An assessment of risk factors for the development of a second primary malignancy in the head and neck

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Abstract
This retrospective database study of 44,862 patients who had a history of a primary head and neck malignancy was conducted to identify any clinical variables that may predict the occurrence of a second primary head and neck malignancy. During a mean follow-up of 42.2 months, a second head and neck primary developed in 941 of these patients (2.1%). Statistical analyses revealed that a higher incidence of a second primary was associated with increased age and a location of the first primary in the larynx/hypopharynx, the oropharynx, a major salivary gland, or the nasopharynx. A lower incidence was associated with the presence of cervical nodal disease or treatment of the first primary with radiation therapy. Factors that had no effect on the risk of a second primary included sex, the size of the first primary tumor, a first-primary site in the oral cavity, and treatment of the first primary with cancer-directed surgery. The risk of a second primary head and neck cancer remained constant for at least 10 years.

Introduction
More than 50,000 new cases of head and neck cancer are diagnosed each year in the United States. The vast majority of these tumors will demonstrate squamous cell carcinoma histology. Because tobacco exposure and alcohol use are strongly synergistic in the promotion of these tumors at multiple sites in the head and neck, patients with an initial head and neck cancer are faced with a long-term risk of developing a second primary malignancy. A second primary typically develops in the upper aerodigestive tract, esophagus, or lung. The reported incidence ranges from 2 to 17%, depending on patient characteristics and the duration of follow-up.

Once a patient has been diagnosed with and treated for a head and neck cancer, frequent and rigorous posttreatment follow-ups are often undertaken. Close follow-up is advisable for two reasons: (1) to detect a local or regional recurrence of the index cancer as early as possible and (2) to identify a second primary malignancy as soon as possible. It is widely held that early detection of a recurrence or a second primary affords a better chance for salvage and cure. As patients survive beyond the actuarial 5-year mark, the emphasis of follow-up generally shifts toward detecting a second primary rather than a recurrence. However, the need for rigorous follow-up of all patients with head and neck cancer to detect a second primary has been questioned. Efficient allocation of follow-up resources—including surveillance endoscopy, imaging studies, and other modalities—would be furthered if we could identify particular clinical risk factors for the development of a second primary.

The study described herein was undertaken from an epidemiologic standpoint to determine if certain clinical factors present at the time of the initial presentation of the index primary head and neck malignancy might serve as markers to identify patients who are at higher risk for a second primary malignancy of the head and neck.

Patients and methods
The patients in this study had been entered into the Surveillance Epidemiology and End Results database between Jan. 1, 1988, and Dec. 31, 1999. The author has used this database for other studies of epidemiology and survival in patients with several types of head and neck malignancy. Data were obtained on primary cancers that had arisen in the oral cavity, larynx/hypopharynx, oropharynx, nasopharynx, major salivary glands, nose, nasal cavity, and middle ear. Index (first) upper aerodigestive tract primaries occurring in the cervical esophagus and trachea were not included in this study.

The author conducted two data extractions. The first included all cases of head and neck cancer at the sites under study in which patients had only one primary; these patients served as the control group. The second data
extraction included all patients with a primary head and neck cancer who subsequently developed one (and only one) head and neck primary at a site under study; patients whose second primary arose in the esophagus, trachea, or lung were excluded from this analysis.

The two data sets were merged and imported into Microsoft Excel software. Patients in the control group who had less than 3 months of follow-up and patients in the second-primary group whose second primary had been diagnosed within 3 months of the first primary were excluded from the study to avoid the possibility of including patients who had purely synchronous primaries that may have been treated simultaneously. In addition to the site of the first primary, other potential predictor variables under consideration were the patient's sex, age at first diagnosis, the size of the first primary tumor, the presence of cervical nodal disease, treatment with cancer-directed surgery, and treatment with radiation therapy. Each of these variables referred to the clinical presentation of the first primary because data on these variables would have been available to the clinician responsible for follow-up surveillance prior to the presentation of a second primary. Overall survival time and the time to diagnosis of a second primary were also recorded.

Data were then exported to SPSS version 10.0 statistical software, and standard descriptive statistics were computed for the two cohorts. Survival time prior to the development of a second primary was computed in accordance with the Kaplan-Meier method. Univariate statistical analysis was conducted for the influence of clinical predictor variables on the development of a second primary by using Pearson's chi-square test or the Student's t test as appropriate. Cox proportional hazards regression analysis was then conducted to determine the multivariate significance of the different potential clinical predictor variables. Missing predictor variables were replaced with the covariate mean. The proportional hazards model was conducted with a backward likelihood ratio, and significance thresholds at entry and exit were set at 0.10 and 0.05, respectively. For clinically significant predictor variables, 95% confidence intervals for the hazard were computed.

Results
A total of 44,862 patients (mean age: 60.9 yr; 70.3% male) in the database met the inclusion criteria (table 1). Of this group, 43,921 patients (97.9%) did not develop a second primary during a mean follow-up of 43.9 months, whereas the remaining 941 patients (2.1%) did develop a second head and neck primary during a mean follow-up of 42.2 months; the difference in the mean length of follow-up was not statistically significant ($p = 0.113$, Student's t test).

