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REVIEW

Prevalence of human Papillomavirus associated oropharyngeal and oral squamous cell carcinoma in Asian countries: A systematic review and large-scale meta-analysis

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Human Papillomavirus (HPV) associated with oropharyngeal and oral squamous cell carcinoma (OPSCC and OSCC) is escalating over the years. Hence, the present review aims to determine the prevalence of HPV-OSCC and HPV-OPSCC in Asian countries over the last decades. An electronic search was conducted using nine online databases to identify English-language articles on the prevalence of HPV-OPSCC and HPV-OSCC in Asian countries from January 2011 to June 2022. The risk of bias was assessed using the JBI critical appraisal checklist and the level of evidence was determined based on the OCEBM guideline. Single-arm meta-analysis was used to estimate the weighted mean prevalence of HPV-OPSCC and HPV-OSCC among patients in Asia. Subgroup analysis meta-regression and Egger's tests were also conducted. 59 eligible studies were included with a higher prevalence of HPV-OPSCC (32.6%-37.4%) as compared to HPV-OSCC (10.9%-23.5%). Subgroup analysis revealed that the weighted mean prevalence of HPV-OPSCC was significantly higher (P<0.001) among East Asians, while the weighted mean prevalence of HPV-OSCC was significantly higher (P<0.001) among South Asians. All studies showed a low to moderate risk of bias with the level of evidence ranked between 2 and 3. The diagnostic tools utilised and geographical locations significantly affect the findings.

Keywords: Asia, epidemiology, mouth neoplasm, HPV, polymerase chain reaction

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Introduction

Squamous cell carcinoma of the head and neck is the sixth most prevalent cancer in the world [1], with oropharyngeal squamous cell carcinoma (OPSCC) and oral squamous cell carcinoma (OSCC) are both malignant neoplasms that occurred commonly in the head and neck region. In contrast to other head and neck cancers, both the incidence and prevalence of OPSCC and OSCC rose considerably over the years [2, 3]. Cancer of the oropharynx and oral cavity has long been linked to tobacco chewing or smoking, as well as the consumption of alcoholic beverages [3]. They also mainly afflict older age groups between the fifth and sixth decades. However, the incidence of OPSCC and OSCC in young population has increased in several countries over the last few decades [4], and one of the risk factors is attributed to the rise in human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (HPV-OPSCC) and HPV-related oral squamous cell carcinoma (HPV-OSCC), particularly high-risk HPV types such as HPV-16 and HPV-18 [5, 6]. HPV is one of the most prevalent infectious agents transmitted sexually across the world, and the main risk factors are sexually acquired behaviours [7]. HPV infection can cause clinical illnesses, such as anogenital warts, cervical neoplasia, cervical cancer, and other anogenital malignancies, even though most infections are asymptomatic and resolve within two years [8].

It is worth noting that, in terms of aetiological variables and gender, the demographic pattern of this disease among young patients differs [9]. Men who are non-smokers, non-drinkers, and have a decent socioeconomic position are more likely to develop oropharyngeal cancers associated with HPV [10]. The bulk of the literature has shown that the incidence and prevalence of HPV-related OPSCC and OSCC were high and continue to escalate [11, 12]. A rapid increase in HPV-OPSCC and HPV-OSCC prevalence would have crucial ramifications for patients, healthcare professionals, and commissioners, since patients would have to deal with substantial treatments and demand greater assistance from healthcare systems [12]. Nonetheless, current evidence on the prevalence of HPV-OPSCC and HPV-OSCC in Asia is relatively scarce in the literature as compared to the United States of America and other Western Europe countries [13, 14]. Previous systematic studies on the prevalence of HPV-related OPSCC and OSCC were either too geographically restricted, focusing solely on South-Central Asia [15], or too general, pooling data from all cases of head and neck cancer without fo-

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cusing on the oral cavity and oropharyngeal regions [16]. Furthermore, the reporting quality of the primary studies included in the previous review was not thoroughly evaluated, which might result in low-quality primary studies being included, and contribute to errors and bias [16].

To the best of the authors' knowledge, there is still a paucity of a well-conducted systematic review and meta-analysis on the prevalence of HPV-related OPSCC and OSCC in Asian countries. Although HPV prevalence rates in OSCC have been reported to be lower than in OPSCC [17, 18], it is unknown if this is only a lag period, or whether HPV prevalence in OSCC is now emerging, imitating the surge of HPV in OPSCC. Therefore, a comprehensive systematic review on this issue was justified since new research has been published and no systematic review evaluating the prevalence of HPV associated OPSCC and OSCC among Asian populations has been reported recently. The objectives of the present study were to determine the prevalence of HPV-related OSCC and OPSCC in Asian countries over the last decades, as well as critically assess the quality of currently available evidence.

Methods

Protocol and registration

The current systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database, University of York with a registration number (CRD42021275003). The study was performed based on Preferred Reporting System for Systematic Reviews (PRISMA) guidelines, which specify a systematic selection of articles to be included [19]. The PIO framework was, Patient or population (P) – patients diagnosed with OSCC or OPSCC, Intervention or indicator (I) – HPV testing, Outcome (O) – Prevalence of HPV-OSCC and HPV-OPSCC in Asian countries. Hence, the PIO question was 'What is the prevalence of patients diagnosed with HPV-OSCC and HPV-OPSCC in Asian countries? In this framework, Asian countries are divided into six regions: North Asia, Central Asia, East Asia, South Asia, Southeast Asia, and West Asia, with a total of 48 countries.

Search strategy

An electronic search was conducted using nine online databases (Google Scholar, PubMed, Web of Science, Science Direct, Cochrane Library, EBSCO, LILACS, Open grey, EMBASE) independently by four investigators (KWSH, YJT, JLSW, GSSL) on the first week of April 2022 to identify potential articles published in English from January 2011 to June 2022. Besides, reference lists of pertinent articles from the electronic search were separately evaluated by two other investigators (WLLK, WNAN) using a computer software (EndNote X9, Thomson Reuters). Extensive databases search were performed using all combination of first keywords ("human papillomavirus", "human papillomaviridae", "HPV") and second keywords ("Oral cancer", "oral tumour", "oral tumor", "oral squamous cell", "oral carcinoma", "oropharyngeal cancer", "oropharyngeal carcinoma", "verrucous carcinoma", "oral malignancy", "oral neoplasm", "mouth malignancy", "mouth neoplasm", "mouth tumour", "mouth tumor", "mouth cancer", "OSCC", "OPSCC", "OPC") using the Boolean operators 'AND' and 'OR'.

Study selection

After the removal of duplicated articles using EndNote software version x9, the articles were screened independently based on the title and the abstract by two investigators (KWSH, YJT). Three investigators (JLSW, WLLK, WNAN) subsequently conducted a full-text evaluation to select eligible studies based on the inclusion and exclusion criteria. The inclusion criteria were: (1). randomized or non-randomized controlled trials, prospective or retrospective cohorts, case-control, or cross-sectional studies. (2). presented in English language only. (3). prevalence of HPV-OSCC or HPV-OPSCC. (4). Asian countries. (5). HPV detected using polymerase chain reaction (PCR)-based methods, in situ hybridization (ISH) or other HPV detection methods. On the other hand, the exclusion criteria of this study were: (1). expert opinions, short communications, reviews, case reports, case series or animal studies. (2). prevalence of HPV associated with tumours other than OSCC or OPSCC. (3). sample obtained using serology or mucosal brushings.

Calibrations between investigators were performed to assess interrater reliability. To compare the investigators' decisions on inclusion and exclusion, the average concordance was calculated using the Kappa value [20]. With the assistance of the sixth investigator (GSSL), any conflicts that developed throughout the search were addressed and resolved.

Data extraction

Four investigators (KWSH, YJT, JLSW, WNAN) used a modified excel spreadsheet extraction form to extract and document the parameters of each article. The following information was extracted: author, country, year, type of studies, total samples, age of patients, clinical signs and symptoms, radiographical signs and symptoms, TNM stage, histological results, specific site, gender predilection, type of HPV, prevalence, and prognosis/ survival. If any discrepancies were identified, the fifth investigator (GSSL) double-checked the accuracy of the filled data, and a further discussion with all investigators was convened.

Risk of bias assessment

The risk of bias for each included study was independently evaluated by five investigators (KWSH, YJT, JLSW, WLLK, WNAN) using four quality assessment tools. Cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies [21]. Either a 'yes', 'no', 'un-

clear' or 'not applicable' was assigned for each domain and the studies were categorized as 'include', 'exclude' or 'seek further info'. The cohort and case-control studies were assessed by using the JBI checklist for cohort and case-control studies, respectively [22, 23]. On the other hand, randomised clinical study was assessed by using the JBI checklist for randomized controlled trials [24]. The Oxford Centre for Evidence-Based Medicine (OCEBM) guideline was used to establish the level of evidence in each study [25]. Any discrepancies in study selection, data extraction, or quality assessment were resolved via discussion among all investigators until a consensus was achieved.

