Human Papillomavirus Type 16 Infection and Squamous Cell Carcinoma of the Head and Neck in Never-Smokers: A Matched Pair Analysis

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ABSTRACT

Purpose: Infection with human papillomavirus (HPV) type 16 has been suggested to be a risk factor for squamous cell carcinoma of the head and neck (SCCHN) and may be of particular importance in HPV-16 exposure, as evidenced by seropositivity, is a risk factor for SCCHN and may be of particular importance in never-smokers.

Experimental Design: To test this hypothesis, we conducted a hospital-based case-control study of 120 patients with SCCHN (60 never-smokers and 60 matched smokers) and 120 cancer-free matched controls. We compared the presence of HPV-16 antibodies in ever-smoker and never-smoker cancer-free control on age (±5 years), sex, and tumor site. Each patient was also matched with a corresponding ever-smoker or never-smoker cancer-free control on age (±5 years) and sex. Serum was collected from study subjects and assayed for IgG reactivity to HPV-16 L1 virus-like particles by using an ELISA.

Results: Forty-nine of the 120 case subjects (40.8%) but only 11 (9.2%) of the control subjects tested positive for HPV-16 antibodies (adjusted odds ratio, 6.69; 95% confidence interval, 3.01–14.90). Among cases, HPV-16 seropositivity was more common in those with oropharyngeal cancer (41 of 70, 58.6%) and poorly differentiated tumors (25 of 43, 58.1%). HPV-16 seropositivity was associated with a significantly increased risk of oropharyngeal cancer (adjusted odds ratio, 59.53; 95% confidence interval, 5.71–620.20). Whereas HPV-16 seropositivity was more common in never-smokers with SCCHN than in ever-smokers (43.3% versus 38.3%, respectively), this difference was not statistically significant.

Conclusions: HPV-16 infection is associated with a significant increased risk for oropharyngeal cancer but not oral cavity cancer. Furthermore, HPV-16 infection does not appear to be more common in never-smokers than ever-smokers with SCCHN.

INTRODUCTION

Tobacco and alcohol are well-established risk factors for SCCHN, but SCCHN also develops in individuals who have never smoked. HPV-16 has been established as an etiological agent in cervical cancer (1–6), and more recently, several investigators have suggested that infection with HPV (especially the high-risk types HPV-16 and HPV-18) is a risk factor for SCCHN (7–10). Numerous studies using methods such as PCR, Southern blotting, and in situ hybridization have detected HPV DNA in the tumor tissue and sera of SCCHN patients (11, 12). However, because these studies did not include cancer-free controls, most of these studies were unable to estimate the risk of SCCHN attributable to HPV-16. Whereas some studies have assessed HPV-16 DNA positivity in the mucosa of cancer-free controls (13, 14), the absence of viral DNA in normal mucosa may not be an accurate indicator of past exposure (15, 16) because HPV DNA can be cleared from normal mucosa (17).

In 1994, an ELISA for detecting HPV-16 VLPs was developed (18). VLP ELISAs have been validated as type-restricted measures of past and present infections (19). Such serological assays may be better than HPV DNA detection for epidemiological studies in which cumulative exposure to specific HPV types is relevant. Serological assays are also not subject to sampling bias, unlike DNA-based assays involving biopsy material.

Recent investigations suggested that the association between cancer and HPV-16 infection may depend on the tumor site within the head and neck region, with oropharyngeal cancers having the highest rates of HPV-16 DNA and seropositivity...
HPV-16 DNA-positive oropharyngeal tumors (but not other SCCHNs) may be less commonly associated with risk factors such as drinking and smoking than HPV-16-negative tumors are (12).

