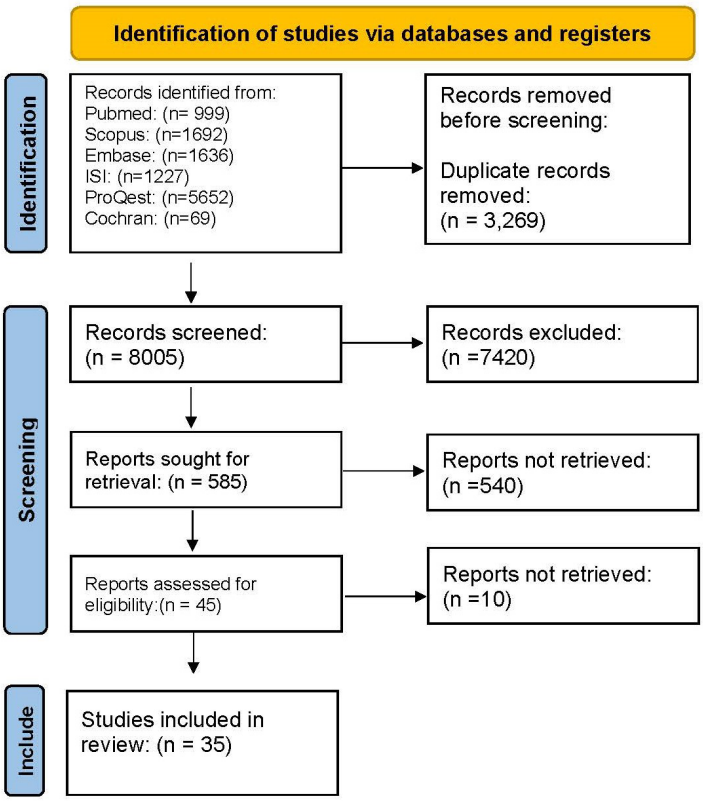

Figure 1. PRISMA 2020 flow diagram demonstrating the studies identified, screened, and included in the review

on a questionnaire or interview.

Comparison

In the case-control studies, the case group included oral cancer patients, and the control group included healthy subjects. In the cohort studies, the smokeless tobacco users were compared with the smokeless-tobacco-free subjects.

Outcomes

Oral cancer.

Information sources for data extraction

An electronic search was conducted by a researcher until January 25, 2021, in the PubMed, Scopus, Embase, Web of Science, ProQuest, and Cochrane Library databases. This study reviewed English articles published from 2010 to 2020, and no restrictions were imposed on the search except for time limit.

Search strategy

The search strategy in PubMed is presented below as an example, and the complete search strategy of each database is available in Supplementary file 1.

PubMed:

((("Tobacco, Smokeless"[Mesh]) AND ("Mouth Neoplasms"[Mesh])) OR (("Smokeless Tobacco"[Title/Abstract] OR "Non-burn Tobacco"[Title/Abstract] OR "Raw Tobacco"[Title/Abstract] OR "Dried Tobacco"[Title/Abstract] OR "Chewing Tobacco"[Title/Abstract] OR "Chew* Tobacco"[Title/Abstract] OR Gutka[Title/Abstract] OR Ghutka[Title/Abstract] OR Gutkha[Title/Abstract] OR "Betel Quid"[Title/Abstract] OR "betel tobacco"[Title/Abstract] OR Snus[Title/Abstract] OR "Dipping Tobacco"[Title/Abstract] OR Dip[Title/Abstract] OR "Oral Tobacco"[Title/Abstract] OR Snuff[Title/Abstract] OR "Mint Snuff"[Title/Abstract] OR Naswar[Title/Abstract] OR "Areca nut"[Title/Abstract] OR "tobacco powder"[Title/Abstract] OR "tobacco tooth powder"[Title/Abstract] OR "tobacco paste"[Title/Abstract] OR "creamy snuff"[Title/Abstract] OR "oral snuff"[Title/Abstract] OR mishri [Title/Abstract] OR masher[Title/Abstract] OR "tobacco water"[Title/Abstract] OR tuibur[Title/Abstract] OR hidakphu [Title/Abstract] OR gul[Title/Abstract] OR mawa [Title/Abstract] OR khaini[Title/Abstract] OR "pan masala"[Title/Abstract] OR "pan masala with tobacco"[Title/Abstract] OR paan[Title/Abstract] OR "pan with tobacco"[Title/Abstract] OR "pan masala-containing tobacco"[Title/Abstract] OR zarda [Title/Abstract] OR tambaku [Title/Abstract] OR "tobacco flakes"[Title/Abstract] OR "tobacco leaf"[Title/Abstract] OR hogesoppu [Title/Abstract] OR gnudi [Title/Abstract] OR Kadapa [Title/Abstract] OR "Mainpuri tobacco"[Title/Abstract] OR qiwam [Title/Abstract] OR kimam [Title/Abstract] OR dohra [Title/Abstract]) AND ("Mouth Neoplasm"[Title/Abstract] OR "Oral Neoplasm"[Title/Abstract] OR "Cancer of Mouth"[Title/Abstract] OR "Mouth Cancer"[Title/Abstract] OR "Oral Cancer"[Title/Abstract] OR "Cancer of the Mouth"[Title/Abstract] OR "Intraoral Cancer"[Title/Abstract] OR "Oral Cavity Cancer"[Title/Abstract] OR "Mouth Mucosa Cancer"[Title/Abstract] OR "oral carcinoma*"[Title/Abstract] OR "oral malignant*"[Title/Abstract] OR "oral tumor*"[Title/Abstract] OR "oral growth"[Title/Abstract] OR "squamous cell carcinoma"[Title/Abstract] OR SCC[Title/Abstract]))

Filters applied: from 2010–2020

Selection process

First, two researchers assessed the titles and abstracts separately. Then, all studies which were not related to the purpose of the study were excluded.