Statistical analysis

A single-arm meta-analysis based on the DerSimonian-Laird random-effects model was used to estimate the weighted mean prevalence of HPV-OPSCC and HPV-OSCC among patients in Asian countries from each study. With a significance level of 0.05 and 95 % confidence intervals, the analysis was carried out using the OpenMeta [Analyst] software (CEBM, Oxford, UK) (CI). The upper limit was defined as 1.0 if the predicted upper limit of the 95 % confidence interval was greater than 1.0. The Higgins' I^2 statistic was also used to evaluate the degree of data heterogeneity across all included studies, with I^2: <30% = acceptable heterogeneity, I^2: 30-60% = moderate heterogeneity, I^2: >60% = substantial heterogeneity [26]. Subgroup analysis and meta-regression were conducted to assess the effect of Asian regions and sample size on the overall prevalence rates of HPV-OPSCC and HPV-OSCC. Furthermore, Egger's test was used to identify publication bias.

Results

Study selection

The initial literature search yielded 2194 items with a search period covering January 2011 to June 2022 (Figure 1). 1489 articles were discarded after duplication was eliminated, followed by 561 articles that were dismissed based on titles and abstracts. The remaining articles were selected for an in-depth full-text assessment according to the inclusion and exclusion criteria. Finally, 59 articles were included in the present review. During the study selection process, the average inter-investigators Kappa score for preliminary article screening (titles and abstracts) and the second screening (full-text assessment) were 0.83 and 0.79, respectively, indicating 'perfect' agreement [27]. The reasons for article exclusion are depicted in Figure 1. The characteristics of the included studies are summarized in Table 1. In general, a total of 64773 samples were included in the current review with the majority of the primary studies originating from India, followed by China and Japan. Most of the primary articles were published in the years 2014 and 2016 with 42 cross-sectional studies, 13 case-control studies, 3 cohort studies, and 1 randomized controlled trial. The patients included in the current review ranged from 18 to 93 years old, and the majority are males. Most of the primary data obtained identified HPV-16 and HPV-18 subtypes.

Risk of bias assessment

All cross-sectional studies were given a 'Yes' for domains 1, 4, 7, and 8, while four studies in domain 2, one study in domain 3, seven studies in domain 5, and fifteen studies in domain 6 were given a 'No'. Besides, two studies were given 'Unsure'. On the other hand, all case-control studies were rated 'Yes' for domains 1,2, 3 and 8, with three studies in domain 6, four studies in domain 7, and one study each for domains 4, 5, and 10 were rated 'No'. Two studies each in domains 4 and 5, and one study each in domains 7 and 9 were rated 'Unclear'. All cohort studies were rated 'Yes' in each domain except for two studies were given 'unclear' in domain 10. In addition, the only randomised controlled study in the present review was rated 'Yes' for all domains except for domains 5 and 6. In general, all included studies demonstrated a low to moderate risk of bias. Most included studies were ranked as Level 3 with three studies ranked Level 2 based on the evidence of OCEBM (Table 2).

Statistical analysis

Table 3 shows the prevalence of HPV-OPSCC and HPV-OSCC using different diagnostic tools. The prevalence rates of both HPV-OPSCC and HPV-OSCC were calculated only if there are three or more studies reporting the number of OPSCC and OSCC patients or tissue samples diagnosed with HPV. For OPSCC, 14 studies used p16 Immunohistochemistry (IHC) to determine the prevalence of HPV-OPSCC, 8 studies used in-situ hybridization (ISH) test, and 18 studies used polymerase chain reaction (PCR) test. On the other hand, 11 studies used p16 IHC to determine the prevalence of HPV-OSCC, while 29 studies used PCR test to determine the prevalence. 4 studies were excluded from the analysis of the prevalence of HPV-OSCC using PCR test due to zero value. Moreover, the analysis of HPV-OPSCC and HPV-OSCC identified using EasyChip HPV blot, as well as the analysis of HPV-OSCC detected with ISH test were not performed owing to a paucity of data.

The weighted mean prevalence of HPV-OPSCC and HPV-OSCC are shown in Figure 2 and Figure 3, respectively. Overall, HPV-OPSCC (ranged from 32.6% to 37.4%) was found to exhibit a higher prevalence among Asian countries as compared to HPV-OSCC (ranged from 10.9% to 23.5%). Further details revealed that HPV-OPSCC identified using HPV ISH test shows a higher prevalence rate [37.4%, CI: (20.0, 54.7)], followed by that using HPV PCR [37.2%, CI: (23.4, 51.0)], and p16 IHC test [32.6%, CI: (26.2, 39.0)]. For HPV-OSCC, a higher prevalence rate was noted when PCR test was used as the diagnostic tool [23.5%, CI: (17.5, 29.4)], followed by that using p16 IHC test [10.9%, CI: (7.3, 14.5)]. The I^2 of the weighted mean prevalence of OPSCC and OSCC ranged

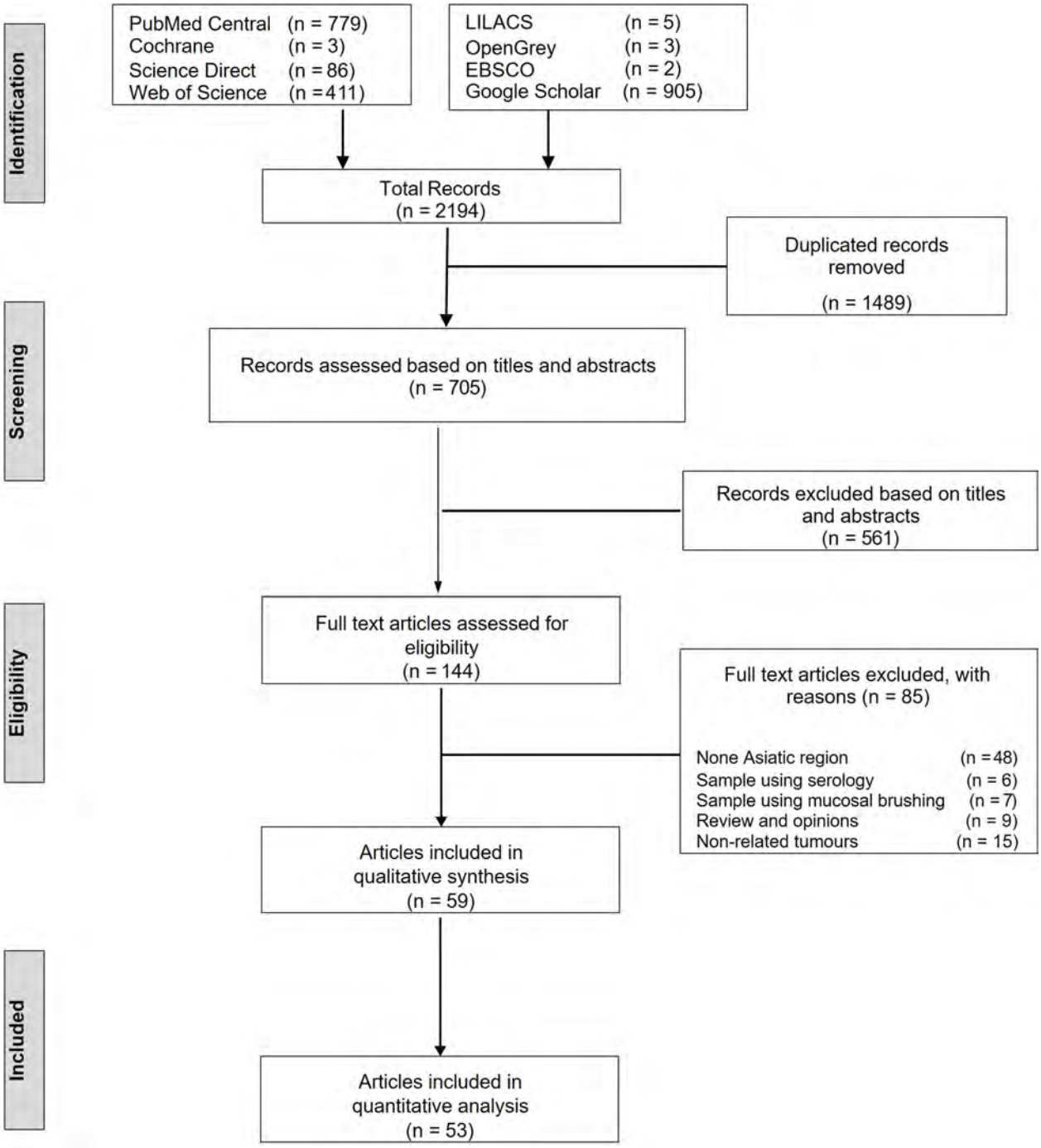

Fig. 1. Study selection according to PRISMA guideline

between 88.80% to 98.06% and 71.19% to 96.49%, respectively, indicating the existence of substantial heterogeneity among the included studies for quantitative analysis.