The chief oncoproteins of HPV-16 are encoded by the genes E6 and E7. The E6 protein targets the tumor suppressor gene p53 for ubiquitination and degradation. In fact, degradation of p53 in HPV-positive cells is fully dependent on the presence of E6 (22). The E7 oncoprotein is involved in suppression of pRb function. Reduced pRb expression is common in HPV-positive tonsillar cancers (23, 24). This leads to the hypothesis that there are two pathways by which head and neck carcinogenesis occurs: (a) HPV-16 inactivates p53 and pRb, leading to tumor formation; or (b) more commonly, SCCHN is induced by tobacco and alcohol. In theory, these two carcinogenic pathways could occur in isolation or in conjunction. We hypothesized that HPV-16 infection, as evidenced by seropositivity, is a risk factor for SCCHN and for oropharyngeal cancer in particular and may be of particular importance in SCCHN occurring in never-smokers. We tested this hypothesis in a matched-pair case-control study of both smokers and never-smokers.

MATERIALS AND METHODS

Subjects. Patients with histologically confirmed, previously untreated SCCHN (excluding cancers of the skin, sinonasal tract, nasopharynx, lip, or salivary glands) were recruited at our institution from May 1996 to January 2001. Cancer-free control subjects were selected from a pool of healthy controls identified during a similar time period from ongoing hospital-based case-control studies. The controls were clients of a local managed-care organization with multiple clinics throughout the Houston metropolitan area. The control subjects were first surveyed by means of a short questionnaire to determine their willingness to participate in research studies and to obtain information about their smoking behavior and demographic factors (25). All participants agreed to donate 30 ml of blood and to complete a self-administered questionnaire that elicited information on age, sex, ethnicity, and tobacco and alcohol consumption. Approximately 95% of eligible cases and 75% of eligible controls agreed to participate. Ever-smokers were defined as those who had smoked more than 100 cigarettes in their lifetimes and ever drinkers were defined as those who had drunk alcoholic beverages at least once a week for more than 1 year. Approximately 95% of eligible cases and 75% of eligible controls agreed to participate. Ever-smokers were defined as those who had smoked more than 100 cigarettes in their lifetimes and ever drinkers were defined as those who had drunk alcoholic beverages at least once a week for more than 1 year. Each never-smoker case subject was matched on age (+/-5 years), sex, and tumor site with an ever-smoker case subject. Each case subject was also matched to a control subject on age, sex, and smoking status. All subjects were non-Hispanic whites.

HPV-16 Serological Testing. VLPs generated from recombinant baculovirus-infected insect cells were used to test for antibodies against HPV-16 in the plasma of study subjects by using a standard ELISA, as described previously (18). The cutoff level used was based on the absorbance value of a standard pooled serum known to be at the threshold of detection (26, 27). All samples were tested in duplicate. Any value above the cutoff value was considered positive, and any value below the cutoff was considered negative. The 38 samples that were within 15% of the cutoff point were tested twice more, and the 17 that were positive in all three assays were considered positive. We also retested a randomly chosen 10% of the samples and obtained 100% concordance on the repeat assays.

To eliminate potential binding interference by heparin, we treated the plasma samples with 43 units/ml heparinase I (Sigma, St. Louis, MO) before use (28). We also obtained heparinized plasma as well as serum from three individuals. There was no discernable difference in the serological reactions between the serum samples and the heparinized plasma samples treated with heparinase (data not shown).

Cotinine Levels. Cotinine is a chemical metabolite of tobacco smoke with a circulating half-life of at least 18 h after exposure to tobacco. We used anti-cotinine antibody-coated microtiter plates (STC Technologies, Inc., Bethlehem, PA) to measure the cotinine levels of all study subjects. The absorbances of known concentrations of cotinine were used as cutoff levels. There were very few subjects whose cotinine levels were intermediate (between 10 and 50 ng/ml), so the data were dichotomized. A subject was considered negative (no recent exposure) if his or her cotinine level was less than 25 ng/ml, positive (recent exposure) if it was greater than 25 ng/ml and intermediate (between 10 and 50 ng/ml), so the data were dichotomized. A subject was considered negative (no recent exposure) if his or her cotinine level was less than 25 ng/ml, positive (recent exposure) if it was greater than 25 ng/ml.

