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REVIEW ARTICLE

Human papillomavirus as a risk factor for oral squamous cell carcinoma: A meta-analysis, 1982-1997

Craig S. Miller, DMD, MS,[a] and Bryan M. Johnstone, PhD,[b] Lexington, Ky, and Indianapolis, Ind
UNIVERSITY OF KENTUCKY COLLEGE OF DENTISTRY AND COLLEGE OF MEDICINE AND ELI LILLY AND COMPANY

Objective. Human papillomavirus (HPV) infection is a significant risk factor for uterine cervical carcinoma. However, the role of HPV infection in oral squamous cell carcinoma (OSCC) is less well defined. To determine the significance of the relationship of this virus in the progressive development of oral cancer, we estimated the risk of HPV detection in normal oral mucosa, precancerous oral tissue, and oral carcinoma using meta-analysis.
Study design. Case reports and clinical series published in English-language journals were retrieved by searching MEDLINE (January 1980-August 1998). Review articles were also examined to identify additional studies. Studies that used biochemical, immunologic, microscopic, or molecular analyses to detect HPV in tissue or cells derived from normal oral mucosa (n = 25), benign leukoplakia (n = 21), intraepithelial neoplasia (ie, dysplasia and carcinoma in situ; n = 27), and oral cancer (n = 94) were included in the meta-analysis. Information on sample size, age, sex, method of tissue preservation (ie, fresh, frozen, paraffin-embedded), assay, primer amplification region (early, late), high-risk versus low-risk genotype, and use of tobacco or alcohol was abstracted by one author (C.S.M.).
Results. Data from 94 reports that analyzed 4680 samples were included in the meta-analysis. Analyses made by means of a random-effects model with and without adjustments for assay sensitivity showed increased probability of HPV detection in tissue with precancerous and cancerous features compared with normal mucosa. The likelihood of detecting HPV in normal oral mucosa (10.0%; 95% confidence interval [CI], 6.1%-14.6%) was significantly less than of detecting benign leukoplakia (22.2%; 95% CI, 15.7%-29.9%), intraepithelial neoplasia (26.2%; 95% CI, 19.6%-33.6%), verrucous carcinoma (29.5%; 95% CI, 23%-36.8%), and OSCC (46.5%; 95% CI, 37.6%-55.5%). Adjustment of findings for differences in assay sensitivity indicated that these estimates may be conservative. Overall, HPV was between 2 and 3 times more likely to be detected in precancerous oral mucosa and 4.7 times more likely to be detected in oral carcinoma than in normal mucosa. The pooled odds ratio for the subset of studies directly comparing the prevalence of HPV in normal mucosa and OSCC was 5.37, confirming the trend observed in the overall sample. The probability of detecting high-risk HPVs in OSCCs was 2.8 times greater than that of low-risk HPVs.
Conclusion. This meta-analysis indicates that HPV is detected with increased frequency in oral dysplastic and carcinomatous epithelium in comparison with normal oral mucosa. The findings provide further quantitative evidence that oral infection with HPV, particularly with high-risk genotypes, is a significant independent risk factor for OSCC.
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[a]Oral Medicine Section, Department of Oral Health Practice, Department of Microbiology and Immunology, University of Kentucky College of Dentistry and College of Medicine, Lexington, Ky.
[b]United States Medical Division, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Ind.
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Oral cancer is a common cancer in the United States, with more than 30,000 cases diagnosed annually.[1] It leads to 7800 deaths per year and has a static 5-year mortality rate of 53% to 56%.[1-3] Known risk factors for oral squamous cell carcinoma (OSCC), the most common form of oral cancer, are long-term tobacco, alcohol, and betel quid use; long-term sun exposure; and immunosuppression.[2,4,5] Although numerous persons are exposed to these risk factors, only a small proportion of these individuals have OSCC develop.

This finding suggests that other factors may play a role in oral carcinogenesis.

Oncogenic human papillomaviruses (HPVs) have a well-established association with uterine cervical and anogenital carcinoma.[6-8] Their relationship to OSCC, however, is less well defined. The role of HPV in OSCC has been examined in numerous epidemiologic studies (reviewed in references 9 and 10). Yet, interpretation of these studies has been limited by the following: the low copy number of HPV in OSCC, the failure to compare dysplastic and carcinomatous tissue with matched normal tissue, the use of molecular assays and HPV probes having different sensitivities and specificities for viral detection, a lack of adequate controls or consideration of confounding factors, and the frequent use of small sample size. We therefore performed a meta-analysis on the available evidence of HPV prevalence in oral lesions to test the hypothesis that HPV infection is a risk factor for OSCC. Pooled estimates were calculated with and without adjustment for assay sensitivity to evaluate this potential confound. To our knowledge, this is the first comprehensive meta-analysis to address the relationship of HPV in oral normal mucosa, oral precancerous tissue, and OSCC.

METHODS

Identification and selection of studies

By means of MEDLINE, the medical literature from January 1980 through August 1, 1998, was searched for English-language case reports and clinical series that reported a relationship between HPV and normal oral mucosa, benign leukoplakia, intraepithelial neoplasia (ie, dysplasia and carcinoma in situ), verrucous carcinoma, or OSCC. In MEDLINE, the keywords *human papillomavirus, oral, oral cancer, head and neck cancer, oral carcinoma, squamous cell carcinoma*, and *oral lesions* were used alone and in combination to search. Reference lists of relevant publications and review articles were examined to identify further studies. Ninety-four articles published in peer-reviewed journals between December 1982 and April 1997 were identified. These were evaluated critically by one of the authors (C.S.M.). Studies were included for analysis if biochemical, immunologic, microscopic, or molecular analyses were used to detect HPV in tissue or in cells derived from normal oral mucosa and mucosal lesions potentially associated with the progression to OSCC. Studies were excluded if the publication was in a non–English language. Data were excluded if tissue had a non–squamous-epithelium origin (eg, in salivary gland tissue), if tissues were from sites distal to the anterior tonsillar pillars (ie, tonsillar, pharyngeal, or aerodigestive tissue), or if insufficient information was available to ascertain a definitive result.

