Human papillomavirus types 16 and 18 in epithelial dysplasia of oral cavity and oropharynx: A meta-analysis, 1985–2010

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SUMMARY

Human papillomavirus (HPV) types 16 and 18 are causally related to a sub-set of oral cavity and oropharyngeal squamous cell cancers. However, a clear estimate of the prevalence of HPV-16/18 in oral cavity and oropharyngeal dysplasia (OOPD) is not available. This literature review and meta-analysis was conducted to provide a prevalence estimate for HPV-16/18 in OOPD. Twenty-two studies that reported prevalence of HPV-16 and/or 18 in 458 OOPD lesions were analyzed. Meta-analysis was used to evaluate the prevalence of HPV-16/18 and logistic regression was used for stratified analysis by age, gender, and histological grade. The overall prevalence of HPV-16/18 in OOPD lesions was 24.5% [95% confidence interval (CI), 16.4–36.7%)]. The individual prevalence for HPV-16 alone was 24.4%. The prevalence of HPV-16/18 in oral cavity lesions alone was 25.3% (95% CI, 14.2–45.2%). The odds of detection of HPV-16/18 in dysplastic lesions in males were twice that of females [odds ratio (OR), 2.44]. HPV-16/18 were 3 times more common in dysplastic lesions (OR, 3.29; 95% CI, 1.95–5.53%) and invasive cancers (OR, 3.43; 95% CI, 2.07–5.69%), when compared to normal biopsies. There was no significant difference in HPV-16/18 rates between dysplastic lesions and cancers or between mild, moderate or severe dysplastic lesions. This meta-analysis provides a quantification of the prevalence of HPV types 16/18 in OOPD lesions. These results also support the assumption that HPV-16/18 infection occurs during the early phase of the oral cavity and oropharyngeal carcinogenesis.

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Keywords

Human papillomavirus; Oral epithelial dysplasia; Oral cancer; Oropharyngeal cancer; Oral precancerous lesion; Epithelial carcinogenesis; Meta-analysis; Prevalence

Introduction

Oral cavity and oropharyngeal squamous cell carcinoma (OOSCC) accounts for over 3% of all cancers, making it the sixth most common cancer worldwide.[1] In 2010, the number of OOSCC-related deaths in the US was estimated to be 7880.[2] Although the overall incidence of OOSCC has gradually decreased in the past few decades,[2] the cancers arising from certain anatomical sub-sites have shown an increase, especially among younger individuals without typical risk factors such as tobacco or alcohol use.[3,4] Human papillomavirus (HPV) is proposed as an etiologic risk factor for this sub-set of OOSCCs.[5]

While over 100 different types of HPV are known[6], only about 15 types have been identified as 'high-risk' serotypes (HR-HPV) with oncogenic potential.[7,8] Currently marketed vaccines offer protection against two HR-HPV types: HPV-16 and 18.[9] HPV-16/18 are associated with about 70% of all cervical cancers and about 35% of OOSCCs.[8,10,11] HPV-16/18 are also the most common (>90%) serotypes detected in the HPV-related OOSCCs.[5,8,12] The successful implementation of prophylactic immunization for cervical cancer has led to discussions on immunizing for other HPV-related cancers including OOSCCs. However, unlike cervical carcinogenesis, the role of HPV-16/18 in the early oral cavity (OC) and oropharyngeal (OP) carcinogenic process has not been clearly defined. Also, while HPV-16/18 have been well established as risk factors for the cancers of OP sites,[5,13–15] they are less strongly associated with the OC cancers. Establishing the timeline and likelihood of HPV-16/18 infection, in relation to early OC and OP carcinogenesis, may improve our understanding of its role and eventually aid in the planning of immunization strategies.

OC and OP squamous carcinogenesis involves sequential histological transformation of normal epithelium, to dysplasia, to in situ carcinoma, and finally to invasive cancer.[16] While the prevalence of different HPV types in OOSCCs has been evaluated in detail,[11,12] there is limited information on its prevalence in histopathologically confirmed dysplastic lesions. Previous studies that evaluated oral cavity and oropharyneal dysplasia (OOPD) have reported widely varying HPV prevalence ranging between 0% and 100%.[17,18] Many of these studies were limited by small sample size. Therefore, a clear estimate of the prevalence of HPV types 16 and 18 in OOPD lesions is not available. We conducted this literature review and meta-analysis to provide an estimate of the prevalence of HPV-16/18 in OOPD.

