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REVIEW

Risk of second primary cancer in patients with head and neck squamous cell carcinoma: a systemic review and meta-analysis

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Abstract

Objectives Second primary cancer is a common event in patients with head and neck squamous cell carcinoma. However, the incidence and relevant factors vary by studies. We conducted a systematic review and meta-analysis of observational studies to estimate the incidence and relevant risk factors.

Materials and methods PubMed and Web of Science were searched for studies published between January 2000 and December 2020 that reported the incidence of SPC in HNSCC patients. Per 1000-person-year incidence and odds ratios were used to estimate the incidence and potential risk factors. Due to the high heterogeneity, random-effects models were used to estimate the incidence and 95% confidence interval.

Results Seven thousand seven hundred thirteen articles were identified from the databases, in which 60 studies were included in this meta-analysis. The pooled incidence of the total, synchronous, and metachronous SPC in patients with HNSCC were 29.116 per 1000-person-year, 6.960 per 1000-person-year, and 26.025 per 1000-person-year, respectively. The head and neck region was the most common area where SPC occurred, followed by the lung (7.472 per 1000-person-year) and upper digestive tract (2.696 per 1000-person-year). Smoking, alcohol consumption, betel quid chewing, primary cancer of T_{1-2}, and N_0 were risk factors, while HPV infection (OR 0.47, 95% CI 0.30–0.72) was the protective factor.

Conclusions SPC is frequently observed in HNSCC patients and had great impact on the prognosis. The findings could promote a more individualized follow-up strategy for SPC in HNSCC patients.

Clinical relevance This systemic review and meta-analysis provide sufficient evidence for the establishment of the follow-up strategy for head and neck squamous cancer patients.

Keywords Second primary cancer · Head and neck squamous cell carcinoma · Risk factors · Meta-analysis · Person-year incidence

Introduction

Cancer survivors are suffering from a great risk of developing and dying from a second primary cancer (SPC), with head and neck cancer (HNC) being one of the regions with highest risk among all kinds of first primary cancers

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[1]. As patients have a lifelong risk of developing an SPC, it has attributed to a quarter to one-third of all deaths in patients with head and neck squamous cell carcinoma (HNSCC) and has been identified as the leading cause of non-HNSCC death [2–4]. The mean incidence of SPC in patients with HNC was 13.2% with 5.3% for synchronous SPC (SSPC) and 9.4% for metachronous SPC (MSPC) reported in a conference report in EGPRN meeting [5]. However, the insufficient involvement of countries and regions leads to the inaccuracy of the results. What's more, the duration of follow-up time was not taken into consideration in the research, which varies considerably among institutions, leading to the heterogeneity in incidence described by the percentage of the occurrence. Therefore, conducting an analysis of SPC incidence based on person-time denominators is essential.

Whether the risk factors of SPC are closely related to that of primary HNSCC remains controversial, where further investigation is required. The increasing risk of SPC is related to various reasons, including genetic predisposition, carcinogenic cancer treatments, and mostly, the environmental and lifestyle-related risk factors shared by the first and second cancers [6]. As one of the most representative risk factors for HNSCC, smoking could elevate the risk of SPC in the head and neck area and other smoking-related SPCs, such as lung cancer [1]. The carcinogenesis of radiotherapy could partially be reflected in SPC development at sites close to primary cancer [7].

SPC has a different choice of appropriate treatment and follow-up strategy comparing with other secondary events such as recurrence and metastasis, emphasizing the importance of its early detection and diagnosis. However, there are still no complete follow-up protocols concerning SPC after HNSCC and further investigation is urgently needed. American Cancer Society Head and Neck Cancer Survivorship Care Guideline and National Comprehensive Cancer Network only emphasize the screening and early detection of the three major sites which have the comparatively high risk of developing SPC, lacking the specific details of more subdivided subsites and the concrete recommendation of follow-up schedule and time interval [8]. It would be of benefit to the clinical work in the detection and diagnosis of SPC if the relatively accurate incidence of the subdivided subsites developing SPC was calculated and the follow-up time in SPC patients after HNSCC was summarized.

This systemic review and meta-analysis aimed to evaluate the SPC risk in HNSCC patients and further explore its predilection sites and risk factors. We tried to provide a more evidence-based approach for establishing an individualized SPC follow-up strategy according to the degree of risk in HNSCC patients and eventually promote earlier diagnosis and better prognosis.

Methods

This systematic review and meta-analysis have been registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020189273). Our study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9].

Search strategy

PubMed and Web of Science were searched for studies concerning SPC in HNSCC patients published between January 2000 and December 2020. The search strategy was as follows: (second primary malignancy OR second primary cancer OR second primary carcinoma) AND ((head and neck OR oral OR nasopharyngeal OR oropharyngeal OR hypopharyngeal OR laryngeal) AND (squamous cell carcinoma OR cancer OR carcinoma)). The initial search had no restriction on language or publication type.

Study selection

Three independent reviewers (XZ, DL, and HS) screened the titles and abstracts to exclude irrelevant studies. Full texts were assessed for eligibility when any information on the occurrence of SPC in HNSCC patients was mentioned in the abstract. The reference lists of included articles were also checked for additional relevant studies. Disagreements were resolved by consensus or involvement of a fourth reviewer as necessary.

