Bidirectional Association of Anogenital and Oral Cavity/Pharyngeal Carcinomas in Men

Andrew G. Sikora, MD, PhD; Luc G. Morris, MD; Erich M. Sturgis, MD, MPH

Objective: To test the hypothesis of a bidirectional association of anogenital and oral cavity/pharyngeal human papillomavirus (HPV)-associated cancers in men.

Design: Population-based epidemiological study using the Surveillance, Epidemiology, and End Results cancer database.


Participants: The study included 47,308 men 20 years and older with an index oral cavity/pharyngeal or anogenital cancer.

Main Outcome Measure: Second primary HPV-associated cancers (anogenital or oral cavity/pharyngeal) or HPV-unrelated cancers (prostate, bladder, or colon).

Results: The standardized incidence ratio (SIR) was elevated for both anogenital cancer following oral cavity/pharyngeal cancer (SIR, 1.9; 95% confidence interval [CI], 1.2-2.7) and oral cavity/pharyngeal cancer following anogenital cancer (SIR, 3.0; 95% CI, 2.1-4.2). The increase in SIR was most pronounced for tonsillar cancer following anal cancer (SIR, 8.4; 95% CI, 2.7-19.6). The risk of second primary HPV-associated cancers did not vary significantly by age, race, year of diagnosis, or geographic location but was greater among never-married men, particularly for anal cancer following oral cavity/pharyngeal cancer (SIR, 6.5; 95% CI, 1.8-16.7 in never-married men, but SIR, 1.6; 95% CI, 0.7-3.1 in ever-married men) and for tonsillar cancer following anogenital cancer (SIR, 13.0; 95% CI, 3.5-33.2 in never-married men, but SIR, 3.8; 95% CI, 1.0-9.7 in ever-married men). Other than a slightly increased risk of tongue cancer following colon cancer (SIR, 1.3; 95% CI, 1.1-1.6), there was no increased risk of oral cavity/pharyngeal or anogenital cancer following HPV-unrelated cancers or vice versa.

Conclusion: The association between index and second primary anogenital and oral cavity/pharyngeal cancers, strongest in never-married men, supports the influence of sexual behavior on the risk of HPV-associated head and neck cancers.


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cases for Oncology histology codes 8050-8089 [squamous]; site codes C00.0-06.9, 09.0-10.9, and 12.9-14.8; anogenital region (histology codes 8050-8089 [squamous], 8094 [basosquamous], or 8023-8024 [basaloid/cloacogenic]; site codes C21.0-21.2 and 60.0-60.9); or selected HPV-unrelated sites, including prostate, bladder, and colon (all histologic subtypes [codes 8000-9889]; site codes C61.9, C67.0-67.9 and C18.0-18.9). We excluded nasopharyngeal carcinoma and salivary gland carcinomas (which are categorized by SEER as pharyngeal and oral cavity tumors, respectively) from analysis. We identified 43,012 men 20 years and older with an index oral cavity/pharyngeal carcinoma (25,789 person-years of follow-up) and 4,926 men with an index anogenital cancer (27,859 person-years of follow-up).

Standardized incidence ratios (SIRs) for second primary cancers were calculated based on the observed number of cases divided by the expected number, which was determined using the incidences of these cancers in the population stratified by age, sex, and marital status. Confidence intervals (CIs) were determined according to the Poisson distribution. The statistical significance of differences between SIRs was evaluated according to the method of Altman and Bland.\(^1\) Marital status was defined as ever-married (married, widowed, and previously married) or never-married (no previous history of marriage). Nonmalignant tumors, second cancers discovered within 1 month of the index cancer, and any cancer diagnosis based solely on death certificate or autopsy report were excluded.