Methods

Study selection

The PubMed, MEDLINE, and SCOPUS databases were used to perform a comprehensive literature search on HPV detection in OOPD. The search was limited to English language studies published between January 1985 and November 2010. The search was conducted using both MeSH terminology and more general search terms. Search terms included, but were not limited to: HPV, head and neck cancer, oral cancer, oropharyngeal cancer, intra-epithelial neoplasia, hyperplasia, dysplasia, leukoplakia, biopsy, polymerase chain reaction (PCR), and in situ hybridization (ISH). References cited in the identified research articles were also reviewed. Based on the preliminary review, 43 studies that reported HPV prevalence in head and neck squamous dysplastic lesions were identified.[19–61] To be

included in the final analysis the articles had to: (1) provide individual estimates for histopathologically confirmed dysplastic lesions, (2) differentiate dysplasia of OP and/or OC from other head and neck sites, and (3) provide type specific prevalence for HPV-16 and/or 18. Only 22 of the 43 articles met all the criteria and were used for this study.[21,22,24,27–31,33–36,40,41,43,44,48,50,53,54,56,60] These articles were evaluated independently by two authors (E.H., V.J.) to identify relevant data points including: number and grade of dysplasia, HPV prevalence, anatomical location, sample type, detection technique and patient demographics. Only the numbers specific to HPV types 16 and 18 and for OC and OP sites were used for this analysis. Studies that did not differentiate between OC and OP lesions were not included for the stratified analysis on anatomical location.

Statistical analysis

The analysis was conducted in two steps. For the first step, the prevalence of HPV-16/18 and 95% confidence intervals (CI) were calculated for each study. Overall prevalence was defined as the number of OOPD samples that tested positive for HPV-16/18 divided by the total number of OOPD samples. The 95% CI were then calculated using the Wilson 'score' method with continuity correction.[62] As a second step, meta-analysis was conducted to estimate the overall pooled prevalence of HPV-16/18 in OOPD. Sub-group analyses were conducted stratified by variables that are potential causes of heterogeneity among the studies. Sub-group meta-analyses were done to identify prevalence based on HPV serotype, detection technique, geographical location and the year of publication of the study. We explored the heterogeneity between study-specific results using the Q statistic at the significance level of $p = 0.05$. Estimates were obtained by both the fixed and random-effects models, and only random-effects model (REM) results were presented if significant heterogeneity was noted. The studies that reported HPV-16/18 prevalence of 0% or 100% were not included in the final meta-analysis. In order to make sure that the studies with prevalence of 0% or100% did not significantly change the overall estimates, we also repeated the meta-analysis by adjusting the estimates by ±1%. Only the results that excluded the studies with 0% or 100% are presented here. Stratified analysis was also conducted based on histological grade, anatomical location, patient age, and gender. However, several studies either did not report stratified data for these variables or reported only very small sample sizes; thereby making it difficult to obtain valid meta-analysis estimates. Therefore, for these variables, crude prevalence estimates and adjusted odds ratios (OR) were reported based on multiple logistic regression. STATA V.10 software was used for this analysis.

Results

The 22 studies together evaluated a total of 458 OOPDs. The number of samples per-study varied from 1 to 60 (Table 1). The detection rate of HPV-16 and/or 18 differed based on study and detection method.

Meta-analysis for overall prevalence based on HPV type

Eight studies reported the prevalence rate of both HPV-16 and 18 types, seven studies reported on HPV-16 alone and the other seven studies did not distinguish between HPV-16/18 (Table 1). Based on REM, the prevalence of either HPV-16/18 types in OOPD lesions was 24.5% [95% confidence interval (CI), 16.4–36.7%; $Q = 59.2$ (p-heterogeneity < 0.001)] (Fig. 1). The individual prevalence of HPV-16 in OOPDs was 24.4% [95% CI, 14.4–41.5%; $Q = 49.8$ (p-heterogeneity < 0.001)] (Fig. 2). Eight studies reported individual estimates for HPV-18, out of which only three studies reported a prevalence of >0%. Therefore, a separate estimate for HPV-18 is not presented.