Sensitivity analyses were performed for the prevalence of HPV-OPSCC and HPV-OSCC. The highest and lowest weighted mean prevalence of HPV-OPSCC diagnosed using p16 IHC were 33.8% [CI: (27.2, 40.4)] and 30.1% [CI: (25.0, 35.3)] when Argirion I *et al*. and Xu T *et al*. were omitted, respectively. For HPV-OPSCC diagnosed using HPV ISH, the highest and lowest weighted mean prevalence were 40.6% [CI: 21.9, 59.4)] and 32.1% [CI: (18.3, 45.9)] when Nopmaneepaisam T *et al*. and Kim Y *et al*. were removed, respectively. Furthermore, the highest and lowest weighted mean prevalence of HPV-OPSCC diagnosed with HPV PCR were 38.2% [CI: (23.8, 52.6)] and 33.5% [CI: (28.5, 38.4)] when Lam EW *et al*. and Kim Y *et al*. were omitted, respectively. On the other hand, for HPV-OSCC diagnosed with p16 IHC, the highest and lowest weighted mean values were 11.7% [CI: (8.5, 15.0)] and 10.3% [CI: (6.7, 13.9)] when Jiarpinitnun C *et al*. and Stritippho T *et al*. were removed, respectively. For HPV-OSCC diagnosed using HPV PCR test, the highest and lowest weighted mean prevalence were 24.3% [CI: (18.5, 30.2)] and 21.7% [CI: (16.0, 27.4)], when Kim Y *et al*. and Mathew A *et al*. were excluded, respectively.

Table 1. Characteristics of the included studies.

Authors	Year	Type of Study	Asian Regions	Country	Sample size	Patient Age	Gender	HPV Subtype	Testing Method	General Outcomes
Gan LL et al.	2014	CC	Eastern	China	200	18-55, more than or equal to 56	Male = 143 Female = 57	16, 18	PCR	The prevalence of HPV of all types in the OSCC group was higher than in the control group (55/200 vs 2/68, OR=11.5, 95% CI=2.6-50.2). HPV-16 and HPV-18 were the main types detected, with the HPV-6 was the only low-risk type identified.
Hama T et al.	2014	C	Eastern	Japan	157	Mean age 61.4	Male = 61, Female = 18	16, 18, 31, 33, 35, 52, 58	PCR	HPV was detected by PCR in 79 (50.3%) out of 157 OPSCC patients.
Joo YH et al.	2014	CC	Eastern	Korea	48	37-80 years	-	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 66	ISH	High risk HPV ISH was positive in 29% of patients (14/48). Of these patients with high-risk HPV, there was a significant difference (p = 0.008) between oral (9.5%) and oropharyngeal (44.4%) cancers.
Ramshankar V et al.	2014	CC	Southern	India	156	-	Male = 108, Female = 48	16	PCR, p16 IHC	HPV prevalence in tongue cancers was 51.2%. HPV-16 being present in 85.2% of the positive cases.
Rushatamukayanunt P et al.	2014	CS	Eastern	Japan	80	-	Male = 54, Female = 26	-	PCR, p16 IHC	Only two (5%) young patients and one (2.5%) older patient were positive for HPV DNA. P16 overexpression was identified in six (!5%) young patients.
Kane S et al.	2015	CS	Southern	India	124	Median (range) = 43 (37-52)	Male = 109, Female = 15	-	p16 IHC	Of 124 patients, 16 patients (12.9%) were HPV-positive.
Wakisaka N et al.	2014	CS	Eastern	Japan	38	-	Male = 33, Female = 5	16	PCR, p16 IHC	Among 38 case analyzed, HPV-DNA was positive in 19 cases in which only HPV-16 was detected. 21 of 38 OPCs were p16-positive. All 19 HPV-DNA positive tumors were p16-positive.
Lee LA et al.	2015	C	Eastern	Taiwan, China	1002	25-89 years	Male = 938, Female = 64	16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68	PCR	The overall prevalence of HPV infections was 19%, with a trend toward decreasing rates from 2004 to 2011.
Parshad S et al.	2015	C	Southern	India	50	Mean = 55.32 + 10.20	Male = 44, Female = 6	16, 18	PCR	42% of OSCC patients were found to harbor HPV-16 an -18 whereas only 8% of patients with benign lesions had HPV-16 and -18
Hwang TZ et al.	2014	CS	Eastern	Taiwan, China	58,448	-	-	-	-	The incidence trends of HPV-related and HPV-unrelated head and neck cancer in Taiwan both rose during 1995-2009.
Singh V et al.	2015	CS	Southern	India	250	-	Male = 200, Female = 50	16, 18	PCR	HPV presence was confirmed in 23/250 (9.2%) OSCC cases, of which 30.4% had HPV-16 infection, 17.4% were positive for HPV-18 and 26.1% had co-infections.
Lam EW et al.	2016	CS	Eastern	China	207	-	Male = 178, Female = 29	-	p16 IHC	20.8% (43/207) of OPSCC was associated with HPV. HPV-16 was identified in all cases except one (HPV-18).
Pongsapich W et al.	2016	CS	South-Eastern	Thailand	23	Mean: OPSCC = 57.7+10.99, OSCC = 61.5+18.41	Male: OPSCC = 20, OSCC = 9 Female: OPSCC = 3, OSCC = 14	16	PCR	The prevalence of HPV-related OPSCC was significantly noted in 26.09% (p = 0.009), while no demonstrable HPV-associated prevalence in OSCC.
Sritippho T et al.	2016	CS	South-Eastern	Thailand	37	Mean (range) = 52.2 (31-82) year	Male = 19, Female = 22	16, 18	PCR, p16 IHC	P16 was overexpressed in 8/37 cases (21.6%) of OSCC. HPV-16 was detected in 4/34 OSCC cases (11.8%) and HPV-18 was detected in 1/34 (3.9%) OSCC cases.
Chen F et al.	2016	CC	Eastern	China	178	Median: = 58.92	Male = 110, Female = 68	16, 18	PCR	The overall HPV prevalence was 14.04% in OSCC patients and 3.17% in controls. HPV-18 was the most prevalent types in cases and controls (10.6% vs 2.12%)
Nakano T et al.	2015	CS	Eastern	Japan	105	Mean (range) = 60 (33-84)	Male = 85, Female = 20	-	ISH, p16 IHC	Fifty-six (53.3%) of the 105 cases were shown by ISH to be positive for high-risk HPV
Toman J et al.	2016	CC	Eastern	Japan	59	-	Male = 39, Female = 5	-	PCR, p16 IHC	The rate of p16 positivity among the oropharyngeal specimens was 29.5%.

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(Table 1 - continued from page 81)

