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REVIEW

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Factors associated with the development of second primary tumours in head and neck cancer patients

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Abstract

Introduction: The development of second primary tumours (SPTs) is one of the main causes of low survival in patients with head and neck cancer (HNC). The aim of this study was to review the evidence about factors associated with developing SPTs in patients with HNC.

Methods: An updated systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, and the search was performed in Pubmed and Scopus. Only original articles with a cohort or case–control design were included. Article quality was assessed with the Newcastle–Ottawa scale.

Results: Thirty-six and two case-control studies were included, with quality medium ($n = 5$) to high ($n = 33$). Tobacco showed a significant association with SPT development, with risks ranging from 1.41 (95%CI: 1.04–1.91) to 5.52 (95%CI: 2.91–10.49). Regarding alcohol, risks ranged from 1.46 (95%CI: 1.12–1.91) to 21.3 (95%CI: 2.9–156). Location of the index tumour in the hypopharynx/oropharynx, absence of human papillomavirus and presence of a premalignant lesion also increased the risk of SPTs. More controversy was found for sex, age and other clinical factors of the tumour.

Conclusion: Toxic lifestyle habits and clinical factors were associated with the risk of SPTs in HNC patients. These findings may improve individualised prevention strategies in its follow-up.

KEYWORDS
head and neck cancer, second primary tumours

1 | INTRODUCTION

Head and neck cancer (HNC) has a significant burden worldwide. This heterogeneous group of tumours (including lip, oral cavity, larynx and pharynx) occupies the eighth position in incidence worldwide, with 858,348 new cases in 2020, that is up to 4.6% of all cancers (Sung et al., 2021). Last trends indicate an expected incidence increase in most of the HNC tumours (Aupérin, 2020; Simard et al., 2014).

In the past decades, an improvement in the locoregional control of HNC has been made as result of early detection, better access to care and treatment advances (Chow, 2020; Hashim et al., 2019; Pulte & Brenner, 2010). However, the 5-year survival rate is still considered low, ranging from approximately 60% for laryngeal cancer to 25% for hypopharyngeal cancer (Gatta et al., 2015). One of the main obstacles for getting a long-term survival is the development of second primary tumours (SPTs) (Massa et al., 2017; Patrucco & Aramendi, 2016; Simpson et al., 2018).

Although with variations, epidemiological studies have demonstrated an excess risk of developing SPTs in HNC patients, with a standardised incidence ratio of up to 2.18 (95% CI: 2.14–2.22) with a minimum follow-up of 31 months (Adjei Boakye et al., 2018; Coca-Pelaz et al., 2020; Hoxhaj et al., 2020; Rubió-Casadevall et al., 2021). Increased risks of SPTs persist 10 years after diagnosis of the first primary (standardised incidence ratio: 1.59, 95% CI: 1.52–1.65) (Chuang et al., 2008). Thus, this risk does not decrease over time, remaining constant during a 30-year follow-up period (León et al., 2020).

Several original studies have explored the location of the index tumour, the clinical stage, the human papillomavirus (HPV) infection, alcohol consumption, smoking habit and treatment received as possible risk factors (Diaz et al., 2016; Ko et al., 2016; León et al., 2009; Patrucco & Aramendi, 2016). Among the recommendations to assist in the surveillance of HNC patients, a risk stratification has been indicated together with health promotion education for those patients who present risk factors for lifestyle-related complications (Nekhlyudov et al., 2017). In order to improve these follow-up approaches, it is necessary to establish the consistency of the evidence regarding risk factors for SPTs, with special emphasis on those modifiable and susceptible to intervention. However, to the best of our knowledge, only one systematic review published in 2014 has summarised this information, and it only evaluated alcohol as a risk factor (Druesne-Pecollo et al., 2014). Thus, the aim of this work was to carry out a systematic review of the latest available evidence on the factors related to the risk of developing SPTs in patients with HNC.

2 | MATERIAL AND METHODS

An updated systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-P 2015 guidelines (Page et al., 2021). The protocol was registered in the International prospective register of systematic reviews (PROSPERO) (registration number CRD42021226850).

2.1 | Data sources and search strategy and selection of articles

The scientific literature search was carried out in the Pubmed search engine and the Scopus (Elsevier) database. The following search terms were used: 'head and neck cancer', 'multiple primary cancer', 'multiple primary malignancies', 'multiple primary neoplasms', 'second primary cancer', 'second primary malignancies', 'second primary neoplasms' and 'risk factors'. The specific search strategies for the two databases mentioned above are available in supporting information Table S1.

We established the following selection criteria to identify the articles that could potentially be included in this review. Inclusion criteria were as follows: (1) original epidemiological studies evaluating the risk of development of a SPT in HNC patients, (2) studies that included participants aged 18 years or older, (3) cohort or case-control studies, and (4) studies published from January 2017 to June 2022. Exclusion criteria were as follows: (1) studies where HNC location was exclusively thyroid, salivary glands and/or maxillary sinuses; (2) studies that evaluated biomarkers as main risk factors; (3) systematic and narrative reviews, books, book chapters, clinical cases, clinical guides, editorials and editor's notes; and (4) studies written in a different language to English or Spanish.

After the elimination of duplicated articles, the selection of studies was performed in two phases: first, based on title and abstract reading; and second, by means of an exhaustive analysis of the full text. Also, a manual search in the reference lists of the relevant selected articles was performed to ensure that eligible articles were not missed out.

2.2 | Data extraction and quality assessment

The following information was collected for each study: (1) *basic information* (first author, country, year of publication); (2) *design features* (study design, follow-up); and (3) *results*: number of patients with primary tumour, number of cases with a SPT, location of the index tumour and of the SPT, risk factors evaluated, and risk estimations of the factors finally associated with the occurrence of SPTs.

To assess the quality of the included studies, the Newcastle–Ottawa Scale (NOS) was applied (Wells et al., 2020). The NOS contains nine items, classified in three dimensions: selection of study groups (four items), comparability between groups (two items), and determination of outcome or exposure for cohort and case-control studies, respectively (three items). The scale ranges from 0 to 9 points. Taking into account that there is no specific categorisation of studies based on the NOS score obtained, we considered scores of 0–3 as low, 4–6 as medium and 7–9 as high methodological quality.

The selection of the studies, data extraction and the evaluation of the quality of studies were conducted by two researchers independently. In case of discrepancy, this issue was discussed with a third investigator.

3 | RESULTS

A total of 3171 articles were identified of which 2258 articles were not eligible because they were not published in English or Spanish between 2017 and 2022. From a total of 829 articles obtained after

deleting duplicates, 703 were excluded based on title and abstract and 126 after reading the full text (Figure 1). Finally, 38 articles were included in this systematic review: 36 cohort studies (Adams et al., 2019; Adjei Boakye et al., 2019; Arie et al., 2021; Bertolini et al., 2021; Bosshart et al., 2021; Bugter et al., 2021; Bukovszky et al., 2022; Cadoni et al., 2017; Chow et al., 2019; Feng et al., 2017; Guo et al., 2021; Harada et al., 2017; Ho et al., 2022; Hosokawa et al., 2018; Inoue et al., 2021; Iwatsubo et al., 2019; León et al., 2020; Leoncini et al., 2018; Li et al., 2020; Lin et al., 2020; Liu et al., 2017; Martel et al., 2017; Milliet et al., 2021; Min et al., 2019; Nishimura et al., 2021; Overwater et al., 2022; Petersen et al., 2022; Piersiala et al., 2020; Sawaf et al., 2022; Stepan et al., 2022; Su et al., 2019; Su et al., 2020; Tseng et al., 2017; Wang et al., 2017; Wang et al., 2019; Zhang et al., 2019) and 2 case-control studies (Ni et al., 2018; Watanabe et al., 2017).

3.1 | Characteristics of the studies

Table 1 shows the main characteristics of the included studies. The study population was always defined as patients diagnosed with a primary cancer in the head and neck region, with the following locations for the index tumour: three studies on the oral cavity (Lin et al., 2020; Liu et al., 2017; Min et al., 2019), two in the nasopharynx (Chow et al., 2019; Zhang et al., 2019), two in the larynx (Adams et al., 2019; Piersiala et al., 2020), one in the hypopharynx (Ni et al., 2018), one in the oropharynx (Martel et al., 2017), one in the lip (Tseng et al., 2017), and the rest of them evaluated a combination of the above or different locations within the head and neck region. The most frequent SPT sites analysed were oesophagus ($n = 22$) and lung ($n = 19$). Four studies did not report the SPT location (Adjei Boakye et al., 2019; Cadoni et al., 2017; Liu et al., 2017; Tseng et al., 2017). Age and sex were variables evaluated in all studies, except in Harada et al. (2017), Sawaf et al. (2022), Stepan et al. (2022) and Bukovsky et al. (2022) (the last one evaluated sex but not age).

