Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review

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Abstract

Mucosal human papillomaviruses (HPV) are the cause of cervical cancer and likely a subset of head and neck squamous cell carcinomas (HNSCC), yet the global prevalence and type distribution of HPV in HNSCC remains unclear. We systematically reviewed published studies of HNSCC biopsies that employed PCR-based methods to detect and genotype HPV to describe the prevalence and type distribution of HPV by anatomic cancer site. Geographic location and study size were investigated as possible sources of variability. In the 5,046 HNSCC cancer specimens from 60 studies, the overall HPV prevalence was 25.9% [95% confidence interval (95% CI), 24.7-27.2]. HPV prevalence was significantly higher in oropharyngeal SCCs (35.6% of 969; 95% CI, 32.6-38.7) than oral SCCs (23.5% of 2,642; 95% CI, 21.9-25.1) or laryngeal SCCs (24.0% of 1,435; 95% CI, 21.8-26.3). HPV16 accounted for a larger majority of HPV-positive oropharyngeal SCCs (86.7%; 95% CI, 82.6-90.1) compared with HPV-positive oral SCCs (68.2%; 95% CI, 64.4-71.9) and laryngeal SCCs (69.2%; 95% CI, 64.0-74.0). Conversely, HPV18 was rare in HPV-positive oropharyngeal SCCs (2.8%; 95% CI, 1.3-5.3) compared with other head and neck sites [34.1% (95% CI, 30.4-38.0) of oral SCCs and 17.0% (95% CI, 13.0-21.6) of laryngeal SCCs]. Aside from HPV16 and HPV18, other oncogenic HPVs were rarely detected in HNSCC. Tumor site–specific HPV prevalence was higher among studies from North America compared with Europe and Asia. The high HPV16 prevalence and the lack of HPV18 in oropharyngeal compared with other HNSCCs may point to specific virus-tissue interactions. Small sample size and publication bias complicate the assessment of the prevalence of HPV in head and neck sites beyond the oropharynx. (Cancer Epidemiol Biomarkers Prev 2005;14(2):467–75)

Introduction

Head and neck squamous cell carcinomas (HNSCC) have broadly varying rates of incidence and mortality around the world, with high rates notably in Southeast Asia and eastern Europe (1). Tobacco smoking and chewing and alcohol consumption are the main risk factors for HNSCC and have been estimated to account for the vast majority of the disease burden worldwide (2). Over the past 15 years, human papillomavirus (HPV), the necessary cause of cancer of the cervix (3, 4), has also been etiologically linked with a subset of HNSCCs (1, 5-8). Among HNSCC biopsies, the true prevalence of HPV DNA remains uncertain, yet studies have estimated that up to 60% of HNSCCs may be HPV positive (5-8). As detection of HPV DNA in tumor biopsies alone is not sufficient evidence of causation, molecular biology studies have helped identify a subset of these cancers that may be the consequence of HPV infection (5, 6, 9-12). Such a subset is mainly found in the oropharynx, particularly the tonsils.

Of the ~40 HPV types known to infect the mucosal surfaces of the genital tract, 14 are detected in nearly all biopsies of invasive cervical cancer and are therefore considered to be either ''high-risk'' or ''oncogenic'' (4). Some of these high-risk types have also been found in the oral cavity and oropharynx of cancer-free adults (13) and in cancer biopsy specimens from HNSCC patients (5-8). HPV16, the most prevalent HPV type in cervical SCCs (14), is also the most common type present in HPV-positive HNSCCs (5-8).

The aim of this study was to determine the worldwide prevalence and type distribution of HPV in tumor biopsies of HNSCCs by use of a systematic review of published studies and to investigate cancer site, geographic location, and study sample size as possible sources of variability.

Materials and Methods

Study Selection. The NIH Pubmed search engine was employed to search for citations published through February 2004 using the MeSH terms ''Papillomavirus'' and ''Head and Neck Neoplasms'' in combination with keywords ''polymerase chain reaction'' or ''PCR.'' The inclusion criteria were (*a*) type-specific HPV results from cancer tissue, (*b*) HPV results on a minimum of 40 cases of HNSCC or 20 cases of site-specific HNSCC (e.g., oropharynx), and (*c*) clearly described PCR-based HPV testing methods. Carcinomas *in situ* were excluded, as were nasopharyngeal cancers and cancers with histologic classifications other than SCC (e.g., tumors of the salivary glands).

For publications that did not include all necessary data but had study methods that suggested additional information might be available, the data were requested from the authors if the publication date was after 1995. If data or subsets of data were published more than once, only the publication with the largest sample size was included. For the one study that involved more than one geographic location (5), the data were divided into components from each continent. Detailed information on the studies included in our analysis is presented in Appendices 1, 2, and 3.

Data Abstraction. Two investigators (A.R.K. and G.M.C.) independently abstracted data on first author and year of publication, study country, number of cases, method of specimen preservation (fresh frozen or paraffin embedded), HPV primers, HPV types genotyped, adequacy of cancer specimen for HPV analysis, and overall and type-specific prevalence of HPV infection. The number of cases was

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stratified by cancer site, specifically oral cavity, oropharynx, hypopharynx, and larynx. Oral cavity included the tongue, gum, floor of mouth, and palate. The oropharynx included the vallecula, walls of the oropharynx, and tonsils. Hypopharynx included the postcricoid region, hypopharyngeal region of the aryepiglottic fold, and posterior wall of the hypopharynx. Finer classification of subsites (base of tongue, etc.) was not possible, as these data were often not provided in the publications. For brevity, and following data abstraction, the few cancers of the hypopharynx (n = 213) were combined with cancers of the larynx (n = 1,222) and henceforth are called ''larynx cancers.'' The location of each study was classified into one of six geographic locations: Africa, Asia, Australia, Europe, North America, and South or Central America. The limited information on Africa (n = 44), Australia (n = 91), and South or Central America (n = 187) were combined into a single category called ''Other.'' To be complete, we present this data in Table 3; however, as generalizations based on the aggregate of countries with such diversity would likely not be valid, we choose not to remark on the results from this category.