The results of univariate statistical analysis suggest that each of the clinical variables may indeed have had some predictive value in assessing the risk of a second primary malignancy (table 2). The Kaplan-Meier hazard rate for development of a second primary continued to increase almost linearly with increasing follow-up (survival) from the time of the first primary and continued beyond 10 years of follow-up (figure).

Factors associated with a higher risk. The results of the Cox proportional hazards analysis revealed that several factors did indeed confer a significantly greater risk of developing a second primary (table 3). Among these was the location of the first primary in the larynx/hypopharynx (hazard ratio [HR]: 7.919), the oropharynx (HR: 5.951), a

Table 1. Distribution of primary sites among the entire study population

<table>
<thead>
<tr>
<th>Site of first primary</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>18,631</td>
</tr>
<tr>
<td>Larynx/hypopharynx</td>
<td>14,346</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>4,122</td>
</tr>
<tr>
<td>Major salivary gland</td>
<td>3,335</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>2,399</td>
</tr>
<tr>
<td>Nose, nasal cavity, and middle ear</td>
<td>2,029</td>
</tr>
<tr>
<td>Total</td>
<td>44,862</td>
</tr>
</tbody>
</table>

Table 2. Comparison of clinical variables and univariate statistics

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>No second primary (n = 43,921)</th>
<th>Second primary (n = 941)</th>
<th>Univariate significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>60.9</td>
<td>62.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>70.4</td>
<td>67.7</td>
<td>0.077</td>
</tr>
<tr>
<td>Mean size of the first primary (cm)</td>
<td>2.8</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of nodal disease (%)</td>
<td>39.3</td>
<td>23.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tx w/cancer-directed surgery (%)</td>
<td>63.4</td>
<td>77.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tx w/radiation therapy (%)</td>
<td>61.8</td>
<td>46.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
major salivary gland (HR: 3.861), or the nasopharynx (HR: 2.073). Another risk factor was greater age at diagnosis of the index primary (HR: 1.012), although this association was weak.

Factors associated with a lower risk. A lower risk of a second primary was associated with treatment of the first primary with radiation therapy (HR: 0.777) and with the presence of nodal disease at presentation of the first primary (HR: 0.955), although the latter association was statistically weak.

Factors not associated with risk. Sex, the size of the first primary tumor, a first-primary site in the oral cavity, and treatment of the first primary with cancer-directed surgery had no influence on the risk of a second primary.

Discussion
Despite advances in radiation therapy, chemotherapy, and reconstructive methods, overall survival for head and neck cancer patients has not improved dramatically during the past 20 years. The increased risk for the development of a second primary in the head and neck among patients who have already undergone successful treatment of a first primary head and neck cancer is related to factors such as “field cancerization” and continued tobacco and alcohol use.

Follow-up of head and neck cancer patients is often scheduled for set intervals and may continue well beyond 5 years after diagnosis and treatment of the first primary cancer. However, such follow-up is time-consuming and expensive. In fact, the need for rigorous follow-up has been the topic of debate in the literature. For example, Haughey et al used the results of their meta-analysis to make a pointed case for an endoscopic screening protocol to promote early detection of second tumors in head and neck cancer patients.

Table 3. Results of multivariate Cox regression analysis for the development of a second primary

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Multivariate significance (p)</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables included in the model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>1.012</td>
<td>1.007 to 1.107</td>
</tr>
<tr>
<td>Presence of nodal disease</td>
<td>0.090</td>
<td>0.955</td>
<td>0.905 to 1.007</td>
</tr>
<tr>
<td>Tx w/radiation therapy</td>
<td>0.002</td>
<td>0.777</td>
<td>0.664 to 0.910</td>
</tr>
<tr>
<td>Nasopharyngeal primary</td>
<td>0.039</td>
<td>2.073</td>
<td>1.036 to 4.147</td>
</tr>
<tr>
<td>Oral cavity primary</td>
<td>0.095</td>
<td>0.971</td>
<td>0.378 to 2.491</td>
</tr>
<tr>
<td>Oropharyngeal primary</td>
<td>&lt;0.001</td>
<td>5.951</td>
<td>3.611 to 9.808</td>
</tr>
<tr>
<td>Laryngeal/hypopharyngeal primary</td>
<td>&lt;0.001</td>
<td>7.919</td>
<td>4.639 to 13.518</td>
</tr>
<tr>
<td>Major salivary gland primary</td>
<td>&lt;0.001</td>
<td>3.861</td>
<td>2.320 to 6.425</td>
</tr>
</tbody>
</table>

| Variables not included in the model     |                               |              |                         |
| Sex                                     | 0.471                         | 0.948        | 0.819 to 1.097          |
| Size of the first primary               | 0.985                         | 1.000        | 0.996 to 1.004          |
| Tx w/cancer-directed surgery            | 0.455                         | 1.078        | 0.885 to 1.315          |

Figure. Graph tracks the percentage of patients who developed a second primary during 13 years of follow-up.
neck cancer. \(^{15}\) Other authors have recommended less intense follow-up, with the frequency of clinic visits guided by patients’ symptoms. \(^{16}\)

A better strategy would be to base follow-up on the presence or absence of each patient’s risk factors for developing a second malignancy. Patients at high risk for a second primary could then be followed more closely than patients deemed to be at low risk. Implementation of such a strategy would require reliable data on pertinent risk factors. Obviously, risk stratification would need to be undertaken for an individual patient at the time of the diagnosis of the first primary in order to prospectively program subsequent follow-up.