Studies were included if they were original studies that reported the incidence of total SPC, SSPC, or MSPC after diagnosis of HNSCC. We included the studies that had investigated SSPC and MSPC according to the definitions reported by International Agency for Research on Cancer (IARC) or by Warren and Gates criteria or by Surveillance Epidemiology and End Results (SEER) program. According to IARC, an MSPC is defined as a SPC occurring more than 6 months after the diagnosis of the primary cancer. According to SEER program, an MSPC is defined as a SPC occurring 2 months after the diagnosis of the primary cancer and an SSPC is defined as that occurring within 2 months after the primary cancer [1, 10]. Where there appeared to be multiple studies concerning the same cohort, the most recent one was included if they contained exactly the same data on SPC. Studies were excluded if they (1) were reviews, meta-analysis, case reports, books, letters, or conference abstracts; (2) were published in non-English language; (3) did not make clear of the histological type of primary HNC;

or (4) reported the incidence of SPC after HNC, including squamous cell cancer as a subtype of primary HNC, but we failed to obtain relevant data after contacting the authors. Total SPC, or tSPC, refers to the combination of SSPC and MSPC, the incidence for which can be obtained in two kinds of situations: firstly, data on SSPC and MSPC were both available and the incidence of tSPC was simply the addition of the two; secondly, SPC was taken as a whole without distinguishment of SSPC and MSPC.

Data extraction and risk of bias assessment

Data extraction was performed independently by three reviewers (XZ, DL, and HS) using a standardized data extraction form and disagreements were resolved by consensus. The following data were extracted from each study: study characteristics, demographic characteristics, primary HNSCC characteristics, and SPC characteristics (the overall and subgroup incidence of SPC, diagnosis criteria, inspection method, inspected sites, and time interval).

The risk of bias in individual studies was evaluated using the Newcastle–Ottawa scale (NOS)[164]. In brief, the list consists of nine items examining the quality of studies based on the selection of cases, factors controlling, and ascertainment of exposure. A full score is 9 points, and a score ≥ 7 indicates high quality, while a score < 6 for low quality. The NOS checklist was assessed independently by two reviewers. Discrepancies in the score were resolved through discussion by the reviewers. The risk of bias across studies was evaluated with funnel plots and the Egger test and considered significant when $p < 0.05$.

Data synthesis and statistical analysis

In each study, the numbers of patients with primary HNSCC, tSPC, SSPC, and MSPC were combined respectively to give a pooled incidence of SPC based on 1000-person-year denominators.

Subgroup analyses were conducted to compare the pooled incidence according to different primary sites and SPC sites and the source of heterogeneity. The risk of SPC was assessed according to proposed risk factors, using an OR, with a 95% confidence interval (95% CI). For the studies that concerned the same cohort with overlapping data on subgroup and risk factors analyses, only the most recent one was used.

Heterogeneity between studies was assessed using the I^2 statistic, with I^2 value $> 50\%$ indicating high heterogeneity. A p-value for $I^2 < 0.05$ was considered statistically significant. Data were pooled using a random-effects model if $I^2 > 50\%$; otherwise, a fixed-effect model was used. R version 4.0.2 was used for all meta-analyses.

Results

The search strategy identified 7717 citations. After removing duplicates, the titles and abstracts of 4921 studies were reviewed, and 334 articles were further assessed in full text. Ultimately, we identified 60 articles that fulfilled the eligibility criteria [11–70] (Fig. 1), representing 60 separate study cohorts, containing 148,534 subjects in 17 countries. Detailed characteristics of all included studies were provided in eTable 1.

The pooled per 1000-person-year incidence of developing a SPC after primary HNSCC was 29.116 per 1000-person-year (95%CI 23.920–34.805, $I^2 = 97.64\%$) for tSPC (Fig. 2), 6.960 per 1000-person-year for SSPC (95% CI 4.461–10.009; $I^2 = 96.76\%$), and 26.025 per 1000-person-year for MSPC (95%CI 19.526–33.427; $I^2 = 98.31\%$).

Pooled incidence of SPC according to different primary cancer sites and SPC sites

We selected 27 studies that took the whole body as a screening area for SPC to estimate the pooled per 1000-person-year incidence according to subsites of primary HNSCC. Hypopharyngeal cancer had the highest incidence of tSPC (41.562 per 1000-person-year) while larynx cancer had the lowest (22.557 per 1000-person-year). The tSPC incidence of other primary HNSCC was 38.729 per 1000-person-year for the oral cavity, 36.811 per 1000-person-year for the oropharynx (Table 1 and eFig1).