Estimation of Overall and Type-Specific Prevalence. Data were abstracted for the following mucosal HPV types: 2, 3, 6, 7, 10, 11, 13, 16, 18, 26-35, 39, 40, 42, 44, 45, 51-59, 61, 62, 64, 66-73, and 81-84. Overall HPV prevalence was defined as persons testing positive for any HPV type divided by the total population. Each type-specific HPV prevalence was measured only among those tested for the specific HPV type in question; therefore, the sample size varies between the type-specific analyses. All but two studies (see Appendices 1, 2, and 3) provided information on both HPV16 and HPV18. Multiple infections were separated into constituent types; thus, type-specific prevalence represents types in either single or multiple infections.

Consensus PCR primers MY09/11 (15), PGMY09/11 (16), GP5+/6+ (17), and SPF10 (18) were considered to amplify the 18 HPV types most commonly associated with cervical cancer (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, 82, and 83; ref. 14) as well as additional high-, intermediate-, and low-risk types (as presented in Table 2). L1C1 and L1C2M (19) primers were considered to amplify all of the above 18 types, except HPV73 and HPV82. GP5/6 (20) was considered to amplify HPV 6, 11, 16, 18, 31, 33, 35, and 45. WD primers amplified 6, 11, 16, 18, 31, 33, 39, 42, 45, and 52. For other consensus and type-specific PCR primers, only those HPV types specified in the individual reports were considered amplifiable. It is important to note that an HPV type was only considered tested for if it was both amplified by the primers and subsequently genotyped.

Statistical Analysis. HPV results were stratified by anatomic cancer site, the variable most strongly correlated with HPV prevalence. HPV findings were further stratified by study-level variables, including geographic location, size of the study population (n, <50, 50-99, and >100), and specimen source. Analysis of heterogeneity by primers used was not possible, as many studies used several combinations of different primers. Analysis of individual-level data (e.g., gender, age, and smoking status) was not possible, as individual data were not available in the literature.

HPV16 prevalence, in addition to overall HPV prevalence, was investigated in the stratified analyses, as it was the only HPV type tested for by all included studies. To evaluate whether prevalence differed significantly by each strata, two-sided 95% confidence intervals (95% CI) were calculated. Sources of variability in prevalence estimates (i.e.: study sample size, laboratory methods) were first investigated by use of unconditional logistic regression analysis and then by use of the *adjust* command in Stata version 7.0, based on probability estimates from the logistic regression model. Crude and adjusted prevalence estimates and the 95% CIs were then compared to assess the presence of any significant differences. Although both crude and adjusted prevalence estimates were calculated, only the prevalence estimates were selected for presentation.

A sensitivity analysis was conducted among a subsample restricted to cases from studies that conducted laboratory assessment of a human gene as a marker of the quality of the DNA as well as the adequacy of the PCR reaction (e.g., β-globin) and explicitly reported the results from this analysis. Only cases confirmed to have adequate cancer specimens for HPV analysis were included in this subanalysis.

Results

Five thousand forty-six cases of SCC were identified from 60 eligible studies from 26 countries. These included 2,642 cases from the oral cavity, 969 cases from the oropharynx, and 1,435 cases from the larynx (Table 1). Twenty-six percent of all HNSCC biopsy specimens were HPV positive. Overall HPV prevalence was significantly higher in oropharyngeal SCCs (35.6%; 95% CI, 32.6-38.7) than in oral SCCs (23.5%; 95% CI, 21.9-25.1) and laryngeal SCCs (24.0%; 95% CI, 21.8-26.3; Table 1).

HPV16 was the most common type detected: it was present in 30.9% of oropharyngeal SCCs, 16.0% of oral SCCs, and 16.6% of laryngeal SCCs (Table 2; Fig. 1). HPV16 thus accounted for 86.7% of all HPV-positive oropharyngeal SCCs compared with 68.2% of HPV-positive oral SCCs and 69.2% of HPV-positive laryngeal SCCs. HPV18 was the next most common oncogenic HPV type detected and was detected in 8.0% and 3.9% of oral and laryngeal SCCs, respectively, yet was only present in 1.0% of oropharyngeal SCCs (Table 2; Fig. 1). The following oncogenic HPV types were detected in at least one of all biopsy specimens: HPV 31, 33, 35, 45, 51, 52, 56, 58, 59, and 68 (Table 2). Additional HPV types considered

Table 1. Studies of HNSCCs by cancer site, geographic location of study, and overall prevalence of HPV

Site	Geographic location	No. studies	No. cases	Overall HPV prevalence (95% CI)
Oral cavity	Australia, Canada, China, Cuba, Finland, France, Germany, India, Ireland, Italy, Japan, Korea, Netherlands, Norway, Poland, Spain, Slovenia, Sudan, Sweden, Switzerland, Taiwan, United Kingdom, United States, Venezuela	35	2,642	23.5 (21.9-25.1)
Oropharynx	Australia, Canada, Cuba, Finland, France, Germany, India, Ireland, Italy, Japan, Netherlands, Norway, Poland, Spain, Slovenia, Sudan, Sweden, Switzerland, United States	27	969	35.6 (32.6-38.7)
Larynx*	Canada, Cuba, Denmark, Finland, France, Germany, Greece, India, Italy, Japan, Netherlands, Norway, Spain, Slovenia, Sweden, Switzerland, United Kingdom, United States	35	1,435	24.0 (21.8-26.3)
Overall	As listed above	60†	5,046	25.9 (24.7-27.2)

*Larynx includes cases of the hypopharynx.
†Does not sum to total number of studies because some studies investigated multiple sites.