Subgroup analyses

The prevalence of HPV was determined with respect to the clinical and histologic (ie, normal, precancerous [benign leukoplakia, intraepithelial neoplasia], carcinoma [verrucous, squamous cell]) nature of the oral epithelium, method of detection, assay sensitivity, and HPV genotype. There were 25 studies of normal mucosa, 21 studies of benign leukoplakia, 27 studies of intraepithelial neoplasia, 14 studies of verrucous carcinoma, and 80 studies of squamous cell carcinoma. Some studies used more than one assay to detect HPV, resulting in 27 data sets involving normal mucosa, 22 data sets involving benign leukoplakia, 28 data sets involving intraepithelial neoplasia, 16 data sets involving verrucous carcinoma, and 90 data sets involving squamous cell carcinoma. Assay sensitivity was determined as described previously.[9] Assays of low sensitivity included electron microscopy, immunoperoxidase, immunofluorescence, and in situ hybridization. Assays of moderate sensitivity included Southern blot, dot blot, and reverse blot hybridizations. Assays of high sensitivity included the polymerase chain reaction (PCR).

Cofactors

Cofactors evaluated included age, sex, method of tissue preservation (ie, fresh, frozen, paraffin-embedded), primer amplification region (early, late), high-risk versus low-risk genotype, and use of tobacco, or alcohol, or both.

Low-risk versus high-risk HPV types

The pooled probability of detecting "low-risk" or "high-risk" HPV types associated with OSCC was evaluated in the subset of studies that reported this information. To be included in this analysis, studies must have used probes to detect both low-risk and high-risk HPVs and have reported the distribution of findings by specimen. Specimens were included in the low-risk virus category if the investigator minimally probed for either virus HPV genotype 6 or 11. HPV types 1-5, 7-10, 12-15, 17, 19-30, 32, 34, 36-44, 46-51, 53-57, and 59 were also included in the low-risk category for the purpose of calculating an overall estimate of prevalence in each study. Specimens were included in the high-risk virus category if the investigator minimally probed for either HPV type 16 or 18. HPV types 31, 33, 35, 39, 45, and 52 were also included in the high-risk category. The denominator for these analyses was that all specimens were probed for HPV genotypes.

If findings from virus probes were reported from studies that used multiple assay procedures to detect

HPV, the results associated with the most sensitive technique were selected. The following guidelines were used: PCR assays were preferable to Southern blot hybridization (SB) and related assays and in situ hybridization (ISH) and associated assays; SB assays were preferable to ISH assays. Findings of this analysis were not further adjusted for putative assay sensitivity because we could not infer the distribution of patients across virus categories in adjusted results. If a range of specimens identified as positive was reported across viruses, the midpoint of the range was selected for inclusion in the analysis. Studies were excluded if investigators did not probe low- or high-risk viruses of interest, if investigators probed only one category of interest, or if the distribution of findings was not reported. A total of 46 studies met inclusion criteria.

Meta-analysis procedures

Outcome: Summary results and selected characteristics of each case report and clinical series were tabulated for analysis. We recorded the observed number of "successes" (ie, positive detection of HPV) and "failures" (negative determination) in each study for the analysis categories of interest: normal mucosa, benign leukoplakia, intraepithelial neoplasia, verrucous carcinoma, and OSCC. We calculated the maximum likelihood estimate of the true probability (θ) of HPV detection for each clinical series, using software for the confidence profile method developed by Eddy and colleagues.[11,12] The likelihood function for this outcome was defined as

$$L(y \mid \theta) \propto \theta^{s}(1-\theta)^{f} \qquad (1)$$

where $y_i = 1$ if the ith outcome is a "success," 0 if the ith outcome is a "failure," $s = \sum_{i=1}^{n} y_i$ [observed number of successes], and

$f = \sum_{i=1}^{n} (1-y_i)$ [observed number of failures].

We compared the probability of detecting low-risk versus high-risk human papillomaviruses in OSCC, using similar procedures on the subsample of studies that reported this information. For each study, we calculated the total number of specimens detected with low-risk HPVs and the total number of specimens detected with high-risk HPVs. The overall probabilities of detection of low-risk and high-risk viruses were determined, with the total number of specimens probed for HPV genotype as the denominator.

We also calculated log odds ratios (ORs) for the subset of studies that included clinical series for both normal tissue samples and one or more of the remaining tissue categories to evaluate the possibility that Simpson's paradox may have influenced the pooled findings.[13] In this case, the effects estimate was the log odds that HPV was detected in tissue samples containing benign leukoplakia, intraepithelial neoplasia, verrucous carcinoma, or OSCC, in comparison with normal tissue samples.

Adjustment for potential errors in measurement of outcomes

Analyses were performed with both unadjusted estimates and assay sensitivity–adjusted estimates. The latter were perceived to be a critical confound because more sensitive assays have the potential for higher detection rates of viruses in tissue. The relationship between the true probability of HPV detection (θ) and the biased parameter (θ′) was estimated with the function

$$\theta' = \theta(1-\alpha) + (1-\theta)\beta \qquad (2)$$

where α is the probability that a true success (detection) is labeled a failure (α = P[failure | success]) and β is the probability a true failure (negative determination) is labeled a success (β = P[success | failure]).[11] On the basis of the literature, findings from assays of high sensitivity (PCR) were accepted at face value, assays of moderate sensitivity (Southern blot, dot blot, and reverse blot hybridizations) were adjusted by using a P(failure | success) value of .2, and assays of low sensitivity (electron microscopy, immunoperoxidase, immunofluorescence, and in situ hybridization) by using a P(failure | success) value of .4. The adjustment was calculated for each relevant clinical series, when computationally feasible. Both unadjusted and adjusted estimates are reported in the tables and figures.

Pooled values

Estimates of the pooled probability of detection of HPV were calculated for each tissue category by means of both fixed effects and random-effects model assumptions,[14] and the heterogeneity of the results across studies was evaluated.[15] We report random-effects model estimates, using the method of DerSimonian and Laird,[16] because an evaluation of the findings indicated significant heterogeneity was present. The average probability of detecting HPV, the 95% confidence interval around this estimate, and the probability density function for the outcome are presented for each tissue category in the tables and figures. For reference, results of a test for homogeneity (Q) for each category are also provided. Values were derived by using software for meta-analysis developed by Eddy and Hasselblad (FAST*PRO, version 1.8).[12] Using the same procedures, we calculated random-effects model estimates of the pooled probability of detecting low-risk HPVs and high-risk HPVs in OSCC for the subset of studies that reported this information.