For studies that could not be judged by examining the title and abstract, the full text was evaluated more comprehensively and accurately by a third researcher. Some studies were eliminated in this stage. Finally, 30 articles were selected, which included 28 case-control studies and two prospective cohort studies. Data extraction of the selected articles was performed, and the following information was extracted from each article:

Study design (study type, setting, and data collection period), sample population (number, gender, and age), cancer type, smokeless tobacco type, effect size, confounder adjustment, and the adjusted odds ratio [OR] or the crude OR of the articles assessed.

Inclusion criteria

1. Prospective cohort and case-control articles
2. Articles with full text available in English
3. Studies about the association of types of smokeless tobacco and oral cancer

Exclusion criteria

1. Irrelevant and duplicate studies, letters to editors, case reports, review articles, systematic reviews, and summaries of congress articles
2. Articles that assessed head and neck cancer and did not report results related to oral cancer

At each stage, in case of disagreement between the two researchers, the final decision was made in consultation with the third researcher.

Assessment of methodological quality, risk of bias, and data extraction

Three researchers assessed the quality of the studies using the Newcastle-Ottawa Quality Assessment Scale checklist.

Each article was reported in three categories: good, fair, and poor.

This research employed adjusted ORs in the case-

control studies and adjusted relative risks (RRs) and hazard ratios (HRs) in the cohort studies to assess the impact of the risk factors.

Results

Study selection

The initial search was done until January 25, 2021, in PubMed, Scopus, Embase, Web of Science, ProQuest, and Cochrane Library databases, and the results obtained from the systematic search included a total of 11 275 articles from 2010 to 2020. Duplicate articles were removed by selecting the "Duplicate" option in Endnote version 20, after that, 8006 articles remained. The search results included 999 papers in PubMed, 1692 papers in Scopus, 1636 papers in Embase, 1227 papers in Web of Science, 5652 papers in ProQuest, and 69 papers in Cochrane.

Then, the titles and abstracts of the studies were surveyed, and irrelevant and duplicate articles were removed. The full texts of 585 articles were reviewed, and according to the inclusion and exclusion criteria, 555 articles were removed. Finally, 30 papers were included in our study. The steps of the article selection according to the PRISMA flow diagram are shown in Figure 1. In all these articles, the relationship between smokeless tobacco and the risk of oral cancer has been investigated. In this study, only two articles were prospective cohorts,[28,29] and 28 were case-control studies. The information of the studies is shown in Table 1.

Geographic pattern

Among these studies, the most significant number was performed in India ($n=13$),[27-39] followed by Pakistan ($n=6$),[40-45] Taiwan,[46,47] Thailand,[48] New England (Greater Boston),[49] Saudi Arabia,[50,51] Sudan,[52] Indonesia,[53] Yemen,[54,55] and East Asia[56] (Table 1).

Gender disparities

In all of these studies, both sexes were examined, except for three studies that examined only the male sex[28,29,46] (Table 1).

Smokeless tobacco and oral cancer

The types of smokeless tobacco in all studies are as follows: Tobacco flakes, supari, gutkha, areca nut, mishri, shammah, snuff, paan, naswar, mainpuri, toombak dipping, betel leaf, betel nut, khat chewing, betel quid, supari (Table 1).

Five studies did not indicate the type of smokeless tobacco,[28,29,34,38,49] while other studies reported the type of smokeless tobacco. Most of the studies evaluated various forms of smokeless tobacco, of which the most oral cancer occurrence was related to betel quid, which was studied in 11 studies,[27,35,36,39,41,43,46-48,53,56] followed by supra, which was evaluated in eight studies.[30-32,35,41,43-45]

In these studies, the largest observed effect size in relation to oral cancer was associated with shammah consumption (OR: 149.5; 95% CI: 12.3–1812).[54] Conversely, the lowest odds ratio for oral cancer was found in relation to khat chewing (OR: 0.67; 95% CI: 0.19–2.36)[51] (see Table 1). These results suggest a strong association between shammah consumption and increased risk of oral cancer, while khat chewing appears to have a protective effect against the disease.

Exposure-response relationships: Frequency and duration of use

The frequency of smokeless tobacco use was reported in 13 studies. Based on statistical tests, obtained ORs, and RRs, nine studies demonstrated a significant and strong relationship between increased frequency of smokeless tobacco consumption and oral cancer development.[29,34,37-39,41,49,53,56] Pednekar et al assessed the frequency of smokeless tobacco use in relation to oral cancer. Their study revealed that the risk of oral cancer increased with a higher frequency of smokeless tobacco use, as indicated by the reported HR.[28]

The duration of smokeless tobacco use was documented in 17 studies. Among them, 10 studies employing OR, RR, and statistical tests illustrated a significant association between prolonged duration of smokeless tobacco use and the development of oral cancer.[29,36-39,47,49,50,53,56] Additionally, the reported HR of a study that investigated the correlation between the duration of smokeless tobacco use and oral cancer risk indicated an elevated risk of oral cancer with longer durations of smokeless tobacco use.[28] These data were not included in the table due to disparate classifications and categorizations utilized in the studies.

Qualitative analysis

The results of the quality assessment performed by the Newcastle-Ottawa Quality Assessment Scale are reported in Tables 2 and 3.

Among the studies, the highest score was related to Pednekar and colleagues' study[28] (Table 3).

In the case-control studies, 26 articles had poor quality, one had good quality,[56] and one had fair quality[42] (Table 2).