Table 2. The type-specific prevalence of HPV in HNSCCs by cancer site

	Oral cavity* (n = 2,642)		Oropharynx* (n = 969)		Larynx*,† (n = 1,435)	
	Positive/tested	Prevalence (%)	Positive/tested	Prevalence (%)	Positive/tested	Prevalence (%)
6‡	59/1,884	3.1	18/706	2.5	52/1,028	5.1
11‡	31/1,904	1.6	5/705	0.7	5/1,015	0.5
16	423/2,642	16.0	299/969	30.9	238/1,435	16.6
18	212/2,642	8.0	9/909	1.0	54/1,387	3.9
16 and 18	44/2,642	1.7	1/909	0.1	6/1,387	0.4
31	3/1,422	0.2	0/656	0.0	2/797	0.3
32‡	1/496	0.2	0/287	0.0	0/178	0.0
33	14/1,678	0.8	9/802	1.1	9/1,051	0.9
35	1/1,350	0.1	2/568	0.4	0/496	0.0
39	0/1,335	0.0	0/496	0.0	0/300	0.0
44‡	1/1,290	0.1	0/466	0.0	0/291	0.0
45	0/1,362	0.0	1/559	0.2	1/439	0.2
51	0/1,350	0.0	0/568	0.0	1/336	0.3
52	0/1,335	0.0	0/496	0.0	1/443	0.2
53‡	1/539	0.2	0/329	0.0	0/327	0.0
56	2/1,350	0.1	0/568	0.0	0/296	0.0
57‡	1/393	0.3	0/220	0.0	0/263	0.0
58	1/1,335	0.1	0/563	0.0	0/443	0.0
59	0/1,335	0.0	1/496	0.2	0/300	0.0
68	1/1,335	0.1	0/496	0.0	0/260	0.0
73	0/524	0.0	0/225	0.0	0/206	0.0
81‡	1/405	0.2	0/220	0.0	0/178	0.0
82	0/496	0.0	0/220	0.0	0/178	0.0

NOTE: HPV types considered ''high-risk'' are in bold.
Abbreviations: HPV, human papillomaviruses; HNSCCs, head and neck squamous cell carcinomas.
*Columns do not sum to total number of HPV-positive cases because multiple infections were broken down into constituent types. Columns sum to total number of infections in study population.
†Larynx includes cases of the hypopharynx.
‡HPV types considered to confer low or intermediate risk based on cervical cancer studies (4).

nononcogenic were also found, including HPV6 and more rarely HPV 11, 32, 44, 53, 57, and 81. Multiple HPV infections were uncommon (3.6%) and biopsy specimens with more than one HPV type detected were in most instances coinfected with HPV16 (data not shown).

In the analysis by study location, HPV prevalence in oral SCCs was similar in Europe (16.0%; 95% CI, 13.4-18.8) and North America (16.1%; 95% CI, 13.2-19.4) but significantly greater in Asia (33.0%; 95% CI, 30.3-35.8; Table 3). In the oropharyngeal SCCs, HPV prevalence was significantly higher in North America (47.0%; 95% CI, 41.1-53.0) compared with Europe (28.2%; 95% CI, 24.4-32.2). HPV prevalence was 46.3% in the small number of cases from Asia (n = 54; 95% CI, 32.6-60.4; Table 3). HPV was detected in 21.3%, 13.8%, and 38.2% of SCCs of the larynx from Europe, North America, and Asia, respectively (Table 3). Patterns for HPV16 prevalence were similar to those for overall HPV prevalence (Table 3). Adjustment of prevalence estimates from the different geographic locations by potential sources of variability on a study level, including study sample size and laboratory methods, did not appreciably affect the magnitude or direction of the unadjusted prevalence estimates by cancer site (data not shown).

In the subanalysis restricted to the 3,445 cases reported to be positive for β-globin or an equivalent marker, the overall HPV prevalence (24.6%; 95% CI, 23.2-26.1) was similar to the results from the total population (Appendices 1, 2, and 3). Similarly, the site- and type-specific HPV prevalence estimates from the restricted sample were not significantly different from those of the total population, nor were the prevalence estimates when stratified by study location (data not shown).

The relationship between HPV prevalence and study size within each of the cancer subsites was assessed in Fig. 2. The majority of studies clustered between 10 and 100 cases of each cancer subsite and showed broad variation in HPV prevalence (between 0% and 80%). The long right tail shows that only five studies of oral cancer (5, 7, 8, 21, 22), one of oropharynx (5), and three of larynx (6, 23, 24) included >100 cases. These larger studies tended to show overall HPV prevalence lower than the average (Fig. 2).

Laboratory methods were also investigated as possible contributors to variability in prevalence. The use of fresh-frozen versus paraffin-embedded biopsy specimens did not affect overall HPV positivity in any of the subsites considered (Appendices 1, 2, and 3).

Discussion

The present review investigated HPV DNA, as measured by sensitive PCR-based assays, in >5,000 HNSCC biopsy specimens from 60 studies. Whereas one-fifth to one-fourth of SCCs from the oral cavity and larynx were HPV positive, the prevalence in oropharyngeal SCCs was significantly greater (more than one-third). The biological explanation for why the prevalence of HPV is higher in tumors from the oropharynx compared with other sites in the head and neck remains unclear. The complicated juxtaposition between squamous cell epithelium and lymphatic tissue in the tonsils may share properties similar to the squamous-columnar junction of the cervix uteri, where the majority of HPV-associated cancers in the female genital tract arise despite the almost ubiquitous

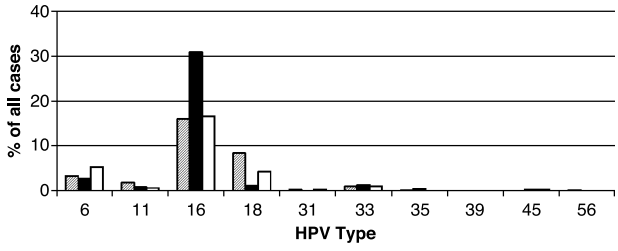

Figure 1. Type-specific prevalence of in full HPV in 2,642 oral cavity in full SCCs, 969 oropharyngeal SCCs, and 1,435 laryngeal SCCs. *Columns with diagonal lines,* oral SCCs; *black columns,* oropharynx SCCs; *white columns,* laryngeal SCCs. Larynx includes SCCs of the hypopharynx.