For the subset of studies that included clinical series

Table I. Characteristics of studies of HPV detection in normal, benign leukoplakia, precancerous oral mucosa, and verrucous carcinoma

	Detection of HPV in specimens of*				
Investigator	*Normal mucosa*†	*Benign leukoplakia*	*Intraepithelial neoplasia*	*Verrucous carcinoma*	*HPV probes used (specimens positive for that genotype)*‡
Abdelsayed[18]			0/18 (ISH)		6/11, 16/18, 31/33
Adler-Storthz et al[19]			1/1 (ISH)	3/9 (ISH)	NP
					$(2)^{III}$, 6, 16
Anderson et al[20]				2/8 (PCR)	$(16/18)^{II}$
Balaram et al[21]		5/5 (PCR)			6, $(11)^{II}$, $(16)^{II}$, $(18)^{III}$
				10/15§ (PCR)	$(6)^{I}$, $(11)^{III}$, $(16)^{VI}$, $(18)^{VI}$
Brandsma et al[22]	*0/18 (SB)*				11, 16, 18
Chang et al[23]	*1/17 (SB)*				6, 11, 16, 18, $(X)^{I}$
Cox et al[24]	*3/5 (SB)*	*3/3 (SB)*	*1/1 (SB)*		$(16)^{III}$, $(16)^{III}$, $(16)^{I}$
Cruz et al[25]	*0/12 (PCR)*				6, 11, 16, 18, 31, 33
Donofrio et al[26]			14/24 (ISH)		$(6/11)^{VI}$, $(16/18)^{VII}$, $(31/33/35)^{I}$
Eike et al[27]	*0/61 (PCR)*				6/11, 16, 18
Fornatora et al[28]			25/48 (ISH)		$(6/11)^{IX}$, $(16/18)^{XVI}$, $(31/33/35)^{XXI}$
Fouret et al[29]			0/3 (PCR)		6, 11, 16, 18, 31, 33
Gassenmaier and		21/202 (ISH)			2, $(6)^{III}$, $(11)^{II}$, $(16)^{VII}$
Hornstein[30]			19/103 (ISH)		$(2)^{II}$, $(6)^{I}$, $(11)^{IV}$, $(16)^{III}$
González-Moles et al[31]		5/13 (ISH)			$(6/11)^{V}$, $(31/33/35)^{III}$
			3/5 (ISH)		$(6/11)^{III}$, $(16/18)^{I}$
Gopalakrishnan et al[32]	1/10 (PCR)				$(16)^{I}$, 18
Greer et al 1987[33]		9/27 (IP)			NP
		5/27 (ISH)			$(2)^{III}$, 4, $(6)^{II}$, 11, 16, 18
Greer et al[34]		16/77 (IP)			NP
Greer et al[35]		7/100 (ISH)			$(2)^{V}$, 4, $(6)^{II}$, 11, 16, 18, 31, 33, 35
			2/60 (ISH)		2, 4, 6, 11, $(16)^{II}$, 18, 31, 33, 35
				4/20 (ISH)	2, 4, $(6)^{I}$, 11, $(16)^{III}$, 18, 31, 33, 35
Greer et al[36]		2/3 (DB)			$(6/11)^{II}$, 16/18, 31/33/35 $(6/11)^{I}$
			1/2 (DB)		6/11, 16/18
Heyden et al[37]	0/52 (ISH)				6, 11, $(16)^{I}$, 18, 33
Holladay and Gerald[38]	1/6 (PCR)				
			9/36 (PCR)		6, $(11)^{I}$, $(16)^{IX}$, 18, 33
				0/2 (PCR)	6, 11, 16, 18, 33
Jalal et al[39]	*21/48 (PCR)*				$(16)^{XXI}$
Jenison et al[40]	*18/56 (PCR)*				$(6)^{XI}$, $(16)^{XII}$
Kashima et al[41]	*2/29 (SB)*				1, $(6)^{I}$, 11, $(16)^{I}$, 18, 31, 57
		1/23 (SB)			1, 6, $(11)^{I}$, 16, 18, 31, 57
			0/4 (SB)		1, 6, 11, 16, 18, 31, 57
Kellokoski et al[42]	*7/262 (DB)*				2, $(6)^{VI}$, $(7)^{I}$, $(11)^{III}$, 13, $(16)^{III}$
Kellokoski et al[43]	*33/212 (SB)*				$(2, 6, 18),^{XXXIII}$ 11, 13, 16
	18/78 (PCR)				2, $(6/11)^{XII\text{-}IXX}$, 13, $(16/18)^{0\text{-}VII}$
Kratochvil et al[44]			1/1 (ISH)		$(16)^{I}$
Lawton et al[45]	*36/60 (PCR)*				$(6/11)^{XI}$, $(16)^{XVI}$, $(18)^{IV}$, $(31)^{II}$, $(33)^{III}$
Löning et al[46]		*3/6 (IF)*			NP
Löning et al[47]		*4/5 (SB)*			11, 16 (NS)
Löning et al[48]	*0/41 (DB)*	*3/4 (DB)*		*0/1 (DB)*	$(6/11)^{I}$, $(16/18)^{I}$
Lookingbill et al[49]			*1/1 (DB)*		6, 11, $(16)^{I}$, 18
Lubbe et al[50]				1/1 (PCR)	$(11)^{I}$, $(16)^{I}$
Maden et al[51]	*11/112 (PCR)*				$(6)^{X}$, $(16)^{I}$
Maitland et al[52]	*5/12 (SB)*				1, 2, 4, 6, 11, 13, $(16)^{V}$, 18
		8/10 (SB)			1, 2, 4, 6, 11, 13, $(16)^{VIII}$, 18
			1/2 (SB)		1, 2, 4, 6, 11, 13, $(16)^{I}$, 18
Mao [53]	*4/26 (PCR)*				$(16)^{IV}$
Mao et al[54]			5/8 (PCR)		$(6)^{0\text{-}I}$, $(16)^{IV\text{-}V}$
Mao et al[55]	0/6 (PCR)		8/23 (PCR)		$(6)^{0\text{-}III}$, $(16)^{0\text{-}VIII}$, 13, $(6/16)^{0\text{-}II}$, 31, 33, 35, 45
Milde and Löning[56]				*1/1 (ISH)*	$(16)^{I}$
Miller et al[57]				1/1 (PCR)	$(16)^{I}$, 18
Murrah et al[59]			2/6 (PCR)	1/1 (PCR)	6/11, $(16/18)^{I}$, 31/33/35
					6/11, $(16/18)^{I}$, 31/33/35

Table I. Continued.