3.2 | Factors associated with the development of SPTs

Table 2 and Figure 2a show the factors significantly associated with the risk of developing SPTs in patients with HNC. Two of the studies

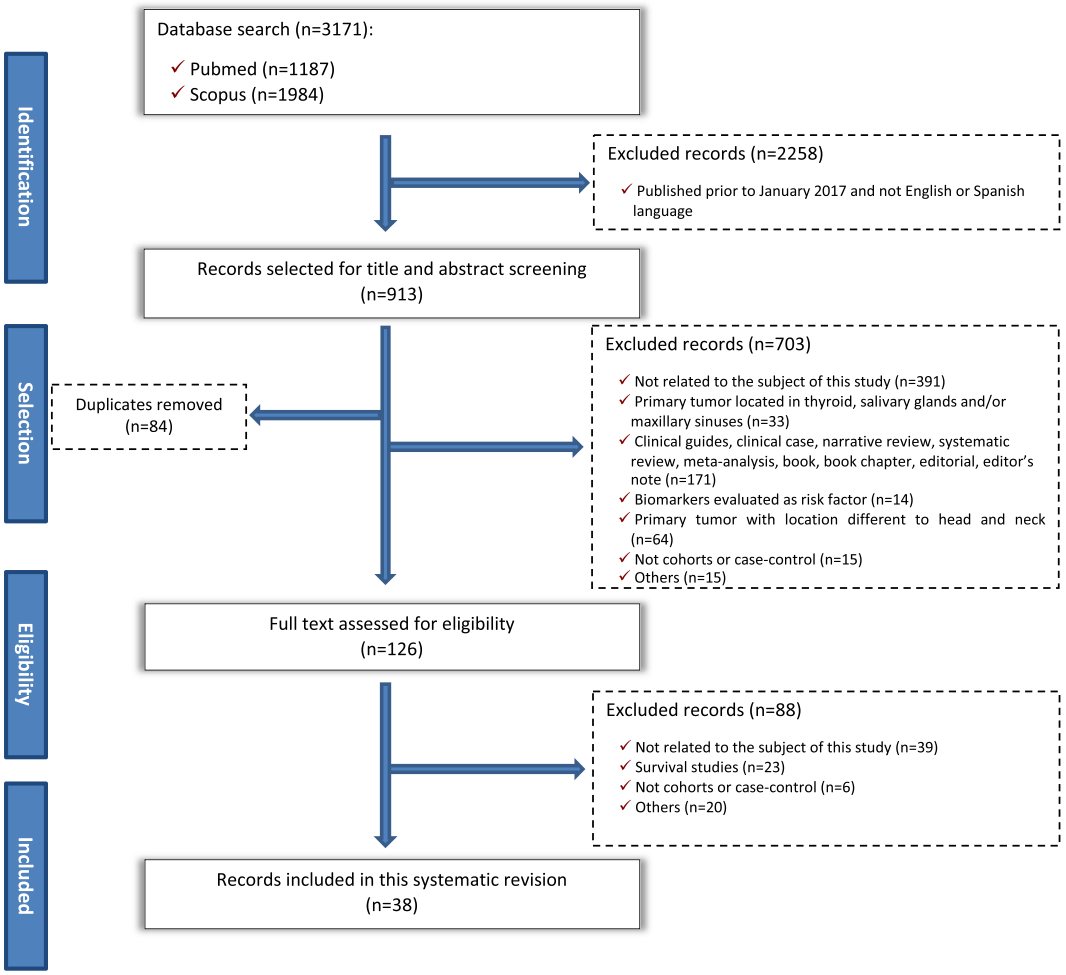

FIGURE 1 Flow chart of article selection

TABLE 1 Characteristics of the included studies

Reference/country	Study design/follow-up	n PT/n SPT	PT/SPT location	Risk factor assessed
Ho et al. (2022)/ Taiwan	Retrospective cohort/at least 5 years	11,882/337	Oral cancer (unspecified)/ oesophagus	Sex, age, endoscopic screening, primary tumour stage, other synchronous head and neck cancer, asymptotic symptoms, Charlson comorbidity index
Petersen et al. (2022)/Denmark	Retrospective cohort/ Median: 107 months Range: 23–220 months	936/219	Oral squamous cell carcinomas floor of mouth, oral tongue, gingiva, other sublocations/ oral cavity, pharyngeal area, laryngeal area, nose and sinuses, lower respiratory and intrathoracic organs, gastrointestinal organs, reproductive organs, skin, other location	Sex, age at diagnosis, primary tumour site, primary tumour stage, smoking habit, alcohol consumption, Charlson comorbidity index
Bukovszky et al. (2022)/Hungry	Retrospective cohort/ Mean: 68 months Range: 5–288 months	124/20	Oral cavity, oropharynx, hypopharynx, larynx/oral cavity, oropharynx, hypopharynx, larynx	Sex, primary tumour site, primary tumour stage, mutagen sensitivity, radiotherapy
Inoue et al. (2021)/Japan	Retrospective cohort/ Median: 54 months Range: 24–184 months	198/64	Hypopharynx, oropharynx, larynx/multiple head and neck tumours	Age, sex, alcohol consumption, smoking habit
Overwater et al. (2022)/ Netherlands	Retrospective cohort/ Median: 18 months Interquartile range: 1–53 months	1708/47	Larynx, oral cavity, oropharynx, hypopharynx/oesophagus	Age, sex, primary tumour site, smoking habit, alcohol consumption
Sawaf et al. (2022)/US	Retrospective cohort/ Mean: NS Range: Up to 36 months	164/8	Oropharynx, larynx, hypopharynx/oropharynx, hypopharynx, larynx, lungs, oesophagus	PET scan, comorbidities, oncologic history, HPV status
Stepan et al. (2022)/US	Retrospective cohort/ Median: 5 months Range: 0–238 months	412/20	Base of tongue, tonsil, palate, posterior pharyngeal wall/ oropharynx, oral cavity, hypopharynx, oesophagus, lung	Primary tumour site, adjuvant radiation treatment
Guo et al. (2021)/US	Retrospective cohort/ Median: NS Range: NS	2495/1275	Hypopharynx/oral cavity and pharynx, digestive system, respiratory system, bones and joints, soft tissue including heart, skin excluding basal and squamous, breast, female genital system, male genital system, urinary system, eye and orbit, brain and other nervous system, endocrine system, all lymphatic and haematopoietic diseases	Year of diagnosis, age, sex, race, marital status, histological grade, primary tumour stage, primary tumour size, surgery
Milliet et al. (2021)/France	Retrospective cohort/ Median: 40 months Range: NS	1291/138	Base of tongue, lateral pharyngeal wall, glosso-tonsillar sulcus, posterior pharyngeal wall, soft palate/ nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, oesophagus, lung, colorectal, prostate, bladder, breast, kidney, liver, ovary, lymphoma, skin	Sex, age, ASA score, KFI, drug consumption (alcohol and tobacco combined), primary tumour size and extension, lymph node invasion, primary tumour site, primary tumour HPV status

TABLE 1 (Continued)

