HPV in Head and Neck Cancers Among 5-Year Survivors

To the Editor:

Human papillomavirus (HPV), in particular the high-risk subtypes such as HPV16 and HPV33 (HR-HPV), has not only a proven role in the pathogenesis of cervical cancer, but is now implicated in some cases of head and neck squamous cell carcinoma (HNSCCA), which can arise in a variety of sites in the upper aerodigestive tract. The overall United State 5-year survival rate for HNSCCA between 1995 and 2001 was 59%. Although the literature shows a wide range in HPV-positivity in unselected HNSCCA (22% [metastudy] to 74%), differential overall 5-year survival based on HPV status (and/or its putative surrogate marker, p16\textsuperscript{INK4a}) has been suggested.

We identified 23-three HNSCCA 5-year survivors whose tumor specimens were positive for presence of p16\textsuperscript{INK4a} (using standard immunohistochemistry, antip16\textsuperscript{INK4a} antibody from Biocare Medical [clone JC8]). Tumor specimen DNA was tested for presence of HPV DNA using our previously published PCR-based method. We obtained results on samples from 17 patients, with the other 6 failing due to insufficient quantity or quality of DNA (Table 1).

Of these 17 cases, 12 (70%) were HPV positive (11 for HPV16, 1 for HPV33). The lack of perfect correlation of p16\textsuperscript{INK4a} and HPV-DNA positivity has been seen in previous studies, and suggests that p16\textsuperscript{INK4a} can be overexpressed without HPV infection, or that the HPV-negative samples were actually from HPV-positive tumors but escaped detection due to tissue sampling. Supporting this latter theory, we had one inconsistency among duplicates HANC4–5, in which PCR analysis of the presurgical biopsy (HANC5) was positive while a fragment from the resection was negative (HANC4) (Table 1). Thus, the frequency of HPV positivity may be underestimated. Our data are consistent with other reports suggesting increased survival in patients with HPV-positive tumors. For example, of 80 patients in another study, 74% had disease-free 5-year survival and were also HPV-positive, compared with only 53% of the HPV-negative cases. Ninety-two percent of our positives were HPV16 and 8% were HPV33, consistent with previous reports of HPV16 predominating in cervical cancer and HNSCCA.

The 17 tumors occurred in the following anatomic locations: larynx (n = 2, 12%), and oropharynx (soft palate, n = 1, 6%), base of tongue (n = 6, 35%), and tonsil (n = 9, 47%). Four of the tongue tumors were HPV-positive (67%), 8 of the tonsil tumors were HPV-positive (89%), and the larynx

TABLE 1. Characteristics and HPV Infections in Head and Neck Cancers

<table>
<thead>
<tr>
<th>Sample</th>
<th>Tumor Location</th>
<th>Age at Diagnosis (yr)</th>
<th>Gender</th>
<th>HPV PCR Test</th>
<th>P16/INK4a Stain</th>
<th>Tobacco Use</th>
<th>Current Alcohol Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>HANC 1</td>
<td>Larynx</td>
<td>54</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 2</td>
<td>Soft palate</td>
<td>68</td>
<td>F</td>
<td>n.d.</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 3</td>
<td>BT</td>
<td>55</td>
<td>M</td>
<td>+16</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 4</td>
<td>BT</td>
<td>68</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>HANC 5*</td>
<td></td>
<td></td>
<td></td>
<td>+16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HANC 6</td>
<td>BT</td>
<td>42</td>
<td>M</td>
<td>+16</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 7</td>
<td>Tonsil</td>
<td>51</td>
<td>F</td>
<td>+33</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>HANC 8</td>
<td>Tonsil</td>
<td>43</td>
<td>M</td>
<td>+16</td>
<td>+</td>
<td>–</td>
<td>++</td>
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<tr>
<td>HANC 9</td>
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<td>56</td>
<td>F</td>
<td>n.d.</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>HANC 10</td>
<td>Tonsil</td>
<td>55</td>
<td>M</td>
<td>+16</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 11</td>
<td></td>
<td></td>
<td></td>
<td>+16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HANC 12</td>
<td>Tonsil</td>
<td>73</td>
<td>M</td>
<td>+16</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 13</td>
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<td>52</td>
<td>M</td>
<td>+16</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>HANC 14</td>
<td>BT</td>
<td>53</td>
<td>M</td>
<td>+16</td>
<td>–</td>
<td>++</td>
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<tr>
<td>HANC 15</td>
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<td></td>
<td>+16</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HANC 16</td>
<td>BT</td>
<td>49</td>
<td>M</td>
<td>+16</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>HANC 17</td>
<td>BT</td>
<td>57</td>
<td>M</td>
<td>n.d.</td>
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<tr>
<td>HANC 18</td>
<td>BT</td>
<td>79</td>
<td>M</td>
<td>n.d.</td>
<td>+</td>
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<tr>
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<td>63</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>HANC 20</td>
<td>BT</td>
<td>47</td>
<td>M</td>
<td>n.d.</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>HANC 21</td>
<td>Tonsil</td>
<td>51</td>
<td>M</td>
<td>+16</td>
<td>+</td>
<td>++</td>
<td>–</td>
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<tr>
<td>HANC 22</td>
<td>BT</td>
<td>28</td>
<td>F</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 23</td>
<td>Tonsil</td>
<td>56</td>
<td>F</td>
<td>+16</td>
<td>+</td>
<td>–</td>
<td>++</td>
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<tr>
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<td>Tonsil</td>
<td>67</td>
<td>M</td>
<td>n.d.</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>HANC 25</td>
<td>Tonsil</td>
<td>54</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>HANC 26</td>
<td>Larynx</td>
<td>55</td>
<td>M</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

HPV: 16, 18, 31, 33 refer to HPV types detected by tests.
Tobacco use: ++ = has smoked at least 100 cigarettes and is a current smoker; + = has smoked at least 100 cigarettes and is a past smoker; – = has never smoked 100 cigarettes and is a nonsmoker.
Alcohol use (current): ++ = >4 times/wk; ++ = 2–3 times/wk; + = 2–4 times/mo; + = monthly or less; – = never drinks.

*Duplicate of HANC4.
†Duplicate of HANC10.
‡Duplicate of HANC14.

n.d. indicates not determined; BT, base of tongue.
and palate tumors were all HPV-negative. This is consistent with previous published data indicating a predilection for HPV-positive tumors in the tonsil and base of tongue. Neither of the 2 cases outside the oropharynx (OP, the 2 larynx cancers) was HPV positive. However, of the 15 OP tumors that were typeable, 12 were HPV positive (80%); these results are consistent with literature indicating that OP tumors are more likely to be HPV-positive than oral cavity or laryngeal sites. Among the 17 patients, 41% reported never having smoked 100 cigarettes and were not current smokers, and 35% reported never drinking alcohol; 50% of these individuals had HPV-positive tumor samples. There was no statistically significant association between HPV status and use of tobacco or alcohol, consistent with these behaviors representing independent risk factors for HNSCCA.

Our data add to growing evidence that patients whose HNSCCA tumors contain HR-HPV have an increased probability of long-term survival. As indicated in our recent review, this has implications for prognosis, and supports the theory that different molecular mechanisms are involved in HPV-positive versus HPV-negative HNSCCA.

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