Investigator	*Detection of HPV in specimens* of*				*HPV probes used (specimens positive for that genotype)‡*
	Normal mucosa†	*Benign leukoplakia*	*Intraepithelial neoplasia*	*Verrucous carcinoma*	
Nielsen et al[58]	0/20 (ISH)	8/18 (ISH)	10/25 (ISH)		6, 11, 16, 18, 31, 33 (NS)
	0/20 (PCR)		1/25 (PCR)		$(16)^{I}$
Noble-Topham et al[60]				12/25 (PCR)	$(6/11)^{I}$, $(16)^{I}$, $(18)^{IX}$, $(16/18)^{I}$
Ostwald et al[61]	*1/97 (PCR)*				6/11, $(16)^{I}$, 18
Palefsky et al[62]		9/21 (PCR)			6, 11, $(16)^{I}$, $(18)^{II}$, $(31)^{II}$, 33, 45, $(X)^{III}$
			10/13¶ (PCR)		6, 11, $(16)^{IX}$, $(18)^{I}$, 31, 33, 45
Shroyer et al[63]		0/10 (ISH)	4/24 (ISH)	0/3 (ISH)	6/11, $(16/18)^{III}$, $(31/33/35)^{I}$
				0/3 (PCR)	
Shroyer et al[64]				7/17 (ISH)	$(6)^{II}$, $(11)^{V}$, 16, 18, 31, 33, 35
				7/17 (PCR)	
Syrjänen et al[65]		1/2 (IP/SH)	1/1 (IP/ISH)		NP
Syrjänen et al[66]			6/21 (ISH)		$(6)^{I}$, $(11)^{II}$, $(16)^{II}$, $(18)^{I}$, 13, 30
Tsuchiya et al[67]		*0/1 (SB)*	*0/1 (SB)*		6/11, 16/18, 31/33/35
Tyan et al[68]	*1/11 (PCR)*				6, 11, $(16)^{I}$, 18, 33
Uobe et al[69]			*5/5 (PCR)*		1, 5, 6, 8, 11, 16, 18, 26, 27, 31, 33, 35, 39-42, 45, 47, 48, 51-5, 57, 59 (NS)
Van Rensburg[70]	1/66 (ISH)				6, 11, 16, $(18)^{I}$
Watts et al[71]	*0/5 (PCR)*				6, 11, 16, 18
Wen et al[72]		2/3 (PCR)			16, $(18)^{II}$
Yeudall and Campo[73]	2/25 (SB)				1-7, 11, 13, 16, $(18)^{II}$
Young and Min[74]		0/36 (ISH)	0/3 (ISH)	0/10 (ISH)	6/11, 16/18, 31/33/35
Zeuss et al[75]		2/20 (ISH)	0/20 (ISH)		6/11, 16/18, 31/33/35

DB, Dot blot hybridization; *ISH,* in situ hybridization; *IP,* immunoperoxidase; *IF,* immunofluorescence; *NP,* nonspecific HPV probe; *NS,* not specified; *SB,* Southern blot hybridization; */,* combination HPV probe; *X,* HPV DNA not defined by type.

*Specimens were paraffin-embedded unless italicized, indicating fresh or frozen tissue.

†Clinically or histologically normal.

‡Number (in Roman numerals) of specimens positive for that genotype, inclusive of dual HPV infections.

§Specimens were paraffin-embedded and frozen.

¶Includes 9 proliferative verrucous leukoplakia specimens.

of both normal tissue samples and one or more of the remaining tissue categories, pooled log ORs, and CIs were estimated by using the formulas and the template statistical analysis system code provided by Shadish and Haddock.[17] Random-effects model estimates of pooled log odds and ORs for unadjusted and adjusted comparisons of normal tissue versus alternative tissue categories are presented.

RESULTS

Characteristics of the studies

Tables I and II show selected characteristics of the studies that met the criteria for analysis. The 94 studies included analysis of 4680 samples from 11 case reports and 83 clinical series. All studies were analyzed independently. Age was identified in only 22% of studies; of these, all cases of OSCC were from adults. Normal mucosa and benign leukoplakia specimens were obtained from a younger population that included adolescents. Most studies included both men and women, but the data necessary to analyze the probability of detecting HPV in normal oral mucosa and precancerous and carcinomatous oral mucosa according to age and sex were not available. In addition, the cofactors (1) method of tissue preservation (ie, fresh, frozen, paraffin-embedded), (2) primer amplification region (early, late), and (3) use of tobacco or alcohol did not contribute to the results in exploratory analyses—in part because of limitations in the availability of detailed exposure of the cofactors. In the normal mucosa category, 25 studies used 3 assays of low sensitivity, 9 assays of moderate sensitivity, and 15 assays of high sensitivity. In the benign leukoplakia category, 24 studies used 13 assays of low sensitivity, 8 studies used moderate sensitivity, and 13 studies used high sensitivity. In the intraepithelial neoplasia category, 28 studies used 14 assays of low sensitivity, 6 studies used moderate sensitivity, and 8 studies used high sensitivity. In the carcinoma (verrucous and OSCC) category, 106 studies used 33 assays of low sensitivity, 26 assays of moderate sensitivity, and 47 assays of high sensitivity.

Table II. Characteristics of studies of HPV detection in oral squamous cell carcinoma

