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REVIEW ARTICLE

The association between oral hygiene and head and neck cancer: a meta-analysis

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ABSTRACT

Objective: Oral hygiene has been suspected to contribute to the aetiology of head and neck cancer (HNC). Based on the meta-analysis, we evaluated the impact of oral hygiene on head and neck cancer (HNC) and its survival.

Materials and methods: Relevant case-control and cohort studies reporting survival data, oral hygiene data were searched *via* PubMed, Embase, Cochrane Library, and Web of Science databases. The odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs) were used. Subgroup analysis was performed.

Results: Oral hygiene was associated with HNC. Tooth brushing $\geq$2 a day, dental floss use, denture wearing, caries $\geq$3, and dental visit $\geq$1 reduced the risk of oral cavity cancer while mouth wash use, missing teeth >5, gum bleeding, and periodontal disease increased the risk of oral cavity cancer. For oropharynx cancer, tooth brushing $\geq$2 and caries $\geq$3 were associated with reduced risk of it. Tooth brushing $\geq$2 and dental visits $\geq$1 decreased the risk of pharynx cancer risk and larynx cancer risk, however, missing teeth >5 increased both of them.

Conclusion: Oral hygiene was associated with HNC and its sub sites. Oral hygiene should be strengthened, a dental floss use and dentist's visits can be recommended.

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KEYWORDS
Oral hygiene; head and neck cancer; survival; meta-analysis

Introduction

Head and neck cancer (HNC), which includes cancers of the oral cavity, oropharynx, hypopharynx, and larynx, is the seventh leading cancer in the world, with approximately 710 000 new cases diagnosed worldwide annually [1]. Over 60% of HNC patients present with stage III or IV, defined as locally advanced HNC [2], which recurs in approximately 50% of cases after primary therapy with surgery and radiation, with or without chemotherapy [3]. Patients with HNC have to cope not only with a life-threatening diagnosis but also with an altered facial appearance and the loss or impairment of important functions as a result of treatment, which has a serious impact on the quality of life of patients [4]. Therefore, it is essential to explore the risk factors for HNC and take appropriate precaution.

Numerous epidemiological studies have consistently demonstrated alcohol, betel quids, and cigarettes are the major risk factors of HNC and contribute to the majority of the HNC cases [5,6]. In addition to the above-mentioned risk factors, oral hygiene indicators have been suspected to contribute to the aetiology of HNCs [7]. A recent meta-analysis demonstrated that good oral hygiene, as characterised by few missing teeth, annual dentist visits, and daily tooth brushing, may modestly reduce the risk of HNC [8]. However, there are still limited studies to explore the relationship between oral hygiene and the risk of HNC in different HNC sites. It is noteworthy that the effect of oral hygiene may vary by different HNC sites [9]. Moreover, studies highlighting the role of oral hygiene in the prognosis of HNC are scarce. To address this gap and to call on patients with HNC to pay attention to oral hygiene, further evaluation of the impact of oral hygiene on HNC is needed.

Herein, we conduct this analysis (1) to assess the association between oral hygiene and the risk of HNC in different HNC sites; (2) to investigate the association between oral hygiene habits and the survival of HNC patients.

Methods

We performed this systematic review using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [10].

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Search strategy

Literature search was performed *via* PubMed, Embase, Cochrane Library, Web of Science databases from inception to November 19, 2021. The search terms were as follows: 'Head and Neck Neoplasm*' OR 'Cancer of Head and Neck' OR 'Head and Neck Cancer' OR 'Upper Aerodigestive Tract Neoplasm' OR 'UADT Neoplasm' OR 'Head Neoplasm*' OR 'Head Cancer*' OR 'Neck Neoplasm*' OR 'Neck Cancer*' OR 'Mouth Neoplasm*' OR 'Oral Neoplasm*' OR 'Cancer of Mouth' OR 'Mouth Cancer*' OR 'Oral Cancer*' OR 'Gingival Neoplasms' OR 'Lip Neoplasm' OR 'Lip Cancer' OR 'Palatal Neoplasm*' OR 'Tongue Neoplasm' OR 'Tongue Cancer' OR 'Pharyngeal Neoplasm*' OR 'Pharynx Neoplasm*' OR 'Cancer of Pharynx' OR 'Pharynx Cancer*' OR 'Cancer of the Pharynx' OR 'Pharyngeal Cancer*' OR 'Hypopharyngeal Neoplasm*' OR 'Hypopharyngeal Cancer*' OR 'Oropharyngeal Neoplasm*' OR 'Oropharynx Neoplasm*' OR 'Oropharyngeal Cancer*' OR 'Oropharynx Cancer*' OR 'Laryngeal Neoplasm*' OR 'Larynx Neoplasm*' OR 'Larynx Cancer*' OR 'Laryngeal Cancer*' OR 'Squamous Cell Carcinoma of Head and Neck' OR 'Head And Neck Squamous Cell Carcinoma*' OR 'HNSCC' OR 'Laryngeal Squamous Cell Carcinoma' OR 'Squamous Cell Carcinoma of Larynx' OR 'Hypopharyngeal Squamous Cell Carcinoma' OR 'Oral Squamous Cell Carcinoma*' OR 'Squamous Cell Carcinoma of the Mouth' OR 'Oropharyngeal Squamous Cell Carcinoma' AND 'Oral Hygiene' OR 'Hygiene, Oral' OR 'Dental Hygiene' OR 'Hygiene, Dental' OR 'Oral health' OR 'Toothbrushing' OR 'Tooth brushing' OR 'Tooth cleaning' OR 'Dental check-ups' OR 'Dental visits' OR 'Gum bleeding' OR 'Missing teeth' OR 'Tooth loss' OR 'Dental factors' OR 'Dental status' OR 'Periodontal disease' OR 'Denture us*' OR 'Wearing dentures' OR 'Mouthwash use'. Detailed search strategies from PubMed are provided in Supplementary File 1.

Inclusion and exclusion criteria

The inclusion criteria were: (1) patients diagnosed with HNC; (2) studies reporting survival data, oral hygiene data, and comparison data between the two groups; (3) case-control and cohort studies; (4) studies published in English.

The exclusion criteria were: (1) animal experiments; (2) conference reports, case reports, meta-analyses, reviews, editorial materials, letters, protocols, errata.

A total of 8,497 articles were identified through the search, and 6,140 studies remained after removing duplicates, 143 full-text articles were eligible for screening. Finally, 44 studies were included.

Data extraction and study quality assessment

For each study, the following were extracted: the authors' names, year of publication, country, study groups, sources, number of participants, gender, age, education, tobacco, alcohol, cancer site, quality of the study, and outcomes.

Study quality was evaluated using a modified version of the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies. The total score of the scale was 10, with <5 as low quality and ≥ 5 as high quality.

Oral hygiene variables and outcomes

Oral hygiene data were obtained from questionnaires administered by dentists and self-report questionnaire interviews. Mouth wash, dental floss, wear denture, gum bleeding, and periodontal disease were defined dichotomously as yes versus no. The number of missing teeth was defined as <5 or ≥ 5 teeth missing. Tooth brushing was categorised by frequency as $2\geq$twice/day versus <2 once/day, and dentist visit frequency as $\geq$ once/year versus $<$ once/year, dental caries was ≥ 3 versus <3 and the number of missing teeth number (<5, ≥ 5).

The outcomes in this study were HNC, overall survival (OS), and disease-free survival (DFS) (from tumour diagnosis to recurrence or end of follow-up). The OS and DFS were assessed by analysing oral health (OH, >5 vs 0-5) and dental care (DC, >2 vs 0-2). A higher OH score indicates worse oral hygiene, and a higher DC score indicates worse DC.

Statistical analysis

All analyses were performed using Stata15.1 software (Stata Corporation, College Station, TX, USA). The odds ratios (ORs) were used as the effect indicators for the enumeration data, hazard ratios (HRs) were chosen for survival data, and the effect size was expressed as 95% confidence intervals (CIs). The heterogeneity was tested for each outcome. The random-effect model analysis was performed for heterogeneity statistic $I^2 \geq 50\%$, otherwise, fixed-effect model analysis was applied. When heterogeneity $I^2 \geq 50\%$. Subgroup analysis was analysed by tobacco smoking (never, ever), alcohol drinking (never, ever), and regions (Europe, North America, Latin America, Asia, and China). Sensitivity analysis was performed on all outcomes, publication bias was tested by Begg's test. And $p < 0.05$ was considered statistically significant.

Results

Basic characteristics of included studies

A total of 8,497 articles were identified through the search, and 6,140 studies remained after removing duplicates, 143 full-text articles were eligible for screening. Finally, 44 studies [7,9,11–52] were included in this study, involving 52,863 patients, with 19,863 patients diagnosed with HNC and 33,000 without HNC. Among the included articles, 40 were case-control studies, 4 were cohort studies, 33 were of high quality and 11 were of low quality. The characteristics of included studies are presented in Table 1. An overview of the search results is depicted in Figure 1.

Oral hygiene and HNC

Tooth brushing (≥ 2 vs <2/d)

Seventeen articles were included to assess tooth brushing and HNC. The result $I^2=73.8\%$, so the random-effect model analysis was performed. The result showed that tooth brushing ≥ 2 times a day was at a lower risk of HNC than tooth brushing <2 times a day (OR: 0.534, 95%CI: 0.461 to 0.618,$p < 0.001$). According to regional subgroup analysis,

Table 1. Basic characteristics of included studies.

Author	Year	Country	Group	Source	Sample size (N)	Sex (Male /Female)	Age (years)	Education	Tobacco	Alcohol	Cancer site	QS	Outcomes
Deng	2021	China	Oral cancer	Hospital	1159	679/480	18-90	Illiteracy, primary-middle school, ≥high school	–	–	Oral	5	Tooth brushing, denture
			Healthy population	Community or the medical examination centre of the same hospital	1159	672/487	18–90	Illiteracy, primary-middle school, ≥high school	–	–	–		
Shewale	2021	USA	HNSCC	Hospital	249	182/67		<high school, high school or equivalent, ≥college	170	178	Oral cavity, oropharyngeal	4	Denture, dental visits, gum bleeding
			Control	Patients with no history of cancer seen for benign conditions	498	364/134		<high school, high school or equivalent, ≥college	257	361	–		
Sharma	2020	India	OSCC	–	200	138/62	53.4	–	–	–	Oral	4	Dental floss, denture, gum bleeding, periodontal disease
			Healthy control	–	200	123/77	51.7	–	–	–	–		
Saira	2019	Pakistan	HNSCC	Hospital	276	177/99	55.0 ± 13.4	–	69	0	Oral cavity, larynx, hypopharynx, oropharynx, pharynx	5	Tooth brushing, mouth wash, denture, periodontal disease
			Control	General visitors to the hospital outpatients department (OPD) without any oral pathology	275	164/111	52.8 ± 14.9	–	32	0	–		
Zeng	2019	China	Hypopharyngeal cancer	Hospital	278	M	60.0	≤primary school 89, junior/senior high school 150, ≥junior college 39	260	258	Hypopharyngeal	5	Missing teeth
			Control	Patients unrelated to alcohol, tobacco, or dietary practices in two hospital centres	693		58.5	≤primary school 137, junior/senior high school 459, ≥junior college 97	454	376	–		
Bornigen	2017	USA	SCC of oral and oropharyngeal	At the outpatient otolaryngology clinic	121	94/27	58	–	99	116	Oral cavity, oropharynx, unknown	5	Periodontal disease
			Control	Outpatient for any benign condition at the same otolaryngology service	242	188/54		–	161	239	–		
Chen	2017	China	Oral cancer	Hospital	250	F		Illiteracy 55, primary/middle school 142, ≥high school 53	0	0	Oral	5	Tooth brushing, missing teeth, denture, dental visits
			Healthy population	Inpatients or outpatients had other acute and non-neoplastic conditions	996			Illiteracy 219, primary/middle school 414, ≥high school 363	0	0	–		
Farquhar	2017	USA	HNSCC	Medical record	1381	1051/330	59.0 ± 10.4	<high school 476, high school 389, >high school 516	–	–	Oral cavity, pharynx, larynx	6	Tooth brushing, missing teeth, dental visit
			Control	The North Carolina department of motor vehicle records	1396	966/430	61.0 ± 12.3	<high school 219, high school 334, >high school 843	–	–	–		
Gupta	2017	Australia	OSCC	Two different multidisciplinary hospitals	187	130/57	56.49 ± 11.96	Illiterate 59, high school 79, >high school 49	163	66	Tongue, floor of mouth, gum, unspecified, hard palate	5	Tooth brushing, missing teeth, denture, gum bleeding
			Control	Non-neoplastic diseases unrelated to tobacco or alcohol consumption, attending or hospitalised at the study sites	240	161/79	58.23 ± 10.32	Illiterate 46, high school 152, >high school 42	119	67	–		
Kawakita	2017	Utah	HNSCC	8 study centres	921	726/195	18–85	Illiteracy 59, primary school 228, junior/middle school 261, senior/ high school 244, ≥college/ university 129	596	446	Oral cavity, oropharynx, hypopharynx, larynx, unspecified/overlapping	5	Tooth brushing, denture, dental visit
			Control	A defined list of nonchronic diseases not related to tobacco smoking or alcohol drinking	806	556/250	18-85	Illiteracy 24, primary school 129, junior/middle school 150, senior/ high school 170, ≥college/ university 333	341	205	–		
Dholam	2016	India	SCC of oral and oropharynx	Hospital	85	151/19	18-45	High educational qualification 15	26	17	Buccal mucosa, tongue, tonsil/oropharynx	3	Dental visit
			Control	General population in the outpatient department.	85			High educational qualification 26	15	5	–		
Laprise	2016	Canada	OSCC	Hospital	306	173/133	59.9 ± 11.1	Low 235, high 71	–	–	Tongue, floor of mouth, gum, buccal mucosa, other	5	Tooth brushing
			Control	Outpatient clinics in the same hospitals with non-neoplastic diseases unrelated to tobacco or alcohol	328	182/146	59.5 ± 11.6	Low 157, high 171	–	–	–		
Zuo	2015	China	OSCC	Hospital	150	111/39	59.35 ± 13.64	–	89	126	Tongue, buccal mucosa, gum, small area of the gum behind the wisdom teeth, floor of the mouth, lips, hard palate, soft palate, maxillary sinus, vestibule, oropharynx, other parts of the mouth	6	Missing teeth

(*continued*)

Table 1. Continued.