Authors	Year	Type of Study	Asian Regions	Country	Sample size	Patient Age	Gender	HPV Subtype	Testing Method	General Outcomes
Kouketsu A et al.	2016	CC	Eastern	Japan	174	Mean = 67.6 (range 32-93 years)	Male = 76, Female = 98	16, 18, others	PCR, ISH, p16 IHC	Twenty-four OSCC samples were found positive for p16 expression; all of them were well-differentiated tumors. HPV DNA was detected in 13 of 24 (54%) p16-positive OSCC by real-time PCR; HPV-16, -18 and other high risk genotypes were the most prevalent.
Chen XJ et al.	2016	CS	Eastern	China	198	37-70	Male = 27 Female = 13	-	PCR	None of the tissue & serum samples of OSCCs were positive for HPV-16 or -18 E6, using both real-time PCR and DNA sequencing.
Palve V et al.	2018	CS	Southern	India	312	-	-	-	PCR, p16 IHC	High prevalence (33-58%) of HPV-16/-18 DNA did not correlate with the presence of transcriptionally active viral genomes (15%) in tumors. 18% of the tumors were p16 positive, and only 6% were both HPV DNA and RNA positive.
Ishibashi M et al.	2011	CC	Eastern	Japan	50	-	-	-	PCR, p16 IHC	The total HPV-positive rate in OSCC was 18.0%. 8 cases (16.0%) of OSCC were positive for p16(INK4a)
Chaturvedi AK et al.	2011	CC	Eastern	Japan	271	-	Male = 217, Female = 54	-	PCR	HPV prevalence in OPSCC significantly increased over calendar time regardless of HPV detection assay.
Kulkarni SS et al.	2011	CC	Southern	India	34	-	-	16, 18	PCR	In OSCC, 70.6% were positive for HPV, among which HPV-16 prevalence was observed in 45.8%, HPV-18 in 54.2%, and HPV-16 and -18 multiple infections in 4.18%.
Mathew A et al.	2011	CC	Southern	India	45	Mean + SD = 53.08 + 11.72	Male = 31, Female = 14	16, 18	PCR	73.3% (33/45) of the OSCC patients were positive for oral HPV-16 while 71.1% (32/45) were positive for HPV-18 and 57.7% were found to have both HPV-16 and -18 infections.
Lee SY et al.	2010	CC	Eastern	Korea	36	-	-	16, 18	PCR	The prevalence of HPV+ among OPSCC cases were 50% (22/44) and 36.0% (9/25) among OSCC cases. Univariate analysis revealed that OPSCC and OSCC were significantly more likely to be HPV+ than hypopharyngeal SCCs ($P < 0.001$ and $P = 0.024$, respectively)
Deng Z et al.	2011	CC	Eastern	Japan	44	-	-	-	PCR	The highest prevalence of the HPV sequence was found in OPSCC (50.0%), especially in tonsillar cancer (63.6%)
Lee LA et al.	2012	CC	Eastern	China	333	-	-	16, 18, 52	PCR	The prevalence of HPV+ OSCC was 22%; HPV-16 (9%) and HPV-18 (7%) were the genotypes most commonly encountered.
Barwad A et al.	2012	CS	Southern	India	40	-	-	-	PCR	HPV was detected in 32.4% cases. Maximum positivity was observed in metastases from primary in the oral cavity (47.1%) with tongue (55%), followed by oropharynx (25%).
Goot-heah K et al.	2012	CS	South-Eastern	Malaysia	30	-	-	18	PCR	From 14 cases of OSCC examined, none of them was found to be positive for HPV18 in this study. The findings of this study revealed that there is a low viral detection of HPV18 in Malaysian OSCC by using saliva samples, suggesting that prevalence of HPV18 may not be important in this group of Malaysian OSCC.
Huang SF et al.	2012	CS	Eastern	Taiwan, China	103	Mean = 49.4, range = 26-81	-	16, 18, 11, 66, 35, 53, 54, 58, 61, MM4, 81	PCR	Thirty-one patients (30.1%) were positive for HPV infection. The most frequent HPV types were types 16 (16 patients, 51.6%) and 18 (seven patients, 22.6%).
Bahl A et al.	2013	CS	Southern	India	105	Median = 55 years, range = 30-80 years	-	-	PCR	HPV prevalence was 22.8%. Results of this study confirms that patients who are HPV positive are younger, and with high-risk sexual behaviour.
Patel KR et al.	2013	CS	Southern	India	97	22 to 75 years	Male = 84, Female = 13	-	PCR	None of the oral cancer patients revealed the presence of HPV type 16 and 18 infection. The results suggested that HPV-16 and -18 do not play an important role in oral carcinogenesis in the population from Gujarat, West India.
Kawakami H et al.	2013	CS	Eastern	Japan	104	Median = 64, range = 35 to 80	Male = 81, Female = 23	16, 18	PCR, p16 IHC	The results showed that 38% of Japanese patients with OPSCC are positive for HPV DNA, with such positivity being an independent prognostic factor for overall survival.

Mizumachi T et al.	2013	CS	Eastern	Japan	71	Median = 63	Male = 63, Female = 8	16, 18, 58	PCR	Of the 71 OPSCC, 20 were positive for HPV-16, two for HPV-18, and one for HPV-58. Kaplan-Meier survival analysis showed improved overall survival rates in patients with HPV-positive tumors (p = 0.0038) compared with HPV-negative tumors
Verma G et al.	2017	CS	Southern	India	102	Mean = 51.8	Male = 110, Female = 25	-	PCR	Overall, 22.9% (31/135) samples were positive for HPV infection. Analysis of type-specific HPV infection by PCR revealed HPV-16 positivity of 29% (9/31) and HPV-18 positivity of 16.1% (5/31).
Chotipanich A et al.	2018	CC	South-Eastern	Thailand	208	<44, 45-65, >66	Male = 77, Female = 27	16	PCR	High-risk HPV was detected in 4 of 52 (7.7%) OSCC cases, 6 of 52 (11.5%) OPSCC cases, and 1 of 104 (0.96%). Although low HPV prevalence was observed, the rate of high-risk HPV infection in the cancer group was still higher than that in the control group.
Yang LQ et al.	2019	CC	Eastern	China	30	-	Male = 14, Female = 16	-	PCR, p16 IHC	The prevalence of HPV DNA in exfoliated cell samples was 3.3% (1/30) among OSCC cases, and 3.3% (1/30) among control cases. A low prevalence of HPV was detected in OSCC though different types of HPV can be detected.
Purwanto DJ et al.	2019	CC	South-Eastern	Indonesia	78	Median = 47	Male = 47, Female = 31	16, 18	PCR	A high prevalence of HPV-16/ -18 was detected in OSCC cases (17.9%). HPV-18 occurred more often than HPV-16 (86%) among OSCC patients who were HPV positive.
Wang F et al.	2017	CS	Eastern	China	95		Male = 130, Female = 58	-	p16 IHC	The p16 results were positive in 25.8% and 9.5% of patients with OPSCC and OSCC, respectively.
Sabu A et al.	2019	CS	Southern	India	21	Mean = 51.3	Male = 11, Female = 10	-	p16 IHC	IHC results revealed p16 positivity in six OPSCC cases.
Nopmaneepaisarn T et al.	2019	CS	South-Eastern	Thailand	110	Mean (range): OPSCC = 59 (28-89) OSCC = 61.3 (29-95)	OPSCC: Male = 95, Female = 15 OSCC: Male = 151, Female = 109	-	p16 IHC, ISH, PCR	A low rate of HPV-related OPSCC was found in Thai patients.
Xu T et al.	2020	C	Eastern	China	170	Median (range): p16- = 58.5 (36-80), p16+ = 55.5 (22-76)	Male = 140, Female = 30	3, 16, 18, 35	p16 IHC, ISH	Out of the 170 tumor tissues evaluated, 57.6% (98/170) samples had positive p16 expressions.
Xu S et al.	2020	C	Eastern	China	170	Mean = 60.55	-	11, 16, 18, 33, 53	p16 IHC, ISH, PCR	The overall HPV infection rate was 18.29% (47/257). HPV-16 was the most widely infected HPV genotype (89.36%), followed by HOV-18, HPV-33, and HPV-35
Argirion I et al.	2020	CS	South-Eastern	Thailand	96	Mean (range): HPV+ = 54.9 (42-73), HPV- = 56.7 (36-81)	Male = 79, Female = 17	16, 18	p16 IHC, PCR	Of the 96 patient samples tested, 17 were found to have to be positive for HPV. Among those with HPV+ OPSCC, 14 were monoinfected with HPV-16, 2 monoinfected with HPV-18 and 1 was co-infected with both HPV-16 and -18. PCR HPV testing results were in complete agreement with p16 staining.
Jiarpinitnun C et al.	2020	CS	South-Eastern	Thailand	93	-	-	-	p16 IHC	The oropharynx was the most common primary site with the distribution of p16-positive status of 37.9%, followed by nasal/paranasal sinus (22.2%), larynx (11.9%), hypopharynx (11.1%), and oral cavity (3.2%)
Kim Y et al.	2020	CS	Eastern	Korea	264	-	-	-	p16 IHC, PCR	The oropharynx showed the highest prevalence of HPV+ 75.1% (154/205), while only 3% (5/166) of oral cavity samples were HPV+

(Continued on page 84

(Table 1 - continued from page 83)