Among men with index anogenital cancers, there was a significantly elevated SIR for second primary oral cavity/pharyngeal cancers, especially of the tonsil or tongue (Table 1). Among men with index cancers of the anus, there was an 8-fold elevated SIR for second primary cancers of the tonsil, and among men with index cancers of the penis, there was a 5-fold elevated SIR for second primary cancers of the tongue (Table 1). Analysis of second primary tumors in women did not reveal an elevated risk of oral cavity/pharyngeal cancers following anal cancer or an elevated risk of anal cancer following oral cavity/pharyngeal cancers (data not shown). However, the much smaller number of index primary anal or oral cavity/pharyngeal tumors in women does not allow conclusions to be drawn from this observation. The rates of second primary anogenital or oral cavity/pharyngeal cancers in men with index cancers at HPV-unrelated sites (prostate, bladder, or colon) were not elevated over what was expected (Table 1), except for tongue cancer following colon cancer.

The SIRs for second primary anogenital and oral cavity/pharyngeal cancers in men did not vary significantly by age, race, year of diagnosis, or geographic location (data not shown). However, the SIR for second primary anogenital cancers following oral cavity/pharyngeal cancers varied significantly by marital status (Figure): the SIR for second primary anal cancers was 6.5 (95% CI, 1.8-16.7) in never-married men but only 1.6 (95% CI, 0.7-3.1) in ever-married men. Also, the age at diagnosis of these second primary anogenital cancers was younger among never-married men than among ever-married men (61.0 years vs 69.6 years, \(P=.03\)).

Similarly, the SIR for second primary oral cavity/pharyngeal cancers following anogenital cancers also varied significantly by marital status (Figure): the SIR for second primary tonsillar cancers was 13.0 (95% CI, 3.5-33.2) in never-married men but only 3.8 (95% CI, 1.0-9.7) in ever-married men. Even more striking, the SIR for second pri-
Among ever-married men (56.4 years vs 70.4 years, significantly younger among never-married men than these second primary oral cavity/pharyngeal cancers was anogenital cancer (Table 2). A tonsillar cancer accounted for 3 of 10 cases of second primary oral cavity/pharyngeal cancer. However, among never-married men, tonsillar cancer accounted for 3 of 10 cases of second primary oral cavity/pharyngeal cancers (30%).

The mean latency (time elapsed between diagnosis of the index tumor and second primary tumor) was 4.2 years for oral cavity/pharyngeal index tumors and 5.6 years for anogenital index tumors. There was no increased risk of HPV-related sites (prostate, bladder, and colon) following index oral cavity/pharyngeal cancers in whom second primary tobacco-related cancers were not dramatic among never-married men than among ever-married men (P = .001). The mean latency (time elapsed between diagnosis of the index tumor and second primary tumor) was 4.2 years for oral cavity/pharyngeal index tumors and 5.6 years for anogenital index tumors. There was no increased risk of HPV-related cancers (prostate, bladder, or colon) following oral cavity/pharyngeal or anogenital cancer, and these findings were not modified by marital status (Figure).

Tonsillar carcinoma is the head and neck cancer with the strongest reported link to oncogenic HPV. Among men with second primary anogenital carcinomas following oral cavity/pharyngeal cancer, the index lesion was a tonsillar cancer in 2 of 5 never-married men (40%) but in 0 of 15 ever-married men. When we examined the subsite distribution of oral cavity/pharyngeal cancers after anogenital cancer (Table 2), we found that among ever-married men tonsillar cancers accounted for 4 of 24 second primary oral cavity/pharyngeal cancers (17%), similar to the proportion of tonsillar cancers (12%) among all men 20 years and older with an index oral cavity/pharyngeal cancer. However, among never-married men, tonsillar cancer accounted for 3 of 10 cases of second primary oral cavity/pharyngeal cancers (30%).

### Table 2. Subsite Distribution of Oral Cavity/Pharyngeal Second Primary Tumors Following an Index Cancer of the Anogenital Region

<table>
<thead>
<tr>
<th>Index Tumor</th>
<th>Never-Married Men</th>
<th>Ever-Married Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other tongue area</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>24</td>
<td>34</td>
</tr>
</tbody>
</table>

*Thirty-four of 38 tumors could be definitively assigned to a subsite. One never-married patient had 2 oral cavity/pharyngeal second primary cancers; therefore, there are 11 tumors distributed among 10 patients.