Author	Year	Country	Group	Source	Sample size (N)	Sex (Male /Female)	Age (years)	Education	Tobacco	Alcohol	Cancer site	QS	Outcomes
			Control	The relatives or friends of OSCC patients	167	125/42	58.83 ± 13.57	–	20	150	–		
Ahrens	2014	Germany	UADT	Hospital	1963	1541/422	59.8 ± 10.1	General secondary school 719, intermediate/advanced secondary school 1147, university 97	1746	1804	Mouth/oropharynx, hypopharynx/larynx, oesophagus, overlapping multiple sites	5	Mouth wash
			Control	Patients admitted to the same hospitals as the cases for a wide spectrum of medical conditions, or randomly selected from the same medical practice list	1993	1442/551	59.8 ± 11.8	General secondary school 517, intermediate/advanced secondary school 1274, university 202	1260	1705	–		
Narayan	2014	India	OSCC	Hospital	242	177/65	53.27 ± 12.62	–	74	47	Buccal mucosa, tongue, gingivo-buccal sulcus, retro molar, others	5	Tooth brushing, mouth wash, missing teeth, dental visit, DMFT
			Control	Randomly selected without previous history of any malignancies	254	178/76	47.48 ± 11.05	–	51	34	–		
Tsai	2014	China	HNSCC	Hospital	436	413/23	54.7 ± 10.4	≤elementary school 128, junior high 137, high/technical school 131, ≥college 40	379	309	Oral cavity, pharynx (oropharynx and hypopharynx), larynx	5	Tooth brushing, mouth wash, dental floss, dental visit
			Control	Patients underwent surgery and had no previous diagnosis of cancer	514	492/22	53.7 ± 9.1	≤elementary school 85, junior high 97, high/technical school 191, ≥college 141	354	275	–		
Chang	2013	China	HNSCC	Hospital	317	300/17	54.6 ± 10.7	≤elementary school 99, junior high 98, high/technical school 94, ≥college 26	277	241	Oral, pharyngeal, laryngeal	5	Tooth brushing, mouth wash, dental floss, dental visit, gum bleeding
			Control	Patients underwent surgery and had no previous diagnosis of cancer	296	280/16	53.1 ± 10.3	≤elementary school 49, junior high 57, high/technical school 118, ≥college 72	213	179	–		
Eliot	2013	USA	HNSCC	Medical facilities	513	377/136	56.0 ± 11.3	Up to high school diploma 186, ≥high school diploma 326	129	462	Oral cavity, pharyngeal, laryngeal	6	Mouth wash, dental visit, periodontal disease
			Control	Massachusetts town lists and town of residence from the same population	567	420/147	60.5 ± 10.8	Up to high school diploma 134, ≥high school diploma 430	233	478	–		
Moergel	2013	Germany	OSCC	Hospital	178	122/56	60 ± 10.7	–	–	38	Mouth floor, tongue, mandible, maxilla, palate, cheek, multiple locations	4	Tooth brushing, dental floss, denture, gum bleeding
			Control	Treated in the same department without malignant diseases	123	58/65	57 ± 9.7	–	–	87	–		
Tezal	2013	USA	HNSCC	Hospital	399	281/118	58.62 ± 11.43	–	328	161	Oral cavity, oropharynx, larynx	5	Dental caries
			Control	General dentistry or benign mucosal lesions patients	221	87/134	54.35 ± 15.57	–	105	65	–		
Sato	2011	Japan	UADT	Hospital	856	700/156	–	–	689	706	Oral cavity, oropharyngeal, hypopharyngeal, laryngeal, oesophageal	6	Tooth brushing
			Control	First-visit outpatients without cancer	2696	2178/518	–	–	1686	1826	–		
Johnson	2010	Canada	HNC	Hospital	162	130/32	63.8	<high school 45, high school 34, trades certificate 16, other post-secondary 24, ≥university 43	115	–	HNC	4	Dental visit
			Control	2004–2005 Canadian Community Health Survey	2679	1302/1377	53.9	<high school 402, high school 579, trades certificate 228, other post-secondary 675, ≥university 799	1377	–	–		
Vaccarezza	2010	Brazil	OSCC	Hospital	124	102/22	–	<5 73, 5-8 30, >8 21	124	–	Cheek mucosa, retromolar area , lower lip, gum, palate, floor of mouth, tongue	5	Denture
			Control	Patients assisted in outpatient-care units of the same hospital, without prior or current experience of cancer	124	102/22	–	<5 53, 5-8 32, >8 39	124	–	–		
Rezende	2008	Brazil	SCC of oral and oropharynx	Hospital	50	45/5	–	–	–	–	Oral, oropharynx	4	Missing teeth, denture, dental caries
			Control	Disease-free and recruited within the same time span	50	43/7	–	–	–	–	–		
Guha	2007	France	SCC of head and neck and oesophagus	Hospital	3210	2728/480	–	<18 432, 18-23 308, >23 180; illiterate 481, primary 1517, secondary 238, university 47	2994	2828	Oral cavity, pharynx, larynx, oesophagus	5	Tooth brushing, mouth wash, missing teeth, denture, dental visit, gum bleeding

(*continued*)

Table 1. Continued.

Author	Year	Country	Group	Source	Sample size (N)	Sex (Male /Female)	Age (years)	Education	Tobacco	Alcohol	Cancer site	QS	Outcomes
			Control	Hospitalised for prespecified conditions thought to be unrelated to tobacco use or alcohol consumption	2733	2151/582	–	<18 324, 18-23 339, >23 265; illiterate 315, primary 1173, secondary 234, university 81	1864	2012	–		
Rosenquist	2005	Sweden	SCC of oral and oropharynx	Hospital	132	91/41	33-87	–	–	–	Tongue, floor of mouth, unspecified, oropharynx	6	Missing teeth, denture
			Control	No previous cancer diagnosis with the exception of skin cancer	320	215/105	33-89	–	–	–	–		
Lissowska	2003	Poland	HNC	Hospital	122	78/44	–	<high school 82, high school 27, >high school 13	100	79	Tongue, oral cavity, oropharynx, unspecified parts of pharynx	6	Dental visit, gum bleeding
			Control	Patients admitted for acute illnesses to major hospitals in the same areas	124	72/52	–	<high school 64, high school 36, >high school 24	81	69	–		
Balaram	2002	India	Oral cancer	Hospital	591	309/282	–	0 292, 1-6 183, ≥7 114	231	178	Oral cavity	4	Tooth brushing, missing teeth, denture, gum bleeding
			Control	Relatives and friends of patients or outpatients	582	292/290	–	0 145, 1-6 160, ≥7 275	170	95	–		
Winn	2001	USA	HNC	Central cancer registry of the department of health of Puerto Rico	342	286/56	–	–	–	–	Oral cavity, pharynx	5	Mouth wash
			Control	Randomly selected for households in the same area, systematic sampling from rosters of Medicare enrolees	521	417/104	–	<high school 306, high school 101, >high school 113	310	349	–		
Moreno-Lopez	2000	Spain	SCC of oral and oropharynx	Hospital	75	63/12	–	<6 41, >6 34	63	63	Labial mucosa, tongue , gingiva , floor of mouth , other mouth areas 1, oropharyngeal 7	6	Dental visit
			Control	Healthy subjects in health care centres that corresponded to these hospitals	150	123/27	–	<6 72, >6 78	94	99	–		
Talamini	2000	Italy	HNC	Hospital	132	99/33	60 (27-86)	<6 54, 6-8 43, ≥9 35	30	123	Tongue 54, mouth 34, oro-pharynx 39, unspecified 5	4	Tooth brushing, mouth wash, missing teeth, denture, gum bleeding
			Control	Patients admitted for acute illnesses to major hospitals in the same areas	148	103/45	60 (30-83)	<6 52, 6-8 53, ≥9 43	40	129	–		
Schildt	1998	Sweden	OSCC	Cancer registry	410	276/134	70.5	–	–	–	Lip, tongue, floor of mouth, gingiva, tonsil/mesopharynx	6	Denture
			Control	National population registry	410	276/134	–	–	–	–	–		
Velly	1998	Canada	HNC	Hospital	717	626/91	–	Illiterate 222, grade school 433, high school 50, college 12	–	–	Mouth, pharynx, larynx	5	Denture
			Control	The same general hospital or catchment area	1434	1252/182	–	Illiterate 396, grade school 886, high school 109, college 42	–	–	–		
Bundgaard	1995	Denmark	Oral cancer	Hospital	161	97/64	–	–	135	77	Retromolar area, buccal mucosa, floor of mouth, hard palate, upper alveolus , lower alveolus, tongue	6	Dental visit
			Control	Select randomly from the Danish Central Population Register	400	250/150	–	–	260	89	–		
Maier	1993	Germany	HNSCC	Hospital	100	–	30-75	–	–	–	Oral cavity, oropharynx, hypopharynx, larynx	4	Tooth brushing, dental visit
			Control	Without carcinoma of the head and neck or oral disease at the same hospital	214	–	30-75	–	–	–	–		
Winn	1991	USA	HNC	Population-based cancer registries	866	573/293	63	–	–	–	Oral cavity, pharynx	6	Mouth wash, denture, gum bleeding, periodontal disease
			Control	Random digit dialling and files of the Health Care Financing Administration from the same geographic areas	1249	821/428		–	–	–	–		
Franco	1989	Brazil	Oral cancer	Hospital	232	201/31	–	Illiterate 66, grade school 141, high school 21, college 4	222	–	Tongue, gum , floor of the mouth, unspecified	5	Dental visit
			Control	Patients in the same hospital, without eoplastic disease or mental disorder	464	402/62	–	Illiterate 112, grade school 303, high school 36, college 12	365	–	–		
Kabat	1989	USA	HNC	In the American Health Foundation's case control study of tobacco-related cancers	125	F	–	–	92	87	Tongue, floor of mouth/gums/ gingiva, buccal mucosa , palate , tonsil, retromolar trigone, pharynx	4	Tooth brushing, mouth wash, denture, gum bleeding

(*continued*)

Table 1. Continued.