Table 3. Prevalence of HPV in HNSCCs by cancer site and geographic location

	No. studies	No. cases	Overall HPV prevalence (95% CI)	HPV16 prevalence (95% CI)
Oral cavity				
Europe	15	744	16.0 (13.4-18.8)	10.8 (8.6-13.2)
North America	8	577	16.1 (13.2-19.4)	10.1 (7.7-12.8)
Asia	13	1,133	33.0 (30.3-35.8)	22.3 (20.3-25.2)
Other*	2	188	18.1 (12.9-24.3)	14.9 (10.1-20.8)
Oropharynx				
Europe	17	529	28.2 (24.4-32.2)	23.8 (20.2-27.7)
North America	7	285	47.0 (41.1-53.0)	42.1 (36.3-48.1)
Asia	4	54	46.3 (32.6-60.4)	35.2 (22.7-49.4)
Other*	2	101	36.6 (27.3-46.8)	33.7 (24.6-43.8)
Larynx†				
Europe	19	799	21.3 (18.5-24.3)	13.8 (11.5-16.4)
North America	7	297	13.8 (10.1-18.3)	10.1 (7.0-14.1)
Asia	8	306	38.2 (32.8-43.9)	26.5 (21.6-31.8)
Other*	1	33	48.5 (30.8-66.5)	45.5 (28.1-63.6)

*Includes Central and South America, Australia, and Africa.
†Larynx includes cases of the hypopharynx.

presence of HPV infection in the vagina and vulva of sexually active women (25). Furthermore, extensive epithelial surface areas are present in the oropharynx due to invaginating crypts that provide an exposed layer of basal epithelial cells.

HPV16, the most common HPV type detected in biopsies from women with cervical SCC (55%; refs. 4, 14), was also the most common type detected in biopsies from HNSCCs. In the oropharynx, HPV16 accounted for the overwhelming majority of HPV-positive cases (86.7%), whereas the predominance of HPV16 was less striking in other head and neck sites. HPV18, the second most common type detected in HPV-positive cancers in this study, was found much less frequently in HPV-positive oropharyngeal SCCs (2.9%) compared with HPV-positive oral SCCs (34.5%) or HPV-positive laryngeal SCCs (17.2%). It therefore seems that the type distribution of HPVs in HNSCCs may also vary by head and neck site. The extreme rarity of HPV18 in the oropharynx is confirmed in all of the largest studies but has not yet been discussed and is difficult to explain. HPV18 has a special tropism for glandular tissue and is the most frequently detected type in adenocarcinomas of the cervix (14). Adenocarcinomas are rare in the head and neck (9%; ref. 26) and occur mainly in salivary gland tumors (26), which were not included in this review. In the cervix uteri, HPV18 seems to be less effective at evading the host immune response and is less likely to persist compared with HPV16 (27). The immunologic response may also differ between oropharynx and other head and neck sites, possibly affecting HPV type-specific prevalence.

Aside from HPV16 and HPV18, other oncogenic HPV types commonly detected in invasive cervical cancer biopsies (e.g., HPV 31, 33, 35, 45, 56, 58, and 59) were rarely or never detected in HNSCC biopsies. Conversely, HPV6, which has been designated as ''low-risk'' or ''nononcogenic'' to the cervix (4) and is the cause of benign tumors in the aerodigestive and genital tract (3), was present in a greater number of HNSCCs than any of the oncogenic types other than HPV16 and HPV18. However, viral detection in biopsy material alone is not evidence of causation. HPV types that have been well described as lacking the ability to induce neoplastic transformation may be coinfecting the tumor, yet not be causally related to tumorigenesis. Findings on HPV serology have not been included in this review, but a few large studies consistent with our present biopsy-based findings showed (*a*) elevated prevalence of different types of antibodies against HPV in HNSCC patients (5, 7); (*b*) especially high seroprevalence in oropharyngeal SCCs (5, 7, 28); and (*c*) predominance of HPV16 over other HPV types (28).

HPV prevalence in oral SCCs from Asia was considerably higher compared with the other geographic locations. Similarly, HPV prevalence was significantly higher in oropharyngeal SCCs from North America and Asia compared with Europe. The geographic heterogeneity might be partly explained by regional differences in the distribution of risk factors other than HPV infection. However, although use of tobacco-related products (smoking or chewing) varies by country and culture, it remains the predominant cause of HNSCC throughout most of the world and likely does not explain the differences seen in HPV prevalence by region. In the IARC study of HPV and oral and oropharyngeal cancers (5), the only multicontinent study conducted to date, HPV prevalence did not differ significantly among Europe, North and South America, Asia, and Africa.

The geographic heterogeneity that emerged from the present review must therefore be interpreted with caution. Studies conducted to date of HPV and HNSCC have been, with rare exception, small (<100 cases). The methods employed for case identification have often been unclear, and it is difficult to differentiate studies that enrolled consecutive patients from studies that used alternative inclusion criteria. HPV prevalence seemed to be inversely proportional to the study sample size, notably among oral and laryngeal SCCs. These findings may be indicative of a selection bias in which certain cases were preferentially included in the study, or certain studies were published based on especially high HPV prevalence. As with geographic location, the heterogeneity was smaller among studies of the oropharynx, thereby supporting the greater certainty of the link with HPV at this rather than other head and neck sites.

Poor quality of some of the cancer specimens may also have affected the prevalence estimates. Slightly greater than half of the studies (n = 36) included in this review reported results from the β-globin or another gene as a marker of the quality of the DNA as well as the adequacy of the PCR reaction. Restriction of the study population to samples with confirmed human DNA did not greatly affect the estimates of HPV prevalence, likely reflecting the fact that most studies assessed, but did not report, findings on β-globin or an equivalent. Nonetheless, some false-negative findings may still derive from the poor quality of biopsy specimens. Specimens may contain variable amounts of cancer cells in addition to normal tissue. In a previous meta-analysis of oral SCC that included biochemical, immunologic, and molecular analyses of HPV in normal as well as dysplastic or malignant oral tissue or cells, HPV was twice to thrice more likely to be detected in precancerous oral mucosa and 4.7-fold more likely to be detected in oral cancers compared with normal oral mucosa (29).