Most of the defects of case-control studies in the qualitative analysis were related to exposure. Twenty-seven case-control studies were deficient in ascertainment of exposure; 24 studies investigated this part using an interview method from the case and control groups without blinding (Interview not blinded to case/control status), and 3 studies did not describe how it was done.[39,50,51] Only Khan and colleagues' study used a structured interview where blind to case/control status[42] (Table 2). After that, the greatest deficiency was in the "non-response rate", and only in two studies the rate was the same for both groups and they received a score.[42,56] In three studies this rate was different in the two groups and no explanation was given about it: "Rate different and no

Table 1. Characteristics of the studies which investigated the association between smokeless tobacco and oral cancer

First author	Study design	Sample population	Cancer type	Smokeless tobacco type	Effect size	Confounder adjusted
Madani[30] (2010)	•Study type: case-control •Setting: India (Pune (•Period: February 2005–September 2006 •Data collection: personal interview questionnaires	•Cases: 350 •Controls: 350 •Total: 700 •Gender included: male & female •Age: >18 years	Oral cancer	Tobacco flakes Gutkha Supari Mishri Betel leaf (paan)	Tobacco flakes OR: 7.6 (4.9–11.9) Gutkha OR: 12.7 (7.0–23.2) Supari OR: 6.1 (2.7–13.9) Mishri OR: 3.0 (1.9–4.9) Betel leaf OR: 1.8 (1.0–3.3)	Age, gender, other tobacco types, and alcohol
Lee[47] (2011)	•Study type: case-control •Setting: Taiwan (Kaohsiung Medical University (KMU) Hospital and Kaohsiung Chang-Gen Memorial) •Period: 2001–2007 •Data collection: interview	•Cases: 2163 •Controls: 2250 •Total: 4413 •Gender included: male & female •Age: mean Case 56.4 ± 13.0 Control (%?) 56.5 ± 12.6	SCC (oral cavity)	Substances with areca nut: Inflorescence Leaf or stem Mixed Betel-quid Juice: Non-swallowing Swallowing Not sure	Substances with areca nut: Inflorescence OR: 25.7 (17.4–38.0) Leaf or stem OR: 11.0 (7.6–15.8) Mixed OR: 5.4 (3.4–8.3) Betel-quid Juice Non-swallowing OR: 11.9 (8.5–16.7) Swallowing OR: 22.0 (15.5–31.2)	Gender, age, ethnicity, education, drink × years of alcohol intake, pack × years of cigarette smoking, and consumption of vegetables and fruits
Madani[31] (2012)	•Study type: case-control •Setting: India (Pune) •Period: February 2005–September 2006 •Data collection: questionnaire and interview	•Cases: 350 •Controls: 350 •Total: 700 •Gender included: male & female •Age: >18	Oral cancer	Chewing tobacco Gutkha Supari Mishri	Chewing tobacco OR: 8.3 (5.4–13.0), *P*: 0.0001 Gutkha OR: 12.8 (7.0–23.7), *P*: 0.0001 Supari OR: 6.6 (3.0–14.8), *P*: 0.002 Mishri OR: 3.3 (2.1–5.4), *P*: 0.0001	Other tobacco and oral dip products, alcohol, non-vegetarian habits, education, occupation, age, and gender
Loyha[48] (2012)	•Study type: case-control •Setting: Northeast Thailand •Period: July 2010–April 2011 •Data collection: questionnaire, interview	•Cases: 104 •Controls: 104 •Total: 208 •Gender included: male & female •Age: ≥25 years	Oral cancer	Betel quid chewing	OR: 9.01 (3.83–21.22) *P* < 0.001	Occupation, tobacco smoking, betel quid chewing, and confounding factors of sex and alcohol drinking
Zhou[49] (2012)	•Study type: case-control •Setting: New England, Greater Boston •Period: Not reported •Data collection: questionnaire, interview	•Cases: 1,046 •Controls: 1,239 •Total: 2,285 •Gender included: male & female •Age: ≥18 years	SCC (oral cavity)	Smokeless tobacco	OR: 0.90 (0.38–2.12)	Age, gender, race (Caucasian, other), education (three categories), smoking (continuous), ever smoker, and alcohol drinking (continuous)
Razmara[32] (2013)	•Study type: case-control •Setting: India (Pune) •Period: February 2005–September 2006 •Data collection: structured questionnaire	•Cases: 350 •Controls: 350 •Total: 700 •Gender included: male & female •Age: >18 years	Oral cancer	Chewing tobacco Gutkha Supari Mishri	Chewing tobacco OR: 8.3 (5.4–13.0) Gutkha OR: 12.8 (7.0–23.7) Supari OR: 6.6 (3.0–14.8) Mishri OR: 3.3 (2.1–5.4)	Other tobacco and oral dip products, alcohol, non-vegetarian habits, education, occupation, age, and gender
Ray [33] (2013)	•Study type: case-control •Setting: India (Kolkata) •Period: 2010–2011 •Data collection: questionnaire person interview	•Cases: 698 •Controls: 948 •Total: 1,646 •Gender included: male & female •Age: 10–99 years	SCC (oral cavity)	Smokeless tobacco (khaini gudhaku snuff) Recount (betel quid gutkha)	Smokeless tobacco OR: Male: 2.876 (1.537–5.421) *P*: 0.001 Female: 6.405 (3.043–13.585) *P* < 0.0011 Areca nut: Male: 0.899 (0.486–1.675) *P*: 0.835 Female: 3.482 (2.026–6.019) *P* < 0.0011	Not adjusted

Table 1. Continued.