Author	Year	Country	Group	Source	Sample size (N)	Sex (Male /Female)	Age (years)	Education	Tobacco	Alcohol	Cancer site	QS	Outcomes
			Control	Patients with cancers, benign neoplasms, and nonneoplastic conditions thought not to be related to smoking or drinking	107		–	–	64	65	–		
Wynder	1983	USA	HNC	–	571	141/157	–	–	508	–	Oral cavity, pharynx	4	Mouth wash
			Control	A large set of hospitalised controls without a tobacco-related disease	6047	4131/1916	30-79	<9 867, 9-12 2825, 13-15 953, ≥16 1373	3661	–	–		
Browne	1977	UK	OSCC	Cancer Registry	75	46/29	28-90	–	36	52	Buccal mueosa, upper alveolus and hard palate , lower alveolus, floor of mouth, pillar of fauces/soft palate, unspecified or multiple	5	Tooth brushing, denture
			Control	Select randomly from the records of a general medical practice serving	150	92/58	37-91	–	68	89	–		
Zhao	2021	China	SCC of lower gingiva	Hospital	143	105/38	–	–	90	53	Lower gingiva	6	OS, DFS
Qian	2020	China	Receive periodontal treatment	Hospital	1385	663/722	≥75	≤6 529, 7-12 471, >12 125	180	253	Oral cavity	6	OS
Chang	2019	China	HNC	Hospital	740	693/47	55.19 ± 10.61	≦elementary school 204, junior high 217, high/technical school 242, ≥college 77	631	–	Oral cavity, oropharynx, hypopharynx, larynx	6	OS
Friemel	2016	Germany	HNSCC	Multicenter	276	230/46	58.0 ± 9.0	<10 189, ≥10 87	–	–	Oral cavity, tonsils, pharynx, larynx	6	OS, DFS

QS: quality assessment; SCC: squamous cell carcinoma; OSCC: oral squamous cell carcinoma; HNC: head and neck cancer; HNSCC: head and neck squamous cell carcinoma; UADT: upper-aerodigestive tract; OS: overall survival, DFS: disease free survival; UADT: upper aerodigestive tract, - represents not available.

tooth brushing ≥2 times a day was associated with a lower risk with HNC in Europe (OR: 0.531, 95%CI: 0.436 to 0.648, $p < 0.001$), North America (OR: 0.631, 95%CI: 0.544 to 0.731, $p < 0.001$), Latin America (OR: 0.640, 95%CI: 0.549 to 0.747, $p < 0.001$), Asia (OR: 0.498, 95%CI: 0.385 to 0.645, $p < 0.001$), and China (OR: 0.666, 95%CI: 0.469 to 0.946, $p = 0.023$). Based on tobacco smoking and alcohol drinking, regardless of whether ever smoked or drank alcohol, tooth brushing was linked to HNC (Table 2, Figure 2(a)).

Mouth wash (yes vs no)

A total of 11 studies assessed mouth wash on HNC. Mouth wash use was not associated with the risk of HNC ($I^2 = 74.1$, OR: 1.027, 95%CI: 0.853 to 1.236, $p = 0.779$). Regarding the regional subgroup analysis, mouth wash use increased the risk of HNC in Latin America (OR: 1.363, 95%CI: 1.107 to 1.679, $p = 0.004$). However, concerning tobacco smoking, no matter never tobacco smoking (OR: 1.470, 95%CI: 1.054 to 2.050, $p = 0.023$), ever tobacco smoking (OR: 1.461, 95%CI: 1.190 to 1.793, $p < 0.001$), mouth wash use was associated with a higher risk of HNC.

Dental floss (yes vs no)

Totally, 3 articles assessed the association between dental floss use and HNC. The result demonstrated that flossing was associated with a lower risk of HNC than non-flossing ($I^2 = 65.2\%$, OR: 0.472, 95%CI: 0.313 to 0.713, $p < 0.001$). Similar results were observed in Europe(OR: 0.271, 95%CI: 0.144 to 0.507, $p < 0.001$), Asia (OR: 0.483, 95%CI: 0.362 to 0.645, $p < 0.001$), China (OR: 0.483, 95%CI: 0.362, to 0.645, $p < 0.001$) (Table 2, Figure 2(b)).

Missing teeth (>5 vs ≤5)

Missing teeth and the risk of HNC were assessed in 12 studies. The more missing teeth, the higher the risk of HNC (OR: 1.891, 95%CI: 1.536 to 2.327, $p < 0.001$). The results were not changed in the subgroup analysis (Table 2, Figure 2(c)).

Wear denture (yes vs no)

A total of 19 studies investigated the association between wear denture and HNC. There was no difference in HNC risk between wearing dentures and not wearing dentures ($I^2 = 86.3\%$, OR: 1.040, 95%CI: 0.848 to 1.274, 0.707). Nevertheless, a higher risk of HNC with denture wearing was noted in North America (OR: 1.343, 95%CI: 1.154 to 1.563, $p < 0.001$) and China (OR: 1.449, 95%CI: 1.262 to 1.663, $p < 0.001$).

Caries (≥3 vs <3)

The influence of caries on HNC risk was assessed in 2 studies. The result indicated that caries ≥3 decreased the risk of HNC (OR: 0.554, 95%CI: 0.388 to 0.792, $p = 0.001$). In North America, a similar result was observed (OR: 0.516, 95%CI: 0.346 to 0.771, $p = 0.001$) (Table 2, Figure 2(d)).

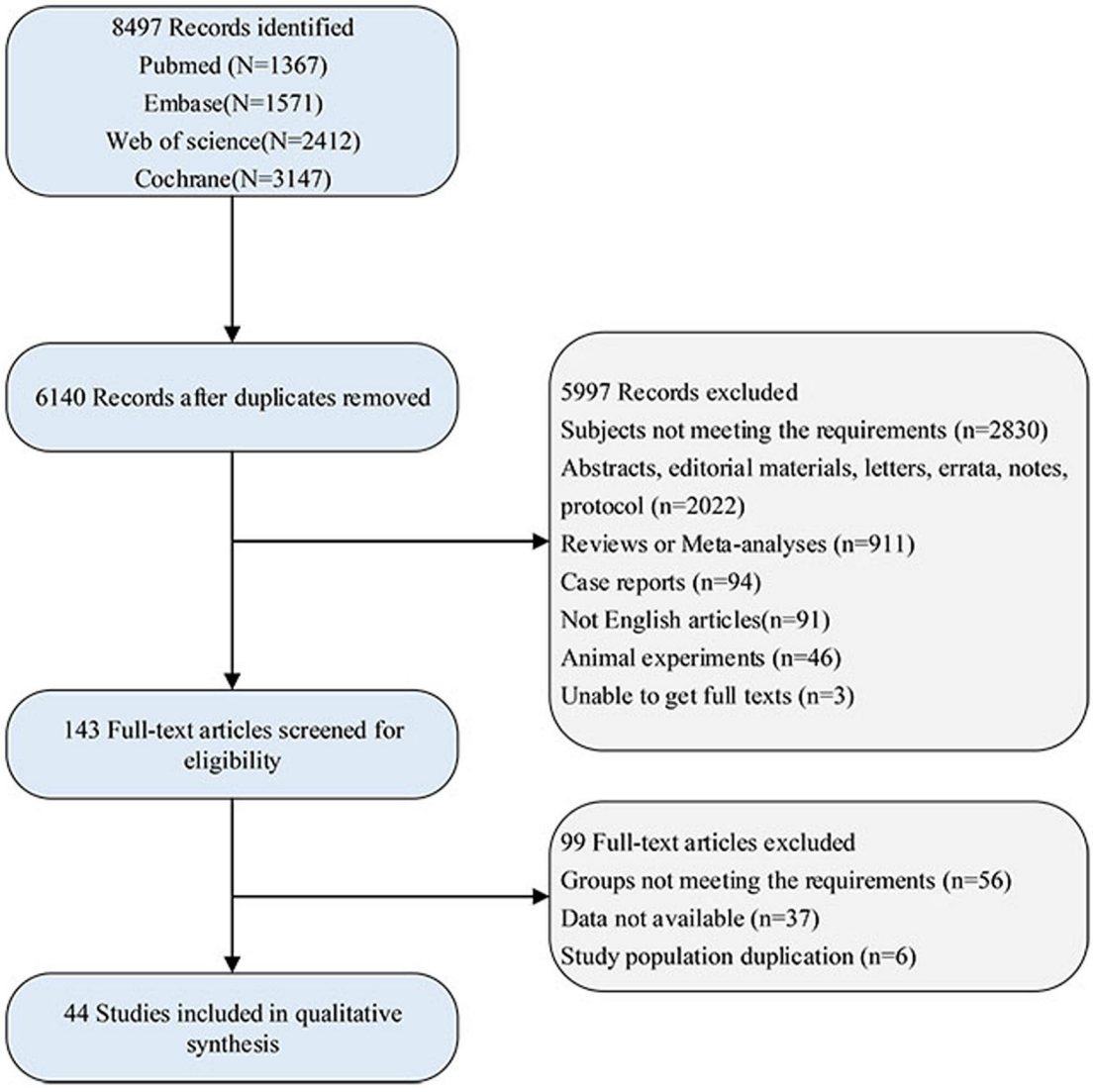

Figure 1. Literature search strategy of included studies.

Dental visit (≥1 vs <1)

Totally, 15 studies evaluated the dental visit and the risk of HNC. The result demonstrated that the more frequent dental visits, the lower the risk of HNC (I^2=88.1%, OR: 0.445, 95%CI: 0.332 to 0.598, $p < 0.001$). Regarding the regional subgroup analysis, frequent dental visit was associated with a reduced risk of HNC in North America (OR: 0.447, 95%CI: 0.328 to 0.611, $p < 0.001$), Latin America (OR: 0.611, 95%CI: 0.479 to 0.778, $p < 0.001$), Asia(OR: 0.319, 95%CI: 0.177 to 0.574, $p < 0.001$), China(OR: 0.260, 95%CI: 0.157 to 0.430, $p < 0.001$). Dental visits ≥1 time a year reduced the risk of HNC among those who smoked tobacco (OR: 0.612, 95%CI: 0.493 to 0.760, $p < 0.001$) (Table 2, Figure 2(e)).

Gum bleeding (yes vs no)

Gum bleeding was evaluated in 11 articles. The result showed that gum bleeding was associated with HNC risk (I^2=86.3, OR: 1.631, 95%CI: 1.220 to 2.181, $p = 0.001$). Nevertheless, this link was also observed in Europe (OR: 1.640, 95%CI: 1.104 to 2.436, $p = 0.014$), Asia (OR: 2.391, 95%CI: 1.575 to 3.630, $p < 0.001$), and China (OR: 1.595, 95%CI: 1.149 to 2.213, $p = 0.005$) (Table 2, Figure 2(f)).

Periodontal disease (yes vs no)

A total of 5 studies were used to assess periodontal disease and the risk of HNC. The result demonstrated that periodontal disease increased the risk of HNC (OR: 2.201, 95%CI: 1.195 to 4.053, $p = 0.011$). Similar results were observed in North America (OR: 1.313, 95%CI: 1.109 to 1.554, $p = 0.002$) and Asia (OR:7.217, 95%CI: 4.917 to 10.592, $p < 0.001$). The periodontal disease was also associated with an increased risk of HNC among those who ever smoked (OR: 1.326, 95%CI: 1.001 to 1.756, $p = 0.049$) (Table 2, Figure 2(g)).

Oral hygiene and oral cavity cancer

Tooth brushing (≥2 vs <2/d)

A total of 11 articles were included to assess tooth brushing and oral cavity cancer. The random-effect model analysis result showed that brushing teeth more often lowers your

Table 2. Overall and sensitivity analysis results.