Reference/country	Study design/follow-up	n PT/n SPT	PT/SPT location	Risk factor assessed
Bosshart et al. (2021)/Switzerland	Retrospective cohort/ Median: 7 months interquartile Range: 31–65 months	91/21	Tonsils, base of tongue, soft palate, pharyngeal wall/oral cavity, oropharynx, larynx, hypopharynx, oesophagus, lung	Sex, age, HPV status, smoking habit, alcohol abuse, primary tumour stage, chemo-radiotherapy
Bugter et al. (2021)/ The Netherlands	Retrospective cohort/ Median: 60 months Interquartile range: 24–83 months	1581/246	Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx/head and neck region (unspecified), lungs, oesophagus	Sex, age, smoking habit, alcohol consumption, comorbidity, anaemia, weight loss, primary tumour site, lymph node invasion, treatment
Arie et al. (2021)/Israel	Retrospective cohort/ Median: 38 months Interquartile range: 19–80 months	184/31	Nasopharynx + nose + paranasal sinuses, oral-cavity + oro-hypopharynx, larynx/ oral cavity + oro-hypopharynx, lung + bronchi, other	Sex, age, ethnicity, alcohol consumption, smoking habit, primary tumour site, treatment, primary tumour stage, lymph node invasion
Bertolini et al. (2021)/Italy	Retrospective cohort/ Mean: 3.5 person-years Range: Up to 60 months	1177/222	Oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx/head and neck, gastrointestinal, lung, gynecologic, breast, haematologic, prostate, bladder, multiple tumours	Age, sex, smoking habit, alcohol consumption, HPV status, primary tumour site, grading of primary cancer, primary tumour stage, lymph node invasion
Li et al. (2020)/China	Retrospective cohort/follow-up NS	11,345/6884	Lip and mouth, salivary glands, larynx and tongue/head and neck, and respiratory, urinary, genital system, digestive and haematologic systems	Age, sex, race, marriage, primary tumour site, histology, primary tumour stage, primary tumour size, primary tumour extent, lymph node invasion, chemotherapy
Lin et al. (2020)/China	Retrospective cohort/ Mean: 63 months Range: 2–132 months	900/60	Oral cavity/Oral cavity: Tongue, buccal, gingiva, oral floor, palate, retromolar	Age, sex, tumour size, chewing betel liquid, alcohol consumption, smoking habit, metastasis, oral precancerous lesion (submucous fibrosis), lymph node invasion, pathological low/medium differentiation, chewing betel liquid + smoking, chewing betel liquid + alcohol, chewing betel liquid + smoking + alcohol, chemoradiation
Nishimura et al. (2021)/Japan	Prospective cohort assembled to clinical trial/ Mean: NS Range: Up to 60 months	43/16	Larynx, oropharynx, hypopharynx/head and neck, lung, oesophagus, bladder, duodenum, colon, prostate, sarcoma, malignant lymphoma, myelodysplastic syndrome	Age, sex, smoking habit, alcohol consumption, primary tumour site, primary tumour stage, synchronous secondary cancer, HPV status, primary tumour shape, primary tumour length, submucosal invasion, pathological differentiation, lymph node invasion, vascular invasion, nerve invasion surgical margin
León et al. (2020)/Spain	Retrospective cohort/ Mean: NS Range: 12–360 months	4458/1203	Oral cavity, oropharynx, hypopharynx, larynx/head and neck, lung, oesophagus, bladder, gastrointestinal, lymphoma, others	Age, sex, drug consumption (alcohol and tobacco combined), primary tumour site

(Continues)

TABLE 1 (Continued)

Reference/country	Study design/follow-up	n PT/n SPT	PT/SPT location	Risk factor assessed
Piersiala et al. (2020)/USA	Retrospective cohort/ Mean: NS Range: At least 36 months	151/9	Larynx/lung	Sex, race, age, smoking history, primary tumour site, primary tumour stage, lymph node invasion
Su et al. (2020)/Taiwan	Retrospective cohort/ Mean: 23.2 months Range: 1–88.6 months	147/43	Nasopharynx, oral cavity, oropharynx, hypopharynx, larynx/oesophagus	Age, sex, primary tumour site, primary tumour stage
Adams et al. (2019)/UK	Retrospective cohort Mean: 45 months Range: 1–98 months	209/16	Larynx/lung	Age, sex, primary tumour site, primary tumour stage
Zhang et al. (2019)/China	Retrospective cohort Mean: 65.4 months Range: 36–154 months	6377/189	Nasopharynx/nasal, oral cavity, oropharynx, hypopharynx, larynx, external auditory canal, lung, sarcoma, leukaemia, multiple myeloma, lymphoma, thyroid, bladder, cervix, breast, skin, nerve, kidney, adrenal gland, oesophagus, stomach, colorectal, liver, pancreas, bile duct	Age, sex, primary tumour size, presence of lymph nodes, smoking habit, alcohol consumption, chemotherapy, re-irradiation, radiation dose
Wang et al. (2019)[a]/Taiwan	Prospective cohort up to 6 months	987/151	Head and neck/synchronous oesophagus	Age, sex, smoking habit, alcohol consumption, betel nut consumption, tumour stage, primary tumour site, tea consumption
Su et al. (2019)/Taiwan	Prospective cohort Mean: 86.8 months Range: NS	4,494/158	Oropharynx, floor of mouth, hard plate, tongue, gum, buccal mucosa, lip, unspecified/hypopharynx or oesophagus	Age, sex, betel quid chewing, smoking habit, alcohol consumption, primary tumour stage, primary tumour site
Min et al. (2019)/ Korea	Retrospective cohort Mean: 58.8 months Range: NS	15,261/1191	Oral cavity/oral cavity, oropharynx, hypopharynx, salivary gland, oesophagus, nose, nasal cavity, ear, larynx, lung, bronchus, bone, joints, soft tissue, and skin	Age, sex, year at diagnosis, histology group, follow-up period, primary tumour subsite, radiation therapy
Chow et al. (2019)/China	Retrospective cohort Median: 90 months Range: NS	759/51	Nasopharyx/lung, sarcoma of head and neck, tongue, liver, prostate, breast, colon-rectum, oropharynx, leukaemia, salivary gland, thyroid, oral cavity, non-melanoma skin	Age, sex, smoking habit, primary tumour stage, chemotherapy, re-irradiation
Iwatsubo et al. (2019)/Japan	Retrospective cohort Median: 41 months Range: 0–154 months	2111/1953	Oral cavity, oropharynx, hypopharynx, larynx/ oesophagus, lung, and others	Age, sex, histological type, primary tumour site
Adjei Boakye et al. (2019)/US	Retrospective cohort Median: 16.5 months Range: NS	113,259/13,900	Oral cavity, oropharynx, larynx, hypopharynx/NS	Age, sex, HPV status, race, marital status, county-level poverty, year of diagnosis, histologic grade, primary tumour stage, surgery, primary tumour site

TABLE 1 (Continued)

Reference/country	Study design/follow-up	n PT/n SPT	PT/SPT location	Risk factor assessed
Ni et al. (2018)[a]/China	Retrospective case-control Median: NS up to 6 months	160/43	Hypopharynx/synchronous oesophagus	Age, sex, family history of cancer, alcohol consumption, smoking habit, primary tumour site, gross tumour type, extent of local invasion, tumour classification, primary tumour size, presence of lymph nodes, distant metastasis
Leoncini et al. (2018)/(Italy, Japan, Brazil)	Retrospective cohort assembled to case-control study/ Median: 26 months Interquartile range: 11–59 months	3982/343	Oral cavity, oropharynx, hypopharynx, larynx/head and neck cancer, lung, others	Age, sex, body mass index, primary tumour site, primary tumour stage, ethnicity, education, smoking habit, alcohol consumption, comorbidities
Hosokawa et al. (2018)/Japan	Retrospective cohort/ Mean: 43.8 months Range: 1–144 months	994/106	Nasopharynx, oropharynx, hypopharynx, larynx, tongue, thyroid, cervical oesophagus, temporal bone, nasal-paranasal, salivary gland, trachea, unknown/head and neck, oesophagus, lung, stomach, colon, prostate, liver, bladder, breast, uterus, kidney, pancreas, gall, ureter	Age, sex, mucosal cancer, primary tumour site, primary tumour stage, smoking habit, alcohol consumption
Watanabe et al. (2017)[a]/Japan	Retrospective case-control/up to 6 months	183/36	Hypopharynx, oropharynx, larynx cancer/synchronous oesophagus	Age, sex, smoking habit, alcohol consumption
Wang et al. (2017)[a]/Taiwan	Retrospective cohort up to 6 months	815/124	Oral cavity, oropharynx, hypopharynx, larynx/synchronous oesophagus	Age, sex, alcohol consumption, betel nut chewing, smoking habit, tumour stage, histologic grade, primary tumour site
Tseng et al. (2017)/Taiwan	Retrospective cohort up to 180 months	133/33	Lip/NS	Age, sex, chronic exposure to sun, smoking habit, alcohol consumption, primary tumour site
Martel et al. (2017)/Spain	Prospective cohort Mean: 1.2 months SD: 51.6 months	412/124	Oropharynx/head and neck, lung, bladder, oesophagus and others.	Age, sex, primary tumour size, presence of lymph nodes, distant metastasis, primary tumour site, HPV, drug consumption (alcohol and tobacco combined)
Liu et al. (2017)/Taiwan	Retrospective cohort at least 36 months or until death	997/157	Oral cavity/NS	Age, sex, primary tumour stage, primary tumour differentiation grade, primary tumour site, alcohol consumption, smoking habit, premalignant lesion
Harada et al. (2017)/Japan	Retrospective cohort median: 59.88 months range: 2.64–145.2 years	150/61	Oral, pharynx, hypopharynx/upper gastrointestinal (oral, oropharynx, hypopharynx, oesophagus, stomach) and not upper gastrointestinal	Flush alcohol reaction, alcohol consumption, smoking habit, primary tumour site