More importantly, the frequency of advanced and multiple-site tumors hampers accurate classification of cancer site in HNSCC. The scope of misclassification of head and neck sites may vary by

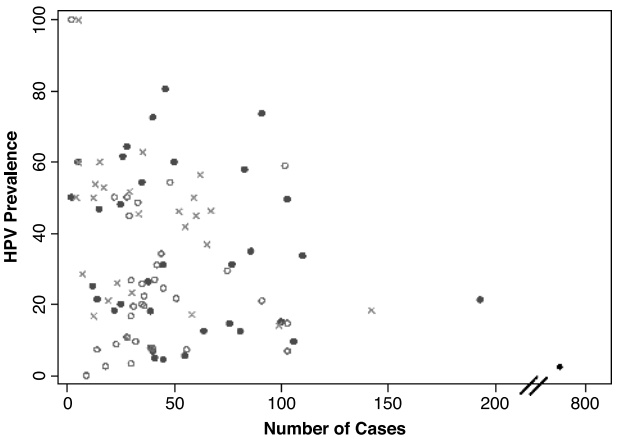

Figure 2. HPV prevalence by number of HNSCCs in each study, stratified by cancer site. ●, oral SCCs; ×, oropharynx SCCs; ○, laryngeal SCCs. Larynx includes SCCs of the hypopharynx.

geographic location: the difference in HPV prevalence between the oropharynx and other sites was greatest, for instance, in North America where advanced-stage cancers are less common than elsewhere (30). Misclassification of advanced oropharyngeal SCCs as oral SCCs might have inflated, conversely, the prevalence of HPV infection in oral cancers in Asia.

Important gaps remain on the topic of HPV prevalence in HNSCC in many parts of the world. In particular, 84% of the information on oropharyngeal SCCs derived from studies conducted in Europe and North America. Furthermore, HPV DNA presence in biopsies is insufficient to prove causation. Several studies (9-12) in which the presence of HPV16 DNA was analyzed jointly with markers of expression of the viral oncogene E6, mutational patterns of the cancer suppressor gene TP53, and levels of allelic loss have suggested methods to identify a subset of HNSCCs where HPV may be the primary cause, as in cervical cancer. Many of the studies included in this review did not conduct such laboratory analyses, nor did they present findings by potentially important covariates (age, gender, smoking and chewing habits, alcohol drinking, etc.). Additionally, only seven of the studies included a cancer-free control group. Whereas pooling the HPV prevalence among the case-control studies would have afforded the estimation of the relative risk of HNSCC by HPV presence, the loss of data from excluding all case-series studies would have been too great. Furthermore, as HPV assessment among cancer-free controls is hampered by the lack of biopsy specimens, HPV status is ascertained by use of surrogate samples (e.g., oral exfoliated cells) that may not accurately reflect HPV status among HNSCC cases (5).

Nonetheless, the fact that HPV16 and HPV18 accounted for almost all oncogenic HPV types detected in HNSCC biopsies suggests that newly developed prophylactic vaccines for cervical cancer (31) should also be relevant for HNSCCs. It remains to be elucidated, however, the fraction of HPV-positive HNSCCs for which HPV is causally related to the cancer and therefore potentially preventable by HPV vaccination.

Appendix 1. Study methods and type-specific prevalence of HPV in oral cavity SCCs by geographic location and by study

First author	Journal abbreviation year	Country	Source	PCR primers used	No. cases	Any	6	11	16	18	31	33	35	45	56
Europe															
Yeudall WA	J Gen Virol 1991	United Kingdom	FF	TS-PCR only	39	7.7	—	—	2.6	2.6	—	—	—	—	—
Ostwald C	J Oral Pathol Med 1994	Germany	FF and PE*	MY09/11 GP5+/6+	26	61.5	—	—	26.9	23.1	—	—	—	—	—
Cruz IB	Eur J Cancer B Oral Oncol 1996	Netherlands	FF*	GP5+/6+ Cpl/CPIIG	35	54.3	2.9	0.0	42.9	0.0	0.0	0.0	—	—	—
Snijders PJ	Int J Cancer 1996	Netherlands	FF and PE*	GP5/6	25	20.0	0.0	0.0	20.0	0.0	0.0	0.0	—	—	—
Fouret P†	Arch Otolaryngol Head Neck Surg 1997	France	PE	WD72/76+ WD66/67/154	12	25.0	—	—	8.3	0.0	16.7	0.0	—	0.0	—
Alvarez AI	Am J Otolaryngol 1997	Spain	Unsure*	TS-PCR only	2	50.0	50.0	—	0.0	0.0	—	—	—	—	—
Andl T†	Cancer Res 1998	Germany	FF*	WD72/76+ WD66/67/154	5	60.0	0.0	0.0	60.0	0.0	—	0.0	—	—	—
Adams V†	Anticancer Res 1999	Switzerland	FF*	MY09/11	15	46.7	0.0	0.0	40.0	6.7	0.0	0.0	0.0	0.0	0.0
Badaracco G	Anticancer Res 2000	Italy	FF*	MY09/11	38	26.3	10.5	5.3	10.5	13.2	2.6	0.0	0.0	0.0	5.3
van Houten VM†	Int J Cancer 2001	Netherlands	FF	GP5+/6+	45	4.4	—	—	4.4	0.0	0.0	0.0	0.0	0.0	0.0
Mork J†	NEJM 2001	Norway, Finland, Sweden	PE*	GP5+/6+ CpI/CpIIG	59	16.9	1.7	1.7	16.0	0.0	—	1.7	—	—	—
Klussman JP†	Cancer 2001	Germany	Unsure*	A10/A5-A6/A8	22	18.2	0.0	0.0	13.6	0.0	0.0	0.0	0.0	0.0	0.0
Koskinen WJ	Int J Cancer 2003	Finland	FF	SPF10 FAP59/64 CP65/70 CP66/69	28	64.3	0.0	0.0	46.4	0.0	0.0	21.4	0.0	0.0	0.0
Herrero R†	J Natl Cancer Inst 2003	Italy, Spain, North Ireland, Poland	FF*	GP5+/6+	338	4.4	0.0	0.0	4.4	0.0	0.0	0.0	0.0	0.0	0.0
Kansky AA	Acta Virol 2003	Slovenia	PE*	PGMY09/11 GP5+/6+ WD72/76+ WD66/67/154	55	5.5	0.0	0.0	1.8	0.0	0.0	1.8	0.0	0.0	0.0
North America															
Maden C‡	Am J Epidemiol 1992	United States	Exf	TS-PCR only	108	NA	19.0	—	6.0	—	—	—	—	—	—
Holladay EB	Am J Clin Pathol 1993	United States	PE	MY09/11	39	17.9	0.0	0.0	17.9	2.6	—	0.0	—	—	—
Noble-Topham SE	Arch Otolaryngol Head Neck Surg 1993	Canada	PE*	TS-PCR only	25	48.0	—	—	8.0	40.0	—	—	—	—	—
Paz IB	Cancer 1997	United States	FF	MY09/11 IU/IUDO	64	12.5	3.1	0.0	7.8	0.0	—	—	—	—	—
Schwartz SM†	J Natl Cancer Inst 1998	United States	PE*	MY09/11	193	21.2	6.2	3.6	11.4	1.0	—	—	—	—	—
Ringstrom E	Clin Cancer Res 2002	United States	FF*	MY09/11	41	4.9	—	—	4.9	0.0	—	—	—	—	—

