Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world with squamous cell carcinoma (SCC) being the most common type affecting the head and neck region (1). Recent advances in diagnostic and multimodal management of Head and Neck Squamous Cell Carcinoma (HNSCC) has resulted in better locoregional control and lower recurrence rates. However, survival outcomes have not demonstrated significant improvements (1-4). This may be attributable to patients with HNSCC being at an increased risk of developing a second primary malignancy.
Epidemiological risk factors such as tobacco and alcohol use, genetic susceptibility and/or the choice of different treatment modalities may account for SPM (1). Risk factors associated with HNSCC include tobacco and alcohol use, human papilloma virus (HPV) and Epstein-Barr virus (EBV) in oropharyngeal cancer and nasopharyngeal cancer (6-8).

The literature reported that the overall survival rate in this patient population continues to be adversely affected by SPM regardless of its location. The role of panendoscopy as a screening tool is pivotal in the early detection of SPM and subsequent treatment with curative intent. Nevertheless, this clinical entity still portends to poorer overall survival despite the substantial improvement in disease free survival rate (1,3,4).

In this study, we report the incidence of SPM (synchronous and metachronous) in HNSCC patients and association between the epidemiological risk factors and the survival outcomes.

**Methods**

We analyzed 790 patients with HNSCCs recorded in the Ear Nose and Throat (ENT) Microsoft Access database at the ENT Department at Fremantle Hospital, Western Australia, between 1993 and May 2011. All patients with cancer who received services through the Department were recorded in this Database, which included the pathology, treatment and follow-up.

The data was extracted into Microsoft Excel for screening and preliminary analysis, and subsequently imported into Statistical Package for Social Sciences (SPSS) version 14 (IBM Corporation, New York, USA) for analysis. Descriptive statistics and Kaplan Meier survival analysis were used as appropriate, and a P value of 0.05 was considered statistically significant. Sites were classified according to Table 1 using free text descriptions and The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) morphology codes included.
and Neck Oncology Database (see Table 2 for Morphology Codes included) (9). Cases were deemed as synchronous, metachronous or metastases based on the Warren and Gates (10) criteria, which was modified by Hong et al. (11,12). Classification for synchronous, i.e., multiple primary HNSCC required (I) each neoplasm to be geographically distinct (separated by normal tissue), and (II) the possibility that the second primary represents a metastasis, or a local relapse must be excluded. A second primary must be separated by at least 2 cm of normal epithelium or occur at least 3 years after the first diagnosis. Any new lung tumor must be solitary and histologically distinct from the first, unless it occurred 3 or more years later. Synchronous carcinomas are second neoplasms occurring at the same time or within a 6-month period of the primary lesion. After this period, they are considered metachronous neoplasms.

For those whose inclusion criteria were met, the demographic data was analyzed, including smoking history (pack-years), smoking status, alcohol consumption (classified by the clinician as never/seldom/social/heavy/not stated), tumor sites, metastases, Tumor, Node, Metastasis (TNM) classification, treatment type (surgical/chemotherapy/radiotherapy/combination/palliative/none), follow-up period and death.

## Results

There were a total of 790 patients, with the age ranging from 15 to 111 (median = 67) years old. There were 600 (75.9%) males and 190 (24.1%) females. Morphology codes M8070/2, M8070/3, M8071/3 and M8075/3 were the cancer types within the population selected (see Table 2).

Of the 790 patients, 442 (55.9%) were smokers, and 281 (35.6%) had a 61–70 pack-year smoking history (see Table 3). There were 291 (36.8%) patients who had a smoking history of over 50 pack-years. Additionally, 334 (42.3%) quit smoking for 5 years or less and 72 (9.1%) quit smoking for more than 10 years, while 5 patients (0.6%) quit smoking after their diagnosis. There were 325 (41.1%) patients who had a history of alcohol use: 20.8% (n=164) were social drinkers and 14.1% (n=111) were heavy drinkers (see Table 3).

Lip and oral cavity primaries comprised the majority (n=299, 37.8%), followed by oropharynx (n=222, 28.1%), larynx (n=209, 26.5%), major salivary glands (n=26, 3.3%), nasal cavity and paranasal sinuses (n=11, 1.4%), nasopharynx (n=9, 1.1%), pharynx (n=8, 1.0%) and hypopharynx (n=6, 0.8%)—see Table 4.