Investigator	*Detection rate of HPV in specimens* by*			*HPV probes used (specimens positive for that genotype)†*
	ISH/IP/IF	*SB/DB/FB*	*PCR*	
Abdelsayed[18]	2/36			(6/11)^{I}, (16/18)^{I}, 31/33/35
Anderson et al[20]			*6/27*	(16/18)^{VI}
Balaram et al[21]			57/76‡	(6)^{XIII}, (11)^{XVI}, (16)^{XXXII}, (18)^{XXXVII}
Brachman et al[76]			*1/13*	16, (18)^{I}
				1, 2, 5, 6, 8, 11, 31, 41, 47, 51, 57
Bradford et al[77]		*1/9*	*1/2*	6, 11, 16, 18, 31, 52 (NS)
Brandsma et al[28]		*2/19*		11, (16)^{II}, 18
Brandwein et al[78]			16/64	6, 11, 16, 18, 31, 35, 57 (NS)
Cerovac et al[79]	5/25			(6)^{I}, (16)^{V}, (16/18)^{I}
Chang et al[23]		*13/17*		6, 11, (16)^{XIII}, 18
Chang et al[80]	1/40			(6/11/16/18)^{I}
			11/40	(6)^{I}, 11, (16)^{IX}, (18)^{I}
Chen et al[81]			*2/3*	(16)^{I}, (18)^{I}
Chiba et al[82]			*8/38*	(16)^{VIII}
Cox et al[24]		*4/8*		(16)^{IV}
Cruz et al[25]			*19/35*	(6)^{I}, 11, (16)^{XV}, 18, 31, 33, (X)^{III}
Dekemezian et al[83]	*4/4*			6, (11)^{IV}, (16)^{I}, 18
de Villiers et al[84]		*3/7*		1, (2)^{I}, 3-15, (16)^{II}, 17-19, 21-25
de Villiers[85]		0/46		1-56 (NS)
Donofrio et al[26]	3/6			(6/11)^{I}, (16/18)^{II}, 31/33/35
Flaitz et al[86]	3/4			(6/11)^{I}, (16/18)^{II}, (31/33/35)^{I}
Fouret et al[29]			2/21	6, 11, 16$^{0\text{-}II}$, 18, 31$^{0\text{-}II}$, 33
Frazer et al[87]	*2/21*		*3/21*	6, 11, (16)^{III}, 18, 31, 33
Gassenmaier and Hornstein[30]	16/63			(2)^{II}, (6)^{II}, (11)^{I}, (16)^{II}
González-Moles et al[31]	10/27			(6/11)^{V}, (16/18)^{I}, (31/33/35)^{V}
González-Moles et al[88]			7/37	(18)^{VII}
Gopalakrishnan et al[32]			3/10	(16)^{III}, 18
Greer et al[35]	3/50			2, 4, 6, 11, (16)^{I}, (18)^{I}, 31, (33)^{I}, 35
Greer et al[36]		*2/2*		(6/11)^{II}, (16/18)^{II}, 31, 33, 35
Holladay and Gerald[38]			7/37	6, 11, (16)^{VII}, (18)^{I}, 33
Hönig[89]	7/12			6, (11)^{IV}, (16)V, (18)^{IV}, 31, 33
Hönig et al[90]	28/40			(6)^{VII}, (11)^{IV}, (16)^{XVII}, (18)^{XX}, (31)^{III}, (33)^{VIII}
Howell and Gallant[91]		*1/7*		(16)^{I}, 18
Ishibashi et al[92]		*0/6*		1, 5, 6, 11, 16, 17, 18, 20
Kashima et al[41]		*5/26*		1-57, (3)^{I}, (6)^{I}, (13)^{I}, (16)^{I}, (57)^{I}
Kiyabu et al[93]		5/15	5/15	(16)^{V}, 18
Kulski et al[94]		1/5		(6/11)^{I}, (16/18)^{I}
Lee et al[95]		*1/2*		6, 11, (16)^{I}, 18
Lind et al[96]	7/10			NP
Lindeberg et al[97]		1/2		(16)^{I}
Löning et al[46]	*1/1*			NP
Löning et al[47]		*3/6*		(11)^{I}, (16)^{I}, (X)^{I}
Löning et al[48]		*5/13*		(6/11)^{I}, (16/18)^{I}, (X)^{III}
Lookingbill et al[49]		1/1		(16)^{I}
Maden et al[51]			*28/118*	(6)^{XXII}, (16)^{VI}
Maitland et al[52]		*7/15*		1, 2, 4, 6, 11, 13, (16)^{VI}, 18, (X)^{I}
Maitland et al[98]			*4/7*	(16)^{IV}
Mao[53]			*8/26*	(16)^{VIII}
Mao et al[54]			2/6	(6)$^{0\text{-}I}$, (16)$^{I\text{-}II}$
Mao et al[55]			12/41	(6)$^{0\text{-}III}$, (16)$^{III\text{-}XI}$, (6/16)$^{0\text{-}II}$, (16/18)$^{0\text{-}II}$, 11, 13, 31, 33, 35, 45
Milde and Löning[56]	3/6			(16)^{III}
Miller et al[99]	0/21			6/11/16/18, 31/33/35/42-45/51/52
Miller at al[57]			20/30	(16)^{XVIII}, (18)^{VII}
Min et al[100]			1/9	16, (18)^{I}
Mukhopadhyay et al[101]	*31/44*			NP
Murrah et al[58]			2/88	6/11, (16/18)^{II}, 31/33/35
Nielsen et al[59]			3/3	(6, 11, 18, 31, 33)^{II}, (16)^{I}
Ostrow et al[102]		*1/2*		6, (16)^{I}, 18
Ostwald et al[61]			*16/26*	(6/11)^{II}, (16)^{VII}, (18)^{VI}, (X)^{II}
Palefsky et al[62]			10/26‡	(6) ^{I}, 11, (16)^{V}, 18, 31, 33, 45, (X)^{IV}

Table II. Continued.

Investigator	*Detection rate of HPV in specimens* by*			*HPV probes used (specimens positive for that genotype)†*
	ISH/IP/IF	*SB/DB/FB*	*PCR*	
Paz et al[103]			*9/71*	$(6)^{II}$, $(16)^{V}$, 18, $(X)^{II}$
Saez et al[104]	8/15			$(6/11)^{II}$, $(16/18)^{VIII}$
Shindoh et al[105]		8/24		$(16)^{VIII}$, $(18)^{I}$, 33
Shindoh et al[106]			24/77	$(16)^{XXIV}$, $(18)^{I}$, 33
Shroyer et al[63]	1/10		1/10	6/11, $(16)^{I}$, 18, 31/33/35
Snijders et al[107]			*5/25*	6, 11, $(16)^{V}$, 18, 31, 33
Steenbergen et al[108]	*1/1*		*1/10*	$(16)^{I}$
Syrjänen et al[109]	8/16			NS
Syrjänen et al[65]	1/2	1/2		6, 11, $(16)^{II}$
Syrjänen et al[66]	6/51			6, 11, 13, $(16)^{III}$, $(18)^{IV}$, 30
Tsuchiya et al[67]	*0/5*			6/11, 16/18, 31/33/35
		3/23		1/3/6/11/16/18/33, $(6/16/18)^{III}$
Tyan et al[68]			*1/9*	6, 11, $(16)^{I}$, 18, 33
Uobe et al[69]			5/5	1, 5, 6, 8, 11, 16, 18, 26, 27, 31, 33, 35, 39-42, 45, 47, 48, 51-5, 57, 59 (NS)
Van Rensburg et al[70]	0/66			6, 11, 16, 18
Watts et al[71]		*16/23*		$(6/11)^{VIII}$, $(16/18)^{XI}$,
			14/14	$(6)^{I}$, $(11)^{VII}$, $(16)^{XI}$, $(18)^{II}$
Wen et al[72]			14/45	$(16)^{IX}$, $(18)^{XI}$
Wong et al[110]		*1/2*		$(16)^{I}$
Woods et al[111]			14/18	$(6/11)^{V}$, $(16)^{II}$, $(18)^{II}$, $(16/18)^{XI}$
Yeudall and Campo[73]		3/39		1-7, 11, 13, $(4)^{I,}$ $(16)^{I,}$ $(18)^{I}$
			18/39	1-7, 11, 13, $(4)^{I}$, $(16)^{X}$, $(18)^{VIII}$
Yeudall et al[112]			*2/8*	$(16)^{II}$
Young and Min[74]	0/17			6/11, 16/18
Zeuss et al[75]	0/15			6/11, 16/18, 31/33/35

ISH, In situ hybridization; *IP,* immunoperoxidase; *IF,* immunofluorescence; *NP,* nonspecific HPV probe; *NS,* not specified; *SB/DB/FB,* Southern blot, dot blot, or filter blot hybridization; */,* combination HPV probe; *X,* HPV DNA not defined by type.
*Specimens were paraffin-embedded unless italicized, indicating fresh or frozen tissue.
†Number (in Roman numerals) of specimens positive for that genotype, inclusive of dual HPV infections.
‡Specimens were paraffin-embedded and fresh or frozen.