(Continued on the following page)

Appendix 1. Study methods and type-specific prevalence of HPV in oral cavity SCCs by geographic location and by study (Cont'd)

First author	Journal abbreviation year	Country	Source	PCR primers used	No. cases	Any	6	11	16	18	31	33	35	45	56
Smith EM[†]	Int J Cancer 2004	United States	PE	MY09/11	106	9.4	0.0	0.0	6.6	0.0	0.0	2.8	0.0	0.0	0.0
Gillison ML[†]	J Natl Cancer Inst 2000	United States	FF*	PGMY09/11	81	12.3	0.0	0.0	12.3	1.2	0.0	0.0	0.0	0.0	0.0
Herrero R[†]	J Natl Cancer Inst 2003	Canada	FF*	GP5+/6+	28	10.7	0.0	0.0	10.7	7.1	0.0	0.0	0.0	0.0	0.0
Asia															
Balaram P	Int J Cancer 1995	India	FF and PE*	MY09/11 GP5/6 TS-PCR	91	73.6	15.4	19.8	41.8	47.3	0.0	0.0	0.0	0.0	0.0
Shindoh M	Cancer 1995	Japan	PE	TS-PCR only	77	31.2	—	—	31.2	1.3	—	0.0	—	—	—
Wen S	Anticancer Res 1997	China	PE*	TS-PCR only	45	31.1	—	—	20.0	24.4	—	—	—	—	—
D'Costa J	Oral Oncol 1998	India	FF	MY09/11	100	17.6	0.0	0.0	17.6	0.0	—	0.0	—	—	—
Mineta H	Anticancer Res 1998	Japan	FF	TS-PCR only	14	21.4	—	—	21.4	0.0	—	—	—	—	—
Tsuhako K	J Oral Pathol Med 2000	Japan	PE*	TS-PCR only	83	57.8	15.7	1.2	33.7	36.1	—	—	—	—	—
Cao J	Chin J Dent Res 2000	China	PE	TS-PCR only	40	72.5	—	—	52.5	27.5	—	—	—	—	—
Shin KH	Int J Oncol 2002	Korea	Unsure	TS-PCR only	76	14.5	—	—	5.3	10.5	—	2.6	—	—	—
Nagpal JK	Int J Cancer 2002	India	FF and PE	MY09/11	110	33.6	—	—	22.7	14.5	—	—	—	—	—
Sugiyama M	Oral Surg Oral Med Oral Pathol Radiol Endod 2003	Japan	PE*	TS-PCR only	86	34.9	—	—	34.9	2.3	—	—	—	—	—
Higa M[†]	Oral Oncol 2003	Japan	FF	TS-PCR only	46	80.4	21.7	2.2	52.2	52.2	—	—	—	—	—
Chang JY	Am J Clin Pathol 2003	Taiwan	PE*	MY09/GP6+	103	49.5	1.0	1.0	28.2	26.2	0.0	1.0	0.0	0.0	0.0
Herrero R[†]	J Natl Cancer Inst 2003	India	FF*	GP5+/6+	262	3.1	0.0	0.0	2.7	0.8	0.0	0.0	0.4	0.0	0.0
Other (includes Central and South America, Australia, and Africa)															
Premoli-De-Percoco G	J Oral Pathol Med 2001	Venezuela	PE	TS-PCR only	50	60.0	0.0	0.0	50.0	16.0	—	—	—	—	—
Herrero R[†]	J Natl Cancer Inst 2003	Cuba, Australia, Sudan	FF*	GP5+/6+	13.8	2.9	0.0	0.0	2.2	1.4	0.0	0.0	0.0	0.0	0.0

Abbreviations: FF, fresh frozen; PE, paraffin embedded; TS, type specific; Exf, exfoliated oral cells.
*Study assessed a human gene marker for the quality of the cancer specimen and reported results for this laboratory assessment.
†Author provided additional data from their study for this review.
‡Study not included in analysis of biopsy specimens.

Appendix 2. Study methods and type-specific prevalence of HPV in oropharyngeal SCCs by geographic location and by study

First author	Journal abbreviation year	Country	Source	HPV primers	No. cases	Any	6	11	16	18	31	33	35	45	56
Europe															
Snijders PJ	Int J Cancer 1996	Netherlands	FF and PE*	GP5/6	7	28.6	0.0	0.0	28.6	0.0	0.0	0.0	—	—	—
Fouret P[†]	Arch Otolaryngol Head Neck Surg 1997	France	PE	WD72/76+ WD66/67/154	58	17.2	—	—	15.5	0.0	0.0	0.0	—	0.0	—
Alvarez AI	Am J Otolaryngol 1997	Spain	Unsure*	TS-PCR only	19	21.1	10.5	—	10.5	0.0	—	—	—	—	—
Hoffman M	Acta Otolaryngol 1998	Germany	FF*	MY09/11 of TS-PCR negative	23	26.1	4.3	0.0	8.7	0.0	0.0	0.0	—	—	—
Andl T[†]	Cancer Res 1998	Germany	FF*	WD72/76+ WD66/67/154	35	62.9	0.0	0.0	60.0	0.0	—	2.9	—	—	—
Adams V[†]	Anticancer Res 1999	Switzerland	FF*	MY09/11	5	60.0	0.0	0.0	60.0	0.0	0.0	0.0	0.0	0.0	0.0
Kleist B	J Oral Pathol Med 2000	Germany	PE*	MY09/11	12	16.7	—	—	8.3	8.3	—	—	—	—	—
Badaracco G	Anticancer Res 2000	Italy	FF*	MY09/11	4	50.0	50.0	25.0	25.0	25.0	0.0	0.0	0.0	0.0	0.0
van Houten VM[†]	Int J Cancer 2001	Netherlands	FF	GP5+/6+	30	23.3	—	—	23.3	0.0	0.0	0.0	0.0	0.0	0.0