Authors	Year	Type of Study	Asian Regions	Country	Sample size	Patient Age	Gender	HPV Subtype	Testing Method	General Outcomes
Thobias AR et al.	2021	CS	Southern	India	127	-	Male = 179, Female = 23	-	PCR	A significant prevalence of HPV infection was detected in all 3 cancers (cervical cancer, OSCC, OPSCC) using the de
Yap LF et al.	2021	CS	South-Eastern	Malaysia	54	Mean (range) = 65.44 + 12.16 (36-93)	Male = 38, Female = 16	-	p16 IHC, ISH	Overall, 15 (25%) tumors were p16 positive by immunohistochemistry, 10 of which were also positive for high-risk HPV DNA by in situ hybridization.
Gaikwad P et al.	2021	CC	Southern	India	80	Mean: Case = 52 + 11; Control = 50 + 10	Male: Case = 16; Control = 16; Female: Case = 24; Control = 24	16, 18, 33, 35, 6, 11	PCR	All of the 80 subjects included in the study (cases, n = 40; controls, n = 40) were tested for HPV DNA, but none of the subjects from either group tested positive.
Venkatesh A et al.	2021	CS	Southern	India	47	-	Male = 35; Female = 12	-	p16 IHC	Out of 50 cases, 3 were deferred due to insufficient tumor sample and 2/47 cases were p16 positive and the site was the lateral border of the tongue.
Heawchaiyaphum C et al.	2021	CC	South-Eastern	Thailand	84	Mean 60.65	Male = 41; Female = 31, Not determined = 12	-	PCR	Prevalence of HPV tumor tissues (33.3%) was significantly higher than normal adjacent tissues (10.7%). HPV-16 was most commonly found in HPV-positive OSCC samples (60.7%)
Ajila V et al.	2021	CC	Southern	India	60	Average (range) = 58 (34-75)	Case only: Male = 25 (83%); Female = 5 (17%)	16, 18	PCR	Among the 30 cases of OSCC, 16.7% (5) tested positive for HPV. Among the controls, one tested positive with an incidence of 3.3%
Ahmed F et al.	2021	CS	Southern	India	60	Mean (standard deviation) = 43.35 + 10.156	Male = 35; Female = 25	16		The prevalence of HPV 16 was 11.7% with no association between habits and histological grading, but there was an association between HPV16 and clinical presentation of OSCC
Hashida Y et al.	2021	C	Eastern	Japan	89	Mean (range) = 68.5 (54-87)	Male = 73; Female = 16	16	p16 IHC, PCR	HPV-16 viral DNA was found in 45 (51%) OPSCCs.
Koksal MO et al.	2021	CS	Western	Turkey	106	Mean = 59.7	Male = 78; Female = 28	16, 18, 82, 45	p16 IHC, PCR	Eighteen out of one hundred and six (19%) OSCCs and OPSCCs showed p16INK4A overexpression, and 26/106 cases (24.5%) were positive for HPV DNA.
Rahbarnia L et al.	2019	CS	Western	Iran	30	Mean (range) = 61.26 (32-88)	Male = 19; Female = 11	18, 19	PCR	Among 30 OSCC samples analyzed, two cases (6.6% of 30) were positive for HPV in PCR performed by MY09/MY11 primer.
Wang CP et al.	2022	CS	Eastern	Taiwan, China	425	-	Male to female ratio = 9.3	16, 18, 26, 33, 35, 51, 52, 56, 58, 67	p16 IHC, PCR	Of the 425 OPSCCs, HPV PCR test was successfully performed on 408 (96%) samples. 119 (29%) of OPSCCs were HPV positive. 369 out of 425 OPSCCs (87%) were successfully p16 stained. The percentage of positive p16 OPSCCs was 31% (114 tumors).
Sri S et al.	2021	CS	Southern	India	40	-	-	16, 18	PCR	High risk HPV-16 was found to be positive in 35% of OSCC cases which showed a statistically significant association of HPV-16 with OSCC.
Rungraungrayabkul D et al.	2021	CS	South-Eastern	Thailand	81	-	Male =	-	p16 IHC, PCR	Of the 81 OSCC specimens, eight (9.9%) exhibited HPV DNA; DNA sequencing confirmed that the viral subtype was HPV-18 in all eight specimens.

*CS: Cross-sectional; CC: Case-control; C: Cohort

Table 2. Risk of bias assessment and level of evidence of each included study using JBI and OCEBM checklists, respectively

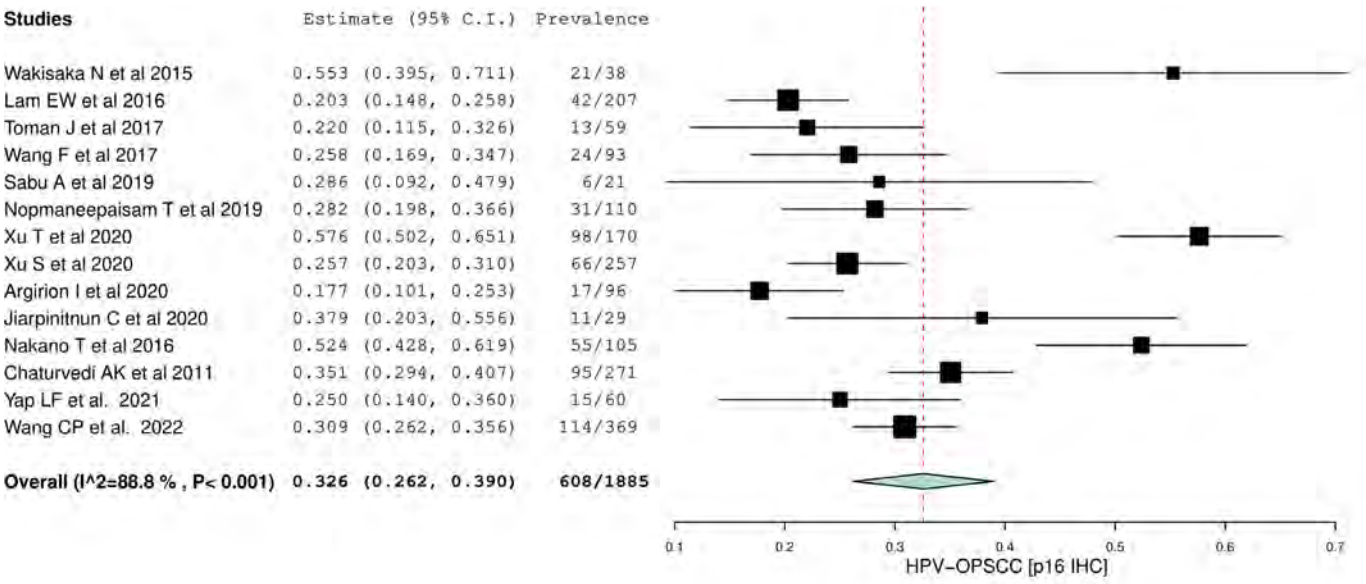
The Risk of Bias Using the Joanna Briggs Institute Checklist for Analytical Cross-Sectional Studies										Level of Evidence
Studies	Domains								Overall appraisal	
	1	2	3	4	5	6	7	8		3
Purwanto DJ et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Hama T et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Wang F et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Sabu A et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Nopmaneepaisarn T et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Xu T et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Argirion I et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Jiarpinitnun C et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Kim Y et al.	Y	Y	Y	Y	N	N	Y	Y	Include	3
Thobias AR et al.	Y	Y	Y	Y	N	N	Y	Y	Include	3
Rushatamukayanunt P et al.	Y	Y	Y	Y	Y	U	Y	Y	Include	3
Kane S et al.	Y	Y	Y	Y	N	N	Y	Y	Include	3
Hwang TZ et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Singh V et al.	Y	Y	N	Y	Y	Y	Y	Y	Include	3
Lam EW et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Pongsapich W et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Sritippho T et al.	Y	Y	Y	Y	N	N	Y	Y	Include	3
Nakano T et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Chen XJ et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Palve V et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Barwad A et al.	Y	N	Y	Y	N	N	Y	Y	Include	3
Goot-heah K et al.	Y	N	Y	Y	Y	N	Y	Y	Include	3
Huang SF et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Bahl A et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Patel KR et al.	Y	N	Y	Y	N	N	Y	Y	Include	3
Mizumachi T et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Joo YH et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Ramshankar V et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Ishibashi M et al.	Y	Y	Y	Y	N	NA	Y	Y	Include	3
Deng Z et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Kouketsu A et al.	Y	Y	Y	Y	Y	N	Y	Y	Include	3
Parshad S et al.	Y	N	Y	Y	Y	N	Y	Y	Include	3
Kawakami H et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Xu S et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Yap LF et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Venkatesh A et al.	Y	Y	Y	Y	Y	U	Y	Y	Include	3
Ahmed F et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Koksal MO et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Rahbarnia L et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Wang CP et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Sri S et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Rungraungrayabkul D et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Gan LL et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Chaturvedi AK et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Kulkarni SS et al.	Y	Y	Y	U	U	N	N	Y	Include	3
Mathew A et al.	Y	Y	Y	U	U	Y	U	Y	Include	3
Lee SY et al.	Y	Y	Y	N	N	N	N	Y	Include	3
Verma G et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Chotipanich A et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Yang LQ et al.	Y	Y	Y	Y	Y	Y	N	Y	Include	3
Chen F et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Toman J et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Gaikwad P et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Heawchaiyaphum C et al.	Y	Y	Y	Y	Y	N	N	Y	Include	3
Ajila V et al.	Y	Y	Y	Y	Y	Y	Y	Y	Include	3
Lee LA et al.	N/A	Y	Y	Y	Y	Y	Y	Y	Include	2
Lee LA et al.	N/A	Y	Y	Y	Y	Y	Y	Y	Include	2
Hashida Y et al.	N/A	Y	Y	Y	Y	Y	Y	Y	Include	2
Wakisaka N et al.	Y	Y	Y	Y	N	N	Y	Y	Include	2