Table III. Results of meta-analysis: probability of detection of HPV and 95% CIs in normal and precancerous oral mucosa, oral verrucous carcinoma, and oral squamous cell carcinoma, unadjusted results

Category	*n**	*Probability†*	*95% CI‡*	*Q (P)§*
Normal mucosa	27	0.0997	0.0613/0.1461	150.0 (<.001)
Benign leukoplakia	22	0.2220	0.1568/0.2994	66.7 (<.001)
Intraepithelial neoplasia	28	0.2616	0.1962/0.3359	45.3 (.005)
Verrucous carcinoma	16	0.2950	0.2295/0.3676	11.1 (.75)
Oral squamous cell carcinoma	90	0.4647	0.3764/0.5547	226.0 (<.001)

*Number of observations (tests of hypothesis) in category.
†Random-effects model estimate, pooled probability of detection of HPV in sample of studies.
‡95% CI around weighted probability.
§Test of homogeneity of weighted probability.

Meta-analysis findings

Fig 1 displays the probability density function for the likelihood of detecting HPV in different tissue categories by using the method of pooled unadjusted estimates. As the figure indicates, the probability of detecting HPV increased with the increasing dysplastic nature of oral mucosa, having a substantial overlap in the probability distributions for benign leukoplakia, intraepithelial neoplasia, and verrucous carcinoma. Table III reports the random-effects model point estimates and 95% CIs for the weighted probability of detecting HPV in each tissue category. The pooled probability of detecting HPV in 27 data sets of normal oral mucosa was 10.0% (95% CI, 6.1% to 14.6%). In 22 tests of the hypothesis in benign leukoplakia, the likelihood of detecting HPV was 22.2% (95% CI, 15.7% to 29.9%). The corresponding probability in 28 samples of intraepithelial neoplasia was 26.2% (95% CI, 19.6% to

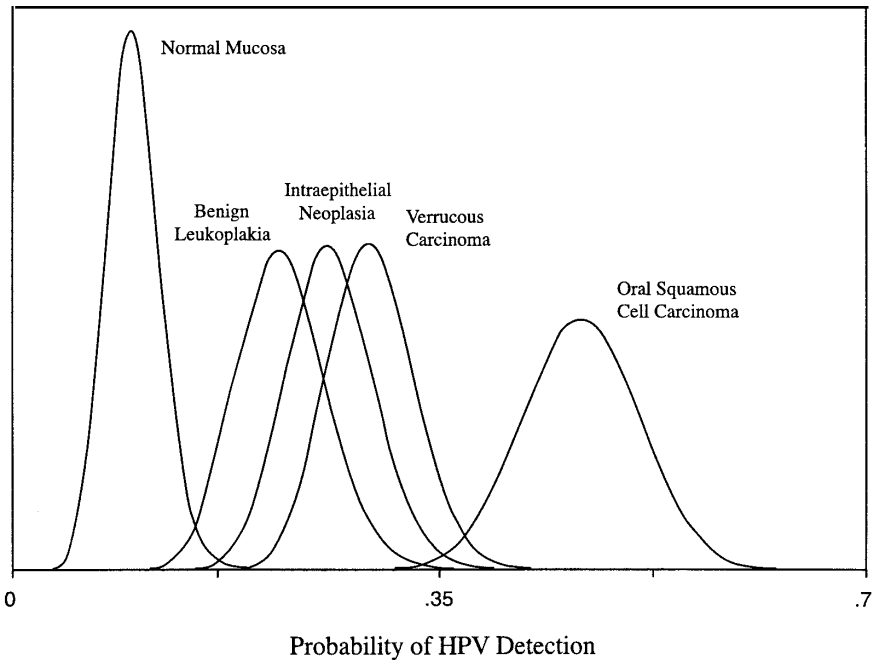

Fig 1. Probability distribution, likelihood of HPV detection in normal and precancerous oral mucosa, oral verrucous carcinoma, and OSCC—unadjusted results.

Table IV. Results of meta-analysis: probability of detection of HPV and 95% CIs in normal and precancerous oral mucosa, oral verrucous carcinoma, and oral squamous cell carcinoma, assay sensitivity–adjusted results

Category	*n**	*Probability*†	*95% CI*‡	*Q (P)*§
Normal mucosa	27	0.1136	0.0732/0.1663	132.9 (<.001)
Benign leukoplakia	22	0.2993	0.2171/0.3924	49.6 (<.001)
Intraepithelial neoplasia	28	0.3314	0.2538/0.4166	38.2 (.03)
Verrucous carcinoma	16	0.3389	0.2620/0.4227	8.5 (.90)
Oral squamous cell carcinoma	90	0.4986	0.4130/0.5843	212.0 (<.001)

*Number of observations (tests of hypothesis) in category.
†Random-effects model estimate, pooled probability of detection of HPV in sample studies.
‡95% CI around weighted probability.
§Test of homogeneity of weighted probability.

33.6%) and 29.5% in 16 samples of verrucous carcinoma (95% CI, 23% to 36.8%). In studies of OSCC, the likelihood of detecting HPV was significantly higher than in other tissue categories, at 46.5% (95% CI, 37.6% to 55.5%). The probability of detecting HPV in oral carcinoma was approximately 4.7 times higher than in normal oral mucosa. Data in Table III demonstrate that significant heterogeneity was observed in 4 of 5 tissue categories (normal mucosa, benign leukoplakia, intraepithelial neoplasia, and OSCC).

The study findings were also pooled by means of assay sensitivity–adjusted estimates to address the potential effects of measurement error on estimates of the probability of detecting HPV in any tissue category or the distribution of estimates across categories. Fig 2 displays the probability density functions for the adjusted findings, and Table IV reports the random-effects model point estimates and 95% CIs for these data. The effects of the adjustment procedure were to increase the estimated probability of detecting HPV in each tissue category by a moderate amount and to homogenize the probability distributions for intraepithelial neoplasia and verrucous carcinoma. The trend toward an increase in the probability of detecting HPV with the increasing dysplastic nature of oral mucosa is preserved in the adjusted findings. As Table IV indicates, significant heterogeneity was again observed in 4 of 5 tissue categories, although the effect of the adjustment for potential measurement error was to reduce the chi-square result by a limited quantity in each case.