Meta-analysis stratified by detection technique

Ten studies used PCR technique, eight used ISH, two used southern or filter blot, and the other two studies utilized both PCR and ISH (Table 1). Based on REM, the overall HPV-16/18 prevalence in OOPD was higher by PCR [26.8%; 95% CI, 15.7–45.8%; $Q = 36.8$ (p-heterogeneity < 0.001)] than by ISH technique [18.7%; 95% CI, 10.5–33.5%; $Q = 13.8$ (p-heterogeneity = 0.02)], but the difference was not statistically significant (p-value: 0.17).

Meta-analysis stratified by anatomical site

Only 15 of the 22 studies clearly differentiated OC dysplasia from OP dysplasia. Of these, 12 studies reported separate prevalence estimates for OC dysplastic lesions.[21,22,27,31,34,36,40,41,43,48,53,54,56,60] One study did not provide location specific estimates for all lesions and was not included in the meta-analysis specific for OC.[36] The OC dysplastic samples from the studies included 44 samples from oral tongue, 24 from floor of the mouth/ventral tongue, 53 from buccal gingiva/vestibule, 4 from hard palate, 14 from oral commissure/lip and another 47 samples from unspecified OC sites. Based on the REM, the overall prevalence of HPV-16/18 in OC dysplastic lesions was 25.3% [95% CI, 14.2–45.2%; $Q = 27.6$ (p-heterogeneity < 0.001)]. There was no significant difference in prevalence among the different OC sub-sites (p-value = 0.95). Only four studies reported individual prevalence estimates for OP dysplastic lesions, thus, separate meta-analysis was not feasible for this sub-group.[34,36,50,53]

Meta-analysis stratified by geographical location of the study

Overall, 9 studies were from Europe and 11 were from the United States (Table 1). The prevalence of HPV-16/18 in OOPD in European studies [28.9%; 95% CI, 18.7–44.8%; $Q = 3.9$ (p-value for heterogeneity = 0.41)] was higher than in the United States [20.3%; 95% CI, 10.8–38.2%; $Q = 34.4$ (p-value for heterogeneity = < 0.001)]; the difference was not statistically significant (p-value 0.18).

Meta-analysis stratified by the year of publication of the study

Ten studies were published up until 1995, and the remaining 12 studies were published in the years after 1995 (Table 1). Based on the random-effects model, the prevalence of HPV-16/18 in OOPD in the studies that were published after 1995 [25.7%; 95% CI, 15.6–42.3%; $Q = 33.5$ (p-heterogeneity < 0.001)] was slightly higher than the prevalence reported by studies published in or before 1995 [21.4%; 95% CI, 9.1–50.5%; $Q = 25.1$ (p-heterogeneity < 0.001)]; this difference was not statistically significant (p-value: 0.51).

Results based on age and gender

Only eight studies reported individual-level data on the age of the patients[31,36,40,41,43,48,53,54] and nine studies reported on gender.[27,31,36,40,41,43,48,53,54] The age distribution of 160 patients was available for analysis, of which 40% were less than 50 years of age. As shown in Table 2, the HPV-16/18 detection rate in OOPD was not significantly different between patients over and under 50 years of age (p-value: 0.16). The odds of detection of HPV-16/18 in OOPD lesions in males were twice that of females (OR 2.44; 95% CI, 1.26–4.74%; p-value: 0.008).

Results based on histological grade of the lesion

Ten studies reported on HPV-16/18 prevalence in benign, dysplastic and OOSCC lesions in the same population.[21,28–31,34,43,44,48,50,56] The odds of detection of HPV-16/18 was over 3 times greater in dysplastic lesions and invasive cancers, when compared with biopsies diagnosed as normal or benign keratosis (Table 3). However, there was no significant

difference in HPV-16/18 rates between dysplastic lesions and OOSCC or between mild, moderate, or severe dysplastic lesions. Separate evaluation of hyperplastic lesions was not feasible because of the small number of lesions and heterogeneity of their clinical and histological description.