In terms of TNM classification, 155 (19.7%) were T1, 190 (24%) were T2, 115 (14.6%) were T3, and 107 (13.5%) were T4. Of the N staging, 297 (37.6%) were...
N0, 91 (11.5%) were N1, 162 (20.5%) were N2, and 19 (2.4%) were N3. Only 23 (2.9%) had metastatic disease at diagnosis, with chest being the most common site (n=10, 1.3%), followed by liver (n=4, 0.5%) and skeletal system (n=2, 0.3%). Eight patients had a second metastatic site: chest (n=3, 0.4%), skeletal system (n=2, 0.3%), liver (n=1, 0.1%), spine (n=1) and other (n=1).

Primary treatment comprised of: surgery (n=244, 30.9%), surgery plus radiotherapy (n=150, 19.0%), chemotherapy only (n=77, 9.7%), surgery plus chemotherapy (n=59, 7.5%), surgery plus chemo-radiotherapy (n=59), radiotherapy only (n=58, 7.3%), chemo-radiotherapy (n=51, 6.5%) and palliative treatment (n=17, 2.2%). Seventy-five (9.5%) patients declined to receive any of the treatment modalities.

Synchronous tumor was found in 29 (3.7%) patients: lung (n=9, 1.1%), larynx (n=5, 0.6%), lip and oral cavity (n=5, 0.6%), oropharynx (n=2, 0.3%), and other sites (n=7, 0.9%)—see Table 5. One was not stated. The TNM staging was: T1 (n=2), T2 (n=5), and T3 (n=1); N0 (n=5), N1 (n=1), and N2 (n=1) (N staging was not documented in one). Of the patients with synchronous tumor, 18 (62.1%) were deceased at the end of the follow-up period (see Table 6).

Fifteen patients (2.3%) had documented metachronous tumor: oropharynx (n=5, 0.6%), lip and oral cavity (n=4, 0.5%), larynx (n=3, 0.4%), lung (n=2, 0.3%), and other sites (n=4, 0.5%)—see Table 5. The recorded T staging was T2 (n=6) and T3 (n=2). Of the patients with metachronous tumor, six patients (33.3%) had deceased tumors at the end of the follow-up period (see Table 6).

The median follow-up period was 25 (range, 0–177) months: 178 (22.5%) were deceased at the end of the follow up period, leading the possibility of attrition bias. Of the 746 patients without synchronous or metachronous HNSCC, 154 (19.5%) were deceased at the end of the follow up period (see Table 6). The overall survival was much poorer in the synchronous group than the metachronous and HNSCC without SPM groups (P<0.05) but there was no significant difference between the metachronous and HNSCC with SPM groups (P<0.2).

**Discussion**

In the era of rapid advancements in diagnostic and therapeutic management for HNSCC, and with better detection and locoregional control rates, the overall survival rate has not experienced significant improvement (1,13). Similar studies have shown that the incidence of synchronous and metachronous carcinoma ranges from

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Table 4: Primary tumor site, whether synchronous or metachronous head and neck squamous cell carcinoma was present

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Synchronous tumor</th>
<th>Metachronous tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Unable to determine</td>
</tr>
<tr>
<td>Lip &amp; oral cavity</td>
<td>299</td>
<td>37.8</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>222</td>
<td>28.1</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td>Pharynx, other</td>
<td>209</td>
<td>26.5</td>
</tr>
<tr>
<td>Nasal cavity &amp; paranasal sinuses</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td>Major salivary glands</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td>Uncertain: inadequate information in database.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>790</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 5: n: total number of patients. %: percentage. Not Present: not present or tumor is a local relapse (i.e., same histology in a site within 2 cm). Present: as per definitions of synchronous and metachronous in introduction. Unable to determine: database had missing fields for date of diagnosis, deceased date (if deceased) or last contact. Uncertain: inadequate information in database.
Table 5 Location of synchronous and metachronous tumor in relation to primary site of head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Lip &amp; oral cavity</th>
<th>Oropharynx</th>
<th>Larynx</th>
<th>Lung</th>
<th>Other*^</th>
<th>Not stated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sync</td>
<td>Meta</td>
<td>Sync</td>
<td>Meta</td>
<td>Sync</td>
<td>Meta</td>
<td>Sync</td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lip &amp; oral cavity</td>
<td>4</td>
<td>0.5</td>
<td>2</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Larynx</td>
<td>1</td>
<td>0.1</td>
<td>1</td>
<td>0.1</td>
<td>1</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td>Nasal cavity &amp; paranasal sinuses</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total                          | 5      | 0.6  | 4      | 0.5  | 2      | 0.3  | 5      | 0.6  | 9      | 1.1  | 2      | 0.3  | 7      | 0.9  | 4      | 0.5  | 1      | 0.1  | 0      | 0    | 29     | 3.7  | 18     | 2.3  

Syr, synchronous tumor; Meta, metachronous tumor; n, total number of patients. %, percentage. *, other synchronous site: neck [3], rectum [2], scalp [1], submandibular [1], chest [1], lymph nodes [1], and cerebral [1]. ^, other metachronous site: rectum [2], esophagus [1], mandible [1], lymph nodes [1], post-auricular [1], and cerebral [1].