First author	Study design	Sample population	Cancer type	Smokeless tobacco type	Effect size	Confounder adjusted
Amtha[53] (2014)	•Study type: case-control •Setting: Indonesia (in five major referral hospitals in Jakarta) •Period: January 2005–April 2006 •Data collection: questionnaire and face-to-face interview	•Cases: 81 •Controls: 162 •Total: 243 •Gender included: male & female •Age: aged 23–74 years	Oral squamous cell carcinoma	Betel quid	OR: 4.59 (1.11–18.91) *P*: 0.035	Alcohol consumption, smoking, and dietary patterns
Lakhanpal[27] (2014)	•Study type: case-control •Setting: India (Aizawl, Gangtok) •Period: December 2005–2010 •Data collection: interview	•Cases: 125 •Controls: 207 •Total: 332 •Gender included: male & female •Age: (mean ± SD) of cases and control was 54.11 ± 12.27 and 52.34 ± 13.5 years	Oral cancer	Tobacco chewing and betel quid chewing	Tobacco chewing OR: 1.12 (0.61–2.04) *P*: 0.712 Betel quid chewing OR: 2.01 (1.05–3.87) *P*: 0.035	Tobacco chewing adjusted for tobacco smoking, betel quid chewing, alcohol consumption, and IL-1β genotypes Betel quid chewing adjusted for tobacco smoking, tobacco chewing, alcohol consumption, and IL-1β genotypes
Nasher[54] (2014)	•Study type: case-control •Setting: Yemen (Sana) •Period: June 2009–February 2011 •Data collection: interview	•Cases: 60 •Controls: 120 •Total: 180 •Gender included: male & female •Age: all ages	Oral squamous cell carcinoma	Shammah use Qat chewing	Shammah use alone OR:149.5 (12.3–1812) *P*: < 0.001 Shammah use + qat chewing OR: 43.1 (7.0–266) *P*: < 0.001	Oral habit combinations, age, gender, and EBV infection
Merchant[40] 2015	•Study type: case-control •Setting: Pakistan (Karachi) •Period: July 1996–March 1998 •Data collection: questionnaire	•Cases: 79 •Controls: 143 •Total: 222 •Gender included: male & female •Age: mean ± SD OSMF: 46.4 ± 12.2 No OSMF: 47.9 ± 13.1	Oral squamous cell carcinoma	Paan without tobacco Paan with tobacco	Paan without tobacco OR: 7.39 (1.01–38.11) * Paan with tobacco OR: 15.68 (3.00–54.90) * *(OR included direct effect and indirect effect)	Paan without tobacco adjusted for age, sex, education, smoking, and alcohol use, and use of paan with tobacco Paan with tobacco adjusted for age, sex, education, smoking, and alcohol use, and use of paan without tobacco
Kadashetti[34] (2015)	•Study type: case-control •Setting: India)Wardha(•Period: September 2008–August 2010 •Data collection: interview	•Cases: 100 •Controls: 100 •Total: 200 •Gender included: male & female •Age: 11–70 years	Oral cancer	Tobacco quid chewing (betel quid, gutkha/kharra tobacco and lime, areca nut only)	Tobacco quid chewing OR: 2.8 (1.2–7.0) *P*: 0.026	Alcohol drinking, smoking, age, and sex
Mahapatra[35] (2015)	•Study type: case-control •Setting: India (Karnataka) •Period: March 2013–July 2013 •Data collection: questionnaire and interview	•Cases: 134 •Controls: 268 •Total: 402 •Gender included: male & female •Age: ≥ 18 years	Oral cancer	Gutkha Supari Snuff Betel quid Chewing tobacco	Gutkha OR: 5.1 (2.0–10.3), *P* < 0.001 Supari OR: 11.4 (3.4–38.2), *P* < 0.001 Snuff OR: 1.0 (0.3–3.0), *P*: 0.975 betel quid OR: 6.4 (2.6–15.5), *P* < 0.001 Chewing tobacco OR: 6.0 (2.3–15.7), *P* < 0.001	Gender, education, age, social class, diet, alcohol, other types of dip products
Quadri[50] (2015)	•Study type: case-control •Setting: Saudi Arabia (Jazan) •Period: Not reported •Data collection: questionnaire	•Cases: 48 •Controls: 96 •Total: 144 •Gender included: male & female •Age: (Mean age of the study sample was 65.3 years)	Oral squamous cell carcinoma	Shammah	OR: 37.24 (12.25–113.18) *P* < 0.05	Smoking, khat use, and pipe

Table 1. Continued.

First author	Study design	Sample population	Cancer type	Smokeless tobacco type	Effect size	Confounder adjusted
Madathil[36] (2016)	•Study type: case-control •Setting: South India (Kozhikode) •Period: 200– 2012 •Data collection: interview and questionnaire	•Cases: 350 •Controls: 371 •Total: 721 •Gender included: male & female •Age: ≥18 Mean ± SD Case: 60.79 ± 11.3 Control: 60.52 ± 11.4	Squamous cell carcinoma	Betel quid chewing (betel quid as products containing either areca nut or tobacco or both)	OR: 11.3 (6.72–19.05)	Age, sex, pack-years of bidi, pack-years of cigarettes, drinks per week of alcohol, number of missing teeth, lifetime material deprivation index, and weekly vegetable consumption
Wu[46] (2016)	•Study type: case-control •Setting: Taiwan •Period: September 1, 2010–June 30, 2014 •Data collection: interview and questionnaire	•Cases: 487 •Controls: 617 •Total: 1,104 •Gender included: men •Age: ≥20 Mean (SE) Case: 54.7 (0.5) Control: 54.1 (0.4)	SCC (oral cavity)	Betel quid	OR: 8.05 (5.10– 12.71)	Age, education, cigarette smoking (pack-year categories), and alcohol drinking (frequency)
Awan[41] (2016 (	•Study type: case-control •Setting: Pakistan (Karachi) •Period: July–December 2014), •Data collection: interview and questionnaire	•Cases: 134 •Controls: 134 •Total: 268 •Gender included: male & female •Age: ≥18 years	Oral cancer	Gutka (tobacco, areca nut, and lime) Betel quid Supari Nascar Mainpuri Chewing tobacco	Gutka (tobacco, areca nut, and lime) OR: 5.54 (2.83–10.83), $P=0$ Betel quid OR: 1.57 (0.80–3.08), $P=0.181$ Supari OR: 3.74 (1.45–9.64), $P=0.006$ Nascar OR: 3.49 (1.24–9.84), $P=0.017$ Mainpuri OR: 4.69 (1.30–16.86), $P=0.017$ Chewing tobacco OR: 5.32 (1.14–24.77), $P=0.033$	Smoked tobacco (cigarette, bidi)
Cherian[37] (2016)	•Study type: case-control •Setting: India •Period: 18 months •Data collection: questionnaire and Interview	•Cases: 76 •Controls: 76 •Total: 152 •Gender included: male & female •Age: in our study, 22.4% ($n=17$) of the cases were young adults less than 40 years of age	Oral squamous cell carcinoma	Betel nut	OR: 14.34 (2.93–70.15)	Age, gender, socioeconomic status, and tobacco
Hassanin[52] (2017)	•Study type: case-control •Setting: Sudan •Period: July–October 2014 •Data collection: questionnaire and directly interview	•Cases: 98 •Controls: 98 •Total: 196 •Gender included: male & female •Age: All ages	Oral squamous cell carcinoma	Toombak dipping	OR: 3.8 (1.7–8.6)	Cigarette smoking, alcohol consumption, and exclusive tombak dipping were significantly associated with OSCC.
Gupta[38] (2017)	•Study type: case-control •Setting: Pune, Maharashtra, India •Period: June 2014–May 2015 •Data collection: face-to-face interview and questionnaire	•Cases:187 •Controls: 240 •Total: 427 •Gender included: male & female •Age: 30–80 years	Oral cancer Squamous cell carcinoma	Tobacco chewing	OR: 8.51 (4.90–14.77) $P<0.001$	Age (continuous), gender, education, income, smoking tobacco, drinking alcohol (never/ever) diet habits (vegetarian/non-vegetarian)
Kadashetti[39] (2017)	•Study type: case-control •Setting: India •Period: not reported •Data collection: pro forma	•Cases: 50 •Controls: 50 •Total: 100 •Gender included: not reported •Age: 11–70 years	Oral cancer	Tobacco/betel quid chewing	OR: 3.1)1.5–6.1(P: 0.012	Smoking and alcohol