Outcomes	Indicators	OR (95%CI)	*p* Value	I^2
HNC	Tooth brush (≥2 vs <2/d)			
	Overall	0.534 (0.461, 0.618)	<0.001	73.8
	Sensitivity analysis	0.534 (0.461, 0.618)		
	Publication bias	Z = 2.10	0.036	
	Region			
	Europe	0.531 (0.436, 0.648)	<0.001	0.0
	North America	0.631 (0.544, 0.731)	<0.001	0.0
	Latin America	0.640 (0.549, 0.747)	<0.001	NA
	Asia	0.498 (0.385, 0.645)	<0.001	85.5
	China	0.666 (0.469, 0.946)	0.023	88.8
	Tobacco smoking			
	Never	0.655 (0.532, 0.807)	<0.001	9.5
	Ever	0.641 (0.576, 0.714)	<0.001	0.0
	Alcohol drinking			
	Never	0.576 (0.473, 0.702)	<0.001	49.3
	Ever	0.655 (0.579, 0.742)	<0.001	0.0
	Mouth wash (yes vs no)			
	Overall	1.027 (0.853, 1.236)	0.779	74.1
	Sensitivity analysis	1.027 (0.853, 1.236)		
	Publication bias	Z = 0.93	0.350	
	Region			
	Europe	1.026 (0.899, 1.170)	0.704	0.0
	North America	1.135 (0.926, 1.392)	0.223	63.8
	Latin America	1.363 (1.107, 1.679)	0.004	NA
	Asia	0.324 (0.075, 1.401)	0.131	83.0
	China	0.877 (0.508, 1.512)	0.636	NA
	Tobacco smoking			
	Never	1.470 (1.054, 2.050)	0.023	0.0
	Ever	1.461 (1.190, 1.793)	<0.001	0.0
	Alcohol drinking			
	Never	0.821 (0.296, 2.275)	0.705	87.5
	Ever	1.353 (1.119, 1.638)	0.002	0.0
	Dental floss (yes vs no)			
	Overall	0.472 (0.313, 0.713)	<0.001	65.2
	Sensitivity analysis	0.472 (0.313, 0.713)		
	Region			
	Europe	0.271 (0.144, 0.507)	<0.001	NA
	Asia	0.483 (0.362, 0.645)	<0.001	NA
	China	0.483 (0.362, 0.645)	<0.001	NA
	Missing teeth (>5 vs ≤5)			
	Overall	1.891 (1.536, 2.327)	<0.001	79.6
	Sensitivity analysis	1.891 (1.536, 2.327)		
	Publication bias	Z = 0.00	1.000	
	Region			
	Europe	1.609 (1.296, 1.997)	<0.001	0.0
	North America	1.917 (1.648, 2.230)	<0.001	NA
	Latin America	1.672 (1.386, 2.017)	<0.001	0.0
	Asia	2.091 (1.380, 3.167)	<0.001	87.1
	China	1.647 (1.090, 2.490)	0.018	72.7
	Tobacco smoking			
	Never	1.703 (1.345, 2.157)	<0.001	56.1
	Ever	1.597 (1.344, 1.897)	<0.001	0.0
	Alcohol drinking			
	Never	1.708 (1.340, 2.177)	<0.001	65.9
	Ever	1.780 (1.500, 2.113)	<0.001	0.0
	Wear denture (yes vs no)			
	Overall	1.040 (0.848, 1.274)	0.707	86.3
	Sensitivity analysis	1.040 (0.848, 1.274)		
	Publication bias	Z = 0.21	0.834	
	Region			
	Europe	0.899 (0.580, 1.393)	0.635	82.5
	North America	1.343 (1.154, 1.563)	<0.001	0.0
	Latin America	0.974 (0.743, 1.276)	0.847	71.1
	Asia	0.867 (0.453, 1.657)	0.665	93.2
	China	1.449 (1.262, 1.663)	<0.001	35.2
	Tobacco smoking			
	Never	1.764 (1.338, 2.326)	<0.001	0.0
	Ever	1.677 (1.025, 2.743)	0.039	18.1
	Caries (≥3 vs <3)			
	Overall	0.554 (0.388, 0.792)	0.001	0.0
	Sensitivity analysis	0.554 (0.388, 0.792)		
	Region			
	North America	0.516 (0.346, 0.771)	0.001	NA
	Latin America	0.724 (0.329, 1.594)	0.423	NA

(*continued*)

Table 2. Continued.

Outcomes	Indicators	OR (95%CI)	*p* Value	I^2
	Dental visit (≥1 vs <1)			
	Overall	0.445 (0.332, 0.598)	<0.001	88.1
	Sensitivity analysis	0.445 (0.332, 0.598)		
	Publication bias	Z = 0.59	0.553	
	Region			
	Europe	0.577 (0.140, 2.387)	0.448	92.6
	North America	0.447 (0.328, 0.611)	<0.001	81.6
	Latin America	0.611 (0.479, 0.778)	<0.001	0.0
	Asia	0.319 (0.177, 0.574)	<0.001	87.8
	China	0.260 (0.157, 0.430)	<0.001	80.6
	Tobacco smoking			
	Never	0.906 (0.473, 1.736)	0.766	75.7
	Ever	0.612 (0.493, 0.760)	<0.001	0.0
	Alcohol drinking			
	Never	0.535 (0.352, 0.814)	0.003	0.0
	Ever	0.710 (0.530, 0.953)	0.022	NA
	Gum bleeding (yes vs no)			
	Overall	1.631 (1.220, 2.181)	0.001	86.3
	Sensitivity analysis	1.631 (1.220, 2.181)		
	Publication bias	Z = 0.93	0.350	
	Region			
	Europe	1.640 (1.104, 2.436)	0.014	0.0
	North America	0.988 (0.815, 1.197)	0.903	0.0
	Latin America	1.149 (0.976, 1.352)	0.096	NA
	Asia	2.391 (1.575, 3.630)	<0.001	80.1
	China	1.595 (1.149, 2.213)	0.005	NA
	Tobacco smoking			
	Never	1.666 (0.871, 3.186)	0.123	42.7
	Ever	1.999 (0.719, 5.562)	0.184	93.3
	Periodontal disease (yes vs no)			
	Overall	2.201 (1.195, 4.053)	0.011	94.5
	Sensitivity analysis	2.201 (1.195, 4.053)		
	Region			
	North America	1.313 (1.109, 1.554)	0.002	11.9
	Asia	7.217 (4.917, 10.592)	<0.001	NA
	Tobacco smoking			
	Never	1.235 (0.783, 1.947)	0.364	NA
	Ever	1.459 (1.045, 2.038)	0.027	NA
	Alcohol drinking			
	Never	4.301 (1.405, 13.169)	0.011	84.4
	Ever	1.326 (1.001, 1.756)	0.049	NA
Oral cavity	Tooth brush (≥2 vs <2/d)			
	Overall	0.522 (0.408, 0.668)	<0.001	80.6
	Sensitivity analysis	0.522 (0.408, 0.668)		
	Publication bias	Z = 1.56	0.119	
	Region			
	Europe	0.490 (0.349, 0.688)	<0.001	0.0
	Latin America	0.716 (0.553, 0.927)	0.011	NA
	Asia	0.511 (0.363, 0.719)	<0.001	87.3
	China	0.703 (0.401, 1.235)	0.221	87.4
	Tobacco smoking			
	Never	0.575 (0.452, 0.732)	<0.001	0.0
	Ever	0.576 (0.418, 0.792)	0.001	0.0
	Alcohol drinking			
	Never	0.594 (0.463, 0.763)	<0.001	72.2
	Ever	0.592 (0.413, 0.848)	0.004	NA
	Mouth wash (yes vs no)			
	Overall	1.340 (1.052, 1.708)	0.018	44.9
	Sensitivity analysis	1.340 (1.052, 1.708)		
	Region			
	North America	1.529 (0.946, 2.470)	0.083	NA
	Latin America	1.494 (1.090, 2.047)	0.013	NA
	Asia	0.702 (0.368, 1.337)	0.282	32.6
	China	0.835 (0.419, 1.665)	0.609	NA
	Dental floss (yes vs no)			
	Overall	0.482 (0.306, 0.757)	0.002	64.7
	Sensitivity analysis	0.482 (0.306, 0.757)		
	Region			
	Europe	0.271 (0.144, 0.507)	<0.001	NA
	Asia	0.520 (0.349, 0.775)	0.001	NA
	China	0.520 (0.349, 0.775)	0.001	NA
	Missing teeth (>5 vs ≤5)			
	Overall	2.005 (1.301, 3.089)	0.002	89.2
	Sensitivity analysis	2.005 (1.301, 3.089)		

(*continued*)

Table 2. Continued.

Outcomes	Indicators	OR (95%CI)	*p* Value	I^2
	Region			
	Europe	1.193 (0.770, 1.848)	0.429	NA
	Latin America	1.349 (0.984, 1.847)	0.063	NA
	Asia	2.524 (1.592, 4.000)	<0.001	85.9
	China	2.051 (1.548, 2.718)	<0.001	NA
	Tobacco smoking			
	Never	2.061 (1.571, 2.704)	<0.001	0.0
	Ever	2.007 (1.103, 3.653)	0.023	NA
	Alcohol drinking			
	Never	2.051 (1.548, 2.718)	<0.001	NA
	Wear denture (yes vs no)			
	Overall	0.739 (0.530, 1.030)	0.074	87.9
	Sensitivity analysis	0.739 (0.530, 1.030)		
	Publication bias	Z = 0.00	1.000	
	Region			
	Europe	0.625 (0.325, 1.202)	0.159	83.3
	Latin America	0.971 (0.638, 1.475)	0.889	79.0
	Asia	0.386 (0.090, 1.660)	0.201	95.6
	China	1.367 (1.160, 1.612)	<0.001	NA
	Tobacco smoking			
	Never	0.708 (0.083, 6.034)	0.752	NA
	Ever	1.677 (1.025, 2.743)	0.039	18.1
	Caries (≥3 vs <3)			
	Overall	0.495 (0.288, 0.849)	0.011	NA
	Region			
	North America	0.495 (0.288, 0.849)	0.011	NA
	Dental visit (≥1 vs <1)			
	Overall	0.531 (0.367, 0.767)	0.001	76.1
	Sensitivity analysis	0.531 (0.367, 0.767)		
	Region			
	Europe	0.515 (0.352, 0.752)	0.001	NA
	North America	0.735 (0.488, 1.106)	0.14	NA
	Latin America	0.831 (0.572, 1.206)	0.33	0.0
	Asia	0.354 (0.153, 0.816)	0.015	88.1
	China	0.255 (0.067, 0.963)	0.044	89.8
	Tobacco smoking			
	Never	0.491 (0.298, 0.809)	0.005	NA
	Alcohol drinking			
	Never	0.491 (0.298, 0.809)	0.005	NA
	Gum bleeding (yes vs no)			
	Overall	2.295 (1.709, 3.081)	<0.001	72.2
	Sensitivity analysis	2.295 (1.709, 3.081)		
	Region			
	Europe	3.125 (0.723, 13.499)	0.127	NA
	Latin America	1.500 (1.149, 1.956)	0.003	NA
	Asia	2.470 (1.714, 3.561)	<0.001	72.1
	China	1.743 (1.214, 2.503)	0.003	NA
	Tobacco smoking			
	Never	2.624 (1.063, 6.478)	0.036	NA
	Ever	3.462 (2.109, 5.685)	<0.001	NA
	Periodontal disease (yes vs no)			
	Overall	1.929 (1.113, 3.342)	0.019	74.1
	Sensitivity analysis	1.929 (1.113, 3.342)		
	Region			
	North America	1.462 (0.993, 2.152)	0.055	NA
Oropharynx	Tooth brush (≥2 vs <2/d)			
	Overall	0.547 (0.308, 0.974)	0.041	NA
	Region			
	Asia	0.547 (0.308, 0.974)	0.041	NA
	Tobacco smoking			
	Never	1.041 (0.192, 5.656)	0.963	NA
	Ever	0.524 (0.269, 1.024)	0.059	NA
	Alcohol drinking			
	Never	0.938 (0.256, 3.430)	0.922	NA
	Ever	0.522 (0.269, 1.015)	0.055	NA
	Caries (≥3 vs <3)			
	Overall	0.396 (0.226, 0.693)	0.001	NA
	Region			
	North America	0.396 (0.226, 0.693)	0.001	NA
Pharynx	Tooth brush (≥2 vs <2/d)			
	Overall	0.506 (0.426, 0.600)	<0.001	49.6
	Sensitivity analysis	0.506 (0.426, 0.600)		
	Region			
	Europe	0.407 (0.257, 0.646)	<0.001	NA

(*continued*)

Table 2. Continued.