We selected the studies that took primary HNSCC as a whole to investigate the site distribution of SPC. SPC sites were divided into five anatomical areas referring to the published studies, including head and neck region (oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and thyroid), lower respiratory system, upper digestive tract (esophagus and stomach), lower digestive tract, and genitourinary system. The head and neck region was the most common area where SPC occurred (13.127 per 1000-person-year, 95% CI 9.282–18.564, $I^2 = 97.57\%$). The SPC-developed incidence of the subsites of head and neck region are as follows: oropharynx (30.258 per 1000-person-year, 95% CI 24.357–37.588, $I^2 = 88.67\%$), (2.254 per 1000-person-year, 95% CI6. 1.013–5.011, $I^2 = 78.89\%$), and oral cavity (10.321 per 1000-person-year, 95% CI6.397–16.654, $I^2 = 95.02\%$). The lower respiratory system (7.472 per 1000-person-year, 95% CI 5.740–9.726, $I^2 = 92.43\%$) and upper digestive tract (2.696 per 1000-person-year, 95%

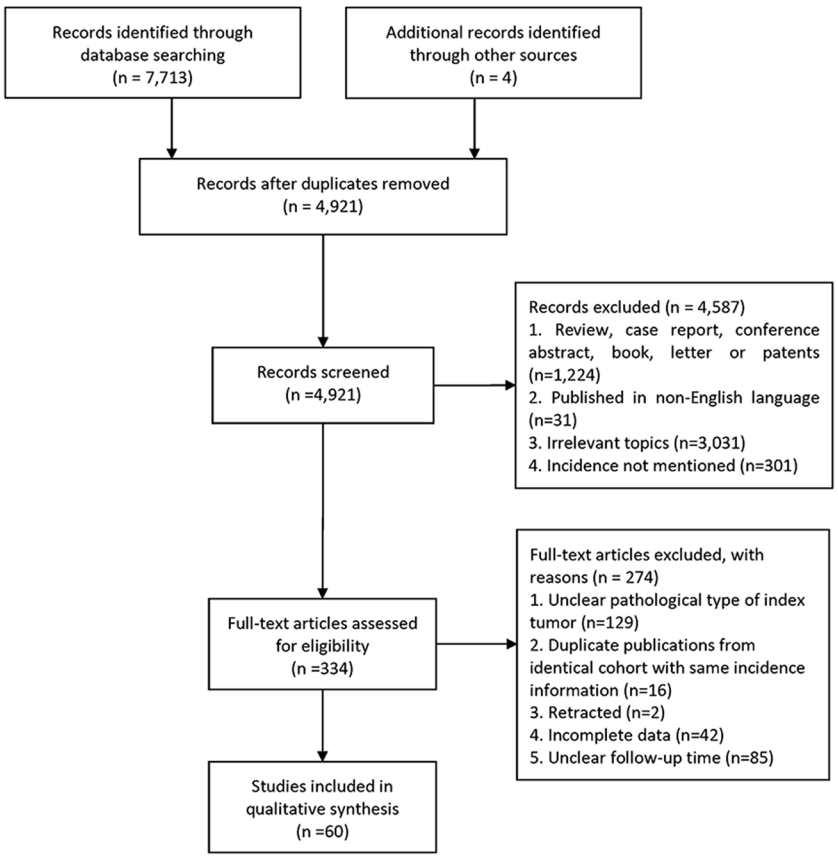

Fig. 1 Flow diagram of study selection

CI 1.739–4.180, $I^2 = 86.85\%$) came the second and the third (Table 1). In order to make out the characteristic of HNSCC survivors for SPC systematical distribution and incidence, we compared the incidence of developing a new primary cancer in the top three anatomical areas as has just been noted (Fig. 3 and Table 1), in HNSCC group, the general population (data extracted from WHO CANCER TODAY in 2020), and all primary cancer survivors without site-limitation (data summarized from five released meta-analyses, see details in the figure legend). Interestingly, for the other two groups, SPC was most likely to occur in the lower respiratory system, while HNSCC survivors have the highest SPC incidence in the head and neck region. Such a distinct difference provided crucial insight into the more individualized follow-up strategy for SPC in HNSCC patients. The head and neck region should be paid prior attention to in HNSCC survivors for better prevention or early detection of SPC.

We further explored the predilection for where SPC occurred according to different primary HNSCC site (Fig. 3). The most common SPC site for patients with oral cancer was the head and neck region (27.685 per 1000-person-year). SPC was also more common for patients with oropharyngeal cancer in the head and neck region (10.959 per 1000-person-year) and lower respiratory system (10.153 per 1000-person-year). For patients with laryngeal cancer, it was the upper digestive tract (6.485 per 1000-person-year).

Pooled incidence of SPC according to potential risk factors

We selected ten potential risk factors frequently discussed in published studies, and 17 studies were included in this analysis (Table 2). In terms of demographic characteristics, those aged ≥ 50 years were at a higher risk of SPC (OR 1.69, 95% CI 1.06–2.69). Gender was proved to be an irrelevant factor (OR 1.72, 95% CI 1.63–1.83).

Unhealthy lifestyles, such as smoking, alcohol consumption, and betel quid chewing, have already been identified as risk factors for HNSCC and were proved to be related to SPC after that as well. The OR in smokers compared with non-smokers (OR 1.79, 95% CI 0.62–5.11; $I^2 = 92.0\%$), alcohol drinkers compared with non-drinkers (OR 1.68, 95% CI 1.32–2.12; $I^2 = 92.0\%$), and betel quid chewers compared with non-chewers (OR 5.62, 95% CI 0.61–51.73; $I^2 = 85.0\%$) indicated these three as risk factors for SPC after HNSCC. HPV infection, however, appeared to be a protective factor (OR 0.47, 95% CI 0.30–0.72).

