Published in final edited form as:

Oral Oncol. 2018 February ; 77: 52–56. doi:10.1016/j.oraloncology.2017.12.008.

Sensitivity and Specificity of Oral HPV Detection for HPV-Positive Head and Neck Cancer

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Abstract

Background—The incidence of HPV-related head and neck squamous cell carcinoma (HPV-HNSCC) is increasing. Oral samples are easy and non-invasive to collect, but the diagnostic accuracy of oral HPV detection methods for classifying HPV-positive HNSCC tumors has not been well explored.

Methods—In a systematic review, we identified eight studies of HNSCC patients meeting our eligibility criteria of having: 1) HPV detection in oral rinse or oral swab samples, 2) tumor HPV or p16 testing, 3) a publication date within the last 10 years (January 2007-May 2017, as laboratory methods change), and 4) at least 15 HNSCC cases. Data were abstracted from each study and a meta-analysis performed to calculate sensitivity and specificity.

Results—Eight articles meeting inclusion criteria were identified. Among people diagnosed with HNSCC, oral HPV detection has good specificity (92%, 95% CI=82–97%) and moderate sensitivity (72%, 95% CI=45–89%) for HPV-positive HNSCC tumor. Results were similar when restricted to studies with only oropharyngeal cancer cases, with oral rinse samples, or testing for HPV16 DNA (instead of any oncogenic HPV) in the oral samples.

Discussion—Among those who already have HNSCC, oral HPV detection has few false-positives but may miss one-half to one-quarter of HPV-related cases (false-negatives). Given these findings in cancer patients, the utility of oral rinses and swabs as screening tests for HPV-HNSCC among healthy populations is probably limited.

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Conflicts: The authors have no conflicts of interest.

Keywords

head and neck squamous cell carcinoma (HNSCC); oropharyngeal squamous cell carcinoma (OPSCC); oral HPV; oral rinse; oral swab; diagnostic accuracy

Introduction

Human papillomavirus (HPV) is a sexually transmitted infection that causes most oropharyngeal cancer cases in the United States^{1,2}. While there are over 100 types of HPV, only 13 are considered carcinogenic, most notably HPV16³. The proportion of oropharyngeal cancers in the U.S. that are caused by HPV has increased from ~20% in 1990 to more than 70%, and the incidence of HPV-related oropharyngeal squamous cell carcinoma (HPV-OPSCC) has increased 225% over the past 20 years². Oral HPV infection is common and most infections will clear spontaneously; however, oral HPV that persists over time can eventually lead to OPSCC.^{4,5}

There are no FDA-approved tests to detect HPV DNA or mRNA in saliva; however, salivary rinse or swab tests for oral HPV have been used in research settings to assess oral HPV infection among both cancer patients and healthy people. Since they are non-invasive and easy to administer, there is interest in considering whether using these oral tests would be helpful to screen for HPV-OPSCC among healthy people. For screening to be advised, these tests should at minimum have high performance characteristics in patients with known OPSCC, and should be proven to benefit those screened (i.e. to decrease morbidity and mortality via early diagnosis of OPSCC). The sensitivity and specificity of these oral rinses are currently unknown both in the setting of diagnosed OPSCC and in the setting of screening.

Therefore, our objective was to review and summarize existing literature describing the diagnostic accuracy (i.e., sensitivity and specificity) of current oral HPV testing methods for correctly identifying HPV-positive head and neck squamous cell carcinomas (HNSCCs), including oropharyngeal squamous cell carcinomas (OPSCCs).

Methods

Identification and Selection of Included Studies

A literature search was performed in PubMed to identify articles that included at least 15 HNSCC cases and, for each patient, reported both 1) oral HPV status in either an oral rinse or oral swab sample (called “oral HPV” hereafter) and 2) primary tumor or neck node HPV status (called “tumor HPV” hereafter). As laboratory methods have changed over time, we restricted to research published in the past 10 years (January 2007 through May 2017, when this abstraction was performed). We used combinations of the following search terms: “oropharyngeal cancer”, “oropharynx”, “sensitivity”, “HPV”, “human papillomavirus”, “oral rinse”, “head and neck cancer”, “screening”, “detection”, “saliva”, and “rinse” to identify articles for review, which yielded 1,787 results. After reviewing these articles and using their lists of references to find additional potentially relevant articles, we identified 29 articles likely to contain sufficient information for sensitivity and specificity calculations.

Among these 29, 21 were excluded because none of the subjects had HNSCC ($n=3$)^{6,7,8}, the necessary information to calculate diagnostic accuracy was not provided ($n=7$)^{9,10,11,12,13,14,15}, the subjects had undergone cancer treatment before sample collection ($n=1$)¹⁶, the study did not perform oral HPV testing ($n=8$)^{17,18,19,20,21,22,23,24}, no tumor HPV DNA status was collected for comparison to oral HPV DNA test results ($n=1$)²⁵, or the subjects were a subset of those in a larger included study ($n=1$)²⁶. The exclusion of these articles gave eight articles meeting inclusion criteria for data extraction. The literature search was performed by a single researcher (BJG).