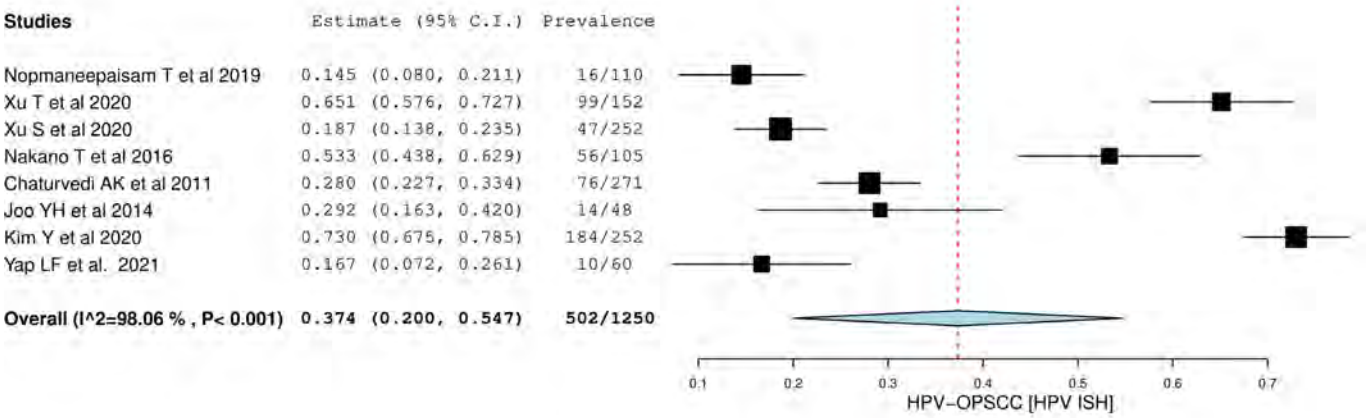
Y: Yes, N: No; U: Unsure; NA: Not available

Table 3. Prevalence of human papillomavirus (HPV) in patients diagnosed with oral or oropharyngeal squamous cell carcinoma using different tests

Study	Prevalence							
	p16 IHC		HPV ISH		HPV PCR		EasyChip HPV blot	
	Oro-pharyngeal	Oral cavity	Oro-pharyngeal	Oral cavity	Oro-pharyngeal	Oral cavity	Oro-pharyngeal	Oral cavity
Gan LL *et al.*	-	-	-	-	-	55/200	-	-
Hama T *et al.*	-	-	-	-	79/157	-	-	-
Joo YH *et al.*	-	-	14/48	-	-	-	-	-
Ramshankar V *et al.*	-	24/156	-	-	-	81/156	-	-
Rushatamukayanunt P *et al.*	-	10/80	-	-	-	3/80	-	-
Kane S *et al.*	-	16/124	-	-	-	-	-	-
Wakisaka N *et al.*	21/38	-	-	-	19/38	-	-	-
Lee LA *et al.*	-	-	-	-	-	-	-	194/1002
Parshad S *et al.*	-	-	-	-	15/50	4/50	-	-
Hwang TZ *et al.*	-	-	-	-	-	-	-	-
Singh V *et al.*	-	-	-	-	-	23/250	-	-
Lam EW *et al.*	42/207	-	-	-	43/207	-	-	-
Pongsapich W *et al.*	-	-	-	-	6/23	0/23	-	-
Sritippho T *et al.*	-	8/37	-	-	-	5/34	-	-
Chen F *et al.*	-	-	-		-	25/178	-	-
Nakano T *et al.*	55/105	-	56/105	-	-	-	-	-
Toman J *et al.*	13/59	-	-	-	-	-	-	-
Kouketsu A *et al.*	-	24/174	-	-	-	13/24	-	-
Chen XJ *et al.*	-	-	-	-	-	0/198	-	-
Palve V *et al.*	-	10/55	-	-	-	135/312	-	-
Ishibashi M *et al.*	-	8/50	-	-	-	9/50	-	-
Chaturvedi AK *et al.*	95/271	-	76/271	-	84/271	-	-	-
Kulkarni SS *et al.*	-	-	-	-	-	24/34	-	-
Mathew A *et al.*	-	-	-	-	-	33/45	-	-
Lee SY *et al.*	-	-	-	-	-	13/36	-	-
Deng Z *et al.*	-	-	-	-	22/44	9/25	-	-
Lee LA *et al.*	-	-	-	-	-	71/333	-	-
Barwad A *et al.*	-	-	-	-	10/40	16/34	-	-
Goot-heah K *et al.*	-	-	-	-	-	1/30	-	-
Huang SF *et al.*	-	-	-	-	-	-	-	31/103
Bahl A *et al.*	-	-	-	-	24/105	-	-	-
Patel KR *et al.*	-	-	-	-	-	0/97	-	-
Kawakami H *et al.*	-	-	-	-	40/104	-	-	-
Mizumachi T *et al.*	-	-	-	-	23/71	-	-	-
Verma G *et al.*	-	-	-	-	13/33	18/102	-	-
Chotipanich A *et al.*	-	-	-	-	-	-	-	-
Yang LQ *et al.*	-	1/30	-	-	-	1/30	-	-
Purwanto DJ *et al.*	-	-	-	-	-	14/78	-	-
Wang F *et al.*	24/93	9/95	-	-	-	-	-	-
Sabu A *et al.*	6/21	-	-	-	-	-	-	-
Nopmaneepaisarn T *et al.*	31/110	-	16/110	-	5/22	-	-	-
Xu T *et al.*	98/170	-	99/152	-	-	-	-	-
Xu S *et al.*	66/257	-	47/257	-	-	-	-	-
Argirion I *et al.*	17/96	-	-	-	-	-	-	-
Jiarpinitnun C *et al.*	11/29	3/93	-	-	-	-	-	-
Kim Y *et al.*	-	-	184/252	20/264	149/159	1/166	-	-
Thobias AR *et al.*	-	-	-	-	20/75	16/127	-	-
Yap LF *et al.*	15/60	-	10/60	-	-	-	-	-
Gaikwad P *et al.*	-	-	-	-	-	0/40	-	-
Venkatesh A *et al.*	-	2/47	-	-	-	-	-	-
Heawchaiyaphum C *et al.*	-	-	-	-	-	28/84	-	-
Ajila V *et al.*	-	-	-	-	-	5/30	-	-
Ahmed F *et al.*	-	-	-	-	-	7/60	-	-
Hashida Y *et al.*	-	-	-	-	47/91	-	-	-
Koksal MO *et al.*	-	-	-	-	20/72	6/34	-	-
Rahbarnia L *et al.*	-	-	-	-	-	2/30	-	-
Wang CP *et al.*	114/369	-	-	-	119/408	-	-	-
Sri S *et al.*	-	-	-	-	-	7/20	-	-
Rungraungrayabkul D *et al.*	-	-	-	-	-	8/81	-	-

HPV: Human papillomavirus; IHC: Immunohistochemistry; ISH: in-situ hybridization; PCR: polymerase chain reaction; (-) indicates not applicable.





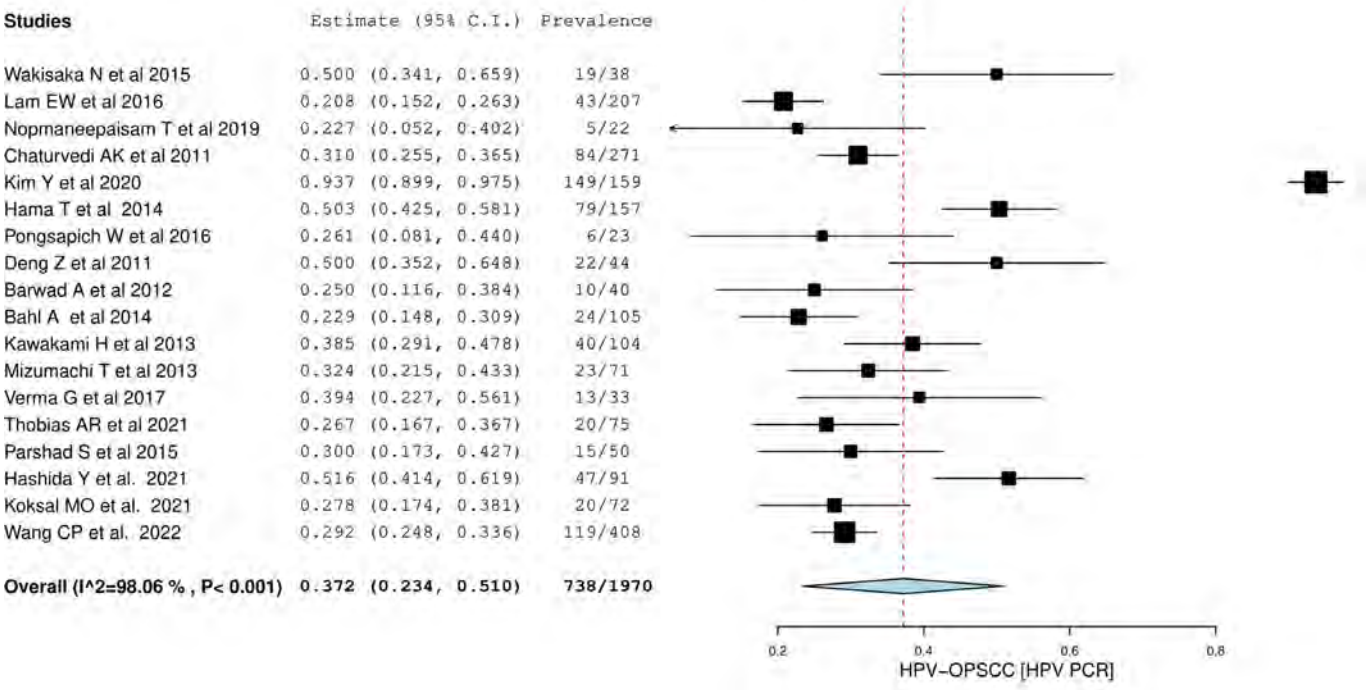


Fig. 2. Weighted mean pooled prevalence of HPV-OPSCC identified using p16 IHC, HPV ISH, and HPV PCR.