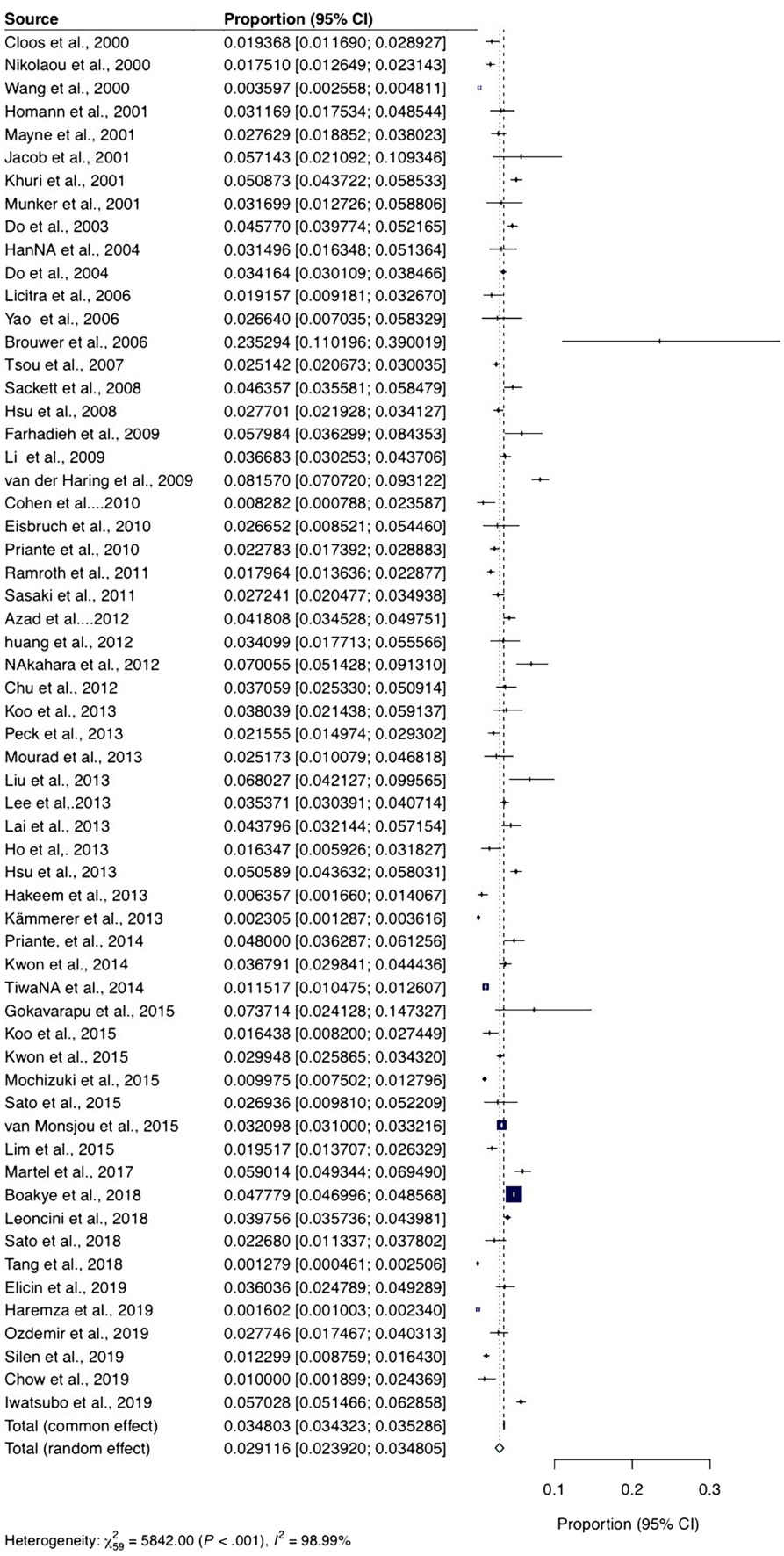

Fig. 2 Forest plots of person-year incidence of SPC

Table 1 Pooled incidence of SPC in HNSCC patients according to different subsites of primary cancer and SPC