Table 6 Treatment provided and deceased at end of follow-up for patients with synchronous and metachronous head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Primary treatment</th>
<th>Total</th>
<th>Without synchronous or metachronous</th>
<th>Synchronous tumor</th>
<th>Metachronous tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% DCD</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Surgical</td>
<td>244</td>
<td>30.9</td>
<td>35</td>
<td>4.4</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>77</td>
<td>9.7</td>
<td>18</td>
<td>2.3</td>
</tr>
<tr>
<td>Radiation only</td>
<td>58</td>
<td>7.3</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Chemo-radiotherapy</td>
<td>51</td>
<td>6.5</td>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td>Surgery plus radiotherapy*</td>
<td>150</td>
<td>19.0</td>
<td>47</td>
<td>5.9</td>
</tr>
<tr>
<td>Surgery plus chemotherapy*</td>
<td>59</td>
<td>7.5</td>
<td>15</td>
<td>1.9</td>
</tr>
<tr>
<td>Surgery plus chemo-radiotherapy*</td>
<td>59</td>
<td>7.5</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Palliative</td>
<td>17</td>
<td>2.2</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td>No treatment</td>
<td>75</td>
<td>9.5</td>
<td>17</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td>790</td>
<td>100.0</td>
<td>178</td>
<td>22.5</td>
</tr>
</tbody>
</table>

*, includes pre-operative and post-operative, but excludes palliative; **, percentage relating to the total number of patients in that sub-category. n, total number of patients; DCD, deceased. Without synchronous or metachronous: includes not confirmed as synchronous or metachronous.
8% to 21%, showing that its presence is a poor prognostic factor with a subsequently poor overall survival rate (1,4,13,14).

In 2009, over 3,800 new cases of HNC were diagnosed in Australia, comprising approximately 3.3% of Australia's 114,137 total new cancer diagnoses that year (15,16). In Australia, lip, oral cavity and pharynx cancers resulted in 763 deaths in 2010 (15). This is comparable to a projected total of 35,540 new oral cavity and pharynx cases and 1,529,560 total new cancer cases (approximately 2.3%) in the United States in 2010 (17). Oral cavity and pharynx related deaths in the United States were predicted to be approximately 1.4% of all cancer related deaths in 2010 (17), with SCC arising from oral mucosal lining accounting for over 90% of tumors (18-20).

Over an 18-year period, 790 new cases of HNSCC were identified at our institution or approximately 44 new cases per year. Annual Australian incidence of new HNC is over 3,800 per year (3.3%) (15,16).

Excluding skin cancers, world-wide, cancer of the mouth and pharynx have been ranked between fifth and sixth overall in the world (behind lung, stomach, breast, colon and rectum, and cervix/corpus uteri), and is the sixth leading cause of cancer mortality (21-23). In developed countries, men are affected two to three times as often as women, possibly due to higher use of alcohol and tobacco.

Our study revealed 5.9% (44 patients) patients developed SPM (29 with synchronous, and 15 with metachronous tumor) within a median follow-up period of 25 months.

Researchers looking at risk of SPM following HNC (24,25) have reported 1.3% of patients (1,294) developing a SPM within a mean 4.9-year follow-up period. This exceeded their expected number of 115.75, and cumulative risk was 36%. However, meta-analysis (26) has found an overall SPM prevalence of 14.2%, with the majority being metachronous and oral cavity. Our findings fall within expected limits for SPM occurrence. Our results revealed a higher occurrence of synchronous (3.7%), rather than metachronous (2.3%) malignancy. Time to diagnosis (early or late) and TNM classification, may impact on the synchronous and metachronous proportions.

Warren and Gates [1932] looked at 1,259 cases of multiple primary tumors arising from unrelated sites (of which 40 were their own cases), and calculated multiple malignancy to be 3.9% of all cancer cases (10). These figures have remained stable over time.

Pooled studies have looked at the risk of SPM following a primary HNC (oral cavity, pharynx and larynx) and the risk of HNC as a SPM. A review of 13 cancer registries from Europe, Canada, Australia and Singapore between 1943 and 2000 noted a total of 99,257 patients (74,988 men and 24,269 women; median age 63) had a first primary HNC (15,985 tongue, 22,378 mouth, 20,758 pharyngeal and 40,190 laryngeal cancer) who contributed 489,855 person-years of follow-up (mean follow-up time: 4.9 years) (24). During the follow-up period, 1,294 of these patients (1.3%) were diagnosed with second HNC at a different site (342 tongue, 345 mouth, 418 pharynx and 189 larynx) compared to an expected 115.75 (24,25). The 20-year cumulative risk was 36% (25).