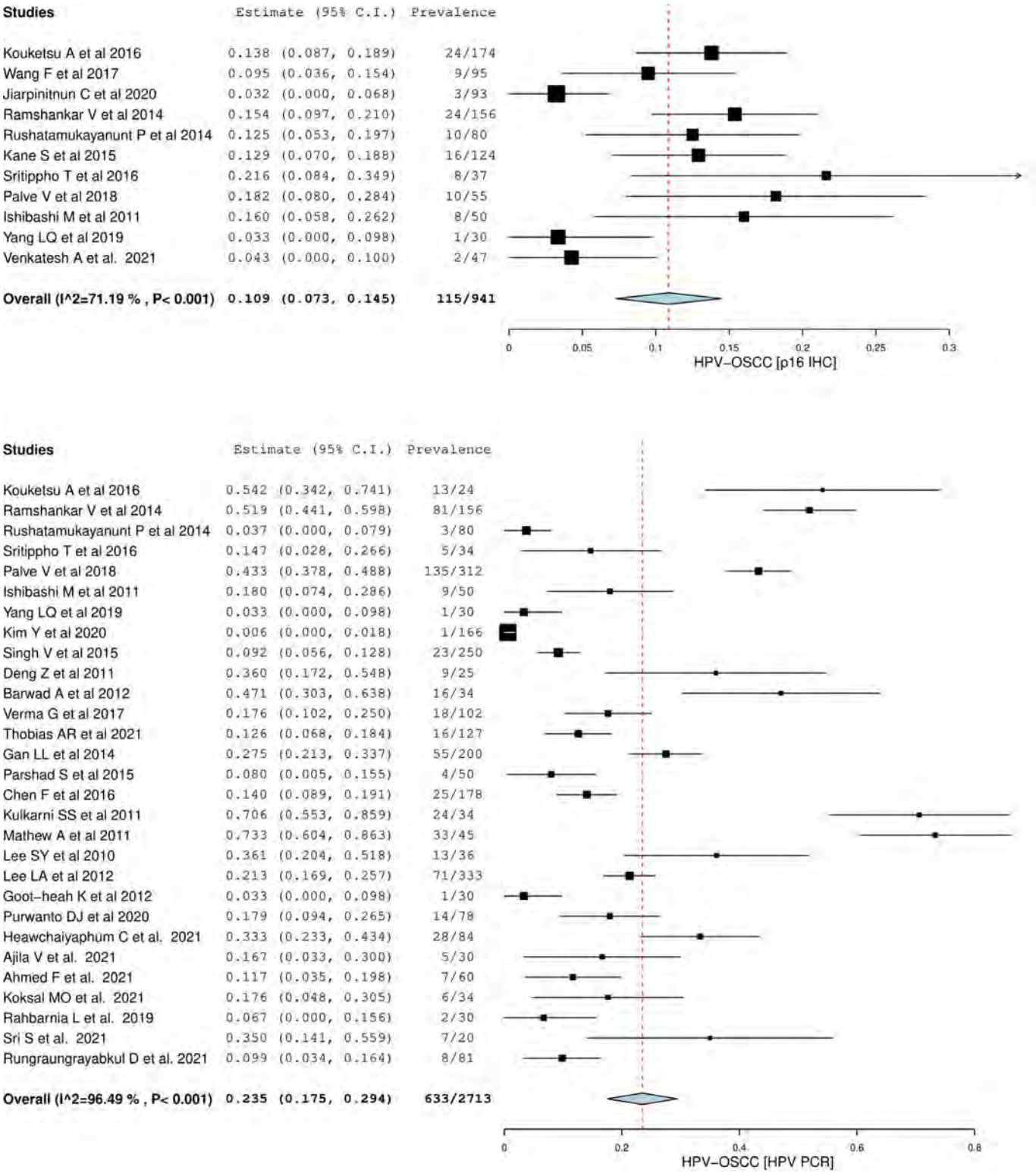


Fig. 3. Weighted mean pooled prevalence of HPV-OSCC identified using p16 IHC and HPV PCR.

Subgroup analysis and meta-regression

Subgroup analysis was conducted to investigate the relationship between different Asian regions and the prevalence of both HPV-OPSCC and HPV-OSCC. The weighted mean prevalence of HPV-OPSCC diagnosed using p16 IHC was significantly higher (P<0.001) among East Asians [35.5%, CI: (27.2, 43.8)], followed by South Asians [28.6%, CI: (9.2, 47.9)], and Southeast Asians [25.2%, CI: (18.0, 32.5)]. Moreover, the weighted mean prevalence of HPV-OPSCC diagnosed using ISH was significantly higher (P<0.001) among East Asians [44.6%, CI: (24.1, 65.1)] as compared to Southeast Asians [15.2%, CI: (9.8, 20.6)]. When PCR was used as the diagnostic tool, the prevalence of HPV-OPSCC was significantly higher (P<0.001) among East Asians [44.7%, CI: (24.9, 64.5)], followed by Western Asians [27.8%, CI: (17.4, 38.1)], South Asians [26.6%, CI: (21.7, 31.6)], and Southeast Asians [24.4%, CI: (11.8, 36.9)]. The degree of subgroup data heteroge-

neity for HPV-OPSCC diagnosed with IHC, ISH and PCR were 90.43%, 97.67% and 98.06%, respectively. On the other hand, the weighted mean prevalence of HPV-OSCC diagnosed using p16 IHC was significantly higher (P<0.001) among South Asians [12.1%, CI: (6.2, 18.1)], followed by Southeast Asians [11.3%, CI: (6.6, 29.2)], and East Asians [10.6%, CI: (6.4, 14.8)]. In addition, a similar pattern was also noted in which the weighted mean prevalence of HPV-OSCC diagnosed using PCR was significantly higher (P<0.001) among South Asians [32.4%, CI: (20.6, 44.2)], followed by Southeast Asians [19.0%, CI: (10.8, 27.1)], East Asians [15.4%, CI: (5.8, 24.9)] and West Asians [11.2%, CI: (6.0, 21.7)]. The degree of subgroup data heterogeneity for HPV-OSCC diagnosed with IHC and PCR were 71.19% and 96.49%, respectively.

Meta-regression was performed to evaluate the effect of the sample size of each study on the prevalence of HPV-OPSCC and HPV-OSCC (Appendix). No significant differences were found for both HPV-OPSCC [P-values: IHC (0.840), ISH (0.490), and PCR (0.960)] and HPV-OSCC [P-values: IHC (0.214) and PCR (0.794)], signifying that the sample size of each study does not have any direct effect on the degree of data heterogeneity. Egger's test revealed no evidence of significant publication bias in the prevalence of HPV-OPSCC [P-values: IHC (0.121), ISH (0.083), and PCR (0.072)] and HPV-OSCC [P-values: IHC (0.087) and PCR (0.091)], respectively.

Discussion

The current study comprehensively summarised, reviewed, and presented concrete evidence on the prevalence of HPV-related OPSCC and OSCC in Asian countries which included 59 primary studies using various diagnostic techniques, particularly p16 IHC, HPV ISH, and HPV PCR. Comparisons of prevalence patterns across different geographical regions can reveal a great deal about the global burden of HPV-related oropharyngeal and oral cavity cancers. Based on the present findings, HPV-OPSCC was shown to have a higher prevalence than HPV-OSCC which corroborates with other previous similar studies [28, 29]. Despite the fact that the previous studies reported a worldwide HPV-OPSCC prevalence rate of approximately 45.8% to 52.9% [29, 30], with the Asian region was found to exhibit a high prevalence of 51.1 % [29], these findings contradicted the results of the current study. Conversely, the prevalence of HPV-OSCC was observed to range from 10.9% to 23.5% in the present study, which is consistent with previous systematic reviews indicating prevalence rates of 23.5% [28], and 24.2% [29], respectively, but contradicts the finding of another meta-analysis which revealed a higher prevalence of 34.5% [31]. Nonetheless, one explanation for the vast differences in prevalence rates across various studies might be attributed to reporting standards as some review studies only included primary research that employed HPV PCR-based diagnostic tools. Hence, a direct comparison of the present findings may not be conceivable.