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Appendix 2. Study methods and type-specific prevalence of HPV in oropharyngeal SCCs by geographic location and by study (Cont'd)

First author	Journal abbreviation year	Country	Source	HPV primers	No. cases	Any	6	11	16	18	31	33	35	45	56
Mork J[†]	NEJM 2001	Norway, Finland, Sweden	PE[*]	GP5+/6+ CpI/CpIIG	18	66.7	0.0	0.0	50.0	0.0	—	0.0	—	—	—
Klussman JP[†]	Cancer 2001	Germany	PE[*]	Degenerate primers A10/A5-A6/A8; CP62/70-CP65/69a	33	45.5	0.0	0.0	36.4	0.0	0.0	3.0	0.0	0.0	0.0
Lindel K	Cancer 2001	Switzerland	PE[*]	SPF10	99	14.1	0.0	0.0	11.1	0.0	0.0	1.0	1.0	1.0	0.0
Szkaradkiewicz A	Clin Exp Med 2002	Poland	Unsure	MY09/11	28	10.7	—	—	0.0	0.0	—	—	—	—	—
Mellin H	Anticancer Res 2003	Sweden	PE[*]	GP5+/6+	60	45.0	—	—	45.0	—	—	1.7	—	—	—
Koskinen WJ	Int J Cancer 2003	Finland	FF	SPF10 FAP 59/64 CP65/70 CP66/69	5	100	0.0	0.0	100	0.0	0.0	0.0	0.0	0.0	0.0
Herrero R[†]	J Natl Cancer Inst 2003	Italy, Spain, North Ireland, Poland	FF[*]	GP5+/6+	89	14.6	0.0	0.0	13.5	0.0	0.0	1.1	1.1	0.0	0.0
Kansky AA	Acta Virol 2003	Slovenia	PE[*]	PGMY09/11 GP5+/6+ WD72/76+ WD66/67/154	4	50.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0
North America															
Paz IB	Cancer 1997	United States	FF	MY09/11 IU/IUDO	15	60	0.0	—	53.3	0.0	—	—	—	—	—
Schwartz SM[†]	J Natl Cancer Inst 1998	United States	PE[*]	MY09/11	55	41.8	12.7	3.6	34.5	0.0	—	—	—	—	—
Gillison ML[†]	J Natl Cancer Inst 2000	United States	FF[*]	PGMY09/11	62	56.5	0.0	0.0	50.0	0.0	0.0	4.8	0.0	0.0	0.0
Ringstrom E	Clin Cancer Res 2002	United States	FF[*]	MY09/11	29	51.7	—	—	51.7	0.0	—	—	—	—	—
Strome SE	Clin Cancer Res 2002	United States	PE[*]	MY09/11 L1 6582-23D/7033-22U	52	46.2	0.0	0.0	40.4	0.0	0.0	0.0	0.0	0.0	0.0
Smith EM[†]	Int J Cancer 2004	United States	PE[*]	MY09/11	65	36.9	0.0	0.0	33.8	1.5	0.0	1.5	0.0	0.0	0.0
Herrero R[†]	J Natl Cancer Inst 2003	Canada	FF[*]	GP5+/6+	7	57.1	0.0	0.0	57.1	0.0	0.0	0.0	0.0	0.0	0.0
Asia															
Mineta H	Anticancer Res 1998	Japan	FF	TS-PCR only	13	53.8	—	—	38.5	15.4	—	—	—	—	—
Tsuhako K	J Oral Pathol Med 2000	Japan	PE[*]	TS-PCR only	17	52.9	17.6	5.9	41.2	11.8	—	—	—	—	—
Higa M[†]	Oral Oncol 2003	Japan	FF	TS-PCR only	12	50.0	25.0	8.3	33.3	16.7	—	—	—	—	—
Herrero R[†]	J Natl Cancer Inst 2003	India	FF[*]	GP5+/6+	12	25.0	0.0	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0
Other (includes Central and South America, Australia, and Africa)															
Li W	Int J Cancer 2003	Australia	PE[*]	GP5+/6+ A10/A5-A6/A8 CP65/70ct-CP66/69ct	67	46.3	0.0	0.0	41.8	0.0	0.0	0.0	0.0	—	0.0
Herrero R[†]	J Natl Cancer Inst 2003	Cuba, Australia, Sudan	FF[*]	GP5+/6+	34	17.6	0.0	0.0	17.6	0.0	0.0	0.0	0.0	0.0	0.0

*Study assessed a human gene marker for the quality of the cancer specimen and reported results for this laboratory assessment.
†Author provided additional data from their study for this review.

Appendix 3. Study methods and type-specific prevalence of HPV in laryngeal SCCs by geographic location and by study

First author	Journal abbreviation year	Country	Source	HPV primers	No. cases	Any	6	11	16	18	31	33	35	45	56
Europe															
Perez-Ayala M	Int J Cancer 1990	Spain	FF	TS-PCR only	48	54.2	—	0.0	54.2	—	—	—	—	—	—
Salam M	Eur J Surg Oncol 1995	United Kingdom	PE[*]	MY09/11	36	22.2	8.3	2.8	5.6	0.0	—	0.0	—	—	—
Snijders PJ	Int J Cancer 1996	Netherlands	FF and PE[*]	GP5/6	31	19.4	0.0	0.0	19.4	0.0	0.0	0.0	—	—	—
Lie ES	Acta Otolaryngol 1996	Norway	FF[*]	MY09/11 CP11/CPIIG GP5+/6+	39	7.7	—	—	2.6	0.0	0.0	0.0	0.0	—	—