Table 1. Continued.

First author	Study design	Sample population	Cancer type	Smokeless tobacco type	Effect size	Confounder adjusted
Khan[42] (2017)	•Study type: case-control •Setting: in two major cities of the Khyber Pakhtunkhwa province of Pakistan •Period: September 2014–May 2015 •Data collection: questionnaire and face-to-face interview	•Cases: 84 •Controls: 174 •Total: 258 •Gender included: male & female •Age: The mean age of: Male cases: 56.3 (±13.0) controls: 57.4 (±12.7) years, females, the mean age of cases: 51.4 (±14.4) controls 57. 3 (±16.9) years	Oral squamous cell carcinoma	Nascar	OR: 27.4 (10.0–74.7)	Age, sex, socioeconomic status (SES), tobacco smoking, and alcohol
Natasha Azhar[43] (2018)	•Study type: case-control •Setting: Pakistan (Karachi) •Period: January 2015–September 2016 •Data collection: interview and questionnaire	•Cases: 62 •Controls: 62 •Total: 124 •Gender included: male & female •Age: The mean age of the respondents was 45 years, with a standard deviation of 11 years for cases (Range: 27–70 years) 40 years with a standard deviation of 16 years for controls (Range: 7–81 years)	Oral squamous cell carcinoma	Betel quid Betel nut Supari Smokeless tobacco	Betel quid OR: 1.170 (1.012–1.352) *P*: 0.034 Betel nut OR: 1.078 (0.970–1.197) *P*: 0.163 Supari OR: 1.111 (0.868–1.423) *P*: 0.403 Smokeless tobacco OR: 1.179 (1.048–1.325) *P*: 0.006	Quantity of consumption
Muhammad Haneef Mugheri[44] (2018)	•Study type: case-control •Setting: Pakistan (Jamshoro) •Period: January 2015–December 2016 •Data collection: interview and questionnaire	•Cases: 291 •Controls: 330 •Total: 621 •Gender included: male & female •Age: Mean age range: [Case: 38.8–45.8 Control: 29.1–43.8]	Oral cancer	Gutkha Supari Pan Nascar Mainpuri	Gutkha OR: 4.354 (0.559–39.384) *P*: 0.088 Supari OR: 4.655 (1.261–17.847) *P*: 0.006 Pan OR: 17.455 (1.954–399.39) *P*: 0.001 Nascar OR: 7.273 (1.167–57.234) *P*: 0.008 Mainpuri OR: 61.091 (8.146–126.01) *P*<0.001	Education, alcohol, smoking, type of ghee/ oil, and exposure to sun
Fahd Alharbi[51] (2018)	•Study type: case-control •Setting: Saudi Arabia) Jazan(•Period: January 2016–March 2017 •Data collection: telephone	•Cases: 70 •Controls: 140 •Total: 210 •Gender included: male & female •Age: The mean age of the sample was 55 years (+20 years)	Oral squamous cell carcinoma	Shammah Khat chewing	Shammah OR=33.01 (3.22–39.88) *P*: 0 Khat chewing OR=0.67 (0.19–2.36) *P*: 0	Shisha Cigarette OSCC adjusted for age, gender, area of residence, and level of education
Yuan-Chin Amy Lee[56] (2019)	•Study type: case-control •Setting: East Asia including 8 centers (Beijing, Fujian, Henan, Jiangsu, Liaoning, Shanghai, Sichuan, and Taiwan) •Period: December 2010–February 2015, •Data collection: face-to-face interview	•Cases: 921 •Controls: 806 •Total: 1,727 •Gender included: male & female •Age: 18–80 years	Oral cancer	Betel quid chewing	OR: 18.50 (10.32–33.17)	Center, education, sex, age, ethnicity, alcohol drinking duration and frequency, and cigarette smoking duration and frequency

Table 1. Continued.