Discussion

The hypothesis that viral infections may play a role in the development of OOSCCs is not new, having been proposed over three decades ago.[63,64] This belief was further strengthened by three studies, published in the early 1980s, that reported the presence of HPV in OOSCCs and pre-malignant lesions.[65–67] In spite of further evidence supporting these findings, the role of HPV in the development of OOSCC has remained controversial.[23,68–76] However, in the past decade, several factors have led to a renewed interest in evaluating the role of HPV in the development of OOSCCs. First, technological advancements leading to more sensitive and broad-spectrum detection methodologies have facilitated more efficient and large-scale studies evaluating HPV prevalence.[77] Second, the simultaneous increase in the rate of OOSCCs in non-users of tobacco and alcohol in the past three decades has led to increased efforts to identify the etiology of these cancers.[78–80] Finally, the success of the prophylactic immunization campaign for cervical cancer has provided an opportunity for prevention, thereby instilling greater interest in preventable HPV-related cancers. Recent molecular and epidemiological studies have established an association between HPV and OOSCCs, specifically those arising from the OP.[5,13–15] The current evidence is strong enough that the monographs of both the International Agency for Research on Cancer and the National Cancer Institute, USA, have listed HPV-16 as a risk factor for OP cancers.[77,81] The prevalence of HPV in OOSCC is estimated to be between 23% and 46%; with the higher prevalence being noted in OP cancers.[11,12,17] HPV-16 is the most common serotype reported in over 90% of these OOSCCs.[82,83]

Several studies have also evaluated HPV in clinically visible potentially malignant oral conditions, like leukoplakia and lichen planus.[29,31,38,49,66,68] However, the prevalence in OOPD lesions has not been thoroughly evaluated. Some studies, based on small cohorts, have reported varying estimates for HPV in OOPD.[21,22,24,27–31,33–36,40,41,43,44,48,53,54,56,60] Miller et al. in a comprehensive meta-analysis on OOSCCs and pre-malignant lesions, reported HPV (both low-risk and high-risk serotypes) prevalence of 22.2% in benign leukoplakia, 26.2% in intra-epithelial neoplasia and 46.5% in OOSCCs.[17] HPV-16 and 18 were the most common high-risk serotypes and were detected in 30% of the OOSCC samples. All other high-risk types were noted in less than 1% of the cases. While Miller et al. provide the most detailed evaluation to-date of the prevalence of HPV in histopathologically diagnosed pre-malignant lesions of OC and OP, they failed to provide separate estimates for HR-HPV-16/18 in these lesions. Additionally, the study does not differentiate HPV prevalence in pre-malignant lesions in OP from those in OC. In the current meta-analysis of 458 OOPD lesions, we estimate that the prevalence of HPV-16/18 to be 24.5%. Because of the strict inclusion criteria for the current analysis, some studies listed in the Miller et al. report are not included in this meta-analysis. The current study, to our knowledge, is the first to provide prevalence estimates of the preventable HPV-16/18 types in OOPD lesions.

It is, however, important to consider the limitations of the current meta-analysis while interpreting these results. The current meta-analysis was limited to English language studies identified on PubMed, MEDLINE and SCOPUS. These criteria may have inadvertently introduced the possibility of language and publication bias. An inherent limitation of meta-analysis methodology is the possibility of heterogeneity of results due to dissimilarities between the individual studies. In the current study, the variability in the patient population,

collection methodology, detection technique, diagnostic criteria, control selection, and anatomical location coding may have resulted in heterogeneity. We tried to address these issues by: (1) reporting REM estimates whenever significant heterogeneity was noted and (2) presenting results stratified by potential confounding and biasing factors. There was little or no information reported on sample selection criteria, collection methodology and on other potentially major confounders such as sexual habits, tobacco, and alcohol use; making adjustment for these factors or a stratified analysis unfeasible. In spite of these limitations, our results were consistent with previously published literature, thus supporting the validity of our study. For example, as previously mentioned, the prevalence of HR-HPV in dysplastic lesions was similar to the rate of HPV in intra-epithelial neoplasia reported by Miller et al..[17] Also as expected, the stratified estimates show that the studies that used the more sensitive PCR technique reported a greater prevalence of HPV-16/18 in OOPD lesions (26.8%), compared to the ones that used the less sensitive ISH technique (18.7%). Additionally, HPV-16/18 was almost 2.5 times more common in OOPD in males than females. This is consistent with reports that HPV-positive OOSCCs are 3 times more common in men as compared to women.[4,84]