Sites	Total SPC					SSPC					MSPC				
	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year incidence	95% CI	I^2 (%)	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year incidence	95% CI	I^2 (%)	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year Incidence	95% CI	I^2 (%)
Primary caner sites															
Oral cavity	10	20641.4	38.729	[29.764, 48.820]	91.33	3	5550.0	6.931	[0.000, 37.143]	98.40	4	4743.5	30.498	[15.668, 50.026]	90.92
Oropharynx	6	7746.9	36.811	[25.325, 50.344]	87.51	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypopharynx	4	2267.8	41.562	[25.822, 60.837]	76.41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Larynx	7	16662.5	22.557	[8.602, 42.902]	98.15	3	5971.3	2.808	[1.626, 4.310]	0.00	4	5702.0	21.046	[14.603, 28.635]	66.87
SPC sites															
General															
Head and neck region	28	191949.1	13.127	[9.282, 18.564	97.57	5	148470.5	2.439	[0.953, 6.239]	97.68	7	146998.0	10.404	[4.890, 22.134]	98.84
Oral cavity	20	35997.2	10.321	[6.397, 16.654]	95.02	4	13334.8	6.130	[1.694, 22.187]	94.78	5	14004.0	10.628	[4.307, 26.223]	95.89
Oropharynx	14	27559.6	30.258	[24.357, 37.588]	88.67	2	7853.7	0.919	[0.413, 2.044]	40.60	2	8522.9	2.438	[0.821, 7.242]	79.73
Hypopharynx	8	16555.5	2.254	[1.013, 5.011]	78.89	NA	NA	NA	NA	NA	2	7853.7	1.287	[0.670, 2.472]	43.30
Larynx	12	27398.3	2.707	[2.098, 3.493]	41.36	NA	NA	NA	NA	NA	4	293052.2	1.414	[1.284, 1.558]	43.18
Thyroid	6	11539.6	1.744	[1.069, 2.845]	27.14	NA	NA	NA	NA	NA	2	283391.0	0.774	[0.678, 0.884]	0.00
Lower respiratory system	29	173255.2	7.472	[5.740, 9.726]	92.43	6	145802.4	0.816	[0.326, 2.040]	86.09	10	434445.5	3.516	[2.108, 5.865]	98.52
Upper digestive tract	19	141440.5	2.696	[1.739, 4.180]	86.85	2	100790.1	0.625	[0.488, 0.800]	0.00	5	108257.4	1.601	[0.769, 3.330]	64.99
Esophagus	25	185162.3	2.605	[1.707, 3.978]	90.88	4	143551.3	0.483	[0.240, 0.974]	71.84	9	440289.9	1.885	[0.728, 4.879]	99.29
Stomach	7	10527.3	2.409	[1.168, 4.973]	59.31	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lower digestive tract	11	25009.4	2.601	[1.347, 5.022]	74.85	NA	NA	NA	NA	NA	3	1005.8	4.003	[1.505, 10.644]	0.00

Table 1 (continued)

Sites	Total SPC				SSPC					MSPC				
	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year incidence	95% CI	I^2 (%)	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year incidence	95% CI	I^2 (%)	Studies (*n*)	Total person-years (*n*)	Per 1000-person-year Incidence	95% CI	I^2 (%)
Genitourinary system	11	34333.3	2.322	[1.238, 4.353]	86.03	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other sites															
Liver	9	20574.5	0.944	[0.536, 1.661]	44.40	NA	NA	NA	NA	NA	3	286764.1	0.534	[0.456, 0.627]	47.15
Skin	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	705.8	3.057	[0.766, 12.196]	0.00
Breast	5	20855.0	0.715	[0.278, 1.837]	53.90	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lymphoma/leukemia	7	20665.5	0.801	[0.444, 1.446]	37.38	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: *SPC*, second primary cancer; *SSPC*, synchronous second primary caner; *MSPC*, metachronous second primary cancer; *CI*, confidence interval; *NA*, not available

We were also able to confirm that primary HNSCC with specific oncologic characteristics were more likely to develop an SPC (Fig. 4). Primary cancers of $T_{1–2}$ (OR 1.57, 95% CI 1.23–2.02) and N_0 (OR 1.58, 95% CI 1.15–2.18) were demonstrated to be at a higher risk of SPC compared with those of T_3–T_4 and N_1–N_3.

Risk of bias assessment and heterogeneity analysis

The details of risk of bias in individual studies using the Newcastle–Ottawa scale (NOS) are available in eTable 3. The number of high-quality studies is 9, which indicates the studies with comprehensive information provided. The details of risk of bias across studies are available in eFig 2. There was no evidence of publication bias with the Egger test ($p = 0.12$).

As we observed significant heterogeneity among included studies, geographical region, sampling method, sample size, and year of primary cancer diagnosis were selected as the potential source of heterogeneity for subgroup analysis (eTable 3). However, we only observed a few faint changes in pooled incidence and a minor decline in I^2. Thus, we failed to find the source of heterogeneity in the baseline by subgroup analysis.

Discussion

In this study, we summarized the incidence of SPC in patients with HNSCC and proved it to be a common event, with the pooled per 1000-person-year incidence of 29.116 for tSPC, 6.960 for SSPC, and 26.025 for MSPC. The most common SPC sites were the head and neck region, lung, and upper digestive tract. Different primary cancers had their predilection for where SPC occurred. Age over 40 years, smoking, alcohol consumption, betel quid chewing, family cancer history, primary cancer of T_1–T_2, N_0, or well/moderate differentiation were found to be risk factors for SPC after HNSCC, while HPV infection and radiotherapy were protective factors. To our knowledge, this is the most extensive systemic review of SPC in patients with HNSCC, the first meta-analysis to assess the risk factors, and the first to calculate the incidence of developing SPC after the HNSCC based on the person-year analysis [71–73].

Site distribution of SPC after primary HNSCC was frequently discussed in previous studies, sharing generally consistent results with slight differences. The most common SPC site for patients with primary SCC in the oral cavity and oropharynx was the head and neck; for patients with hypopharyngeal cancer, it was the lung and esophagus; for those with laryngeal cancer, it was the lung [69, 71, 73–77]. These findings are not surprising as the SCC of the lung, head and neck, and esophagus shares similar risk factors and morphologic features as well as mechanisms