HPV-16 in Tumor Tissue. DNA was extracted from the paraffin-embedded tumors samples of 34 of the case subjects. Tumor tissue was not available from the rest of the patients because it was archived at another institution or because only a cytologic aspirate was collected. The integrity of the DNA was determined by PCR amplification of the FAS gene. The DNA of 27 samples was intact and tested for the presence of HPV-16 viral DNA by using PCR with primers specific for E6 and E7, as described previously (29, 30).

Statistical Analyses. χ² analyses were performed to determine the difference in the distribution of each demographic and exposure variable in cases and controls. Conditional logistic regressions were completed using LogXact 4 for Windows (Version 4.1; Cytel Software Corp., Cambridge, MA). ORs and 100% concordance on the repeat assays.
Table 2  Matched pair analysis of HPV-16 serological status and SCCHN risk estimates

<table>
<thead>
<tr>
<th>Matched pairs</th>
<th>Control</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>Adjusted OR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>Adjusted OR&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>HPV-16+</td>
<td>3</td>
<td>5.75 (2.71–12.18)</td>
<td>6.21 (3.83–10.61)</td>
</tr>
<tr>
<td></td>
<td>HPV-16−</td>
<td>8</td>
<td>5.00 (1.94–13.06)</td>
<td>5.30 (1.95–14.37)</td>
</tr>
<tr>
<td></td>
<td>HPV-16+</td>
<td>1</td>
<td>7.00 (1.98–22.43)</td>
<td>9.87 (2.26–43.13)</td>
</tr>
<tr>
<td></td>
<td>HPV-16−</td>
<td>2</td>
<td>2.00 (0.50–8.20)</td>
<td>2.50 (0.60–10.50)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditional logistic regression analyses on matching variables.
<sup>b</sup> Conditional logistic regression analyses on matching variables, adjusted for alcohol status.
<sup>c</sup> Conditional logistic regression analyses on matching variables, adjusted for alcohol and cotinine level.

Results

Table 1 demonstrates the matching variable distributions between cases and controls. One HPV-16-negative control subject was miscoded as a smoker before matching. The two groups were similar in their exposure history to alcohol (Table 1). Their similar plasma cotinine levels showed that similar percentages were similar in their exposure history to alcohol (Table 1). The two groups between cases and controls. One HPV-16-negative control subject was miscoded as a smoker before matching. The two groups were similar in their exposure history to alcohol (Table 1). Their similar plasma cotinine levels showed that similar percentages were similar in their exposure history to alcohol (Table 1).

Patients with supraglottic cancer were also frequently positive, but the number of laryngeal cancer cases was relatively small (n = 14). The prevalence of seropositivity increased with the tumor grade; 25 of 43 patients (58.1%) with poorly differentiated tumors were serologically positive (Table 3). The 38 patients with poorly differentiated oropharyngeal tumors, 24 (63.2%) were serologically positive for HPV-16, whereas only 2 of the 30 patients with moderate or well-differentiated oral cavity tumors (6.7%) were serologically positive (data not shown). HPV-16 viral DNA was detected in 8 tumors of the 27 tumors tested. Five of the 8 tumors positive for HPV-16 DNA were found in the oropharynx, and 3 were found in the oral cavity, whereas 15 of the 19 tumors negative for HPV-16 DNA were found in the oral cavity, 3 were found in the larynx, and only 1 was found in the oropharynx. Overall concordance between HPV-16 DNA being detected in the tumor and HPV-16 seropositivity was 74.1% [20 of 27 (14 of 18, 5 of 6, and 1 of 3 for oral cavity, oropharynx, and larynx, respectively)]. Five of the eight tumors positive for HPV-16 DNA (62.5%) occurred in serologically positive patients, whereas 15 of the 19 HPV-16-negative tumors (78.9%) occurred in serologically negative patients.