Outcomes	Indicators	OR (95%CI)	*p* Value	I^2
	Latin America	0.560 (0.459, 0.682)	<0.001	NA
	Asia	0.344 (0.204, 0.579)	<0.001	NA
	China	0.344 (0.204, 0.579)	<0.001	NA
	Mouth wash (yes vs no)			
	Overall	1.384 (0.966, 1.985)	0.077	51.7
	Sensitivity analysis	1.384 (0.966, 1.985)		
	Region			
	North America	1.345 (0.940, 1.925)	0.105	NA
	Latin America	1.653 (1.283, 2.129)	<0.001	NA
	Asia	0.487 (0.142, 1.669)	0.252	NA
	China	0.487 (0.142, 1.669)	0.252	NA
	Dental floss (yes vs no)			
	Overall	0.310 (0.157, 0.614)	0.001	NA
	Region			
	Asia	0.310 (0.157, 0.614)	0.001	NA
	China	0.310 (0.157, 0.614)	0.001	NA
	Missing teeth (>5 vs ≤5)			
	Overall	1.497 (1.201, 1.865)	<0.001	0.0
	Sensitivity analysis	1.497 (1.201, 1.865)		
	Region			
	Europe	1.539 (0.965, 2.454)	0.07	NA
	Latin America	1.485 (1.157, 1.905)	0.002	NA
	Wear denture (yes vs no)			
	Overall	3.493 (0.444, 27.469)	0.235	97.8
	Sensitivity analysis	3.493 (0.444, 27.469)		
	Region			
	Europe	0.944 (0.646, 1.380)	0.765	NA
	Latin America	17.876 (0.000, 2.0e + 07)	0.685	99
	Dental visit (≥1 vs <1)			
	Overall	0.461 (0.239, 0.887)	0.02	82.8
	Sensitivity analysis	0.461 (0.239, 0.887)		
	Region			
	North America	0.805 (0.581, 1.117)	0.195	NA
	Latin America	0.451 (0.311, 0.655)	<0.001	NA
	Asia	0.183 (0.071, 0.470)	<0.001	NA
	China	0.183 (0.071, 0.470)	<0.001	NA
	Gum bleeding (yes vs no)			
	Overall	1.214 (0.806, 1.829)	0.353	56.8
	Sensitivity analysis	1.214 (0.806, 1.829)		
	Region			
	Latin America	1.043 (0.842, 1.292)	0.699	NA
	Asia	1.619 (0.958, 2.734)	0.072	NA
	China	1.619 (0.958, 2.734)	0.072	NA
	Periodontal disease (yes vs no)			
	Overall	1.313 (0.965, 1.787)	0.083	NA
	Region			
	North America	1.313 (0.965, 1.787)	0.083	NA
Larynx	Tooth brush (≥2 vs <2/d)			
	Overall	0.713 (0.602, 0.844)	<0.001	0.0
	Sensitivity analysis	0.713 (0.602, 0.844)		
	Region			
	Europe	0.792 (0.574, 1.091)	0.154	NA
	Latin America	0.693 (0.565, 0.851)	<0.001	NA
	Asia	0.555 (0.256, 1.201)	0.135	NA
	China	0.555 (0.256, 1.201)	0.135	NA
	Mouth wash (yes vs no)			
	Overall	0.909 (0.699, 1.183)	0.479	0.0
	Sensitivity analysis	0.909 (0.699, 1.183)		
	Region			
	North America	1.057 (0.576, 1.941)	0.858	NA
	Latin America	0.880 (0.651, 1.188)	0.403	NA
	Asia	0.835 (0.187, 3.731)	0.814	NA
	China	0.835 (0.187, 3.731)	0.814	NA
	Dental floss (yes vs no)			
	Overall	0.355 (0.132, 0.955)	0.04	NA
	Region			
	Asia	0.355 (0.132, 0.955)	0.04	NA
	China	0.355 (0.132, 0.955)	0.04	NA
	Missing teeth (>5 vs ≤5)			
	Overall	2.221 (1.757, 2.809)	<0.001	0.0
	Sensitivity analysis	2.221 (1.757, 2.809)		
	Region			
	Europe	1.892 (1.281, 2.795)	0.001	NA
	Latin America	2.419 (1.802, 3.247)	<0.001	NA

(*continued*)

Table 2. Continued.

Outcomes	Indicators	OR (95%CI)	*p* Value	I^2
	Wear denture (yes vs no)			
	Overall	0.974 (0.838, 1.132)	0.732	0.0
	Sensitivity analysis	0.974 (0.838, 1.132)		
	Region			
	Europe	0.922 (0.680, 1.252)	0.605	NA
	Latin America	0.991 (0.834, 1.178)	0.92	0.0
	Caries (≥3 vs <3)			
	Overall	0.800 (0.442, 1.448)	0.461	NA
	Region			
	North America	0.800 (0.442, 1.448)	0.461	NA
	Dental visit (≥1 vs <1)			
	Overall	0.541 (0.408, 0.717)	<0.001	32.7
	Sensitivity analysis	0.541 (0.408, 0.717)		
	Region			
	North America	0.411 (0.243, 0.695)	0.001	NA
	Latin America	0.636 (0.452, 0.895)	0.009	NA
	Asia	0.285 (0.084, 0.965)	0.044	NA
	China	0.285 (0.084, 0.965)	0.044	NA
	Gum bleeding (yes vs no)			
	Overall	1.089 (0.883, 1.345)	0.426	0.0
	Sensitivity analysis	1.089 (0.883, 1.345)		
	Region			
	Latin America	1.118 (0.900, 1.390)	0.314	NA
	Asia	0.746 (0.317, 1.752)	0.501	NA
	China	0.746 (0.317, 1.752)	0.501	NA
	Periodontal disease (yes vs no)			
	Overall	1.616 (0.954, 2.738)	0.074	NA
	Region			
	North America	1.616 (0.954, 2.738)		
Hypopharynx	Missing teeth (>5 vs ≤5)			
	Overall	2.002 (1.375, 2.913)	<0.001	NA
	Region			
	Asia	2.002 (1.375, 2.913)	<0.001	NA
	China	2.002 (1.375, 2.913)	<0.001	NA

HNC: head and neck cancer; OR: odds ratios; CI: confidence interval;.

risk of oral cavity cancer (I^2=80.6%, OR: 0.522, 95%CI: 0.408 to 0.668, $p < 0.001$). Tooth brushing ≥2 decreased the risk of oral cavity cancer in Europe (OR: 0.490, 95%CI: 0.349 to 0.688, $p < 0.001$), Latin America(OR: 0.716, 95%CI: 0.553 to 0.927, $p = 0.011$), and Asia (OR: 0.511, 95%CI: 0.363 to 0.719, $p < 0.001$), while there was no significantly difference in China (OR: 0.703, 95%CI: 0.401 to 1.235, $p = 0.221$) (Table 2, Figure 3(a)).

Mouth wash (yes vs no)

Four studies assessed the impact of mouth wash on oral cavity cancer. A higher risk of oral cavity cancer was found in mouth wash use (OR: 1.340, 95%CI: 1.052 to 1.708, $p = 0.018$). Regarding the regional subgroup analysis, mouth wash use was also related to an increased risk of oral cavity cancer in Latin America (OR: 1.494, 95%CI: 1.090 to 2.047, $p = 0.013$) (Table 2, Figure 3(b)).

Dental floss (yes vs no)

Totally, 3 articles assessed the association between dental floss use and oral cavity cancer. Our result demonstrated that dental floss was beneficial to the reduced risk of oral cavity cancer (OR: 0.482, 95%CI: 0.306 to 0.757, $p = 0.002$) (Table 2, Figure 3(c)).

Missing teeth (>5 vs ≤5)

Missing teeth were evaluated in 6 articles. The random-effect analysis result indicated that more missing teeth were associated with a higher risk of oral cavity cancer (OR: 2.005, 95%CI: 1.301 to 3.089, $p = 0.002$). Even though the number of missing teeth was not associated with oral cavity cancer risk in Europe (OR: 1.193, 95%CI: 0.770 to 1.848, $p = 0.429$) and Latin America (OR: 1.349, 95%CI: 0.984, 1.847, $p = 0.063$) more missing teeth were associated with higher oral cavity cancer risk in Asia (OR: 2.524, 95%CI: 1.592 to 4.000,$p < 0.001$) and China (OR: 2.051, 95%CI: 1.548 to 2.718, $p < 0.001$). Moreover, people who never drank alcohol but had missing teeth >5 were also at higher risk of developing oral cavity cancer (OR: 2.051, 95%CI: 1.548 to 2.718, $p < 0.001$) (Table 2, Figure 3(d)).

Wear denture (yes vs no)

A total of 11 studies investigated the association between wear denture and oral cavity cancer. We found that wearing dentures was not statistically associated with oral cavity cancer risk (OR: 0.739, 95%CI: 0.530 to 1.030, $p = 0.074$). However, subgroup analysis showed that wearing dentures in China (OR: 1.367, 95%CI: 1.160 to 1.612, $p < 0.001$) and ever smoking (OR: 1.677, 95%CI: 1.025 to 2.743, $p = 0.039$ increased the risk of oral cavity cancer.

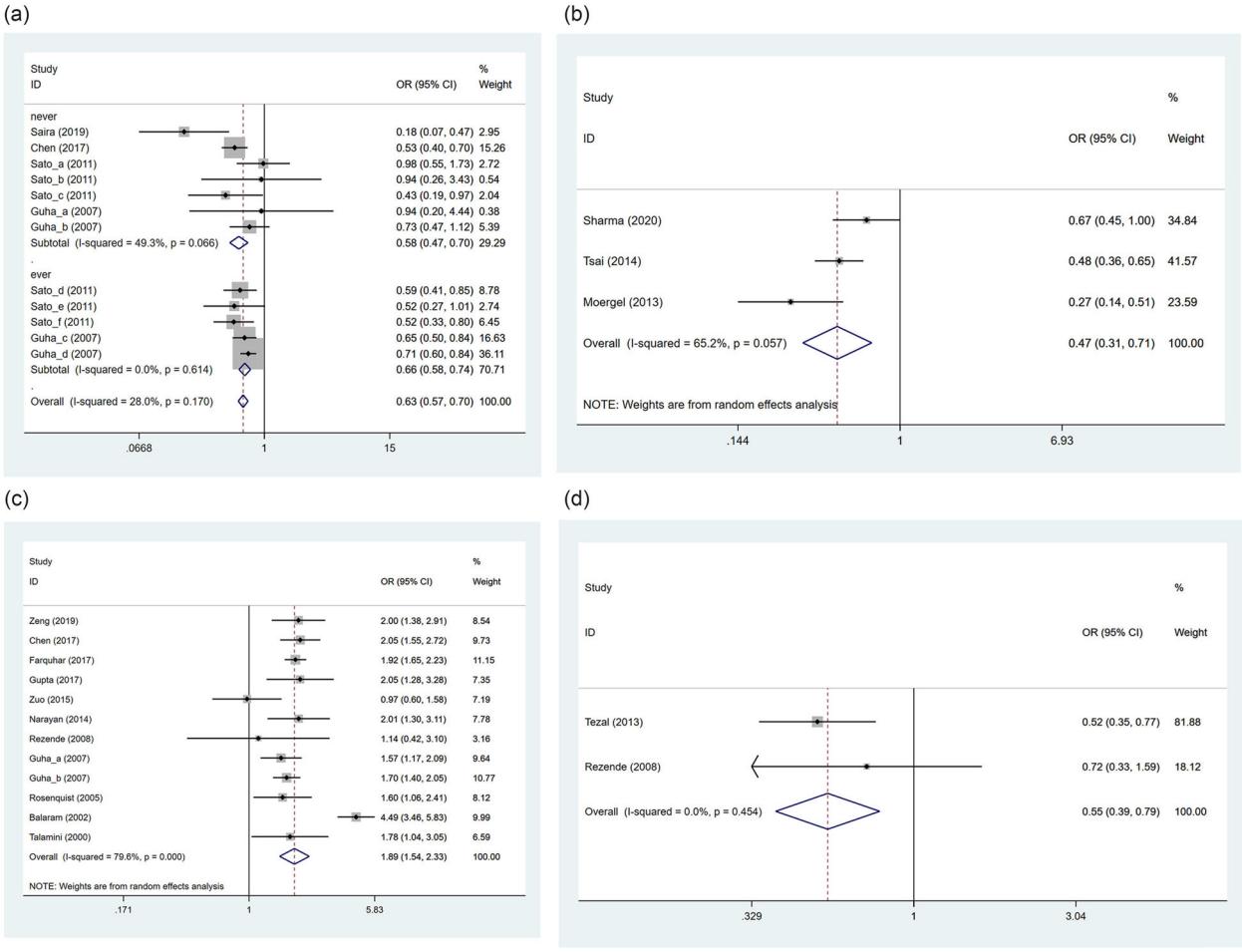

Figure 2. Oral hygiene and the risk of HNC; (a) tooth brush (≥2 vs <2/d); (b) dental floss (yes vs no); (c) missing teeth (>5 vs ≤5); (d) caries; (e) dental visit (≥1 vs <1); (f) gum bleeding (yes vs no); (g) periodontal disease (yes vs no).

Caries (≥3 vs <3)

The influence of caries on oral cavity cancer risk was assessed in 1 study in North America. Dental caries ≥3 had a lower risk of oral cavity cancer than dental caries <3 (OR: 0.495, 95%CI: 0.288 to 0.849, $p = 0.011$) (Table 2, Figure 3(e)).

Dental visit (≥1 vs <1)

Totally, 7 studies evaluated the dental visit and the risk of oral cavity cancer. The result showed that frequent visits to the dentist reduced the risk of oral cavity cancer (OR: 0.531, 95%CI: 0.367 to 0.767, $p = 0.001$). The Frequent dental visits were also associated with lower risk of oral cavity cancer in Europe (OR: 0.515, 95%CI: 0.352 to 0.752, $p = 0.001$), Asia(OR: 0.354, 95%CI: 0.153 to 0.816, $p = 0.015$), and China (OR: 0.255, 95%CI: 0.067 to 0.963, $p = 0.044$) (Table 2, Figure 3(f)).