To explore the potential rationale underlying the present findings, a deeper understanding of the epidemiology of both HPV-associated OPSCC and OSCC is needed. It has been reported that oral benign papillomatous lesions appear to be strongly related to low-risk HPV, primarily HPV-6 and 11, while High-risk HPV, such as HPV-16 and 18 subtypes, is linked to OPSCC and OSCC [32]. Most HPV-associated OPSCC and OSCC differ from HPV-negative oral malignancies in terms of demographic features, clinical response, and overall survival rates [33]. There is a distinct trend in the literature that HPV-negative OPSCC and OSCC patients are often older and have a history of alcohol consumption and smoking, whereas those HPV-positive patients on the other hand are often younger, male, and sexually active patients [34, 35]. Furthermore, a direct relationship has also been discovered between high-risk HPV 16-positive individuals and frequent sexual activity [36]. Although oral sexual behaviour may explain some of the epidemiological differences in HPV-OPSCC and HPV-OSCC among various ethnic groups and genders [34], such a conjecture may not be appropriate to extrapolate to Asian countries since collecting comprehensive sexual behaviour histories can be uncomfortable for both patients and researchers, limiting data availability. As a result, more in-depth research into the association between sexual behaviour and epidemiological differences in HPV-associated OPSCC and OSCC in Asian countries is needed to elicit the relationship between these two variables [37].

The present study revealed that the prevalence of HPV-OPSCC was highest among East Asians, followed by West Asians, South Asians and Southeast Asians which is consistent with the findings of Shaikh MH *et al*. [38]. On the other hand, South Asians had the greatest prevalence of HPV-OSCC, followed by Southeast Asians, East Asians, and lastly West Asians, contrasting a previous systematic review that indicated HPV-OSCC to be most common among Southeast Asians, followed by East Asians, and finally South Asians [38]. This implies that HPV-OSCC cases have been on the rise in South Asia over the past ten years, outpacing those in Southeast, East, and West Asia. Though minimal investigation on the prevalence of HPV-OSCC in the Asian population based on different geographical regions has been conducted, the current finding must be considered in light of genetic variations and ethnic subpopulations throughout the Asian nations. Additionally, more research is required to examine the potential confounding effects of risk factors, such as cigarette and tobacco use, which is prevalent in South Asia rendering it difficult for the current study to draw evidence on the specific role of HPV infection in OSCC [39]. As primary studies derived from West Asia were scarce and led to highly uneven regional contributions, the current finding mostly reflects the situation in South, Southeast, and Eastern Asia, and disregards the evident disparity in the prevalence of HPV-related OPSCC and OSCC. Hence, the au-

thors speculate that prevalence differs widely across Asian countries, and that a generalisation of the Asian figure is likely to be an underestimation or overestimation.

One interesting finding is that while the reported East Asia demonstrated a greater incidence of HPV-OPSCC fits with the overall observation of a rise in developed countries globally [40], the causes for this specific increase remain unknown. Evidence suggested that the occurrence of HPV infection is likely followed by the emergence of OPSCC after a few years or even decades, and this relationship between increased OPSCC incidence rates and higher HPV prevalence has been established [41]. Therefore, the plausible explanation for this observation could be that while tobacco use significantly reduced in developed East Asian countries such as Japan, South Korea, China, Taiwan, and Hong Kong [42], sexual behaviour has changed over time [6], which has coincided with the rise in HPV-positive OPSCC. The number of oral sex partners has been found as the most predictive factor of HPV-OPSCC, which might explain the high prevalence of HPV-OPSCC in East Asia, since premarital sexual behaviour and multiple sex partners have increased in recent years [43, 44]. Besides, it has also been suggested that prophylactic vaccinations targeting specific HPV16 and HPV18 may have the potential to avert a significant portion of head and neck squamous cell carcinomas globally [29, 45], particularly OPSCC and OSCC. Thus, with the increased adoption of HPV vaccines, a decline in HPV-OPSCC and HPV-OSCC could be predicted. Nevertheless, the disparity in prevalence between HPV-OSCC and HPV-OSCC among Asian population is still unknown. Considering how the various Asian nations differ in terms of social norms, religions, and cultural backgrounds, it is not surprising that such a difference, notably in developed countries, contributed to greater societal acceptance of more sexually active behaviours, particularly those involving oral contact. Consequently, this argument may provide an explanation for the trend of a higher prevalence of HPV-OPSCC in East Asians.

The great range of currently available HPV detection tools necessitates a review of their benefits and drawbacks in testing protocols. According to the current meta-analyses, the prevalence of HPV-OPSCC and HPV-OSCC in Asian regions varies depending on the diagnostic tool used, with those detected with the HPV PCR test exhibiting a greater prevalence which is in-line with a previous meta-analysis [31]. This can be explained by the diagnostic tool's reliability, since PCR has been shown to have higher sensitivity than ISH in identifying HPV DNA [31]. Moreover, it has been reported that HPV PCR has a sensitivity of 97-98% and a specificity of 84-87%, whilst HPV ISH has a sensitivity of 85-88% and a specificity of 83-88% [46, 47]. Prior studies have also underlined the significance of p16 IHC expression as a surrogate marker for HPV infection in head and neck squamous cell carcinomas (HNSCC), which also predicts the survival outcome of patients with HNSCC [48, 49]. It is worth noting that PCR cannot tell if the HPV came from tumour cells or non-tumour tissues, and both PCR and ISH-based methods can only show the presence of HPV without confirming the viral activity, but p16 IHC can identify cancer cells with transcriptionally active HPV [50].

Although testing for viral E6/E7 mRNA expression in OPSCC and OSCC is a valid alternative to HPV association testing, it is less widely utilised and lacks standardisation [51]. Nevertheless, the ideal standard for HPV identification in HNSCC remains the combination of p16 IHC followed by HPV PCR or HPV ISH [46], because p16+ HNSCC with HPV-independent carcinogenesis can occur in a limited number of cases [44]. Despite the majority of the studies included in the present review employed HPV PCR as a diagnostic tool, followed by p16 IHC, and HPV ISH, it is still reasonable to infer that the reported prevalence of HPV-OPSCC and HPV-OSCC can be used as a guide for future public health predictions as the percentage does not differ much among various diagnostic tools.

The current study opted to limit data synthesis and focus on HPV prevalence over the last decade since HPV-OPSCC and HPV-OSCC have escalated over the previous years and are thus influenced by the time of diagnosis. One limitation of the present review is the lack of extensive quantitative measurements of the associating factors such as patients' age, gender, educational background, and social behaviour due to the pooling of the primary data. Multivariate regression using these covariates would have been fascinating to be explored if the available data are not limited. Nevertheless, the present review is still unable to separate the data for oropharyngeal and oral cavity sublocations, which might offer relevant insight into explaining the prevalence of HPV in different subsites [52]. Some Asian regions were also under-represented in the present study.

In addition, despite the great reliability and specificity of HPV diagnostic techniques, the lack of false-positive results may also render the present data to a certain level of biasness. Due to the high degree of data heterogeneity, varied study designs, and the extensive pooling of primary data across different countries in Asia with various patients' inclusion and exclusion criteria, it is challenging to assimilate solid conclusions drawn from the current meta-analysis. Nonetheless, data heterogeneity is still present in the current review despite stratifying data based on diagnostic tools and sub-regions in Asia. Other methods employed to mitigate heterogeneity include performing subgroup analysis, meta-regression, and study elimination.

Conclusions

The association between HPV and cancers of the oropharyngeal and oral cavity has gained broad consensus. Although the prevalence of HPV-OPSCC and HPV-OSCC in the Asian region has been consistent over the last decade, the present findings are strongly influenced by the diagnostic tools utilised and geographical locations. Other con-

founding variables must be considered, such as age, gender, race, and specific anatomical sites of the oropharyngeal and oral cavities. Nevertheless, future studies into the standardisation of diagnostic tools and the implementation of cancer prevention and treatment programmes emphasising the importance of HPV vaccination are warranted.

Authors' contribution

YJT: Data curation, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft
KWSH: Data curation, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft
GSSL: Conceptualization, Formal Analysis, Methodology, Project administration, Software, Validation, Writing – review & editing
JLSW: Data curation, Investigation, Methodology, Visualization, Writing – original draft
WNAWAAN: Data curation, Investigation, Methodology, Visualization, Writing – original draft
LWLK: Conceptualization, Data curation, Methodology, Writing – review & editing

Conflict of interest

None to declare.

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Appendix

Supplementary table 1. Meta-regression evaluating the effect of sample size of each study on the prevalence of HPV-OPSCC and HPV-OSCC.

	Coefficient	Confidence intervals		Standard error	P-value
		Upper bound	Lower bound		
HPV-OPSCC					
IHC	0.336	0.456	0.217	0.061	0.840
ISH	0.227	0.589	0.035	0.159	0.490
PCR	0.371	0.499	0.244	0.065	0.960
HPV-OSCC					
IHC	0.068	0.134	0.002	0.034	0.214
PCR	0.248	0.353	0.144	0.053	0.794

*HPV: Human papillomavirus; OPSCC: Oropharyngeal squamous cell carcinoma; OSCC: Oral squamous cell carcinoma; IHC: Immunohistochemistry; ISH: in-situ hybridization; PCR: polymerase chain reaction.