HPV-16 seropositivity was associated with a 38-fold increased risk of oropharyngeal cancer (P < 0.001; Table 4). This risk remained significant after adjusting for alcohol status and cotinine level. When stratified by smoking status, HPV-16 seropositivity was more common in the never-smokers with oropharyngeal cancer [24 of 35 (68.6%)] than in the ever-smokers with oropharyngeal cancer [17 of 35 (48.6%)]. Whereas the never-smokers with oropharyngeal cancer had more pairs in which the case was HPV-16 positive and the control was HPV-16 negative than the ever-smokers with oropharyngeal cancer (23 versus 15 pairs, respectively; Table 4), and we observed higher ORs associated with risk of oropharyngeal cancer in the never-smokers than in the ever-smokers (Table 4), these differences were not statistically significant.

To further explore the interaction of HPV-16 status and smoking status, we performed a case-case matched pair analysis (Table 5). Fourteen of the 60 matched case-case pairs (23%) had a never-smoker who was HPV-16 positive and a smoker who was HPV-16 negative, whereas 11 pairs (18%) had a smoker...
who was HPV-16 positive and a never-smoker who was HPV-16 negative. The remaining 35 pairs (59%) were concordant for HPV-16 serological status (Table 5). Never smoking was not associated with an increase in risk of HPV-16 positivity among SCCHN patients (OR, 1.16; 95% CI, 0.58–2.78). Furthermore, after adjustment for alcohol status and cotinine level or in oropharyngeal subgroup analysis, never smoking was not associated with HPV-16 serological status (Table 5).

**DISCUSSION**

In this matched pair analysis, we demonstrated that HPV-16 seropositivity was associated with an approximately 7-fold increased risk for SCCHN. It is noted that we did not find an increase in HPV-16 seropositivity for oral cavity cancer patients, suggesting that the association of HPV-16 with SCCHN risk is primarily limited to the oropharyngeal cancer subsite. This finding is in support of existing subsite data in the literature. These risk estimates were independent of alcohol use and cotinine levels, suggesting that HPV-16 is associated with a significant risk independent of alcohol use or recent tobacco exposures. Sexual history is a potential confounding variable, which was not controlled for in this study, and it is possible that a difference between the cases and controls exists with respect to sexual history that could in part account for the different HPV-16 seropositivity rates.

This matched pair serological case-control study adds to the molecular epidemiological evidence suggesting that HPV-16 exposure is a risk factor for oropharyngeal cancer and explores the importance of HPV-16 in the never-smoker with SCCHN. In a nested case-control study of 292 cases and 1568 controls from a Scandinavian cohort of almost 900,000 subjects, Mork et al. (21) recently reported that HPV-16 seropositivity was associated with a 2.2-fold increased risk of SCCHN after adjustment for cotinine levels. However, 25% of the cases in that study were not classic SCCHN (3% were nasopharynx cancer, 20% were lip cancer, and 2% were sinus cancer). Because subjects with cancers of these sites were less frequently HPV-16 seropositive, Mork et al. (21) may have underestimated the risk of SCCHN associated with HPV-16 exposure. In addition, differences in the proportion of cases with oropharynx cancer may also account for the differences in risk estimates. In fact, in their subgroup analysis of oropharyngeal cancer, Mork et al. (21) reported an estimated risk of 14.4 (95% CI, 3.6–58.1). In a retrospective case-control study of 259 subjects with prevalent cancers of the oral cavity and oropharynx and 446 population-based controls, Schwartz et al. (31) found seropositivity to HPV-16 viral capsids associated with an adjusted risk of SCCHN of 2.3 (95% CI, 1.6–3.3). The highest risk estimates were associated with oropharyngeal cancers, and data suggested that HPV-16 seropositivity and current cigarette smoking were associated with a greater than additive increased risk for SCCHN. These landmark studies demonstrated the utility of HPV-16 serological screening and demonstrate that HPV-16 infection is a risk factor for oropharyngeal cancer.