Data Extraction

The following information was extracted from each of the eight eligible articles: the years in which the article's data were collected, geographical location of the study, cancer type (HNSCC or OPSCC specifically), number of cancer cases, tumor testing method (in situ hybridization [ISH], polymerase chain reaction [PCR], or p16), HPV type used to define positivity for tumor and oral samples (HPV16 only or any oncogenic HPV), and the number of true positives, false positives, true negatives, and false negatives when using oral HPV testing to identify HPV-positive tumors. Data were extracted separately by two researchers (BJG and HAR) and discrepancies were resolved by the senior author (GD).

Statistical Analysis

Data were analyzed in Stata/MP 14 (64-bit) using the metandi package, which conducts bivariate meta-analysis for diagnostic accuracy using hierarchical logistic regression²⁷. Estimates of sensitivity and specificity were calculated overall and for subsets of interest (when sample size allowed), including by tumor type, oral HPV testing method, and tumor HPV testing method. The midas package²⁸ was used to generate figures depicting sensitivity and specificity estimates across studies.

Results

Among the eight articles meeting our inclusion criteria, half described patients from the United States, and all data were collected in 1999 or later (Table 1). Three studies included HNSCC patients, and five restricted to OPSCC patients. Five studies used strictly oral rinses, two used strictly oral swabs, and one study tested all subjects with both an oral rinse and an oral swab. In oral samples, two studies tested for any oncogenic HPV, five studies tested specifically for HPV16, and one study reported results for both any oncogenic HPV and HPV16. All studies tested for oral HPV DNA except for one²⁹ which tested instead for HPV16 E6/E7 mRNA. The method of tumor HPV testing included ISH only ($n=2$), p16 only ($n=3$), PCR only ($n=1$), ISH or p16 ($n=1$), and ISH or qPCR ($n=1$).

Among patients with HNSCC (including OPSCC specifically), and including all studies regardless of oral or tumor testing method, sensitivity of oral HPV for detecting HPV-related tumor was 72% (95% CI: 45–89%) and specificity was 92% (95% CI: 82–97%) (Table 2, Figure 1). Specificity estimates were consistently high across studies, though confidence intervals were wide (Figure 1). In contrast, there was considerable variability in the

sensitivity estimates, which ranged from a maximum of 93% (95% CI: 81–99%)³⁰ to a minimum of 12% (95% CI: 7–19%)³¹.

When restricting to the five studies that used an oral rinse, results were similar with good specificity of 95% (95% CI: 70–99%) but moderate sensitivity of 77% (95% CI: 61–87%) (Table 2). Results were also similar when considering oral HPV16 positivity specifically. Among the five studies describing OPSCC patients only, sensitivity of oral HPV for OPSCC tumor HPV positivity was 55% (95% CI: 25–82%) and specificity was 94% (95% CI: 85–98%).

Discussion

This meta-analysis synthesized existing literature regarding the utility of oral HPV detection to identify HPV-positive OPSCC tumors. Our results suggest that oral HPV detection methods, including oral rinses and oral swabs, have good specificity and moderate sensitivity for HPV-positive tumor among diagnosed HNSCC cases. Although a specificity of 92% is good, it is unlikely to be high enough for use in general population screening. A lack of specificity produces false-positive results, and since oropharyngeal cancer is rare in the general population, the number of resulting false-positives would be much higher than the number of true-positives detected – i.e., the positive predictive value of the test would be low in the general population.³²

Since our meta-analysis describes people already diagnosed with HNSCC, our results do not directly relate to the utility of oral HPV detection as a screening test for HPV-positive HNSCC or OPSCC. However, the false-positive rate observed in patients with HPV-negative HNSCCs (8%) is consistent with the observation that about 11% of older individuals in the general population have oral HPV infection³³. Since most oral HPV infections clear within 2 years^{34,35}, identifying these infections is not likely to be useful as a screening test for HNSCC, and these false positives could cause substantial psychological harm and misuse of resources. It is likely that identifying persistent HPV infection (i.e., requiring oral HPV positivity at multiple time-points to define a positive test) would improve test specificity, but this would produce a concomitant decrease in sensitivity.

There is no FDA-approved biomarker for screening healthy people for OPSCC, although a serum test for HPV16 oncogene antibodies has been suggested to have high specificity and may detect cancer 10 or more years before symptoms occur³⁶. This test may have utility for screening in some settings and subgroups³⁷ but is not currently commercially available and requires further study before it could be implemented as a screening test. There is also interest in developing biomarkers based on miRNA expression profiles in HNSCC.³⁸ If and when an acceptable screening test is developed, implementation is likely to begin among groups at high risk for HPV-OPSCC and/or oral HPV. OPSCC incidence in the U.S. is highest among white males aged 60–69,³⁹ while risk factors for oral HPV acquisition and/or persistence include immunosuppression, male sex, older age, smoking, higher numbers of oral sex partners, and poor oral hygiene.^{40–44}

There was substantial variation across the studies included in our meta-analysis with regard to methods of oral and tumor HPV testing, as well as patient characteristics such as geographical location. This is a limitation of our study and is one possible explanation for the wide variation across studies in sensitivity estimates. In addition, we assumed that there were no errors in measurement of tumor HPV positivity, but it is possible that some false-positive and false-negative oral HPV tests actually represent errors in the tumor HPV test. The number of studies identified by our literature review was also small, which limited our ability to produce meta-analysis estimates for specific tumor types (including OPSCC sub-sites) and testing methods.