(Continues)

TABLE 1 (Continued)

Reference/country	Study design/follow-up	n PT/n SPT	PT/SPT location	Risk factor assessed
Feng et al. (2017)/China	Retrospective cohort Median: 66 months Range: NS	1,818/188	Tongue, lower gingiva, buccal mucosa, floor of the mouth oropharynx, upper gingiva, hard palate/oral cavity, head and neck, lung, oesophagus, breast, uterus, liver. Colorectum, penis, stomach, leg, gallbladder, kidney, bladder	Age, sex, primary tumour site, primary tumour size, presence of lymph nodes, pathological grade, growth pattern, smoking habit, alcohol consumption, extracapsular spread, perineural invasion, vascular/lymphatic emboli, diffuse infiltration, multiple oral dysplastic lesion
Cadoni et al. (2017)/Italy	Retrospective cohort Median: 49 months Interquartile range: 19–86 months	448/169	Oral cavity, oropharynx, hypopharynx, larynx/NS	Age, sex, smoking habit, alcohol consumption, primary tumour stage

Note: *n*: sample size, PT: primary tumour, SPT: secondary primary tumour, NS: not specified, HPV: human papillomavirus, PET: positron emission tomography, ASA: American Society of Anesthesiologists, KFI: Kaplan-Feinstein index.
[a]Only assessed predictor factors to synchronous tumors.

(Piersiala et al., 2020; Sawaf et al., 2022) did not perform multivariable analysis and did not provide a risk estimator. Thus, only the *p* value was indicated in the table.

3.2.1 | Sociodemographic characteristics

Sex was found to be a risk factor for developing a SPT in seven articles, with six of them showing that men had a higher risk than women (Adjei Boakye et al., 2019; Ho et al., 2022; Hosokawa et al., 2018; León et al., 2020; Min et al., 2019; Zhang et al., 2019). Leoncini et al. (2018) found a higher risk in women for SPTs located in the region of head and neck [HR: 1.54 (95% CI: 1.01–2.35)] or lung [HR: 4.29 (95% CI: 2.24–8.23)] but not when the risk was evaluated combining these and other locations.

Ten studies found that age at diagnosis of index tumour was associated with SPT, showing a higher probability with increasing age (eight of them) (Adjei Boakye et al., 2019; Chow et al., 2019; Hosokawa et al., 2018; León et al., 2020; Li et al., 2020; Piersiala et al., 2020; Zhang et al., 2019). Conversely, Min et al. (Min et al., 2019), Iwatsubo et al. (2019) and Liu et al. (2017) found an increased risk in the younger patients, and Ho et al. (Ho et al., 2022) a reduced risk in patients older than 64 years.

Leoncini et al. (2018) was the only study evaluating the educational level, and they found that having high school studies or higher reduced in 41% (95% CI: 0.39–0.82) the likely of having a second malignancy. Adjei Boakye et al. (2019) found that living in a county with 10–19% of poverty reduced the risk of second neoplasm a 5% (95% CI: 0.91–0.98) compared to countries with <10% of poverty. In addition, they found that having a marital status different to married also decreased the risk. However, Guo et al. (2021) found that to be unmarried increased the risk of a SPT. Lastly, two studies evaluated race and found an increase risk among black people compared to white (Adjei Boakye et al., 2019; Li et al., 2020).

3.2.2 | Lifestyle habits

Ten out of 22 studies found that drinking alcohol increased the risk of developing SPTs (Bertolini et al., 2021; Bugter et al., 2021; Hosokawa et al., 2018; Inoue et al., 2021; Leoncini et al., 2018; Ni et al., 2018; Overwater et al., 2022; Su et al., 2019; Wang et al., 2017; Wang et al., 2019), whereas 12 of those studies did not find any association. The categories to define alcohol consumption varied among studies, but overall, a dose response was observed, with risks ranging from 1.006 (95% CI: 1.004–1.009) to 8.12 (95% CI: 4.15–15.92) for the increase of units per week or for highest category compared to never or non-heavy drinkers. Of note, most of the studies that found an association between alcohol and the risk of SPTs reported the oesophagus as the main location of the SPT (Bugter et al., 2021; Hosokawa et al., 2018; Ni et al., 2018; Overwater et al., 2022; Su et al., 2019; Wang et al., 2017; Wang et al., 2019).

Six out of the 24 studies that evaluated the smoking habit showed a statistically significant and positive association with the risk of developing SPTs, with risks ranging from 1.007 (95% CI: 1.004–1.011) to 5.52 (95% CI: 2.91–10.49), for pack per year or comparing smokers with never smokers. Regarding the duration of the habit, Cadoni et al. (2017) indicated that those patients with a smoking habit for more than 40 years had a risk 3.68 (CI 95% 1.10–12.30) times higher of occurrence of SPTs than patients who had never smoked. Only two studies (Hosokawa et al., 2018; Leoncini et al., 2018) analysed the effect of being ex-smokers and did not find any association with the risk of SPTs, compared to never smokers.

In a combined analysis of alcohol and tobacco exposure, Milliet et al. (2021) and León et al. (2020) reported that patients with both habits had a higher risk of developing SPTs, with a positive dose–response association in the later article (HR: 2.19; 95% CI: 1.59–3.03, for patients with severe consumption compared with the non-consumers). However, Martel et al. (2017) did not find a significant association with a similar approach.

TABLE 2 Factors associated with the risk of second neoplasms in patients with an index tumour in the head and neck area

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
Sociodemographic factors			
Sex	Ho et al. (2022)	Male	aSHR: 4.32 (1.77–10.50)
		Female	Reference
	León et al. (2020)	Male	Reference
		Female	aHR: 0.60 (0.46–0.79)
	Adjei Boakye et al. (2019)	Male	aHR: 1.09 (1.05–1.14)
		Female	Reference
	Min et al. (2019)	Male	aRR: 1.17 (1.01–1.35)
		Female	Reference
	Zhang et al. (2019)	Male	aHR: 1.64 (1.09–2.45)
		Female	Reference
	Hosokawa et al. (2018)	Male	aOR: 4.02 (2.06–7.84)
		Female	Reference
	Leoncini et al. (2018)	Male	Reference
		Female	aHR: 1.54 (1.01–2.35)[a]
	Leoncini et al. (2018)	Male	Reference
		Female	aHR: 4.29 (2.24–8.23)[b]
Age at diagnosis (years)	Ho et al. (2022)	20–44	Reference
		45–54	aSHR: 1.24 (0.92–1.68)
		55–64	aSHR: 1.21 (0.87–1.67)
		65+	aSHR: 0.63 (0.40–0.98)
	León et al. (2020)	< 50	Reference
		50–65	aHR: 1.34 (1.13–1.58)
		> 65	aHR: 1.73 (1.44–2.08)
	Li et al. (2020)	18–49	Reference
		50–64	aHR: 1.67 (1.36–2.03)
		65–79	aHR: 2.13 (1.72–2.64)
	Piersiala et al. (2020)	Under 70	Reference
		Over 70	Increased presence. *p* value: 0.003[c]
	Adjei Boakye et al. (2019)	≤ 54	Reference
		55–64	aHR: 1.58 (1.50–1.65)
		≥ 65	aHR: 1.61 (1.54–1.69)
	Chow et al. (2019)	Advanced (>50 years)	aHR: 1.05 (1.03–1.08)
	Iwatsubo et al. (2019)	< 65	aOR: 1.75 (1.27–2.41)[d]
		≥ 65	Reference
	Min et al. (2019)	< 45	Reference
		45–64	aRR: 0.63 (0.51–0.78)
		≥ 65	aRR: 0.39 (0.31–0.49)
	Zhang et al. (2019)	≤ 50	Reference
		>50	aHR: 1.68 (1.25–2.26)
	Hosokawa et al. (2018)	< 65	Reference
		≥ 65	aOR: 1.02 (1.00–1.04)
	Liu et al. (2017)	≤ 40	aOR: 2.27 (1.18–4.39)
		40–60	aOR: 1.60 (0.91–2.82)
		> 60	Reference