Three additional case-control studies have been conducted using PCR to identify HPV-16 DNA in tumor tissue from SCCHN patients and head and neck mucosal tissue from cancer-free controls (13, 14, 32). A study of oral cavity cancer (13) in which the HPV DNA in oral cavity was amplified and sequenced revealed that 15% of 93 oral cavity cancer cases and only 5% of 205 cancer-free controls were positive for HPV DNA (OR, 3.70; 95% CI, 1.47–9.32). A second study (14) found only a slight difference in high-risk HPV DNA types in 44 cases with laryngeal cancer, 10 cases with leukoplasia, and 12 cancer-free controls (18.2%, 20.0% and 16.7%, respectively). More recently, a retrospective case-control study of 52 patients with squamous cell carcinoma of the tonsil and 48 age- and sex-matched patients with benign tonsillar hyperplasia demonstrated a 18.2-fold risk of tonsillar carcinoma associated with the presence of HPV in tonsillar tissue (32). Whereas these studies were relatively small, retrospective, unmatched, lacked smoking information, or did not include patients with oropharyngeal cancer, two of the three support the hypothesis that HPV-16 is a risk factor for SCCHN.

Our findings are also consistent with many case-series reports of HPV-16 DNA in the tumors of SCCHN patients. Past studies have also indicated that HPV-associated tumors are more likely to be in the oropharynx than in other parts of the head and neck (12, 14, 31). In our study, 58.6% of the patients with oropharyngeal tumors were seropositive, compared with 8.3% and 35.7% of the patients with oral cavity and larynx cancer, respectively. This is in agreement with the previous results of both serological and tumor DNA studies reported by other investigators (11–13, 21, 32). The subgroups within the oropharynx (the base of the tongue and the tonsil) did not differ significantly in HPV seropositivity. Furthermore, HPV-positive tumors are poorly differentiated and nonkeratinizing and have a basaloid morphology, which is more common in oropharyngeal tumors and is also consistent with our findings (11, 23, 33–36). Whereas the association between HPV seropositivity and poorly differentiated tumors may be restricted to tumors of the oropharynx, we are unable to confirm this due to a sample size of only four patients with poorly differentiated tumors of the oral
cavity (one seropositive) and only a single patient (seronegative)
with a poorly differentiated laryngeal cancer. We did find a high
prevalence of seropositivity in the patients with supraglottic
cancer, which was also consistent with previous reports (21, 37).
Also, the 27 case subjects with HPV-16-positive tumors were
three times more likely to be serologically positive than those
with HPV-16-negative tumors. Although the number of cases
was small, the correlation between serological data and tumor
data is consistent with previous reports on head and neck (21)
and gynecological cancer (18, 38).

Finally, we did not find that never-smokers with SCCHN
were significantly more frequently HPV-16 seropositive than
ever-smokers with SCCHN. We did observe that almost 70% of
oropharyngeal cancer patients who never smoked were
serologically positive for HPV-16 and a higher risk of orophar-
yngeal cancer associated with HPV-16 seropositivity in the
never-smokers than in the ever-smokers, but these differences
were not statistically significant. Whereas our study included
only 60 never-smokers with SCCHN, this is the largest number
of never-smokers previously examined for HPV-16 status and is
the first to systematically explore the role of HPV-16 in never-
smokers with SCCHN. Other studies have also found that HPV
is more common in SCCHN in never-smokers, but those studies
had few never-smokers and no matching (particularly for tumor
site) between ever-smokers and never-smokers. Fouret et al.
(20) found that 5 of 10 SCCHNs (50%) in nonsmokers but only
15 of 177 SCCHNs (8.5%) in smokers had HPV DNA. Smith et
al. (13) found that 7 of 18 oral and pharyngeal cancers (38.9%)
in nonsmokers but only 7 of 75 oral and pharyngeal cancers
(9.3%) in smokers were HPV positive. Strome et al. (32) found
6 of 7 (86%) tonsil cancers occurring in never-smokers to be
HPV positive and 18 of 45 (40%) tonsil cancers in smokers to
be HPV positive. Based on previous case-control studies and
case series and the findings reported here, we conclude that
HPV-16 is a clear risk factor for oropharyngeal cancer in ever-
smokers and also a substantial risk factor for oropharyngeal
cancers in never-smokers.