Oral HPV rinses and swabs are not currently FDA approved for use in any clinical setting in the United States, but the presence of oral HPV is known to be a biomarker for the presence of OPSCC¹ and an indicator of disease prognosis²⁰. Indeed, among HPV-OPSCC cases who have completed treatment, detection of oral HPV is a marker for recurrence¹⁶, which supports its ability to be a marker of pre-cancer or cancer among people who otherwise have no evidence of disease. Whether oral HPV tests could be useful as an adjunct (triage) test in people with potentially malignant oral lesions has also been of interest; however, the American Dental Association recently concluded in a systematic review that oral HPV tests do not have sufficient diagnostic accuracy for this use⁴⁵.

As the incidence of HPV-OPSCC rises in the United States, research efforts continue to understand its biology and explore tools that can reduce disease morbidity and mortality. Our data do not support oral HPV detection as a tool for screening in healthy people. Further study is needed to determine whether repeated detection of oncogenic oral HPV might be useful, and whether knowledge of persistent infection would affect clinical management. Other studies suggest that oral HPV may have utility as a marker of cancer recurrence⁴⁶.

Acknowledgments

Funding: R35DE026631, F31CA210660 (HAR)

Role of Funding Source: The funding source had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation of the manuscript.

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Research Highlights

- Among people with HNSCC, oral HPV detection has good specificity (92%) and moderate sensitivity (72%) for HPV-positive HNSCC.
- The utility of oral HPV detection to screen for HNSCC among healthy populations is probably limited, as there would be many false-positives.

Figure 1.
Study-specific and pooled sensitivity and specificity estimates of oral HPV detection for classifying HPV-positive head and neck tumors

Characteristics of 8 studies included in meta-analysis of the diagnostic accuracy of oral HPV detection for classifying HPV-positive head and neck tumors

Table 1

Study	Cancer type	Number of patients	Geographical location	Data collection years	Oral HPV detection method and HPV type	Tumor HPV detection method
D'Souza (2007) ^{1,a}	OPSCC	100	USA	2000–2005	Rinse, HPV16	HPV16 ISH
Tsao (2016) ^{31,b}	OPSCC	144	USA	2007–2010	Swab, HPV16 Swab, Oncogenic	ISH or p16
Chai (2016) ³⁰	HNSCC	82	Australia	2013–2015	Rinse, HPV16	p16
Gillison (2008) ⁴⁷	HNSCC	240	USA	2000–2006	Rinse, HPV16	HPV16 ISH
Koslubova (2013) ⁴⁸	HNSCC	141	Czech Republic	2001–2007	Rinse, Oncogenic	PCR
Yoshida (2017) ^{49,c}	OPSCC	19	Japan	Not stated	Rinse, Oncogenic Swab, Oncogenic	p16
Ahn (2014) ⁵⁰	OPSCC	83	USA	1999–2010	Rinse, HPV16	HPV16 ISH or qPCR
Isaac (2017) ²⁹	OPSCC	52	Canada	2015–2016	Swab, HPV16 E6/E7 RNA	p16

HNSCC, head and neck squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; ISH, in situ hybridization; PCR, polymerase chain reaction.

^aThis study was included only for the OPSCC-specific sensitivity and specificity estimates, as cases in this paper were a subset of the HNSCC cases described in Gillison et al.

^bWhere not specifically noted, data from the oncogenic HPV oral swab were used for meta-analysis.

^cWhere not specifically noted, data from the oral rinse were used for meta-analysis.

Table 2

Meta-analysis estimates of the sensitivity and specificity of oral HPV detection for classifying HPV-positive head and neck tumors

Cancer type	Oral HPV type	Oral HPV detection method	Tumor HPV detection method	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)
HNSCC	Any Oncogenic	Rinse or Swab	ISH or p16 or PCR	7	72% (45–89%)	92% (82–97%)
HNSCC	Any Oncogenic	Rinse Only	ISH or p16 or PCR/qPCR	5	77% (61–87%)	95% (70–99%)
HNSCC	HPV16 Only	Rinse or Swab	ISH or p16 or qPCR	5	68% (27–92%)	95% (83–99%)
OPSCC	Any Oncogenic	Rinse or Swab	ISH or p16 or qPCR	5	55% (25–82%)	94% (85–98%)

HNSCC, head and neck squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; ISH, in situ hybridization; PCR, polymerase chain reaction. Tumor site “HNSCC” includes studies that restricted to OPSCC. Oral HPV type and tumor HPV type “any oncogenic” includes studies that tested specifically for HPV16.