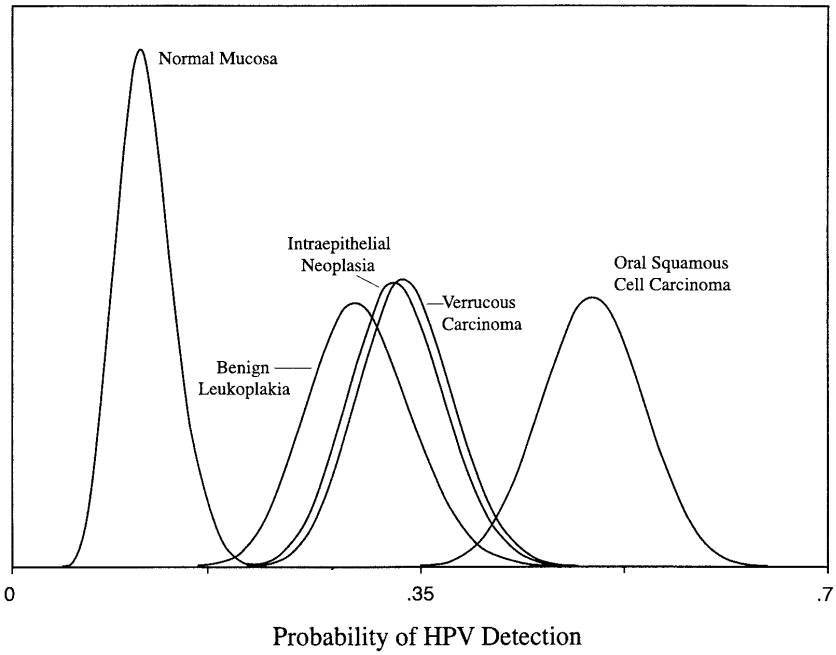

Fig 2. Probability distribution, likelihood of HPV detection in normal and precancerous oral mucosa, oral verrucous carcinoma, and OSCC—assay sensitivity–adjusted results.

Table V. Meta-analysis of studies that reported prevalence of HPV in both normal tissue and precancerous oral mucosa, oral verrucous carcinoma, or oral squamous cell carcinoma

		Unadjusted estimates			*Adjusted estimates*		
Category	*n**	*Ln (OR)†*	*OR‡*	*95% CI (OR)§*	*Ln (OR)†*	*OR‡*	*95% CI (OR)§*
Benign leukoplakia	6	1.96	7.10	1.32/38.25	2.05	7.80	1.18/51.45
Intraepithelial neoplasia	5	1.05	2.85	1.60/5.07	0.64	1.91	0.85/4.29
Verrucous carcinoma	2	1.30	3.68	0.11/125.6	1.45	4.28	0.11/163.15
Oral squamous cell carcinoma	19	1.65	5.21	2.49/10.89	1.68	5.37	2.49/11.55

*Number of studies.
†Random-effects model estimate of pooled log odds, weighted variance method.
‡Random-effects model estimate of pooled OR, weighted variance method.
§95% CI around pooled OR.

We pooled observations across samples within each tissue category rather than evaluating differences in proportions or the odds of detecting HPV within studies, because few reports provided comprehensive comparative data. It is therefore possible that aggregation bias (Simpson's paradox) may have influenced the pooled results. To evaluate this possibility, we pooled the comparative likelihood of detecting HPV within studies in the subset of the overall sample of studies that reported both findings for both normal mucosa and one or more alternative tissue categories. Table V reports these findings. The number of observations in any single category meeting the criterion for this analysis was small, ranging from 2 to 19. However, the overall trend of the findings was similar to the results observed in the full sample. Summary ORs indicated that the likelihood of detecting HPV was higher in precancerous oral mucosa, oral verrucous carcinoma, and OSCC than in normal mucosa, although CIs were broad and in 2 cases (intraepithelial neoplasia, verrucous carcinoma) extended below 1.0. Perhaps the best available estimate was obtained for OSCC. The pooled OR for this comparison indicated that HPV was more than 5 times more likely to be detected in squamous cell carcinoma clinical series than in normal mucosa. These findings, in general consonant with the observed results for the full sample, provide additional evidence in support of the hypothesis.

Table VI compares the pooled probability of detecting low-risk versus high-risk HPVs in OSCC in

Table VI. Results of meta-analysis: comparison of probability of detection of low-risk HPV versus high-risk HPV in oral squamous cell carcinoma tissue

Category	*n**	*Probability†*	*95% CI‡*	*Q (P)§*
Low-risk virus	46	0.0857	0.0547/0.1268	162.8 (<.001)
High-risk virus¶	46	0.2371	0.1634/0.3248	294.8 (<.001)

*Number of observations (tests of hypothesis) in category. To be included in the meta-analysis, each study must have minimally probed for low-risk HPV (viruses 6 or 11) and high-risk HPV (viruses 16 or 18).
†Random-effects model estimate, pooled probability of detection of low- or high-risk HPV in sample of studies.
‡95% CI around weighted probability.
§Test of homogeneity of weighted probability. To be included, studies must have minimally probed for HPV types 6 or 11.
¶To be included, studies must have minimally probed for HPV types 16 or 18.

46 studies that reported this information. High-risk viruses were significantly more likely to be detected in OSCC specimens than were low-risk viruses. HPV 16 and 18 were detected in 30% (369/1223 cases), whereas other high-risk types were detected in less than 1% of cases. The pooled probability of detecting any high-risk HPV in OSCC was 0.2371 (95% CI, 0.1634 to 0.3248), for a difference of approximately 2.8 times the probability of detecting low-risk viruses of interest (0.0857; 95% CI, 0.0547 to 0.1268). This finding confirms the expectation that high-risk HPV is more commonly associated with OSCC than is low-risk HPV. It should also be noted, however, that tests for homogeneity (Q) indicated that significant heterogeneity in findings was present between studies in both categories (Table VI). Although significant heterogeneity was observed in both groups, the level of heterogeneity was especially marked in the high-risk group (high-risk $Q = 294.8$ [$P < .001$]; low-risk $Q = 162.8$ [$P < .001$]). This finding indicates that substantial variability existed in the detection rates between samples included in the analysis and that the variability was particularly concentrated in the high-risk virus group.