First author	Study design	Sample population	Cancer type	Smokeless tobacco type	Effect size	Confounder adjusted
Azmawati Mohammed Nawi[55] (2019)	•Study type: case-control •Setting: Yemen (Hodeida) •Period: December 2013–June 2014 •Data collection: self-constructed and pre-tested questionnaire and face-to-face guided interview	•Cases: 74 •Controls: 74 •Total: 148 •Gender included: male & female •Age: Mean Case: 53.5 (16.4) Control: 41.5 (18.2)	Oral cancer	Khat chewing Shammah	Khat chewing OR: 2.59 (1.12–5.97) *P*:0.026 Shammah Adjusted OR: 3.34 (1.43–7.83) *P*: 0.005	Age, area of residence, shammah usage, oral hygiene status
Shah Zeb Khan[45] (2020)	•Study type: case-control •Setting: Pakistan (Lahore) •Period: November 2016–September 2017 •Data collection: questionnaire, interview	•Cases: 90 •Controls: 120 •Total: 210 •Gender included: male & female •Age: mean age of the controls was 52.04 years (range: 22–69, ± SD 11.17); for; for cases it was 57.38 years (range: 40–70, ± SD 6.88).	Oral cancer	Snuff Betel leaf Supari/chalia	Snuff OR: 32.65 (10.6–100.4) Betel leaf OR: 23.18 (6.23–86.2) Supari/chalia OR: 21.09 (3.59–123.6)	For age (< 50 and > 50 years), gender, and smoking (never vs. ever smokers)
Padmavati Amma Jayalekshmi[29] (2010)	•Study type: prospective cohort study •Setting: India (Karunagappally, Kerala) •Period: January 1, 1990–December 31, 1997 (the end of follow-up (December 31, 2005) Follow up: 15 years •Data collection: interview and questionnaire	•Sample: 66,277 160 cases of oral cancer •Gender included: male •Age: 30–84 years	Oral cancer	chewing tobacco	RR: 2.4 (1.7–3.3) *P* < 0.001	Age, income, education, bidi smoking, and alcohol
Mangesh S. Pednekar[28] (2011)	•Study type: prospective cohort study •Setting: India (main city of Mumbai) •Period: 1991–1997 Follow up during 1997–2003 Follow up: 5.5 years •Data collection: questionnaire and interview	•Sample: 87,222; 1267 cases of oral cancer •Gender included: male •Age: ≥ 35 years	Lip, oral cavity, and pharynx Tongue Gum Mouth	Smokeless tobacco	Lip, oral cavity, and pharynx HR: 1.48 (1.03–2.13) Tongue HR: 0.85 (0.42–1.74) Gum HR: 2.05 (0.55–7.64) Mouth HR: 0.78 (0.40–1.54)	Age, education, religion, mother tongue, BMI, and smoking

designation".[36,46,49] Other studies did not report this item (Table 2).

All studies used the same method of ascertainment for cases and controls, with the exception of the study performed by Lakhanpal et al[27] (Table 2).

Regarding selection category, the greatest shortcoming was in selection of controls, with hospital controls selected in 24 studies and no explanation given in one study.[39] Only three studies selected community controls and received a score[30,32,49] (Table 2).

Considering the "comparability of cases and controls on the basis of the design or analysis", most studies had good quality. Only Ray and colleagues' study was of poor quality and did not receive any score in this regard[33] (Table 2).

The two cohort studies were of good quality considering "selection", "comparability", and "exposure"[28,29] (Table 3).

Case-control studies

Of the 28 studies, 21 studies showed a positive relationship between smokeless tobacco consumption and oral cancer (OR range: 0.67–149.5) (Table 1).

In these studies, the greatest effect on the risk of oral cancer was related to shammah consumption (OR: 149.5, 95% CI: 12.3–1812).[54] The lowest OR regarding oral cancer was related to khat chewing (OR: 0.67, 95% CI: 0.19–2.36).[51] Seven studies assessed one or two smokeless tobacco products, and they found no significant correlation[27,30,33,35,41,43,44] (Table 1).

In Madani and colleagues' study, which evaluated several smokeless tobacco products, a positive relationship was observed between tobacco flakes, gutkha, supari, mishri, and oral cancer. However, there was no relationship between betel leaf (paan) and oral cancer (OR = 1.8)[30] (Table 1).

In Ray and colleagues' study, there was no association between areca nut consumption and oral cancer in the male population ($P = 0.835$). However, there was a

Table 2. Quality assessment performed using the Newcastle-Ottawa Quality Assessment scale checklist (case-control studies)

First author	Selection				Comparability	Exposure			Total score	Power
	Question 1	Question 2	Question 3	Question 4	Question 1	Question 1	Question 2	Question 3		
Madani[30] (2010)	*	*	*	*	**	__c	*	__b	7	Poor
Lee[47] (2011)	*	*	__b	*	**	__c	*	__b	6	Poor
Madani[31] (2012)	*	*	__b	*	**	__c	*	__b	6	Poor
Loyha[48] (2012)	*	*	__b	*	**	__c	*	__b	6	Poor
Zhou[49] (2012)	__b	__b	*	__b	**	__c	*	__c	4	Poor
Razmara[32] (2013)	*	*	*	__b	**	__c	*	__b	6	Poor
Jay Gopal Ray[33] (2013)	*	*	__b	__b	__	__c	*	__b	3	Poor
Rahmi Amtha[53] (2014)	*	*	__b	__b	**	__c	*	__b	5	Poor
Meena Lakhanpal[27] (2014)	*	__b	__b	__b	**	__c	B	b	3	Poor
Akram T. Nasher[54] (2014)	*	__b	__b	__b	**	__c	*	__b	4	Poor
Merchant[40] 2015	*	*	__b	*	**	__c	*	__b	6	Poor
Kadashetti[34] (2015)	*	__b	__b	*	**	__c	*	b	5	Poor
Mahapatra[35] (2015)	*	*	__b	*	*__	__c	*	__b	5	Poor
Quadri[50] (2015)	*	*	__b	__b	**	__d	*	__b	5	Poor
Madathil[36] (2016)	*	__b	__b	*	**	__c	*	__c	5	Poor
Wu[46] (2016(	*	__b	__b	*	**	__c	*	__c	5	Poor
Awan[41] (2016)	*	*	__b	__b	*	__c	*	__b	4	Poor
Cherian[37] (2016)	*	__b	__b	__b	**	__c	*	__b	4	Poor
Hassanin[52] (2017)	*	*	__b	__b	**	__c	*	__b	5	Poor
Gupta[38] (2017)	*	*	__b	*	**	__c	*	__b	6	Poor
Kadashetti[39] (2017)	*	__b	__c	__b	**	__d	*	__b	4	Poor
Khan[42] (2017)	*	__b	__c	*	**	*b	*	*	7	Fair
Azhar[43] (2018)	*	__b	__c	__b	*	__c	*	__b	3	Poor
Mugheri[44] (2018)	__c	__b	__c	__b	*__	__c	*	__b	2	Poor
Alharbi[51] (2018)	*	*	__c	*	**	__d	*	__b	6	Poor
Amy Lee[56] (2019)	*	*	__c	*	**	__c	*	*	7	Good
Mohammed Nawi[55](2019)	__C	*	__b	__b	*__	__c	*	__b	3	Poor
Khan[45] (2020)	*	*	__b	*	**	__c	*	__b	6	Poor