Furthermore, a meta-analysis of the Washington University Department of Otolaryngology Head and Neck Tumor Registry and 24 studies reported an overall SPM prevalence of 14.2% in 40,287 patients (26). Most tumors were metachronous, with oral cavity tumors having the highest rate of SPM.

The risk of developing synchronous and metachronous HNSCC is well correlated with tobacco and alcohol use (2,15,16,27), and this relationship is dose-dependent (28-31). Leon et al. found that the risk of developing a SPM was doubled in patients who used tobacco and alcohol, compared to non-users (2). In patients with tumors related to tobacco and alcohol use (oral cavity, oropharynx and larynx), 80% of SPM occurred in the oral cavity, oropharynx and larynx (2,28). This was less than 50% for non-alcohol or tobacco users.

Leon reported that (2,28) among never alcohol-users, cigarette smoking was associated with an increased risk of HNC and this was dose and exposure dependent (pack-years). Furthermore, in never tobacco-users, high-frequency alcohol consumption was associated with increased risks of cancers of the oropharynx, hypopharynx and larynx only.

Our findings also support the phenomenon that patients with HNSCC are at increased risk for the development of SPM. Although, the patterns were consistent with malignancies related to smoking and alcohol, our statistical analysis was limited and dependent on the accuracy of the patient records. In terms of tobacco use, 55.9% of patients reported tobacco use, 9.2% did not, while 34.8% was undeterminable. Similarly, for alcohol, 41.1% reported alcohol use, 7.3% did not, while 51.1% was undeterminable. Of determinable use, 37.2% reported both and 1.8% reported neither. These results support the phenomenon that patients with HNSCC are at an increased risk for developing a SPM. However, due to the retrospective nature of the study, the missing data may affect the final
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Primary tumors of the lip and oral cavity were most common (37.8%) and these most commonly recurred as synchronous and metachronous tumors again in the lip and oral cavity. While only 1.8% of patients reported neither tobacco nor alcohol use, our findings support previous research that HNC relating to tobacco and alcohol use have SPM pertaining to the oral cavity (2,28). This is due to the chronic and accumulative toxic insult to the oral mucosa by the tobacco and alcohol use. Those patients who continued to smoke after the diagnosis of the HNSCC with SPM had poorer overall survival rates.

Due to both the rate of SPC and the majority of synchronous and metachronous tumors occurring in the oral cavity, oropharynx, larynx and lung, clinical attention must focus on prevention. Once malignancy is established, the focus must shift to regular surveillance. Patient education on smoking and alcohol cessation may reduce incidence of multiple primaries.

Limitations of this study include that being a retrospective analysis, while data was screened; there were limitations on information captured. The data was dependent on the accuracy of personnel entering the data, which resulted in incomplete and omitted fields. Patients with multiple or important omissions were excluded from analysis. The ENT Database may not include all patients that presented to our institution. Unfortunately, there was missing data for tobacco and alcohol use which reduced the strength of association and the deductions that could be made. Some fields were predetermined. For example, pack years could be calculated, however alcohol use was recorded subjectively (e.g., socially vs. heavily), which depends on the honesty of the patient and interpretation of the clinician collecting the data.

While this study found a lower rate of SPM in patients with HNSCC than some other studies, there is a clear association between smoking and the development of HNSCC. Fatality in patient with HNSCC is high and the development of a SPM has a higher fatality than without. Once malignancy is established, the focus must shift to regular surveillance. Given the anatomical location of HNSCC and SPC, prevention and early treatment of SPC will impact on a patient’s quality of life. Patient education on smoking and alcohol cessation may reduce incidence of multiple primaries. While this study did not look at the role of viruses (such as HPV and EBV) in the development of HNSCC, growing research supports this association, and future data collection could include DNA testing for such viruses.

**Conclusions**

This retrospective study demonstrates that the SPM occurred at the rate of 5.9% and that there is a clear association between tobacco and alcohol use with the development of HNSCC with SPM. In our patient population, 3.7% developed synchronous and 2.3% metachronous malignancy. Metachronous malignancy was associated with much poorer overall survival rate. This study contributes to the literature in that it strengthens the notion that public health efforts should target alcohol and smoking cessation in Australia, and that our study specifies specific malignancies that patients are at risk for.

**Acknowledgements**

None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This study was exempt from the Fremantle Hospital ethical review board due to the negligible risk on collections of non-identifiable data.

**References**


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