(Continues)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
Education level	Leoncini et al. (2018)	Less than high school	Reference
		College/high school graduate	aHR: 0.59 (0.39–0.82)
Country-level poverty	Adjei Boakye et al. (2019)	< 10%	Reference
		10–19%	aHR: 0.95 (0.91–0.98)
		≥ 20%	aHR: 1.03 (0.98–1.09)
Race	Li et al. (2020)	White	Reference
		Black	aHR: 1.37 (1.14–1.64)
		Other	aHR: 0.75 (0.75–1.31)
	Adjei Boakye et al. (2019)	White	Reference
		Black	aHR: 1.06 (1.01–1.13)
		Others	aHR: 0.74 (0.68–0.81)
Marital status	Guo et al. (2021)	Married	Reference
		Unmarried	aHR: 1.31 (1.07–1.60)
	Adjei Boakye et al. (2019)	Married	Reference
		Divorced/separated	aHR: 0.94 (0.90–0.99)
		Widowed	aHR: 0.86 (0.81–0.91)
		Never married	aHR: 0.95 (0.91–1.00)
		Unknown	aHR: 0.90 (0.84–0.96)
Habits			
Alcohol	Overwater et al. (2022)	< 30 g ethanol/day	Reference
		> = 30 g ethanol/day	3.25 (1.33–7.93)
	Inoue et al. (2021)	Before technique of transoral surgery (per +10 units/week)	aHR: 1.15 (1.04–1.28)
	Bugter et al. (2021)	Units per week	aHR: 1.006 (1.004–1.009)
	Bertolini et al. (2021)	Non-drinker	Reference
		Drinker	sHR: 1.46 (1.12–1.91)
	Wang et al. (2019)	Non-drinker	Reference
		Drinker	aOR: 21.3 (2.9–156.6)[e]
	Su et al. (2019)	Yes	aRR: 1.65 (1.10–2.48)
		No	Reference
	Hosokawa et al. (2018)	Never	Reference
		Occasional (1 or 2 per week)	aOR: 1.19 (0.48–2.99)
		Drinker (everyday)	aOR: 8.12 (4.15–15.92)
	Leoncini et al. (2018)	Never drinkers	Reference
		≤ 1 drink per day	aHR: 1.51 (1.00–2.29)
		>1 drink per day	aHR: 1.37 (0.89–2.10)
	Ni et al. (2018)	Non-heavy drinkers (< 250 g/day)	Reference
		Heavy drinkers (≥ 250 g/day)	aOR: 4.79 (1.11–6.37)
	Wang et al. (2017)	Non-drinker	Reference
		Low dose	aOR: 6.2 (1.2–33.6)[e]
		High dose	aOR: 7.9 (1.5–41.4)[e]
Tobacco	Bugter et al. (2021)	Pack per year	aHR: 1.007 (1.004–1.011)
	Chow et al. (2019)	No	Reference
		Yes	aHR: 1.76 (1.00–3.08)
	Zhang et al. (2019)	No	Reference
		Yes	aHR: 1.41 (1.04–1.91)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
	Hosokawa et al. (2018)	Never	Reference
		Former	aOR: 1.28 (0.40–4.11)
		Smoker	aOR: 5.52 (2.91–10.49)
	Leoncini et al. (2018)	Never	Reference
		Former	aHR: 1.05 (0.66–1.68)
		Current	aHR: 1.57 (1.01–2.44)
	Cadoni et al. (2017)	Never	Reference
		≤ 20 years	aHR: 1.91 (0.42–8.75)
		21–40 years	aHR: 2.34 (0.69–7.93)
		> 40 years	aHR: 3.68 (1.10–12.30)
Drug consumption (alcohol and tobacco)	Milliet et al. (2021)	No	Reference
		Yes	Increased presence. *p* value: 0.005
	León et al. (2020)	No	Reference
		< 20 cigarettes/day and/or < 80 g alcohol/day	aHR: 1.84 (1.30–2.59)
		≥ 20 cigarettes/day or ≥ 80 g alcohol/day	aHR: 2.19 (1.59–3.03)
Chewing betel quid	Lin et al. (2020)	No	Reference
		Yes	aOR: 9.99 (7.36–12.60)
Chewing betel quid+smoking	Lin et al. (2020)	No	Reference
		Yes	aOR:12.39 (9.32–15.45)
Tea consumption	Wang et al. (2019)	No	Reference
		Yes	aOR: 0.50 (0.30–0.90)[e]
Clinicopathological factors			
Primary tumour site	Overwater et al. (2022)	Larynx	Reference
		Oral cavity	aHR: 2.81 (1.07–7.40)
		Oropharynx	aHR: 4.03 (1.49–10.91)
		Hypopharynx	aHR: 1.18 (0.22–6.15)
	Bugter et al. (2021)	Oral cavity	Reference
		Nasopharynx	aHR: 0.190 (0.026–1.368)
		Oropharynx	aHR: 1.018 (0.739–1.402)
		Hypopharynx	aHR: 0.740 (0.437–1.252)
		Larynx	aHR: 0.707 (0.441–0.835)
	Bertolini et al. (2021)	Oral cavity	Reference
		Oropharynx	sHR: 2.03 (1.30–3.18)
		Hypopharynx	sHR: 1.10 (0.55–2.17)
		Glottis	sHR: 1.63 (1.07–2.49)
		Supraglottis	sHR: 2.89 (1.80–4.63)
	Li et al. (2020)	Lip and mouth	Reference
		Salivary glands	aHR: 0.90 (0.67–1.21)
		Larynx	aHR: 0.82 (0.66–1.02)
		Tongue	aHR: 0.70 (0.57–0.85)
	Nishimura et al. (2021)	Larynx	Reference
		Hypopharynx	aOR: 3.96 (1.07–14.6)
	Su et al. (2020)	Nasopharynx/oral cavity/oropharynx	Reference
		Hypopharynx/larynx	aOR: 4.7 (1.26–17.55)