a, b, and c are defined in the "Newcastle-Ottawa Quality Assessment scale checklist" which is attached (Supplementary File 2).

Table 3. Quality assessment performed by the Newcastle-Ottawa Quality Assessment scale checklist (cohort studies)

First author	Selection				Comparability	Outcome			Total score	Power
	Question 1	Question 2	Question 3	Question 4	Question 1	Question 1	Question 2	Question 3		
Jayalekshmi[29] (2010)	* a	*	* b	*	*	* a	*	*b	8	Good
Pednekar[28] (2011)	* b	*	* b	*	**	* b	*	* b	9	Good

positive and significant association between oral cancer and the use of smokeless tobacco in men and women and the use of areca nut in women ($P=0.001$ and $P=0.0001$, respectively)[33] (Table 1).

In Lakhanpal and colleagues' study, there was a positive relationship between oral cancer and betel quid chewing ($P=0.035$). However, there was no association between tobacco chewing and oral cancer ($P=0.712$).[27] In addition, Mahapatra and colleagues' study showed a positive and significant relationship between consuming gutkha, supari, betel quid, and chewing tobacco and oral cancer ($P=0.000$). However, there was no relationship between snuff and oral cancer ($P=0.975$)[35] (Table 1).

Furthermore, in Awan and colleagues' study, a positive and significant relationship was observed between oral cancer and consumption of gutkha, supari, naswar, mainpuri, and chewing tobacco ($P=0$, $P=0.006$, $P=0.017$, and $P=0.017$, respectively). However, there was no relationship between oral cancer and betel quid consumption ($P=0.181$)[41] (Table 1).

Azhar et al found a positive and significant relationship between oral cancer and the consumption of Betel quid and

smokeless tobacco ($P=0.006$ and $P=0.034$, respectively). However, no association was found between oral cancer and the consumption of Betel nut and supari ($P=0.403$ and $P=0.163$, respectively).[43] Moreover, in Mugheri and colleagues' study, a positive and significant relationship between oral cancer and the consumption of supari, pan, naswar, and mainpuri was observed ($P=0.000$, $P=0.008$, $P=0.001$, and $P=0.006$, respectively), but there was no association between oral cancer and gutkha consumption ($P=0.088$)[44] (Table 1).

Prospective cohort studies

Regarding cohort studies, only two prospective cohort studies from 2010 to 2020 met the inclusion criteria for this study. Both prospective cohort studies were conducted on the male population[28, 29] (Table 1).

The largest sample size was related to Pednekar and colleagues' study, which was performed in India. Their study included 87222 samples, and the period of the follow-up was 5.5 years. They reported a positive and significant relationship between tobacco use and oral cancer (HR: 1.48 (1.03– 2.13))[28] (Table 1).

Moreover, Jayalekshmi and colleagues' study was conducted in India and included 66277 samples and a 15-year follow-up. A positive and significant relationship was found between chewing tobacco and oral cancer ($P<0.001$, HR: 5. 26 (2.51–11.01))[29] (Table 1).

Adjustment for risk factors

Cancer of the oral cavity has other risk factors, including smoking, alcohol, age, sex, etc. Therefore, to evaluate the association between oral cancer and smokeless tobacco, adjustment for other risk factors should be performed.

Various studies adjusted for some factors, including age, gender, other types of tobacco use, alcohol, cigarettes, ethnicity, consumption of vegetables and fruits, race (Caucasian and other), education, dietary pattern, number of missing teeth, IL-1β genotypes, oral habit combinations, EBV infection, material deprivation index, socioeconomic status, type of consumed ghee/oil, exposure to sun, area of residence, oral hygiene status, religion, mother tongue, BMI, and spicy food and hot drink consumption. Only one study reported an OR without any adjustment[33] (Table 1).

Among the studies that reported adjusted OR, three studies did not adjust for cigarette use[35,43,54]; eight studies did not adjust for alcohol consumption[28,37,41,43,45,50,51,54]; ten studies did not adjust for age,[27,39,41,43,44,48,50,52,53,55] and nine studies did not adjust for sex[27,39,41,43,44,50,52,53,55] (Table 1).

Discussion

During these ten years, 30 articles were finally selected for our study. Because some studies, especially retrospective cohort studies, were cross-sectional, or the exact information about case selection and their inclusion criteria were not described,[1] we decided to evaluate only prospective cohort and case-control studies. Among all the cohort studies from 2010 to 2020, only two studies were prospective cohort studies. Out of the 28 case-control studies, 21 studies showed a significant association between oral cancer and smokeless tobacco consumption (OR: 0.67–149.5).