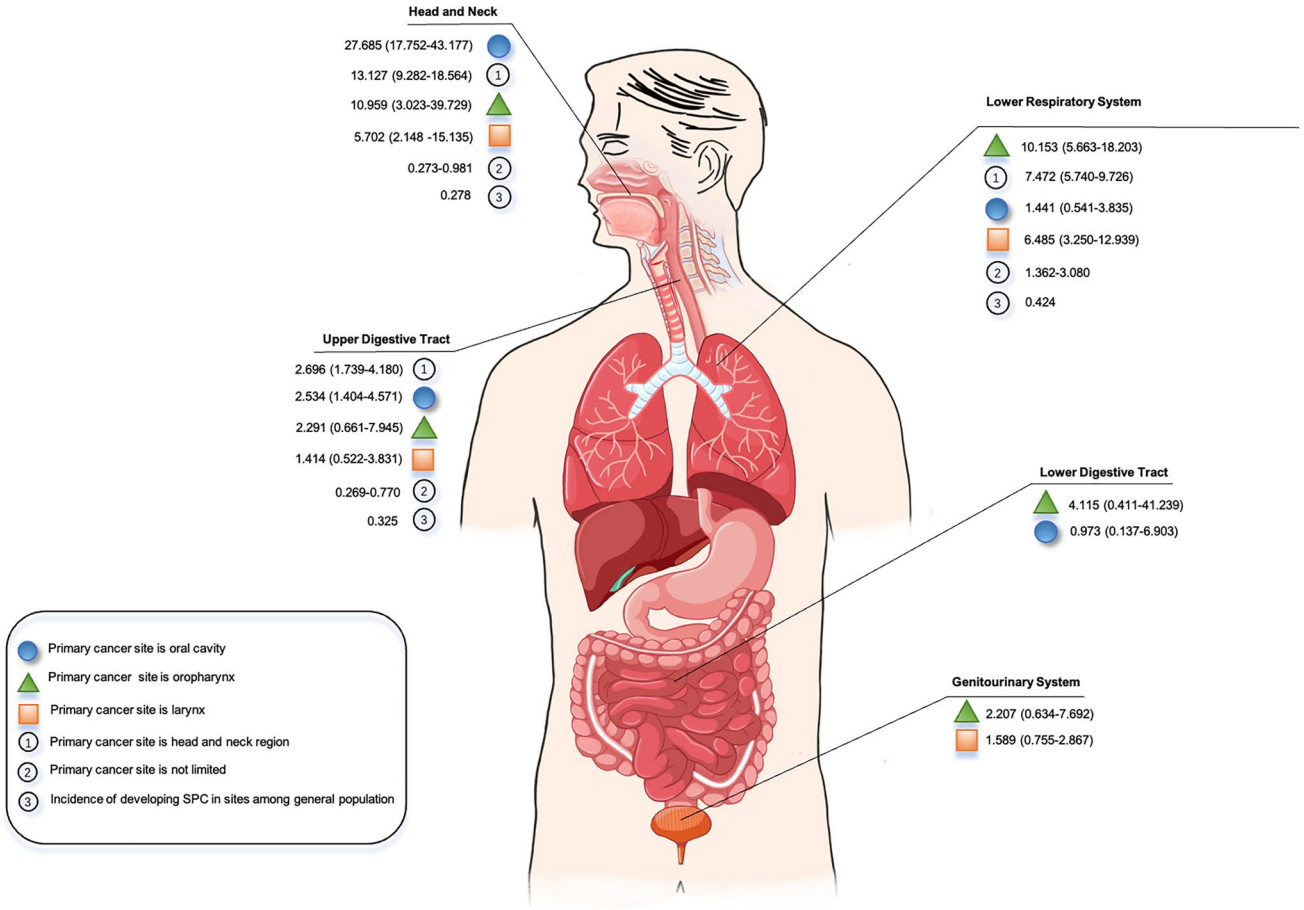

Fig. 3 Site distribution of tSPC occurring after the four primary cancers. For each figure, the SPC site was listed above the horizontal line. Primary cancer sites were represented by dots of different colors and listed below the line in order of incidence from highest to lowest. 95% confidence interval was shown within the brackets. (**A**) SPC sites were divided into five anatomic areas: head and neck region, lower respiratory system, upper digestive tract, lower digestive tract, and genitourinary system; (**B**) SPCs in the head and neck region were further divided into those occurred in the oral cavity, oropharynx, hypopharynx, larynx, and thyroid; (**C**) incidence of developing SPC from not-limited primary cancer sites was summarized from study Sung, H. et al., 2020, Feller, Anita et al., 2020, Jégu, Jérémie et al., 2014, Donin, Nicholas M et al., 2016, Donin, Nicholas et al., 2019; c: Pooled incidence of developing SPC in three sites above among patients with HNSCC, according to our meta-analysis; (D) the crude rate of estimated new cancer cases among general population was extracted from WHO CANCER TODAY in 2020; abbreviations: SPC, second primary cancer

of tumorigenesis. Genetic predisposition could also play a role. The HNSCC has been confirmed to be associated with molecular-level changes such as the epidermal growth factor receptor (EGFR) and the genetic polymorphism of p21 [78, 79], which may explain the reason why second primary cancer of HNSCC is most likely to occur in the head and neck. Studies have confirmed that the fibroblast growth factor receptor 1 (FGFR1) gene located on chromosome 8 in HNSCC is highly variable, while frequent amplification of FGFR1, a cell surface receptor of fibroblast growth factor involved in the regulation of cell proliferation and differentiation, can also be detected in primary lung squamous cell carcinoma [80]. This may provide guidance for HNSCC treatment and prognostic testing programs to reduce the incidence of secondary primary cancer.