Gum bleeding (yes vs no)

The association between gum bleeding and the risk of oral cavity cancer was evaluated in 6 articles. Random effect model results showed that gum bleeding was associated with an increased risk of oral cavity cancer (OR: 2.295, 95%CI: 1.709 to 3.081, $p < 0.001$). Concerning the regional subgroup analysis, although gum bleeding was not associated with oral cavity cancer risk in Europe, gum bleeding increased oral cavity cancer risk in Latin America (OR: 1.500, 95%CI: 1.149 to 1.956, $p = 0.003$), Asia (OR: 2.470, 95%CI: 1.714 to 3.561, $p < 0.001$) and China (OR: 1.743, 95%CI: 1.214 to 2.503, $p = 0.003$) (Table 2, Figure 3(g)).

Periodontal disease (yes vs no)

A total of 2 studies were used to assess periodontal disease and the risk of oral cavity cancer. Periodontal disease was found to be associated with oral cavity cancer risk (OR: 1.929, 95%CI: 1.113 to 3.342, $p = 0.019$) (Table 2, Figure 3(h)).

Oral hygiene and oropharynx cancer

Tooth brushing (≥2 vs <2/d)

A study based in China demonstrated that tooth brushing ≥2 per day decreased the risk of oropharynx cancer (OR: 0.547, 95%CI: 0.308 to 0.974, $p = 0.041$) (Table 2, Figure 4(a)).

Caries (≥3 vs <3)

A study conducted in North America demonstrated that more caries were significantly associated with a lower risk of

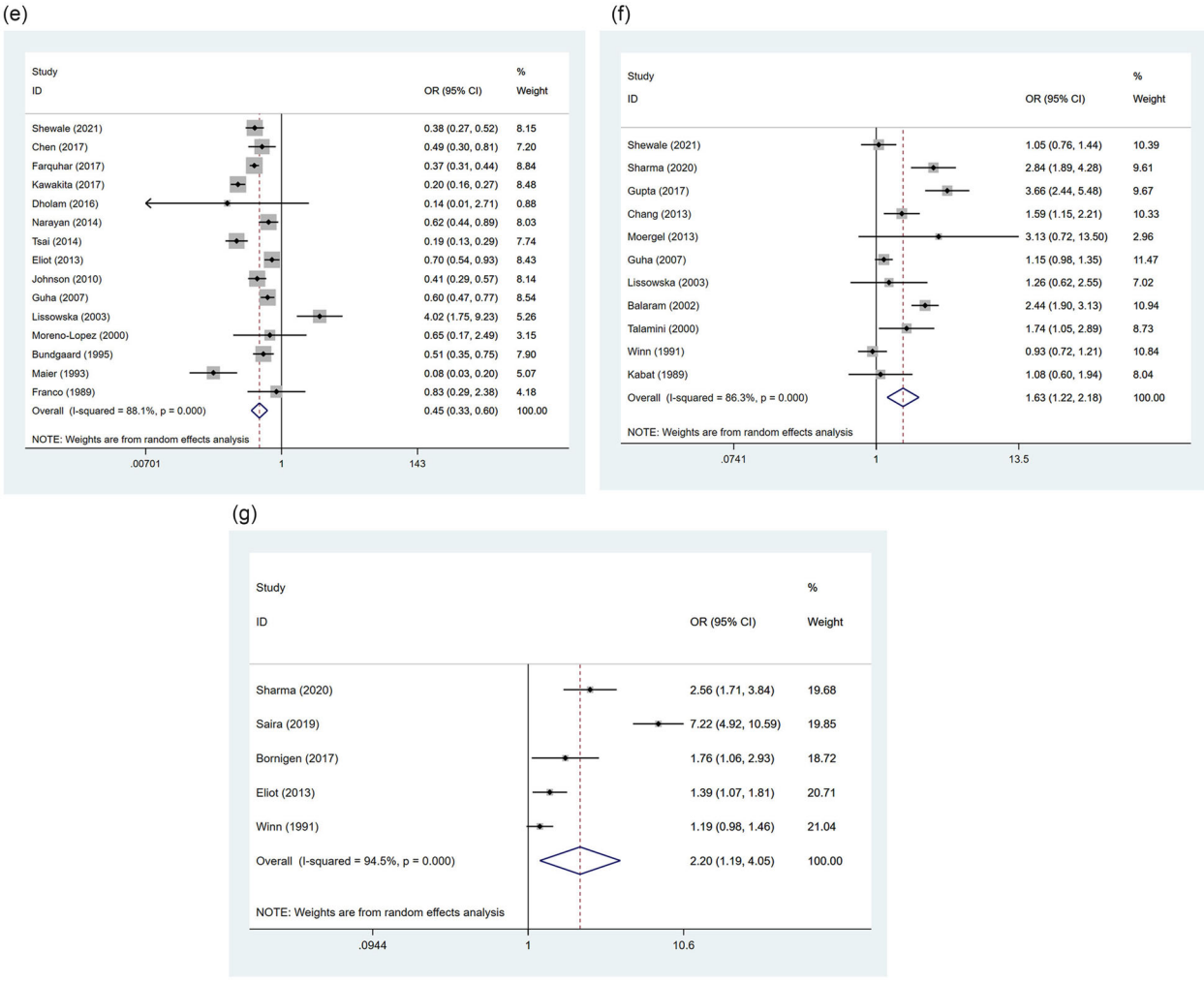

Figure 2. Continued.

oropharynx cancer (OR: 0.396, 95%CI: 0.226 to 0.693, $p = 0.001$) (Table 2, Figure 4(b)).

Oral hygiene and pharynx cancer

Tooth brushing (≥2 vs <2/d)

The impact of tooth brushing on the risk of pharynx cancer was evaluated in 3 studies. The result showed that brushing more than twice a day reduced the risk of pharynx cancer (OR: 0.506, 95%CI: 0.426 to 0.600, $p < 0.001$). Regional subgroup analysis also demonstrated that tooth brushing ≥2 per day was associated with a reduced risk of pharynx cancer in Europe, Latin America, Asia, China (Table 2, Figure 5(a)).

Mouth wash (yes vs no)

Three studies were used to investigate mouth wash use and pharynx cancer risk. We found that mouth wash use was not associated with pharynx cancer risk (OR: 1.384, 95%CI: 0.966 to 1.985, $p = 0.077$). However, a study conducted in Latin America reported that mouth wash use increased the risk of pharynx cancer (1.653 (OR: 1.653, 95%CI: 1.283 to 2.129, $p < 0.001$).

Dental floss (yes vs no)

A study conducted in China reported that dental floss use was related to a lower risk of pharynx cancer (OR: 0.310, 95%CI: 0.157 to 0.614, $p = 0.001$) (Table 2, Figure 4(b)).

Missing teeth (>5 vs ≤5)

Missing teeth and the risk of pharynx cancer were assessed in 2 studies. A higher risk of pharynx cancer was noted with missing teeth >5 (OR: 1.497, 95%CI: 1.201 to 1.865, $p < 0.001$). A similar relationship was also observed in Latin America (OR: 1.485, 95%CI: 1.157 to 1.905, $p = 0.002$) (Table 2, Figure 5(c)).

Wear denture (yes vs no)

A total of 3 studies assessed denture wearing on the risk of pharynx cancer. The results showed that wearing dentures

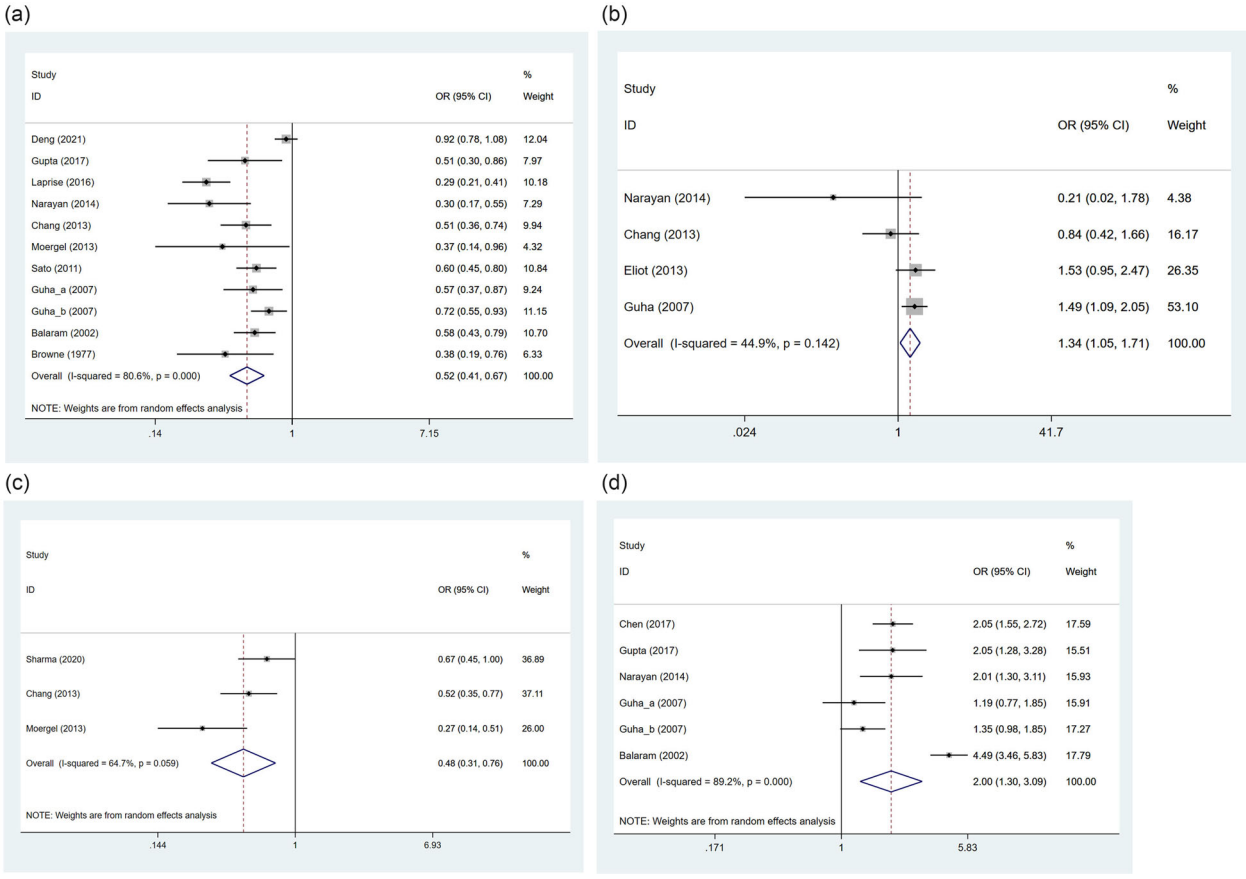

Figure 3. Oral hygiene and the risk of oral cavity cancer; (a) tooth brush (≥2 vs <2/d); (b) mouth wash (yes vs no); (c) dental floss (yes vs no); (d) missing teeth (>5 vs ≤5); (e) caries; (f) dental visit (≥1 vs <1); (g) gum bleeding (yes vs no); (h) periodontal disease (yes vs no).

was not statistically related to pharynx cancer risk (OR: 3.493, 95%CI: 0.444 to 27.469, $p = 0.235$).

Dental visit (≥1 vs <1)

Three studies assessed the dental visit. The random-effect model result showed that dental visit ≥1 a year reduced the risk of pharynx cancer (OR: 0.461, 95%CI: 0.239 to 0.887, $p = 0.02$). The dental visits ≥1 a year was also found to be associated with a decreased risk of pharynx cancer in Latin America (OR: 0.451, 95%CI: 0.311 to 0.655, $p < 0.001$), in Asia (China) (OR: 0.183, 95%CI: 0.071 to 0.470, $p < 0.001$) (Table 2, Figure 5(d)).

Gum bleeding (yes vs no)

Totally 2 studies evaluated the gum bleeding on the risk of pharynx cancer. Gum bleeding was not found to be associated with the risk of pharynx cancer (OR: 1.214, 95%CI: 0.806 to1.829, $p = 0.353$).

Oral hygiene and larynx cancer

Tooth brushing (≥2 vs <2/d)

The impact of tooth brushing on the risk of larynx cancer was assessed in 3 studies. Brush tooth ≥2 has been found to be associated with the reduction of larynx cancer risk (OR: 0.713, 95%CI: 0.602 to 0.844, $p < 0.001$). Subgroup analysis also indicated that tooth brushing time was associated with the risk of larynx cancer in Latin America (OR: 0.693, 95%CI: 0.565 to 0.851, $p < 0.001$) (Table 2, Figure 6(a)).