In the two prospective cohort studies, a significant positive relationship was found between smokeless tobacco and oral cancer (HR: 1.48 (1.03–2.13) and HR: 5.26 (2.51–11.01), respectively).[28,29]

Seven case-control studies did not find a significant correlation between oral cancer and the one or two evaluated forms of smokeless tobacco products

Seven case-control studies did not find a significant correlation between oral cancer and the one or two evaluated forms of smokeless tobacco products.[27,30,33,35,41,43,44]

Previous case-control study in Mumbai have shown an association between oral cancer and betel leaf chewing.[57] Another study performed by Madani et al reported a relationship between oral cancer and tobacco flake, gutkha, supari, and mishri. However, they found no relationship between betel leaf and oral cancer,[30] which could be because most subjects are in the habit of spitting out the quid rather than swallowing, so the carcinogenic and toxic substances do not come into contact with the oral epithelium.[30]

In Mahapatra and colleagues' study,[35] the lack of an association between snuff and oral cancer is likely due to the fact that betel quid and gutkha are very popular in India among non-smoking subjects.[16] Therefore, the small number of snuff users enrolled in that study probably affected the result regarding this substance.

In Mugheri and colleagues' study,[44] no association was found between gutkha and oral cancer. However, the number of users in the study was low, which may have affected the final result; it is also noteworthy that in the qualitative analysis, the study was poor according to the selection point of view.

A systematic review of Indian manuscripts showed that all Indian case-control studies demonstrated a significant association between oral cancer and tobacco chewing. The majority of these studies confirmed that the risk of tobacco chewing was higher than the risk of smoking. In addition, an increased risk was reported in all tobacco chewers, whether they were ever chewers, past chewers, or present chewers.[58]

A similar systematic review was conducted in 2018, which evaluated the association between various cancers and the consumption of smokeless tobacco products in different studies. They reported that in most of these studies, which were conducted in the southeastern and eastern Mediterranean regions, there was a significant positive association between non-predictive tobacco use and oral cancer (OR: 1.48–27.4) and esophageal cancer

(OR: 2.06–12.8).[59]

In Asthana and colleagues' study, the articles up to 2016 were reviewed, and they concluded that consumers of smokeless tobacco products, mostly in Southeast Asia (SEAR (4.44, 95% CI: 3.51–5.61)) and the Eastern Mediterranean (EMR (1.28, 95% CI: 1.04–1.56)), are at high risk for oral cancer.[60]

In Awan and colleagues' study, the articles were collected up to July 2015. In their study, a significant positive association was observed between oral cancer and consumption of different types of smokeless tobacco. The OR for betel quid and the risk of oral cancer ranged from 3.1 to 15.7, and for chewing tobacco, the risk of oral cancer varied from 1.2 to 12.9.[61]

Two systematic reviews revealed that the risks of head, neck, oral, and pharyngeal cancers decreased after quitting smoking and betel quid within the five and ten years of cessation, respectively.[62,63]

In a meta-analysis by Quadri et al, the relationship between smokeless tobacco and oral cancer in North Africa and the Middle East was evaluated, which assessed the studies had evaluated only one type of smokeless tobacco, shammah. In the case-control studies, the cumulative OR was 38.74 (95% CI: 19.50–76.9696), indicating that oral cancer was almost 39 times more likely to occur among shammah users than non-users. This study concludes that shammah is a potential risk factor for oral cancer.[64]

The mentioned studies were conducted at different time intervals, and they reviewed various types of substances in different databases.[62-64] Therefore, it was impossible to accurately compare our study's results with similar previous studies. However, in our study, unlike previous studies, the evaluated articles were from a different period, i.e., from 2010 to 2020. Moreover, more comprehensive keywords were used for the search, and more databases were searched.

According to a 2017 report by the WHO, smokeless tobacco consumption is generally 5.1% among young people, 4.8% among women, and 5.4% among men. However, no statistics were provided for adults.[65]

In total, 27 studies were performed on both sexes, and three examined only the male population. Therefore, the results of these three studies can be generalized only to the male population.[12,13,22] Women in some countries consume these substances due to cultural issues, which places them at increased risk of oral cancer.[23,24] Research has also shown that the oral mucosa in women is more vulnerable to smoking.[25] Furthermore, lack of knowledge and awareness[66] increases the risk of oral cancer in women.

With regard to age, the wide variety of classifications and subgroups makes analysis difficult.

Smokeless tobacco is used in 121 countries around the world, but more than 80% of the users are in Southeast Asian countries because its use is more accepted in their culture and traditions.[18,67]

Therefore, most studies were related to these areas. In the present study, most of the studies were related to India.

The different methods, designs, and sample sizes of the included studies complicated the analysis. Moreover, a critical issue was the frequency and duration of smokeless tobacco consumption, as well as different classifications and definitions of users, which were not mentioned in some studies. Also, some studies classified subjects as former and current users, but some did not, so it was difficult to compare the results.[9,10]

Generally, it can be stated that this study had several limitations. One of the most important limitations was that all major confounders had not been adjusted in the included studies. Therefore, it is suggested that future studies adjust the effects of smokeless tobacco on oral cancer for all confounders, especially major risk factors.

In addition, cohort studies should have longer follow-up periods and larger sample sizes. Also, since different studies use different criteria to define the duration and frequency of consumption, using a comprehensive definition in studies can help better compare the results in the future.

Considering the large volume of studies in this area, this study included articles published from 2010 to 2020, using comprehensive keywords in six databases. However, as this study was conducted in 2021, it is suggested that future studies include studies published before and after this date in different databases, as well as non-English studies, such comparative studies may lead to more definitive conclusions about the association between the risk of oral cancer and smokeless tobacco.

Conclusion

This systematic review confirms the positive and significant association between oral cancer and non-smoking tobacco. However, the important issue was the different classifications and definitions for users and the frequency and duration of smokeless tobacco consumption, which made comparison difficult.

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Competing Interests
The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval
The protocol of this research was approved by the Ethics Committee of Mashhad University of Medical Sciences (ethical code: IR.MUMS.DENTISTRY.REC.1397.045).

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Supplementary Files
Supplementary files 1. Database search strategy
Supplementary files 2. Newcastle – Ottawa quality assessment scale

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