DISCUSSION

Since Syrjänen et al[109] first reported a relationship between HPV and OSCC, in 1983, numerous epidemiologic studies of HPV in oral cancerous tissue have been reported. Despite these reports and several reviews of the topic,[9,10,113-115] the meaning of these observed associations remains unclear and a systematic quantitative evaluation of the data has been lacking. Therefore, we conducted a meta-analysis to clarify the relationship between HPV and OSCC. Our results indicate that HPV is a significant independent risk factor for OSCC. Results of our pooled unadjusted estimates indicate that HPV is 2 to 3 times more likely to be detected in precancerous oral mucosa and 4.7 times more likely to be detected in OSCC than in normal mucosa. These findings were preserved in the pooled odds analyses. The OR for HPV in benign leukoplakia was 7.1 (95% CI, 1.32-38.25); in intraepithelial neoplasia it was 2.85 (95% CI, 1.60-5.07), in oral verrucous carcinoma it was 3.68 (95% CI, 0.11-125.6), and in OSCC it was 5.21 (95% CI, 2.49-10.89). Raw data were not published in a manner to draw any conclusion about the relationship of HPV and age, sex, method of tissue preservation, primer amplification region, and use of tobacco, alcohol, or both.

Before this analysis, the prevalence of HPV in OSCC was reported to be 20% to 30%.[9,10] This is in contrast to several reports indicating that HPV DNA has been detected in more than 50% of OSC tumors.[21,23,25,57,61,71,111] Our meta-analysis suggests that the 20%-to-30% figure could be an underestimation of HPV prevalence in OSCC. Factors contributing to the underestimation include small sample size, method of tissue collection and preservation, assay sensitivity, and extent of sample analyzed. We addressed the issue of assay sensitivity by weighting the data conservatively on the basis of the sensitivity of the assay performed. These analyses produced results similar to the unadjusted analyses. That is, the OR for the detection of HPV in precancerous oral tissues ranged from 1.91 to 7.8, the OR for verrucous carcinoma was 4.28 (95% CI, 0.11-163.15), and the OR for OSCC was 5.37 (95% CI, 2.49-11.55) in comparison with that of normal oral mucosa.

Our findings indicate that the likelihood of detecting HPV in patients with OSCC is approximately 1 in 2. The results are concordant with the findings of 3 large well-controlled studies of the past decade that demonstrated that HPV infection is associated with an increased risk (3 to 6 times) of OSCC independent of exposure to alcohol or tobacco.[51,116,117] These studies further demonstrated that the relative risk of HPV and OSCC is equal to or exceeds the risk associated with tobacco and alcohol consumption. However, HPV's role in oral carcinogenesis at present appears to be epidemiologically minor, because the prevalence of HPV infection is less than the prevalence of tobacco smoking and alcohol consumption.

In addition to these findings, the following lines of evidence suggest that high-risk HPVs are involved in oral carcinogenesis: (1) high-risk HPV DNA has been identified in OSCC and derivative cell lines,[67,73,77,98,110] (2) oral keratinocytes can be transformed with high-risk HPVs in vitro through mechanisms involving E6 and E7 oncoproteins,[108,118-121] and (3) high-risk HPVs identified in primary OSCC are maintained in nodal metastases.[83,91,102,111] Consistent with this theory, our analysis found that high-risk HPVs were 2.8 times more likely to be detected in OSCC than were low-risk HPVs. In contrast, low-risk HPVs were more likely to be detected in leukoplakia (data not shown), a finding we have reported previously.[9] The most frequently detected high-risk HPVs in OSCC were types 16 and 18. These findings are similar to observations reported for cervical and anogenital carcinomas[122,123] and support the hypothesis that OSCCs that contain HPV 16 and HPV 18 DNA may arise as a result of HPV 16 and HPV 18 infection. Although the purpose of our study was not to investigate the molecular mechanisms by which high-risk HPVs may induce oral carcinogenesis, we note that a parallel mode of viral activity may occur at both epithelial sites. The different anatomical sites and age of onset suggest that unique host factors may also be involved.

The reported findings must be interpreted in light of limitations, including the post hoc nature of the analysis, the small sample size and power, the combination of data from studies that are nonequivalent in terms of quality and methods, the inability to assess the role of uncontrolled confounding factors, and possible misclassification. No effort was made in case selection to determine whether the assays were performed accurately, whether appropriate positive and negative controls were used, whether confounding factors were analyzed, and whether the data were collected in an unbiased manner. In addition, the fact that normal mucosal cells are often collected (1) in a manner that excludes basal undifferentiated keratinocytes that are the target of HPV infection and (2) from younger populations was not taken into consideration.[114]

The fact that meta-analysis is prone to "publication bias," whereby studies with positive findings are more likely to be reported in the literature,[124] may have caused the overestimation of the risk of HPV and OSCC. Non–peer-reviewed reports (ie, abstracts) were included for analysis to address this possibility. Non–peer-reviewed reports, however, represented only 3.2% of the reports analyzed. Nevertheless, the strength of the results comes from the fact that the samples were obtained from geographically diverse regions, including Africa, Asia, Australia, Europe, and North America. In addition, significant heterogeneity between the findings of the studies was observed in 4 of 5 tissue categories evaluated. This indicates that it is unlikely that the differences in the observed results of the individual studies occurred by chance alone and unmeasured systematic variation may have been present.[11] As is common in meta-analyses, the studies included in the full sample varied substantially in terms of setting, patient composition, and procedures. We reported random-effects estimates for all parameters, as is recommended in the presence of significant heterogeneity. To avoid the possibility of aggregation bias, it would be desirable to calculate differences between tissue categories in the probability of detecting HPV within studies and then to pool these estimates of effect across studies.[13] It was possible to do this in a subset of studies. Results from meta-analysis of the full sample were robust in light of the findings observed in studies that permitted direct comparisons among normal mucosa and other tissue categories.

In summary, our meta-analysis confirms quantitatively that HPV is an important risk factor for OSCC. Although this study does not determine the etiologic role of HPV in OSCC, several molecular studies have shown that HPV is carcinogenic. The findings raise important questions with respect to the need for (1) screening of patients who may harbor latent high-risk HPV in oral mucosa, (2) decision analyses when oral lesions are dysplastic and HPV is detected, and (3) treatment strategies of HPV-associated OSCCs versus tobacco- or alcohol-associated OSCCs.

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Reprint requests:

Craig S. Miller, DMD, MS
Oral Medicine Section MN 118
Department of Oral Health Practice
University of Kentucky College of Dentistry
800 Rose St
Lexington, KY 40536-0297
cmiller@pop.uky.edu