The evaluation of risk factors for SPC is of great importance during the follow-up of cancer survivors, contributing to earlier diagnosis and treatment of SPC, and eventually improves the prognosis of HNSCC. Lifestyle factors such as smoking, alcohol consumption, and betel quid chewing have already been proved to be risk factors for sure, and those who continued smoking after a cancer diagnosis seem to have a higher risk of SPC [81, 82]. The phenomenon could be partly explained by the classic theory of field cancerization [82]. This theory hypothesizes the tissue in a certain site is exposed to carcinogenic factors such as tobacco, alcohol for a long time, and those genes in the tissue cells are abnormally changed, which leads to an increased risk of malignant lesions in the epithelial layer of the entire area, and multiple malignant lesions may occur simultaneously or

Table 2 OR for SPC[a] in HNSCC patients according to potential risk factors

Variable	Studies (*n*)	OR	95% CI	I^2 (%)
Age	5	1.72	1.63–1.83	0
> 50				
< 50				
Gender	8	1.01	0.56–1.84	85
Male				
Female				
Alcohol consumption	6	1.68	1.32–2.12	34
Yes				
No				
Smoking	8	1.79	0.62–5.11	92
Yes				
No				
Betel quid chewing	2	5.62	0.61–51.73	85
Yes				
No				
T stage	4	1.57	1.23–2.02	43
T_1–T_2				
T_3–T_4				
N stage	3	1.58	1.15–2.18	0
N_0				
$N_{1–3}$				
Clinical stage	7	1.01	0.77–1.44	30
1–2				
3–4				
HPV infection	3	0.47	0.30–0.72	0
Positive				
Negative				
Treatment	3	0.53	0.32–0.89	0
With radiotherapy				
Without radiotherapy				

[a]SPC in this table did not tell a difference between total SPC, SSPC, or MSPC. For the studies that had relevant data on tSPC, SSPC, and MSPC, the data on tSPC was used

Abbreviations: *SPC*, second primary cancer; *SSPC*, synchronous second primary cancer; *MSPC*, metachronous second primary cancer; *CI*, confidence interval; *OR*, odds ratio

successively. That is to say, risk factors for primary cancer affect other sites at the same time (for example, continuous exposure to tobacco harms the esophagus and airway), which may increase their incidence of SPC. This reminds us of the importance of encouraging healthy lifestyles and routine comprehensive examination in cancer survivors.

HNSCC of advanced stage or poor differentiation is more likely to undergo recurrence and metastasis within the 5 years after treatment. On the contrary, those of T_1–T_2 and N_0 stage or well/moderate differentiation tend to suffer from SPC. Part of the reason may be that they have a longer survival time to develop a second cancer and the incidence of SPC rises with the extension of follow-up time.

The impact of radiotherapy on the occurrence of SPC in HNSCC patients still remains controversial [6]. So far, the most consensus view is that the risk of SPC in patients receiving radiotherapy decreases during the first 5–10 years after HNSCC diagnosis, but then increases beyond the risk in those without radiotherapy [6, 83]. A possible theory is that radiation may sterilize occult synchronous malignancies and premalignant tissues, thus reducing the incidence of SPC in or near the irradiated fields [84, 85]. While in terms of its carcinogenic effect, it often takes years of latency to be revealed. So it may result in underestimating actual incidence due to limited follow-up time [65, 86]. As the mean follow-up time of all included studies was mainly within 5 years, it is not surprising that radiotherapy was a protective factor in the present study.

Some problems in follow-up strategy of SPC still exist nowadays. For example, the need of an individually tailored approach that considers the specific performance status and the impact on quality of life of the diagnosis of SPC in asymptomatic patients [87]. The incidence based on person-year analysis, which takes the follow-up time into considerations as a part of the denominator, provides relatively more accurate data. The three major sites with high risk in developing the SPC after HNSCC are head and neck region, lung, and upper digestive tract, which is almost the same as the result of the sites developing SPC after HNC [8]. The subsites with highest incidence in head and neck region are as follows: oropharynx, oral cavity, and hypopharynx, suggesting that more targeted inspections are needed in screening and diagnosis of head and neck region and upper digestive tract. The data of the ranking of most common SPC sites in different primary HNSCC sites can provide the detailed evidence in personalized follow-up strategy in clinical work. For example, the patients with larynx primary cancer should pay more attention to lung SPC than head and neck region according to the data.

Some limitations of the present study should be interpreted. Firstly, there was significant heterogeneity in most of our analyses and we failed to explain it through subgroup analysis. We assumed that the heterogeneity might be partly attributed to the differences in the diagnostic criteria for SPC, which were diversely modified according to the Warren and Gates criteria and strikingly varied among the included studies. Even though we tried to categorize the studies according to different criteria throughout the analysis process, similar results were obtained as those shown in the present study. Secondly, ORs were calculated using raw data extracted from studies, not adjusting for potential underlying differences between individuals. The connections between the first and second primary cancer were mediated by complex interactions between them, including genetic predispositions, aging, treatment exposures, lifestyle factors, socioeconomic status, and access to health care [88], which could not be independently