(Continues)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
	Adams et al. (2019)	Glottis	Reference
		Supraglottis	aHR: 4.14 (1.16–14.85)
	Adjei Boakye et al. (2019)	Oropharynx	Reference
		Oral cavity	aHR: 1.12 (1.07–1.17)
		Hypopharynx	aHR: 1.15 (1.06–1.25)
		Larynx	aHR: 1.18 (1.12–1.23)
	Iwatsubo et al. (2019)	Oral cavity	Reference
		Oropharynx	aOR: 1.08 (0.68–1.72)[d]
		Hypopharynx	aOR: 3.17 (2.25–4.48)[d]
		Larynx	aOR: 1.92 (1.34–2.74)[d]
	Min et al. (2019)	Tongue	Reference
		Lips	aRR: 1.15 (0.91–1.45)
		Gums	aRR: 1.03 (0.83–1.29)
		Floor of mouth	aRR: 1.45 (1.21–1.75)
		Palate	aRR: 1.32 (1.09–1.59)
		Others	aRR: 1.12 (0.95–1.32)
	Su et al. (2019)	Lip	Reference
		Oropharynx	aRR: 19.98 (4.72–84.55)
		Floor of mouth	aRR: 12.13 (2.67–55.15)
		Hard palate	aRR: 7.31 (1.65–32.37)
		Tongue	aRR: 3.15 (0.76–13.16)
		Gum	aRR: 3.57 (0.81–15.79)
		Buccal mucosa	aRR: 1.24 (0.29–5.31)
	Hosokawa et al. (2018)	Non-mucosal	Reference
		Mucosal	aOR: 6.99 (3.78–12.93)
	Harada et al. (2017)	Oral cavity and pharynx	Reference
		Hypopharynx	aHR: 4.86 (2.19–10.8)
	Tseng et al. (2017)	Non-lower lip	Reference
		Lower lip	aOR: 2.91 (1.10–7.69)
	Wang et al. (2017)	Oral cavity	Reference
		Oropharynx	aOR: 2.8 (1.2–6.2)[e]
		Hypopharynx	aOR: 6.8 (3.2–14.5)[e]
		Larynx	aOR: 4.6 (1.3–15.4)[e]
Primary tumour stage	Petersen et al. (2022)	I	Reference
		II	aHR: 0.75 (0.47–1.20)
		III	aHR: 0.69 (0.42–1.14)
		IV a/b/c/x	aHR: 0.48 (0.30–0.77)
	Ho et al. (2022)	0–II	Reference
		III–IV	aSHR: 1.26 (1.01–1.59)
	Wang et al. (2019)	0–I	Reference
		II	aOR: 2.8 (0.7–11.7)[e]
		III	aOR: 2.9 (0.8–10.7)[e]
		IV	aOR: 4.3 (1.3–14.3)[e]
	Cadoni et al. (2017)	I–II	Reference
		III–IV	aHR: 2.75 (1.39–5.44)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
Size	Li et al. (2020)	≤ 30 mm	Reference
		≥ 31 mm	aHR: 0.85 (0.74–0.98)
Lymph node involvement	Li et al. (2020)	Negative	Reference
		Positive	aHR: 0.83 (0.69–0.98)
	Lin et al. (2020)	Lymph node negative	Reference
		Lymph node positive	aOR: 7.32 (5.63–9.02)
	Zhang et al. (2019)	0–1	Reference
		2–3	aHR: 1.34 (1.00–1.79)
	Feng et al. (2017)	No pathologic nodal status	Reference
		Pathologic nodal status	aOR: 0.72 (0.56–0.93)
Metastasis	Guo et al., 2021	M_0	Reference
		M_1	aHR: 1.91 (1.13–3.23)
	Wang et al. (2017)	M_0	Reference
		M_1	aOR: 7.1 (1.2–42.0)[e]
Invasion	Li et al. (2020)	Localised	Reference
		Regional	aHR: 0.92 (0.74–1.15)
		Distant	aHR: 0.78 (0.61–0.99)
	Adjei Boakye et al. (2019)	Localised	Reference
		Regional	aHR: 0.80 (0.77–0.83)
		Distant	aHR: 0.62 (0.58–0.66)
		Unstaged/unknown	aHR: 0.79 (0.72–0.86)
	Ni et al. (2018)	< 3 anatomical sites	Reference
		≥ 3 anatomical sites	aOR: 14.39 (2.24–12.56)
Pathological differentiation	Lin et al. (2020)	Medium/low	Reference
		Well	aOR: 3.83 (2.60–5.06)
	Adjei Boakye et al. (2019)	Well	Reference
		Moderately	aHR: 1.08 (1.03–1.14)
		Poor	aHR: 0.99 (0.93–1.05)
		Undifferentiated/unknown	aHR: 1.03 (0.97–1.09)
Histological type	Li et al. (2020)	Squamous cell carcinoma	aHR: 1.48 (1.11–1.98)
		Others	Reference
	Iwatsubo et al. (2019)	Squamous cell carcinoma	aOR: 7.50 (1.02–55.2)[d]
		Others	Reference
Presence of premalignant lesion	Lin et al. (2020)	No	Reference
		Yes	aOR: 14.63 (12.05–17.21)
	Liu et al. (2017)	No	Reference
		Yes	aOR: 2.62 (1.82–3.77)
	Liu et al. (2017)	Homogenous leukoplakia	Reference
		Heterogeneous leukoplakia	aOR: 2.17 (1.17–4.00)
		Erythroplakia	aOR: 1.58 (0.13–18.56)
	Feng et al. (2017)	No multiple oral dysplastic lesion	Reference
		Multiple oral dysplastic lesion	aOR: 4.56 (2.79–7.45)
Others			

(Continues)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
HPV status	Bosshart et al. (2021)	Negative	Reference
		Positive	aHR: 0.362 (0.155–0.847)
	Milliet et al. (2021)	No	Reference
		Yes	Decreased presence. *p* value: 0.003
	Adjei Boakye et al. (2019)	Potentially HPV related	Reference
		Non-HPV related	aHR: 1.15 (1.10–1.20)
	Martel et al. (2017)	Positive	Reference
		Negative	aHR: 3.70 (1.60–8.30)
Treatments	Stepan et al. (2022)	No adjuvant treatment	Reference
		Radiation with or without chemotherapy	aHR: 0.25 (0.08–0.78)
	Guo et al. (2021)	Surgery	Reference
		No surgery	aHR: 1.31 (1.04–1.64)
	Li et al. (2020)	No chemotherapy	Reference
		Chemotherapy	aHR: 0.85 (0.73–0.98)
	Adjei Boakye et al. (2019)	Surgery	Reference
		No surgery	aHR: 0.88 (0.85–0.91)
	Min et al. (2019)	No radiation therapy	Reference
		Any radiation therapy	aRR: 1.34 (1.17–1.54)
***Flush* alcohol**	Harada et al. (2017)	No	Reference
		Yes	aHR: 2.63 (1.25–5.52)
	Wang et al. (2017)	Non-drinker	Reference
		Low-dose	aOR: 12.2 (2.7–54.1)[e]
		High-dose	aOR: 16.9 (3.8–75.2)[e]
Year group of diagnosis	Guo et al. (2021)	2004–2009	Reference
		2004–2009	aHR: 1.39 (1.13–1.71)
	Adjei Boakye et al. (2019)	2000–2004	Reference
		2005–2009	aHR: 0.88 (0.85–0.91)
		2010–2014	aHR: 0.67 (0.64–0.70)
	Min et al. (2019)	1993–2000	Reference
		2001–2007	aRR: 1.21 (1.06–1.39)
		2008–2014	aRR: 1.02 (0.85–1.23)
Follow-up	Min et al. (2019)	6–23 months	Reference
		24–59 months	aRR: 0.89 (0.76–1.05)
		60–119 months	aRR: 0.82 (0.69–0.97)
		≥ 120 months	aRR: 0.68 (0.55–0.83)
Asymptotic symptoms	Ho et al. (2022)	No	Reference
		Dysphagia	aSHR: 2.88 (1.61–5.16)
		Gastrointestinal bleeding	aSHR: 0.70 (0.29–1.71)
		Body weight loss	aSHR: 1.61 (0.23–11.33)
		Oesophageal disease	aSHR: 1.12 (0.72–1.76)
		Trismus	aSHR: 1.94 (0.26–14.20)
		Anaemia	aSHR: 1.82 (0.98–3.39)
		Chest pain	aSHR: 1.84 (0.67–5.05)

TABLE 2 (Continued)

Risk factor	Study	Categories	Adjusted risk (confidence interval 95%)
Synchronous HNC cancer	Ho et al. (2022)	No	Reference
		Yes	aSHR: 5.80 (3.97–8.46)
Endoscopic screening	Ho et al. (2022)	No	Reference
		Yes	aSHR: 2.92 (2.30–3.71)
PET scan results	Sawaf et al. (2022)	Negative	Reference
		Positive	Increased presence. *p* value: 0.006[c]
Comorbidity[f]	Bugter et al. (2021)	None	Reference
		Mild	aHR: 1.568 (1.138–2.159)
		Moderate	aHR: 1.435 (0.998–2.062)
		Severe	aHR: 1.854 (1.165–2.950)

aSHR: adjusted subdistribution hazard ratio, aHR: adjusted hazard ratio, aOR: adjusted odds ratio, aRR: adjusted relative risk; sHR: subdistribution hazard ratio, HPV: human papillomavirus, HNC: head and neck cancer, PET: positron emission tomography.
[a]For second primary tumour in head and neck.
[b]For second primary tumour in lung.
[c]Univariate analysis.
[d]For second primary tumour in oesophagus.
[e]High-grade dysplasia primary second tumour.
[f]Comorbidity was scored by the ACE-27.

Only one out of the four studies evaluating the betel chewing found an increased risk of SPTs, reaching an OR of 12.39 (95% CI: 9.32–15.45) when it was combined with smoking consumption (Lin et al., 2020). A single study evaluated the influence of tea consumption in the development of second tumours in HNC, showing that tea drinkers had a 50% lower risk of presenting a high grade SPT (95% CI: 0.30–0.90) than non-tea drinkers, even in patients with a habit of alcohol, tobacco and/or betel nut consumption (Wang et al., 2019).