Factors associated with a higher risk. In the study described herein, it is not surprising that first primaries located in the larynx/hypopharynx and in the oropharynx were associated with a higher risk for a second primary. Both hazard ratios were rather high—7.919 and 5.951, respectively. This finding is very much in concert with the theory of field cancerization or “condemned mucosa,” which was popularized by Slaughter et al. \(^{17}\) Patients who develop primary malignancies at these sites are likely to experience local field changes beyond the area of surgical excision and/or radiation therapy, and these changes may subsequently mature into mucosal malignancy.

The significantly higher hazard ratio for laryngeal/hypopharyngeal first primaries is especially worth noting. The most abundant data regarding the incidence of second neoplasms in head and neck cancer specifically relate to patients with a laryngeal index primary. \(^{3,18}\) Higher rates of a second primary malignancy (4.8 to 8.2% higher) in patients with a laryngeal first primary have been reported by others, including Nikolaou et al. \(^{3}\) Yamamoto et al, in a large study of the site-dependent specificity of second primary tumors, identified the larynx and the oropharynx as the index primary sites most likely to be associated with a second primary. \(^{3}\)

Quite often, the second primary will appear in the respiratory tract, usually the lung. \(^{15,19}\) The present study did not examine the risk of second primaries outside of the head and neck because the study’s focus was on otolaryngology, and therefore follow-up of esophageal and lung second primaries was outside the scope of this study. Nonetheless, it is extremely important to remember that there is a risk for a second primary in the esophagus (most often after a pharyngeal first primary) and in the lung.

In the present study, it was somewhat surprising that patients with a salivary gland first primary were also more likely to develop a second primary; the reason for this is not intuitively clear, and this finding may merit further study. Less of a surprise was the association between increased risk and nasopharyngeal carcinoma. Smoking is a well-known risk factor for both nasopharyngeal carcinoma and the development of a second primary. \(^{20}\) Still, the hazard ratio for nasopharyngeal carcinoma was relatively small (2.073), a finding that is consistent with those of previous studies. \(^{2}\) Nevertheless, patients with nasopharyngeal carcinoma should be followed closely.

Factors associated with a lower risk. The apparent protective effect of radiation therapy may be attributable to the fact that irradiation treats not only the site of the first primary, but it “pretreats” adjacent areas of field cancerization, thereby preventing many second primaries.

The lower risk associated with the presence of nodal disease is more difficult to understand. It is possible that patients with nodal disease received irradiation over a wider area and therefore received a similar benefit in adjacent mucosal areas.

Duration of increased risk. In one of the larger published series with adequate follow-up of head and neck cancer patients, Leon et al reported that the risk of a second neoplasm is approximately 4% per year, and this risk persists well beyond 5 years after the index diagnosis. \(^{21}\) The results of the present study reinforce the continuation of the extended risk. The percentage of second primary tumors encountered in the present study (2.1%) is slightly lower than that reported in the literature because this study did not include patients who had two or more subsequent head and neck second primaries. And again, the present study also excluded patients whose second primary neoplasms arose in the esophagus, lung, and elsewhere outside the head and neck.

Other predictors. Other investigators have attempted to use other biologic markers to determine the relative risk of a second head and neck primary. For example, Schantz et al demonstrated that sensitivity to chromatid breaks of lymphocytes treated with bleomycin was one such marker. \(^{22}\) Shin et al showed that p53 was not a reliable marker. \(^{23}\) Currently, most marker studies are experimental and cannot be easily applied to most humans with head and neck cancer, but they may hold some promise in the future.

One potential drawback to the present study is that data were not available regarding the history of tobacco and alcohol use leading up to the index primary or during the interval between primaries. It is well known that continued smoking and alcohol use significantly elevate the risk for a second primary malignancy within the head and neck. \(^{2}\) Certainly, data on these social habits would be useful in determining the need for closer clinical follow-up of patients diagnosed with a first head and neck primary. The predictor variables analyzed in this study were those that were available to the otolaryngologist immediately following the diagnosis and treatment of the first primary, and they are therefore fixed. Smoking and alcohol intake are modifiable (and in head and neck cancer patients, often continuously changing) risk factors for the development of a second primary, and they should be reassessed at regularly scheduled intervals during follow-up. Because these social habits are so variable during follow-up, it is difficult to include them in any predictive model. However, they should not be ignored.
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References

References