The presence of HPV-16/18 in one-fourth of OOPD lesions is consistent with the hypothesis that HPV plays a significant role in the early phase of OC and OP carcinogenesis. HPV infection can however be transient and HPV detection alone might not prove a causal association. Several studies have previously shown that HPV can be detected even in normal oral tissue.[85–90] On the other hand, based on a review of 18 studies, Kreimer et al. estimated the prevalence of oral HR-HPV in healthy individuals to be 3.5%, only about 1.3% being HPV-16.[91] This is a much lower prevalence than the estimates in OOPD lesions reported by the current study. It is also important to note that, in the current study, HPV-16/18 were over 3 times more common in OOPD and OOSCC lesions than in normal samples. This finding is consistent with other recent studies showing a significantly greater prevalence of HPV in oral pre-malignant and malignant lesions compared to normal tissue.[17,92,93] While the greater prevalence in OOPD compared to normal samples suggests a role for HPV in the early carcinogenic process, it does not by itself directly imply a causal relationship. Further studies are needed to evaluate the significance of this upsurge in HPV-16/18 infection during the early carcinogenic process and its role in the progression of dysplastic tissues to invasive cancers.

Although this study included lesions from both OC and OP sites, only 15 of the 22 studies differentiated between biopsies from these two anatomical locations. Twelve of these studies evaluated only OC dysplasia, thereby limiting our ability to determine a clear estimate of HPV-16/18 prevalence for OP dysplasia alone. It is also possible that samples from the remaining 10 studies were also pre-dominantly from the OC. The reason may be that pre-malignant changes in the OP are hard to identify and biopsy as compared to OC sites. Therefore, it is possible that the restrictive inclusion criteria, including only histologically confirmed squamous dysplasia, inadvertently biases these results towards the lower OC prevalence. Despite this limitation, this is the first study to report a clear estimate of HPV-16/18 in dysplasia of the OC alone. Contrary to the opinion that HPV is a risk factor primarily for OP cancers, our results suggest the possibility that HPV-16/18 may play a role in the development of a sub-set of OC cancers also.

In summary, the current meta-analysis provides a quantification of the prevalence of HR-HPV-16/18 in OOPD lesions. This study also supports the hypothesis that HPV-16/18 infection may be a risk factor not only for OP cancers, but also in a sub-set of OC cancers. Understanding the process of HPV-related carcinogenesis is critical for the development of efficient HPV-targeted prevention strategies. This data on the prevalence of HPV-16/18 in OOPD lesions may be useful in the future to evaluate the effect of prophylactic vaccines in

the prevention of carcinogenic HPV-16/18 infections. However, large and well-designed prospective studies are needed to confirm these results and to further understand the prognostic significance of HPV infection in oral dysplasia.

Abbreviations

OOSCC	oral cavity and oropharyngeal squamous cell carcinoma
HPV	human papillomavirus
HR-HPV	high risk human papillomavirus
OC	oral cavity
OP	oropharynx
OOPD	oral cavity and oropharyngeal dysplasia
REM	random-effects model
PCR	polymerase chain reaction
ISH	in situ hybridization
OR	odds ratio
CI	confidence interval