3.2.3 | Clinicopathological factors related to the index tumour

Twenty-eight studies included in this review evaluated the location of the index tumour as an associated factor for SPTs, and 15 of them showed a significant association (Adams et al., 2019; Adjei Boakye et al., 2019; Bertolini et al., 2021; Bugter et al., 2021; Harada et al., 2017; Hosokawa et al., 2018; Iwatsubo et al., 2019; Li et al., 2020; Min et al., 2019; Nishimura et al., 2021; Overwater et al., 2022; Su et al., 2019; Su et al., 2020; Tseng et al., 2017; Wang et al., 2017). Hypopharynx and oropharynx were the locations more consistently associated. Increased risks were found in hypopharynx that ranged from HR = 1.15; 95% CI: 1.06–1.25 to OR = 6.8; 95% CI: 3.2–14.5 compared to oral cavity (Bertolini et al., 2021; Iwatsubo et al., 2019; Wang et al., 2017), HR: 3.96; 95% CI: 1.07–14.6 compared to larynx (Nishimura et al., 2021), HR: 1.15; 95% CI: 1.06–1.25 compared to oropharynx (Adjei Boakye et al., 2019), and HR: 4.86; 95% CI: 2.19–10.8 compared to oral cavity and pharynx (Harada et al., 2017). With respect to oropharynx, the risks ranged from 2.03 (95% CI: 1.30–3.18) compared to oral cavity, to 19.98 (95% CI: 4.72–84.55) compared to lips. By subsites, floor of mouth and palate had an increased risk of appearance of SPTs than other locations within the oral cavity and supraglottis in the larynx.

Twenty-eight studies measured some parameters related to extension of the primary tumour (stage, size, lymph node involvement, metastasis or invasion), and 12 of them found an association with the appearance of SPTs. Except for Feng et al., Li et al., Adjei Boakye et al. and Petersen et al. (Adjei Boakye et al., 2019; Feng et al., 2017; Li et al., 2020; Petersen et al., 2022), the rest of the articles showed that the higher the extension of the index tumour, the higher the risk (Cadoni et al., 2017; Guo et al., 2021; Ho et al., 2022; Lin et al., 2020; Ni et al., 2018; Wang et al., 2017; Wang et al., 2019; Zhang et al., 2019).

The three studies that evaluated the presence of a premalignant oral lesion at the time of diagnosis of the index tumour found it to be a risk factor with OR that ranged between 2.62 (95% CI: 1.82–3.77) and 14.63 (95% CI: 12.05–17.21) (Feng et al., 2017; Lin et al., 2020; Liu et al., 2017). Moreover, Liu et al. indicated that the heterogeneous leukoplakia increased the risk compared to homogeneous leukoplakia (OR: 2.17; 95% CI: 1.17–4.00) (Liu et al., 2017).

3.2.4 | Other factors

Four out of the seven studies that evaluated the influence of the HPV reported that the risk of developing a second tumour was lower for those HPV-related HNC tumours (Adjei Boakye et al., 2019; Bosshart et al., 2021; Martel et al., 2017; Milliet et al., 2021). Twelve studies

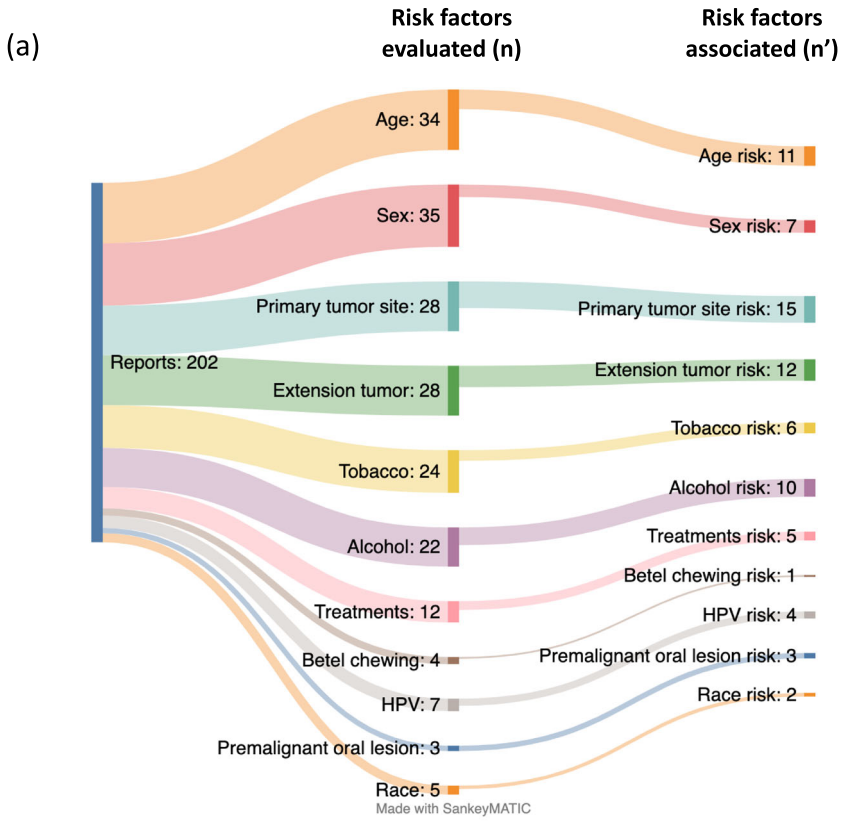

FIGURE 2 Graphical summary of the articles included in this review. (a) For each risk factor evaluated in this review, the number of articles that studied that factor (*n*) and the number of articles that found a significant association for that factor (*n'*) is provided. (b) A summary of the quality of the articles according to their study design is provided

evaluated the influence of treatments, and five of them found an association with the appearance of SPT; the results were contradictories.

The two studies that analysed the influence of facial flushing reaction (flush) to alcohol found a risk of SPTs up to 17 times higher (95% CI: 3.8–75.2) compared with patients who did not present that reaction (Harada et al., 2017; Wang et al., 2017). By last, Min et al. found an inverse dose–response risk of SPTs with the increasing follow-up (Min et al., 2019).

3.3 | Quality assessment of studies

Table 3 and Figure 2b show the evaluation of the quality of the studies included in this review. Thirty-three of them were classified as having a high methodological quality (7–9 points). The remaining five studies scored 5–6 points and were therefore considered as of medium quality (Bukovszky et al., 2022; Ni et al., 2018; Piersiala et al., 2020; Sawaf et al., 2022; Watanabe et al., 2017).

In the selection category, the item that the studies most frequently failed to fulfil was 'representativeness of the exposed cohort'. Thus, in most cohorts many patients (more than 10%) were excluded from the eligible population because of restrictive selection criteria including not having a 'sufficient' or 'complete' follow-up, that is, being alive at the end follow-up, or for reasons not provided (Bukovszky et al., 2022; Chow et al., 2019; Harada et al., 2017; Ho et al., 2022; Leoncini et al., 2018; Lin et al., 2020; Martel et al., 2017; Ni et al., 2018; Nishimura et al., 2021; Piersiala et al., 2020; Sawaf et al., 2022; Stepan et al., 2022; Su et al., 2019; Wang et al., 2017; Wang et al., 2019; Zhang et al., 2019), thus introducing a potential selection bias. Other authors did not perform an exposure description (Bertolini et al., 2021; Feng et al., 2017; León et al., 2020; Liu et al., 2017; Su et al., 2020), and in another study, the exposure was self-reported (Adjei Boakye et al., 2019).

TABLE 3 Evaluation of the methodological quality of the included studies

	NOS scale criteria		
Reference/country	**S**	**C**	**E/O**
Ho et al. (2022)/Taiwan	+++[a]	++	+++
Bukovszky et al. (2022)/Hungry	+++		++
Inoue et al. (2021)/Japan	++++[a]	++	+++
Overwater et al. (2022)/Netherlands	++++[a]	++	+++
Sawaf et al. (2022)/US	+++[a]		+++
Stepan et al. (2022)/US	+++[a]	++	+++
Petersen et al. (2022)/Denmark	++++	++	++
Guo et al. (2021)/US	++++	++	+++
Milliet et al. (2021)/France	++++	++	+++
Bosshart et al. (2021)/Switzerland	++++[a]	++	+++
Bugter et al., 2021/The Netherlands	++++[a]	++	++
Arie et al. (2021)/Israel	++++	++	+++
Bertolini et al. (2021)/Italy	+++[a]	++	+++
Li et al. (2020)/China	++++	++	++
Lin et al. (2020)/China	++	++	+++
Nishimura et al. (2021)/Japan	++[a]	++	+++
León et al. (2020)/Spain	+++[a]	++	+++
Piersiala et al. (2020)/US	+++		+++
Su et al. (2020)/Taiwan	+++	++	+++
Adams et al. (2019)/UK	++++	++	+++
Zhang et al. (2019)/China	+++[b]	++	+++
Wang et al. (2019)/Taiwan	+++	++	+++
Su et al. (2019)/Taiwan	++	++	+++
Min et al. (2019)/Korea	++++	++	+++
Chow et al. (2019)/China	+++	++	+++
Iwatsubo et al. (2019)/Japan	++++	++	+++
Adjei Boakye et al. (2019)/US	+++	++	+++
Ni et al. (2018)/China	++	++	++
Leoncini et al. (2018)/(Italy, Japan, Brazil)	+++[b]	++	+++
Hosokawa et al. (2018)/Japan	++++[b]	++	+++
Watanabe et al. (2017)/Japan	++++		++
Wang et al. (2017)/Taiwan	+++	++	+++
Tseng et al. (2017)/Taiwan	++++	++	+++
Martel et al., 2017)/Spain	+++[b]	++	+++
Liu et al. (2017)/Taiwan	+++[b]	++	+++
Harada et al. (2017)/Japan	+++[b]	++	+++
Feng et al. (2017)/China	+++[b]	++	++
Cadoni et al. (2017)/Italy	++++[b]	++	+++

NOS scale criteria: *The Newcastle–Ottawa* Scale S: selection (0–4 stars), C: Comparability (0–2 stars), E/O: Exposure/Outcome (0–3 stars).