Mouth wash (yes vs no)

Mouth wash use and the risk of larynx cancer were evaluated in 3 studies. Mouth wash use was not associated with the larynx cancer risk (OR: 0.909, 95%CI: 0.699 to 1.183, $p = 0.479$).

Dental floss (yes vs no)

A study based on Chinese people showed that dental floss use decreased the risk of larynx cancer (OR: 0.355, 95%CI: 0.132 to 0.955, $p = 0.04$) (Table 2, Figure 6(b)).

Missing teeth (>5 vs ≤5)

Two studies were used to evaluate the association between missing teeth and the risk of larynx cancer. Missing teeth >5 was found to be associated with a higher risk of larynx cancer (OR: 2.221, 95%CI: 1.757 to 2.809, $p < 0.001$). Similar results were found in Europe (OR: 1.892, 95%CI: 1.281 to 2.795, $p = 0.001$) and Latin America (OR: 2.419, 95%CI: 1.802 to 3.247, $p < 0.001$) (Table 2, Figure 6(c)).

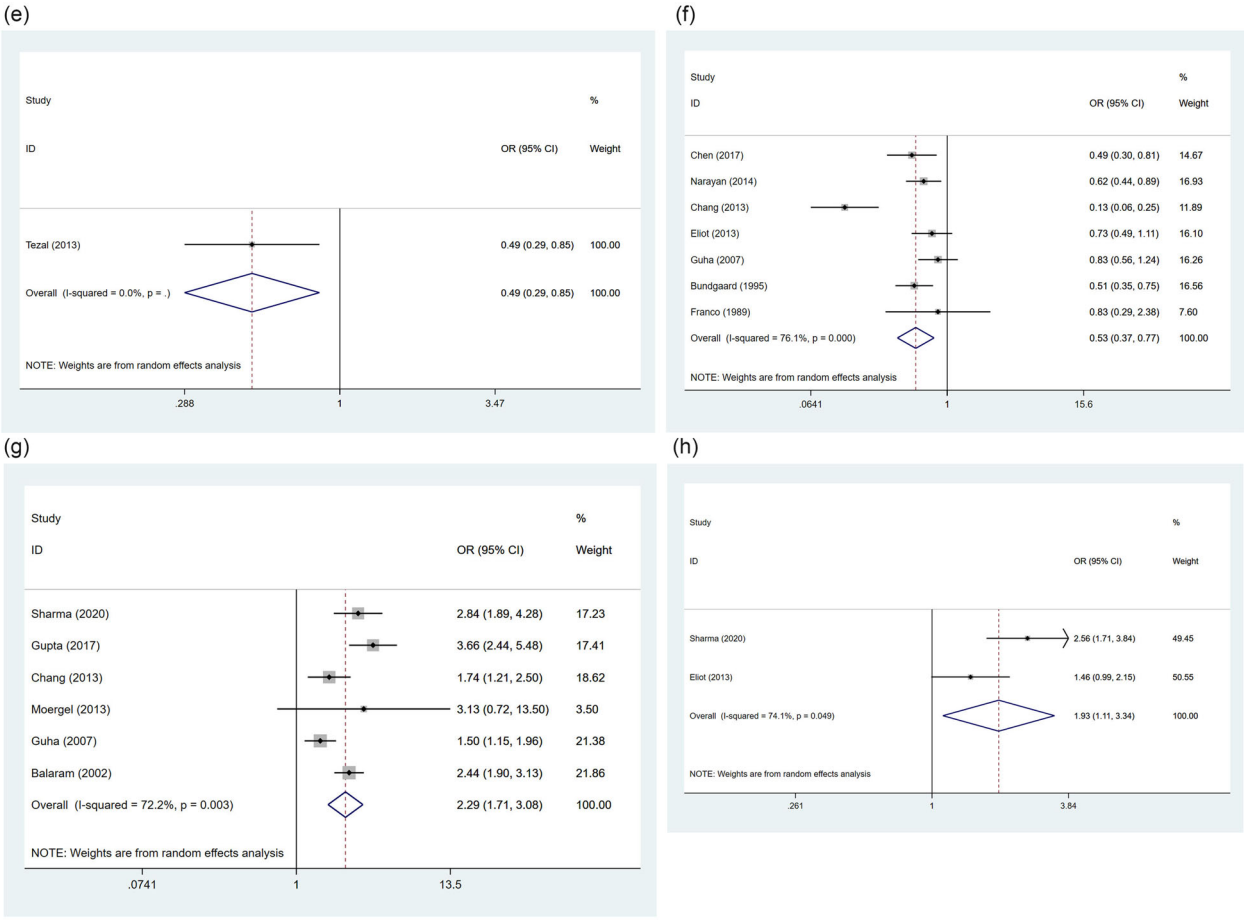

Figure 3. Continued.

Dental visit (≥1 vs <1)

Three studies assessed dental visits on the risk of larynx cancer. Dental visits ≥1 a year reduced the risk of larynx cancer (OR: 0.541, 95%CI: 0.408 to 0.717,$p < 0.001$) (Table 2, Figure 6(d)).

Oral hygiene and hypopharynx cancer

Missing teeth (>5 vs ≤5)

A study base in China demonstrated that missing teeth >5 increased the risk of hypopharynx cancer risk (OR: 2.002, 95%CI: 1.375 to 2.913, $p < 0.001$) (Table 2, Figure 7(a)).

Oral hygiene and HNC survival

OS

OH > 5 vs 0-5. Two studies were identified in the literature reporting OS in patients with HNC basedon their OH. The heterogeneity test showed I2 = 71.8%, so the random effect model was used for analysis. The result reported that there was no difference in the OS risk between the poor and good oral hygiene groups (HR: 1.419, 95%CI: 0.760 to 2.649, $p = 0.272$). In addition, studies by Qian et al. [50] demonstrated that the more severe periodontitis disease and a more missing tooth, the higher the risk of oral cancer death. The HR and 95%CI of mild, moderate, and severe periodontitis patients were 4.46 (0.94–21.06), 5.16 (1.14–23.39), and 6.65 (1.51–29.36), respectively, with the HR and 95%CI of a missing tooth, was 1.05(1.01–1.09) (Table 3).

DC > 2 vs 0-2. Two studies assessed DC > 2 vs 0-2. The fixed effect analysis results showed that the group with poor DC had a higher risk of OS than the group with better DC (I^2=24.9%, HR: 1.598, 95%CI: 1.108 to 2.304, $p = 0.012$) (Table 3).

DFs

OH > 5 vs 0-5. A total of 2 articles were included, and the random-effect model was used for analysis. There was no statistical significance after all studies were combined (I^2=67.9%, HR: 1.366, 95%CI: 0.977 to 1.910, $p = 0.068$) (Table 3).

DC > 2 vs 0-2. Two studies were included to assess DFS. The risk of DFS was higher in the poor DC group than in the good DC group (I^2=13.9%, HR: 1.755, 95%CI: 1.176 to 2.619, $p = 0.006$) (Table 3).

Publication bias and sensitivity analysis

Sensitivity analysis was conducted to assess the reliability of the findings of this study. Sensitivity analysis showed that our results are reliable. Begg's funnel plots were used to

Figure 4. Oral hygiene and the risk of oropharynx cancer; (a) tooth brush (≥2 vs <2/d); (b) caries (≥3 vs <3).

estimate the potential publication bias. The results showed that there was a publication bias in tooth brushing ≥2 (Table 2).

Discussion

In this systematic review and meta-analysis exploring the impact of oral hygiene on HNC and its sub-sites, we found that oral hygiene was associated with HNC. Tooth brushing ≥2 a day, dental floss use, denture wearing, caries ≥3, and dental visit ≥1 reduced the risk of oral cavity cancer while mouth wash use, missing teeth >5, gum bleeding, and periodontal disease increased the risk of oral cavity cancer. For oropharynx cancer, tooth brushing ≥2 and caries ≥3 was associated with reduced risk of it. Tooth brushing ≥2 and dental visits ≥1 decreased the risk of pharynx cancer risk and larynx cancer risk, however, missing teeth >5 increased both of them. Based on our subgroup analysis, dental visit ≥1 time a year reduced the risk of HNC among those who smoked tobacco. The periodontal disease was also associated with an increased risk of HNC among those who ever smoked.

Previous researches have indicated that there is a positive relationship between poor oral hygiene and HNC [8,51]. Poor oral hygiene may interfere with oral microbiome homeostasis and induce chronic inflammation in the oral environment (periodontitis). Inflammatory cytokines or chemokines produced during this process can promote cell proliferation, oncogene activation, and tumour angiogenesis [8,53]. These microorganisms are in a microbiological imbalance (dysregulation) that can produce carcinogens that promote the carcinogenic effects of other carcinogens (e.g. nitrosamines) or metabolise alcohol into genotoxic substances (e.g. acetaldehyde), leading to DNA damage [54].

A higher frequency of tooth brushing that gives a reduction in the risk of oral cavity cancer was observed in this study, which was consistent with several epidemiological studies [17,55,56]. Increasing the frequency of brushing can effectively remove plaque and buildup and reduce the number and type of oral pathogens, thus preventing or delaying the carcinogenic process [56]. The role of dental hygienists in

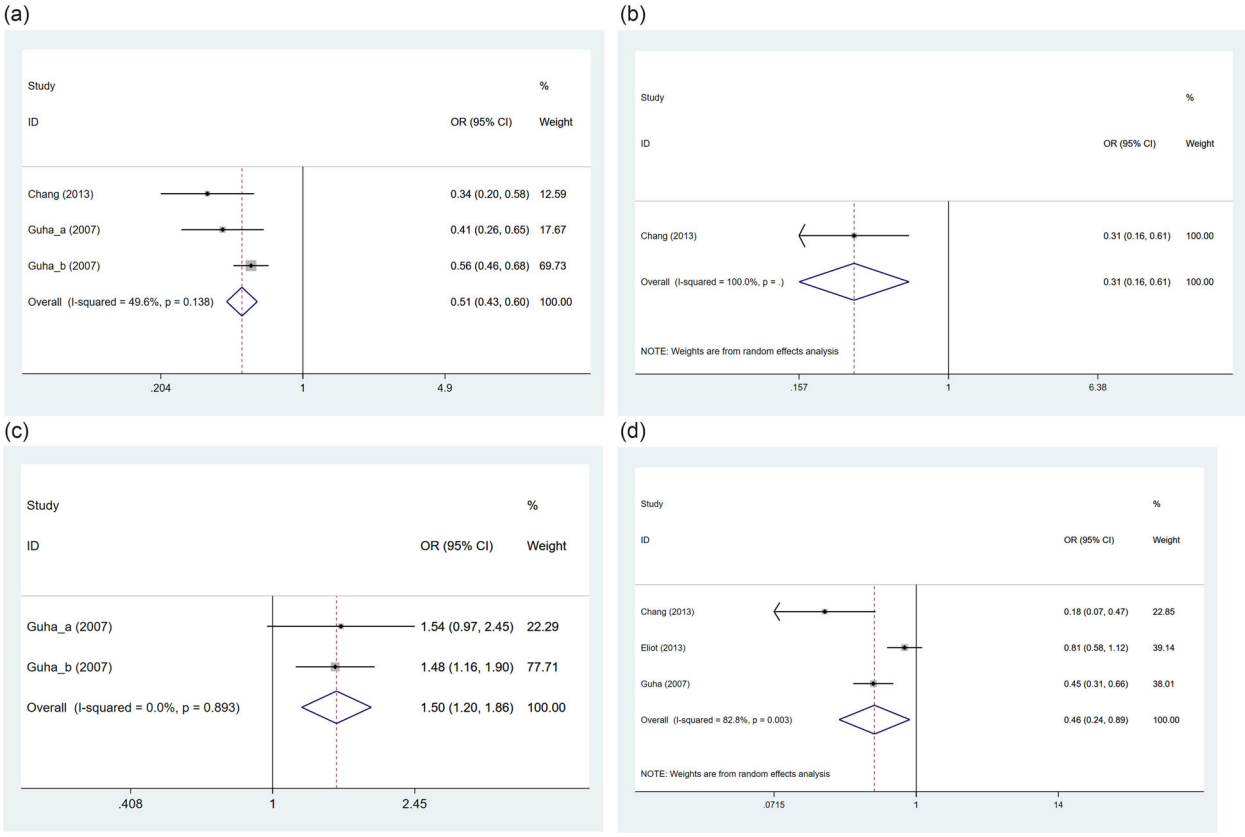

Figure 5. Oral hygiene and the risk of pharynx cancer; (a) tooth brush (≥2 vs <2/d); (b) dental floss (yes vs no); (c) missing teeth (>5 vs ≤5); (d) dental visit (≥1 vs <1).