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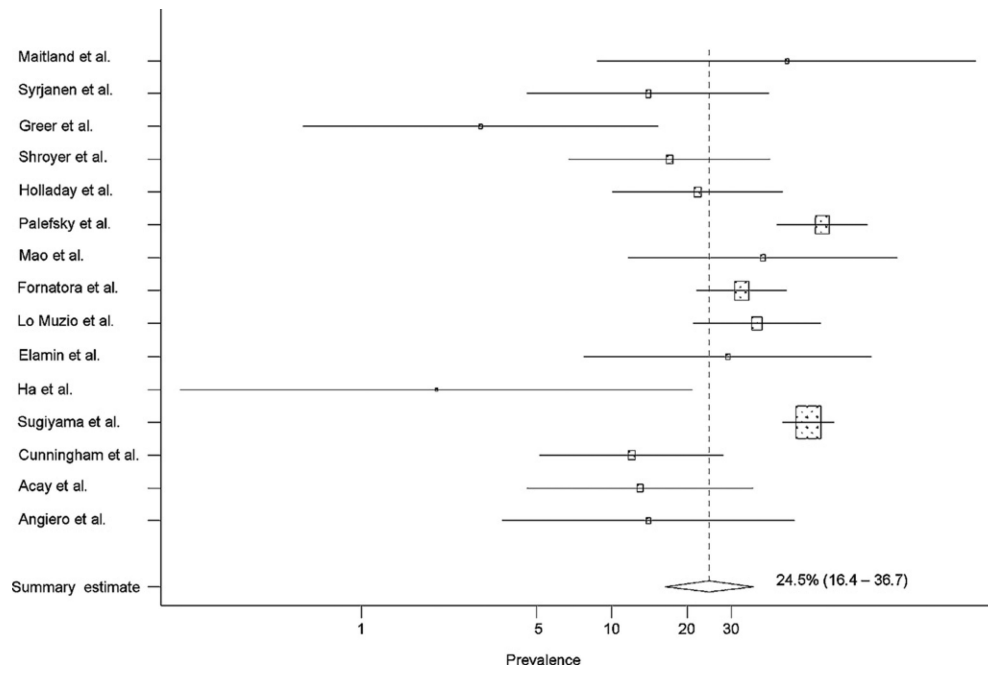
Fig. 1.
Pooled prevalence of HPV-16/18 in all dysplastic lesions. ◇, summary estimate; ▫,
random weight of each study; ●——●, 95% confidence interval.
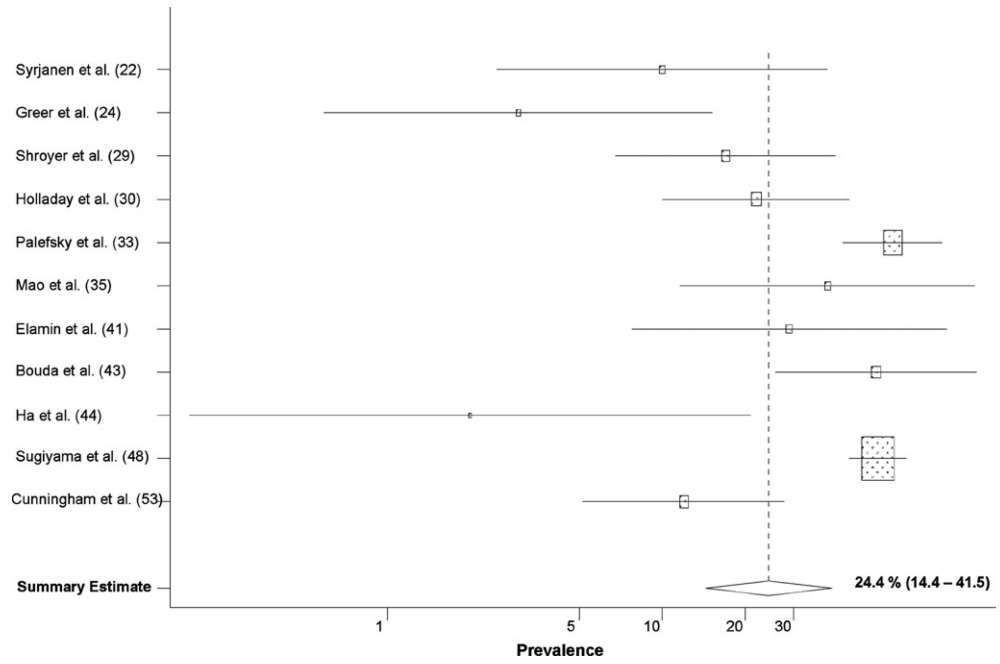
Fig. 2.
Pooled prevalence of HPV-16 alone in all dysplastic lesions. ◇, summary estimate; ⊡, random weight of each study; ●——●, 95% confidence interval.

Table 1

Characteristics of 22 studies that evaluated HPV-16 and/or 18 in dysplastic oral or oropharyngeal lesions.