[a]This study assessed for the presence of synchronous secondary tumours, which included some diagnosed at the start of the study. Because of the singularity of the study in which synchronous tumours are part of the outcome, for the *Newcastle–Ottawa* Scale (NOS) item 'Demonstration that outcome of interest was not present at start of study', a star was allocated to this study despite the outcome being present.

[b]For the NOS scale item "Demonstration that outcome of interest was not present at start of study", this study assessed for the presence of synchronous s secondary tumours, which included some diagnosed at the start of the study. Because of the singularity of the study in which synchronous tumours as part of the outcome, a star was allocated in these cases.

With regards to comparability, only 4 out of the 38 studies did not get the maximum score; three because the authors did not perform multivariate analysis (Bukovszky et al., 2022; Piersiala et al., 2020; Sawaf et al., 2022), and another one because they did not mention the variables included in the multivariate analysis (Watanabe et al., 2017).

In the third category (exposure/outcome), only seven studies did not reach the maximum possible score. Ni et al. (2018) and Bukovszky et al. (2022) did not describe how they analysed the exposure or outcome, Watanabe et al. (2017), Petersen et al. (2022), Bugter et al. (2021) did not mention the rate of non-response in the measurement of exposure, the follow-up in Li et al. (2020) was not long enough for outcomes to occur, and Feng et al. (2017) had a high loss (more than 10%) at follow-up.

4 | DISCUSSION

This systematic review provides a comprehensive and actualised synthesis of the existing evidence about the factors associated to the risk of developing second primary neoplasms in HNC patients. Our results suggest that alcohol consumption and location of the index tumour in hypopharynx are the variables with the highest consistency of association with the risk of SPTs. Smoking was also consistently associated with an increase of the risk in those studies that found a significant association. More controversy was found in variables such as age and sex. Information is still scarce for factors as presence of premalignant oral lesions, but the results pointed towards a risk association. Only five studies were classified with moderate quality, and their results were in consonance with the rest of the selected articles.

All articles that found a significant association between tobacco and alcohol consumption and appearance of SPTs indicated an increased risk. On the one hand, it was an expected result as these factors are the main promoters of the appearance of a head and neck index tumours (Rettig & D'Souza, 2015). Moreover, it has been described that their cessation is effective in reducing the risk of SPTs (von Kroge et al., 2020; Yokoyama et al., 2017). Nevertheless, this issue highlights a fail in cancer prevention policies as there is a high prevalence of smokers and, even more, drinkers among HNC survivors (Barrios-Rodríguez et al., 2019; Gritz et al., 2020; Sanford et al., 2020). On the other hand, it should be noted that some studies did not find a significant risk attributable to these lifestyle factors. It may be possible that alcohol and tobacco have an impact in the appearance of SPTs only in determinate locations. Thus, alcohol consumption was mostly reported to be a risk for second neoplasms in the oesophagus. It should also be kept in mind that some studies just included patients with complete follow-up, and this could lead to an underestimation in smokers and alcohol drinkers as these variables are related to high mortality rates (Peacock et al., 2018). Some of these articles that did not find associations had a low frequency in one of the categories that might have made it difficult to find differences as well. Also, the different number and type of variables evaluated in each study could explain an absence of associations of alcohol and smoking habit with SPTs because of competitive causes.

Facial flushing reaction to alcohol consumption was strongly associated to increased risk of STPs. Acetaldehyde is metabolised by alcohol dehydrogenase 2. The deficiency of this enzyme produces accumulation of acetaldehyde, enhancing its carcinogenic action, and it is related to alcohol flushing response (Harada et al., 1981). Harada et al. (2017) found that flushers and non-drinkers had significant lower SPTs rate than flushers and drinkers, which cessation of this habit may reduce the risk of SPTs in flushers.

The location of the index tumour in hypopharynx or oropharynx was related to an increased risk of appearance of SPTs, with a stronger association when the SPT was of high grade. These tumours have a higher difficulty in early diagnosis than other HNC sites (Hamada et al., 2018), and this might favour the persistence of preneoplastic fields of genetically altered cells ('field cancerisation' phenomenon) described in the head and neck area (Bansal et al., 2020; Leemans et al., 2011). This peculiar characteristic could also explain the higher risk found with the presence of premalignant lesions that comprise other clones of stigmatised cancer cells invisible to routine clinical and histological examination (Holmstrup & Dabelsteen, 2016). Considering the possible implication in the risk of appearance of SPTs, further research is needed in this direction to overcome these diagnostic challenges.

An increased risk of SPTs was found when HPV was not present. This finding is in consonance with the favourable prognosis found in patients with HPV expression tumours (Sedghizadeh et al., 2016). HPV-related tumours have a biologically distinct behaviour compared to HPV-negative tumours which contribute to the pathophysiology of the disease. Because of its complexity, more research focussing on this issue is needed to better understand its role in the decreased risk of SPT (Dong et al., 2021).

Some other factors were assessed in a very limited number of studies, which preclude arriving to strong conclusions. A possible explanation for the disparity in the variables under assessment in the different studies may be the fact that most of them were retrospective and therefore used clinical records or cancer registries as a source of information, what conditioned the available data. Some of these variables like race, educational level or tea consumption have been previously associated with the risk and prognosis of HNC patients (Crooker et al., 2018; Ingarfield et al., 2018). Thus, in future studies evaluating the development of SPTs, it would be interesting to include these variables to confirm the potential roles found in this study.

Regarding other frequently investigated factors—sex, age and variables of tumour extension—in general terms, men, older people and patients with a more advanced index tumour seemed to have a higher risk of developing a SPT, even after adjusting for relevant risk factors as lifestyle and other clinical variables. In the case of the sex variable, it has been described an inverse association between women and HNC because of endogenous and exogenous hormonal factors (Aupérin, 2020), and this could also explain the association with second malignancies. However, there were more inconsistency in results as some studies showed contrary results.

This review has potential limitations to take into account in the interpretation of results. As it has been mentioned previously, most of the included studies were retrospective and used variables registered in records or registries. Besides, this could lead to information bias or uncompleted information of associated factors. Thus, we cannot rule out the role of third uncontrolled variables or the influence of possible changes in them over time. In this sense, conclusions about whether stopping drinking alcohol may prevent STPs appearance could not be done because only one article considered the category 'former' in its analysis (Cadoni et al., 2017). Other potential limitation was that there was a great heterogeneity in the included studies regarding sample size, locations for both the first and second head cancer, and variables studied, and all these issues could have an implication in the results described. Nevertheless, the limitations have not prevented us from identifying the most updated evidence about relationships between risk factors and second neoplasms in HNC patients, reinforcing previous findings on well-known risk factors, that is, smoking habit, and highlighting several factors that require further research. The language exclusion criteria could be another limitation. However, most part of the scientific literature is written in English, so the risk of selection bias is low.

As conclusions, smoking, alcohol consumption, location of the index tumour in hypopharynx/oropharynx, abscense of HPV, and presence of a premalignant lesion were associated with the risk of SPTs in HNC patients. These findings indicate the necessity of reinforcing the education about unhealthy behaviours and cessation techniques. Moreover, they highlight that prevention strategies may be more effective in patients with a tumour index located in hypopharynx or with presence of a premalignant lesion.

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CONFLICT OF INTEREST

The authors declare not having any conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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