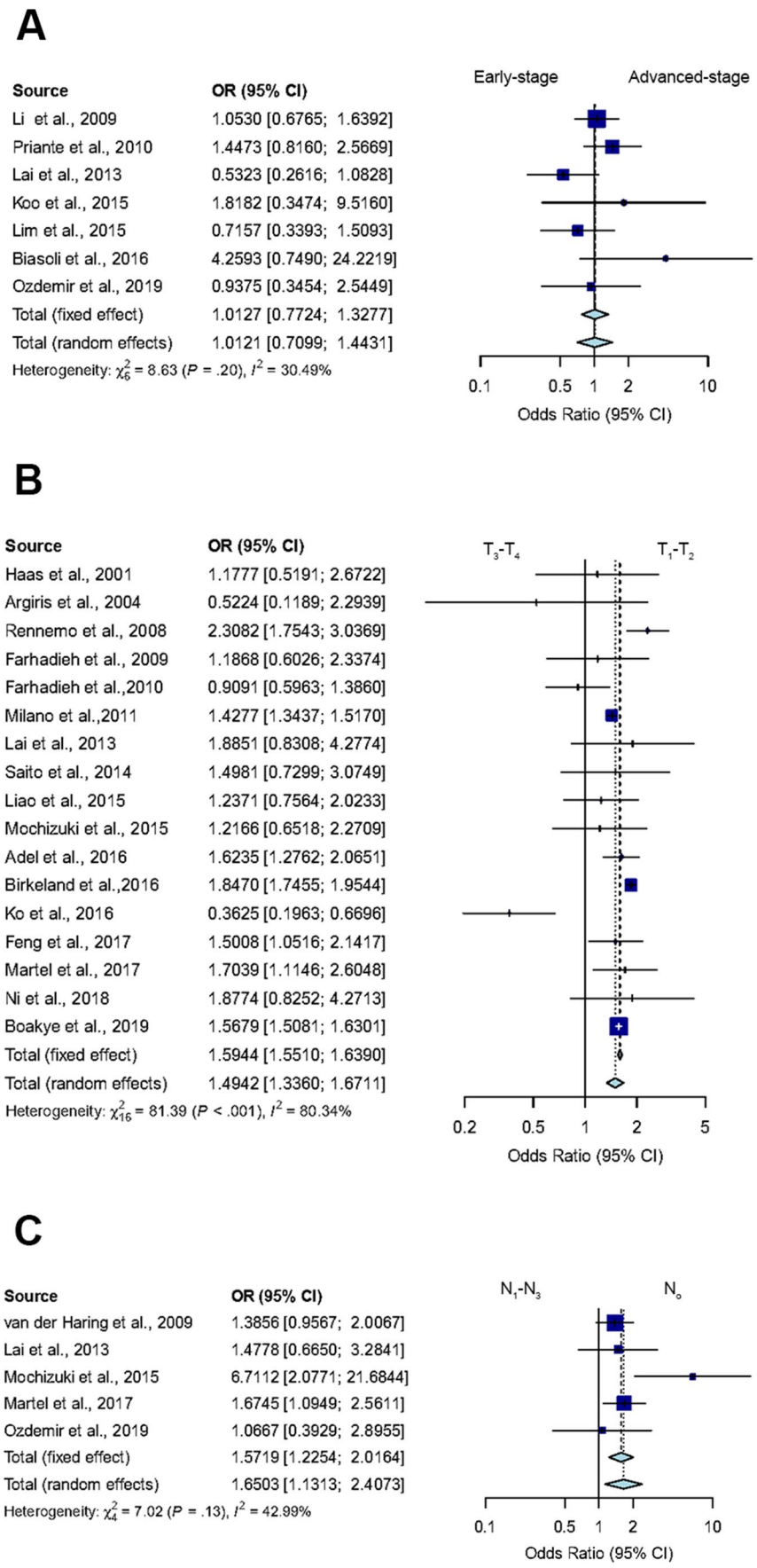

Fig. 4 Forest plots of OR for SPC according to potential risk factors. (**A**) OR for tSPC, SSPC, and MSPC in patients with HNSCC of early stage versus advanced stage; (**B**) OR for SPC in patients with HNSCC of $T_{1–2}$ versus $T_{3–4}$; (**C**) OR for SPC in patients with HNSCC of N_0 versus $N_{1–3}$. Abbreviations: OR, odds ratio; CI, confidence interval; SPC, second primary cancer; tSPC, total second primary caner; SSPC, synchronous second primary caner; MSPC, metachronous second primary cancer

analyzed. However, the direction of the effect, protective or harmful, could still be identified in the present study.

Conclusions

SPC is frequently observed after the diagnosis of HNSCC and the incidence varies with different sites of primary cancer and SPC. Unhealthy lifestyles, anatomical subsites, initial treatments, and other oncological factors of primary HNSCC should all be taken into consideration when assessing the risk of SPC. Thus, a more individualized screening and follow-up strategy should be applied according to different degrees of risk, with the reasonable arrangement of various examinations at the proper time of points.

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Author contribution GL, YL, and LY contributed to conception and design of the study. XZ, DL, and HX contributed to data extraction. XZ organized the data. DL, BZ, and JG performed the statistical analysis. XZ, DL, HX, and JF wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Data availability The original contributions presented in the study are included in the supplementary material. Further inquiries can be directed to the corresponding authors.

Declarations

Competing interests The authors declare no competing interests.

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