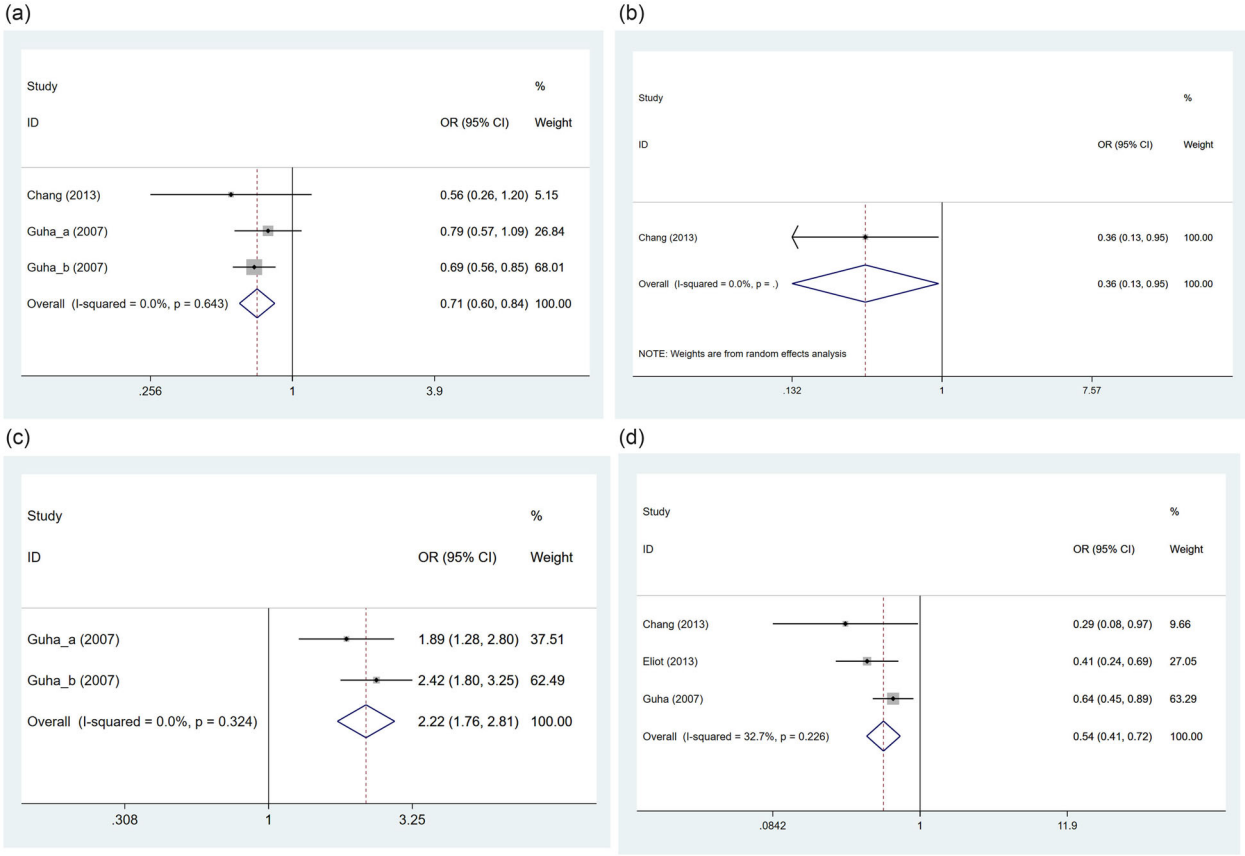

Figure 6. Oral hygiene and the risk of larynx cancer; (a) tooth brush (≥2 vs <2/d); (b) dental floss (yes vs no); (c) missing teeth (>5 vs ≤5); (d) dental visit (≥1 vs <1).

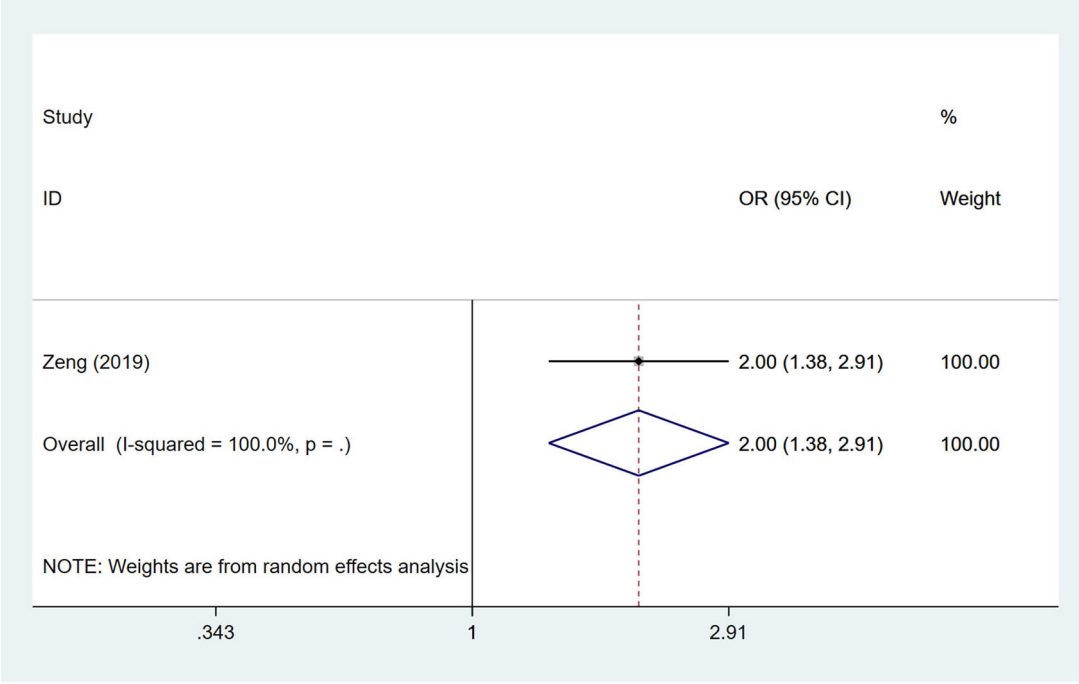

Figure 7. Oral hygiene and the risk of hypopharynx cancer; (a) missing teeth (>5 vs ≤5).

Table 3. Oral hygiene and HNC survival.

Outcomes	Indicators	HR (95%CI)	*p* Value	I^2
OS	OH > 5 vs 0-5			
	Overall	1.419 (0.760, 2.649)	0.272	71.8
	Sensitivity analysis	1.419 (0.760, 2.649)		
	DC > 2 vs 0-2			
	Overall	1.598 (1.108, 2.304)	0.012	24.9
	Sensitivity analysis	1.598 (1.108, 2.304)		
DFS	OH > 5 vs 0-5			
	Overall	1.366 (0.977, 1.910)	0.068	67.9
	Sensitivity analysis	1.366 (0.977, 1.910)		
	DC > 2 vs 0-2			
	Overall	1.755 (1.176, 2.619)	0.006	13.9
	Sensitivity analysis	1.755 (1.176, 2.619)		

HNC: head and neck cancer; HR: hazard ratio; CI: confidence interval; OS: overall survival; OH: oral health; DC: dental care.

the early detection of oral cancer and the management of precancerous lesions has also been emphasised [57]. The decreased frequency of dental visits has been linked to an increased risk of oral cancer in previous studies, which were similar to our results [22,58]. Consistent with our study, Sharma et al. reported the presence of gum bleeding and periodontal pathologies were significant risk factors for the occurrence of oral cancer [12]. Additionally, the current results also demonstrate that missing teeth could result in an increased risk of oral cancer. It is biologically plausible that missing teeth reflects poor oral health maintenance (irregular tooth brushing and dental visits), mechanical trauma, inflammation (secondary to diabetes, nutritional deficits), infection (secondary to periodontitis or gingivitis), and exposures such as nitrosamines, tobacco use, and alcohol which also result in tooth loss [59]. Missing teeth may be causally related to dentures and inflammation, resulting in gingiva trauma in addition to receding gums, jawbone weakening, and teeth collapsing [60]. The use of dental floss showed a positive trend with HNC risk [25]. We found an interesting finding that mouth wash use was associated with a higher risk of oral cavity cancer. Some authors have stated that oral cancer is increased or contributed to by the use of alcohol-containing mouth rinses [26]. Guha et al. [27] described that daily mouth wash use may be an independent cause of HNC. In daily life, good oral hygiene should be encouraged, increasing the frequency of brushing, flossing, and regular visits to the dentist, and reducing the use of alcohol-based mouth washes to reduce the risk of oral cancer.

Oral hygiene is related to oropharynx, pharynx, and larynx cancers in addition to oral cancer. Sato et al. found that brushing twice or more was associated with a reduction of upper aerodigestive tract cancer risk, including oropharynx cancer [29]. Consistent with our study, a study by Chang et al. [25] demonstrated that a positive association was observed between pharynx cancer risk and larynx cancer risk and no regular dental visits, brushing teeth <2 times/day, frequent gum bleeding. Therefore, individuals with poor oral hygiene, in addition to the prevention of oral cavity cancer, should also be vigilant against oropharyngeal cancer, pharyngeal cancer, and larynx cancer.

Our analysis showed that the positive association between poor oral hygiene and HNC was also among those who consumed alcohol and tobacco. In our subgroup analysis, dental visits ≥1 time a year reduced the risk of HNC among those who smoked tobacco, the periodontal disease was associated with an increased risk of HNC among those who ever smoked. Chang et al. reported that combined regular dental visits, tooth brushing, and use of dental floss and mouthwash, showed a positive trend with HNC risk, particularly

among alcohol drinkers and cigarette smokers [25]. A study by Sato et al. reported that the reduced risk of HNC associated with brushing teeth 2 or more times daily was especially significant among heavy smokers and drinkers [29]. Similarly, Chang et al. showed that the reduced risk of HNC associated with routine dental visits was more prominent among ever smokers and ever drinkers [25]. For smokers and drinkers, routine dental visits may even lessen the negative effects of smoking and alcohol on oral health because dental providers can evaluate oral health, check for early signs of oral and pharyngeal cancers, clean their teeth, and counsel them about oral hygiene behaviours such as brushing and flossing [61]. Although it is important to promote abstinence from or reduction of alcohol drinking to decrease the occurrence of HNC, improving oral hygiene practices may provide additional benefits among participants who consumed alcohol and tobacco.

A study has shown that regular dental visits lead to earlier detection of HNC and lower stage at diagnosis, which are crucial components of HNC prognosis [62]. Chang et al. reported that a lack of regular dental visits and overall poor oral hygiene was associated with worse survival of HNC patients [51]. Farquhar et al. reported that poor oral health directly affects cancer progression by altering tumour development and host immune response [16]. Poor oral hygiene may result in the overgrowth of pathogenic bacteria in the oral cavity. These pathogenic bacteria may induce inflammation [63]. Inflammation in turn may lead to poorer survival among HNC patients [64,65]. In addition to inducing inflammation, pathogenic bacteria may promote the progression of HNC through other mechanisms. Fusobacterium nucleatum a well-known species of periodontopathogenic bacteria, has been shown to promote cell proliferation and increase cellular migration and invasion [66] and thus has a potential to promote the progression of HNC.

This study has several limitations. First, the sub sites analysis might have suffered from the lack of statistical power due to the smaller sample size for each sub site. In addition to the lack of statistical power, smaller sample size in the stratified analyses may increase the probability of chance findings. Our analysis is limited by factors influencing oral hygiene indicators and behaviours that could not be adjusted for. Moreover, variables of oral hygiene are subjective in nature. It is possible that these subjective exposures may have been misclassified, depending on whether an interviewer or dentist was performing the examination to assess oral hygiene. We were not able to evaluate interviewer bias by stratifying the results of the oral hygiene assessment by whether the oral examinations were conducted by dentists versus nondentists. In addition, the different dosages of smoking and drinking may affect the risk of HNC. Generally, the more smoking and drinking, the higher the risk of cancer. However, most of the included studies did not mention dosage, so it could not be divided into subgroups.

Conclusions

Oral hygiene is associated with the risk of HNC. It is important to maintain oral hygiene in daily life to reduce the risk of cancer, including tooth brushing $\geq$2 a day, dental floss use, and dentist's visits $\geq$1 a year.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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