The literature and our findings together support many of
the classic criteria for disease causality [including at least three
of the five used by the Surgeon General in the official report
linking smoking to lung cancer (39)]. These criteria include
the strength of the association (between HPV-16 and oropharyn-
geal cancer), the consistency in the literature (of HPV-16 DNAs
being identified frequently in oropharyngeal cancers and asso-
ciated with risk of oropharyngeal cancer in case-control studies),
the specificity (of HPV-16 and not other HPV types), the consis-
tency (of the cancer site associated with HPV-16), the coherence
of the explanation and the analogy (of HPV-16-induced oropharyngeal
cancer to cervical carcinogenesis), and the bio-
logical plausibility (of the HPV-16 carcinogenesis model).
However, these studies could not demonstrate either a dose-
response effect on risk or (with one exception) a clear temporal

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Table 4  Matched pair analysis of HPV-16 serological status and oropharyngeal cancer risk estimates

<table>
<thead>
<tr>
<th>Matched pairs</th>
<th>Control</th>
<th>OR* (95% CI)</th>
<th>Adjusted ORb (95% CI)</th>
<th>Adjusted ORc (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>HPV-16+</td>
<td>HPV-16−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-16+</td>
<td>3</td>
<td>38</td>
<td>38.0</td>
<td>60.40 (5.67–631.4)</td>
</tr>
<tr>
<td>HPV-16−</td>
<td>1</td>
<td>28</td>
<td>(5.22–276.8)</td>
<td></td>
</tr>
<tr>
<td>HPV-16+</td>
<td>1</td>
<td>23</td>
<td>32.68d</td>
<td>27.17d (4.36–∞)</td>
</tr>
<tr>
<td>HPV-16−</td>
<td>0</td>
<td>11</td>
<td>(5.75–∞)</td>
<td>(4.36–∞)</td>
</tr>
<tr>
<td>HPV-16+</td>
<td>2</td>
<td>15</td>
<td>15.00</td>
<td>19.70d (3.32–∞)</td>
</tr>
<tr>
<td>HPV-16−</td>
<td>1</td>
<td>17</td>
<td>(1.98–113.6)</td>
<td></td>
</tr>
</tbody>
</table>

*a Conditional logistic regression analyses on matching variables.
*b Conditional logistic regression analyses on matching variables, adjusted for alcohol status.
*c Conditional logistic regression analyses on matching variables, adjusted for alcohol and cotinine level.
*d Exact logistic regression analysis.

Table 5  Matched pair analysis of HPV-16 serological status and smoking status risk estimates among cases

<table>
<thead>
<tr>
<th>Matched pairs</th>
<th>Ever-smoker</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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<tr>
<td>Never-smoker</td>
<td>HPV-16+</td>
<td>12</td>
<td>1.32 (0.58–2.78)</td>
<td>1.16 (0.47–2.86)</td>
</tr>
<tr>
<td>HPV-16−</td>
<td>11</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-16+</td>
<td>11</td>
<td>13</td>
<td>2.17 (0.83–5.56)</td>
<td>1.79 (0.54–6.67)</td>
</tr>
<tr>
<td>HPV-16−</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Conditional logistic regression analyses on matching variables.
*b Conditional logistic regression analyses on matching variables, adjusted for alcohol status.
*c Conditional logistic regression analyses on matching variables, adjusted for alcohol and cotinine level.
link between infection and tumor development. Consequently, a larger prospective cohort study is needed to verify the etiological role of HPV-16 in oropharyngeal cancer, to accurately quantify the risk of oropharyngeal cancer in those with serological evidence of HPV-16 exposure, and to explore the interaction between HPV-16 and degree of tobacco exposure. Ultimately, such studies may lead to improved cancer prevention by identifying individuals at high-risk of oropharyngeal cancer, who may benefit from aggressive smoking cessation efforts, screening for early detection, chemoprevention protocols, and possibly even prophylactic tonsillectomy.

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REFERENCES


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