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Appendix 3. Study methods and type-specific prevalence of HPV in laryngeal SCCs by geographic location and by study (Cont'd)

First author	Journal abbreviation year	Country	Source	HPV primers	No. cases	Any	6	11	16	18	31	33	35	45	56
Fouret P†	Arch Otolaryngol Head Neck Surg 1997	France	PE	WD72/76+ WD66/67/154	103	6.8	—	—	6.8	0.0	0.0	0.0	—	0.0	—
Alvarez AI	Am J Otolaryngol 1997	Spain	Unsure*	TS-PCR only	35	25.7	22.9	—	5.7	0.0	—	—	—	—	—
Poljak M	Acta Otolaryngol Suppl 1997	Slovenia	PE*	MY09/11 GP5/6 WD72/76+ WD66/67/154	30	3.3	0.0	0.0	3.3	0.0	—	0.0	—	—	—
Cattani P	Clin Cancer Res 1998	Italy	FF*	MY09/11	75	29.3	0.0	0.0	12.0	10.7	0.0	1.3	—	—	—
Hoffman M	Acta Otolaryngol 1998	Germany	FF*	MY09/11 of TS-PCR negative	51	21.6	0.0	0.0	3.9	2.0	0.0	0.0	—	—	—
Andl T†	Cancer Res 1998	Germany	FF*	WD72/76+ WD66/67/154	30	26.7	0.0	0.0	26.7	0.0	—	0.0	—	—	—
Adams V†	Anticancer Res 1999	Switzerland	FF*	MY09/11	36	19.4	0.0	0.0	19.4	0.0	0.0	0.0	0.0	0.0	0.0
Lindelberg H	Cancer Lett 1999	Denmark	Unsure*	MY09/11 GP5+/6+ CPI/CPII	30	3.3	—	—	0.0	0.0	0.0	0.0	0.0	—	—
Gorgoulis VG	Hum Pathol 1999	Greece	PE	MY09/11 GP5/6	91	20.9	3.3	0.0	14.3	3.3	0.0	3.3	0.0	—	—
Badaracco G	Anticancer Res 2000	Italy	FF*	MY09/11 HPV6 and 16 E6/E2	22	50.0	18.2	0.0	27.3	0.0	0.0	0.0	0.0	4.5	0.0
Kleist B	J Oral Pathol Med 2000	Germany	PE*	MY09/11	35	20.0	—	—	11.4	5.7	—	—	—	—	—
Mork J†	NEJM 2001	Norway, Finland, Sweden	PE*	GP5+/6+ CpI/CpIIG	40	12.5	0.0	0.0	2.5	0.0	—	0.0	—	—	—
Klussman JP†	Cancer 2001	Germany	Unsure*	A10/A5-A6/A8	30	16.7	0.0	0.0	13.3	0.0	0.0	0.0	0.0	0.0	0.0
van Houten VM†	Int J Cancer 2001	Netherlands	FF	GP5+/6+	9	0.0	—	—	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Koskinen WJ	Int J Cancer 2003	Finland	FF	SPF10 FAP 59/64 CP65/70 CP66/69	28	50.0	10.7	3.6	42.9	0.0	0.0	14.3	0.0	0.0	0.0
North America															
Brandwein MS	Ann Otol Rhinol Laryngol 1993	United States	PE	Bauer L1 consensus primers	40	7.5	0.0	0.0	2.5	0.0	0.0	0.0	0.0	0.0	—
Fliss DM	Laryngoscope 1994	Canada	PE*	TS-PCR only	29	44.8	—	—	31.0	31.0	—	—	—	—	—
Shen J	Mod Pathol 1996	United States	PE*	MY09/11	32	9.4	3.1	3.1	0.0	3.1	—	—	—	—	—
Paz IB	Cancer 1997	United States	FF	MY09/11 IU/IUDO	56	7.1	0.0	—	5.4	0.0	—	—	—	—	—
Gillison ML†	J Natl Cancer Inst 2000	United States	FF*	PGMY09/11	103	14.6	0.0	0.0	14.6	0.0	1.0	0.0	0.0	0.0	0.0
Smith EM†	Ann Otol Rhinol Laryngol 2000	United States	FF and PE	MY09/11	23	8.7	0.0	0.0	4.3	0.0	4.3	0.0	0.0	0.0	0.0
Ringstrom E	Clin Cancer Res 2002	United States	FF*	MY09/11	14	7.1	—	—	7.1	0.0	—	—	—	—	—
Asia															
Ogura H	Jpn J Cancer Res 1991	Japan	Unsure	TS-PCR only	28	10.7	—	—	10.7	3.6	—	—	—	—	—
Shidara K	Laryngoscope 1994	Japan	PE	L1C1/L1C2	45	24.4	0.0	0.0	20.0	4.4	0.0	0.0	0.0	0.0	0.0
Suzuki T	Jpn J Cancer Res 1994	Japan	PE	L1C1/L1C2	41	26.8	0.0	0.0	22.0	4.9	0.0	0.0	—	—	—
Ma XL	J Med Virol 1998	Japan	PE	pU-1M/pU-2R	102	58.8	24.5	2.0	29.4	21.6	—	1.0	—	—	—
Mineta H	Anticancer Res 1998	Japan	FF	TS-PCR only	42	31.0	—	—	26.2	4.8	—	—	—	—	—
Tsuhako K	J Oral Pathol Med 2000	Japan	PE*	TS-PCR only	2	100	100	0.0	100	0.0	—	—	—	—	—
Jacob SE	J Surg Oncol 2002	India	PE	TS-PCR only	44	34.1	0.0	0.0	34.1	0.0	—	—	—	—	—
Higa M†	Oral Oncol 2003	Japan	FF*	TS-PCR only	2	100	100	0.0	100	0.0	—	—	—	—	—
Other (includes Central and South America, Australia, and Africa)															
Garcia-Milian R	Acta Otolaryngol 1998	Cuba	FF*	MY09/11	33	48.5	3.0	0.0	45.5	3.0	—	—	—	—	—

*Study assessed a human gene marker for the quality of the cancer specimen and reported results for this laboratory assessment.
†Author provided additional data from their study for this review.

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