Study	Year	Country	Number of samples (HPV positive/all dysplastic samples)								
			HPV-16/18[b]			HPV-16 alone			HPV-18 alone		
			ISH	SB/FB	PCR	ISH	SB/FB	PCR	ISH	SB/FB	PCR
Maitland et al.[21]	1987	UK	–	1/2	–	–	–	–	–	–	–
Syrjanen et al.[22]	1988	Finland	3/21	–	–	2/21	–	–	1/21	–	–
Greer et al.[24]	1990	USA	2/60	–	–	2/60	–	–	0/60	–	–
Zeuss et al.[27]	1991	USA	0/15	–	–	–	–	–	–	–	–
Young et al.[28]	1991	USA	0/3	–	–	–	–	–	–	–	–
Shroyer et al.[29]	1991	USA	3/24	–	4/24	–	–	4/24	–	–	–
Holladay et al.[30]	1993	USA	–	–	6/27	–	–	6/27	–	–	0/27
Cox et al.[31]	1993	UK	–	1/1	–	–	1/1	–	–	–	–
Palefsky et al.[33]	1994	USA	–	–	9/13	–	–	9/13	–	–	1/13
Fouret et al.[34]	1995	France	–	–	0/7	–	–	0/7	–	–	0/7
Mao et al.[35]	1996	USA	–	–	2/5	–	–	2/5	–	–	–
Fornatora et al.[36]	1996	USA	16/48	–	–	–	–	–	–	–	–
Lo Muzio et al.[40]	1997	Italy	8/21	–	–	–	–	–	–	–	–
Elamin et al.[41]	1998	UK	–	–	2/7	–	–	2/7	–	–	–
Bouda et al.[43]	2000	Greece	–	–	5/5	–	–	3/5	–	–	4/5
Ha et al.[44]	2002	USA	–	–	1/52	–	–	1/52	–	–	–
Sugiyama et al.[48]	2003	Japan	–	–	31/51	–	–	31/51	–	–	0/51
Begum et al.[50]	2005	USA	9/9	–	–	9/9	–	–	–	–	–
Cunningham et al.[53]	2006	USA	–	–	5/41	–	–	5/41	–	–	–
Bagan et al.[54]	2007	Spain	–	–	0/2	–	–	0/2	–	–	0/2
Acay et al.[56]	2008	Brazil	4/30	–	–	–	–	–	–	–	–
Angiero et al.[60]	2010	Italy	–	–	2/14[a]	–	–	2/14[a]	–	–	–

Abbreviations: ISH, in situ hybridization; SB/FB, Southern Blot / Filter blot; PCR, polymerase chain reaction.

[a] Only moderate and severe dysplasia included.

[b]HPV-16 alone or HPV-18 alone or both HPV-16/18.

Table 2

Odds of HPV-16/18 detection in oral dysplastic lesions, stratified by age and gender.

Characteristic	Number of studies	Number of samples	Crude prevalence (%)	Adjusted odds ratio[a]	p-Value
Age group [b]	8				
<50 years		66	39.1	1	
50 years		94	45.7	2.06 (0.76-5.62)	0.16
Gender [b]	9				
Female		75	29.3	1	
Male		98	46.9	2.44 (1.26-4.74)	0.008

[a] Adjusted by study ID and type of diagnostic test.

[b] Only dysplastic lesions.

Table 3

Odds of HPV-16/18 detection in oral cavity and oropharyngeal lesions, stratified by histologic grade.

Characteristic	Number of studies	Number of samples	Crude prevalence (%)	Adjusted odds ratio [b]	p-Value for trend
Type of lesion	10				
Benign[a]		207	14.0	1	
Squamous dysplasia		204	30.4	3.29 (1.95–5.53)	<0.001
OOSCC		241	30.7	3.43 (2.07–5.69)	
Grade of dysplasia	8				
Mild dysplasia		67	28.4	1	
Moderate dysplasia		73	28.8	1.05 (0.50–2.23)	0.92
Severe dysplasia		50	26.0	0.95 (0.41–2.20)	

[a]Includes normal and simple keratotic lesions.

[b]Adjusted by study ID and type of diagnostic test.