### Table 3. Subsite Distribution of Oral Cavity/Pharyngeal Index Tumors Preceding a Second Primary Cancer of the Anogenital Region

<table>
<thead>
<tr>
<th>Index Tumor</th>
<th>Never-Married Men</th>
<th>Ever-Married Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other tongue area</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

*Twenty of 20 tumors could be definitively assigned to a subsite.

The elevated and reciprocal risk of second primary anogenital and oral cavity/pharyngeal cancers in men supports HPV as a link between these cancers. The dramatically elevated risk among never-married men compared with ever-married men suggests that never-married status may be a surrogate for sexual practices associated with HPV transmission. The earlier age at diagnosis of these second primary cancers in never-married men is consistent with observations that HPV-associated oral cavity/pharyngeal cancers present earlier than cancers caused by smoking and/or use of alcohol.

A significant limitation of our study relates to the lack of tobacco use information in SEER: smoking may be more common among never-married men than among ever-married men, potentially causing spurious differences in the risk of second primary tumors. Such confounding may have been present in the analysis of men with index oral cavity/pharyngeal cancers in whom second primary tobacco-related cancers (of the lung, larynx, and esophagus) are common and among whom we found that elevated SIRs for second primary tobacco-related cancers occurred more often in the never-married men (Figure). However, in men with index anogenital cancers, the SIRs for second primary tobacco-related cancers were not dramatically elevated, nor were there differences by marital status. Also, analysis of oral cavity/pharynx second pri-
mary cancer by subsite suggests that tobacco use may have actually been more prevalent in ever-married men with index anogenital cancer. Carcinomas of the floor of the mouth and hypopharynx (subsites with the strongest link to smoking) were more common second primary cancers following index anogenital cancers in ever-married men (Table 2) and were more common index cancers in ever-married men as well (Table 3). Furthermore, the disproportionate representation of second primary tonsillar cancers among never-married men in our study is more consistent with HPV than smoking as a common etiologic agent. Another limitation is the inability to extract HIV status (which is strongly associated with risk of anal carcinoma16) from the SEER registry, making it impossible to control for different rates of HIV positivity among ever- and never-married men.

Understanding risk factors for additional primary tumors in patients with HPV-related head and neck carcinomas is essential for proper patient counseling and risk reduction. While the attention of both the medical community and the lay population are understandably focused on the dramatic impact of oncogenic HPV on women’s health, physicians who treat HPV-associated cancers must be mindful that sexual transmission of HPV also places men at risk for HPV-related cancers at other body sites. The present data identify a patient population (never-married men) that may be at increased risk for additional HPV-related cancers after an index diagnosis of oral cavity/pharyngeal or anogenital carcinoma. Population-based databases that address behavioral risk factors, including smoking and sexual practices, are needed to further define the interaction between marital status and reciprocal increased risk of second primary anogenital and oral cavity/pharyngeal cancers.

Submitted for Publication: July 24, 2008; final revision received September 25, 2008; accepted October 29, 2008. Correspondence: Andrew G. Sikora, MD, PhD, Department of Otolaryngology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1189, New York, NY 10029 (agsikora@gmail.com).

Author Contributions: Dr Sikora had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sikora and Sturgis. Acquisition of data: Sikora and Morris. Analysis and interpretation of data: Sikora and Sturgis. Drafting of the manuscript: Sikora, Morris, and Sturgis. Critical revision of the manuscript for important intellectual content: Sikora and Sturgis. Statistical analysis: Sikora and Morris. Administrative, technical, and material support: Sturgis. Study supervision: Sikora and Sturgis.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the Seventh International Conference on Head and Neck Cancer of the American Head and Neck Society; July 23, 2008; San Francisco, California.

Additional Contributions: Rosalind Gary assisted with manuscript preparation, and Stephanie P. Deming edited the manuscript.

REFERENCES