Secondary Salivary Gland Malignancy in Thyroid Cancer: A United States Population Based Study

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Abstract

Background: There is an increased risk of second primary malignancies with thyroid cancer. However, the risk and characters of secondary salivary gland malignancy (sSGM) in patients with thyroid cancer have not been evaluated before.

Methods: We used the Surveillance Epidemiology and End Results (SEER) 18 registry to identify thyroid cancer patients from 1973 to 2014. We then calculated the risk of sSGM using standardized incidence ratio and excess risk. Separately, all cases of primary salivary gland malignancy (pSGM) diagnosed between 1973 - 2014 were extracted from the SEER 18 registry, and their characteristics compared with sSGM using independent samples t-test for continuous variables and Chi-square tests for categorical variables.

Results: There were a total of 68,339 cases of primary thyroid cancer. Of these, 18 patients developed sSGM with the observed to expected ratio being 3.58 (95% CI: 2.12 to 5.65; P < 0.05) and excess risk being 0.48 per 10,000 population. The incidence of sSGM remained higher between 6 months to 10 years from the time of diagnosis of thyroid carcinoma. The risk of developing sSGM was significantly higher if they were below 60 years of age (O/E: 4.51; 95% CI: 2.33 - 7.88; P < 0.05), were females (O/E: 4.91; 95% CI: 2.80 - 7.97; P < 0.05), were whites (O/E: 3.04; 95% CI: 1.62 - 5.19; P < 0.05), had well-differentiated thyroid carcinoma (O/E: 9.70; 95% CI: 3.90 - 19.98; P < 0.05) or were treated with radioactive iodine (O/E: 5.26; 95% CI: 2.72 - 9.19; P < 0.05). While the proportion of females developing sSGM was significantly greater than those developing pSGM (88.9% vs. 44%; P < 0.05), there was no statistical difference between pSGM and sSGM in terms of the age at diagnosis, the proportion of patients diagnosed before 60 years of age, anatomic site of origin or the histological grade of tumor.

Conclusions: Patients with thyroid cancers are at an increased risk of developing sSGM than the general population. This risk is greater if the person is below 60 years of age, female, white, with well-differentiated thyroid carcinoma or is treated with radioactive iodine.

Keywords: Salivary gland malignancy; Thyroid cancer; Second primary malignancy; SEER database

Introduction

Salivary gland tumors are heterogeneous group of uncommon tumors. They are predominantly benign. Malignant tumors of salivary gland comprise less than 1% of all cancers of head and neck [1]. Salivary gland malignancy (SGM) may occur as a primary malignancy or as a second malignancy in people with prior history of other neoplasms. Increased risk of SGM in people with benign salivary gland tumors, Hodgkin’s lymphoma, medulloblastoma and basal cell carcinoma has been reported [2-5]. This may be related to the genetic predisposition to malignancy or to the associated treatments like radiation exposure. The risk and characters of such secondary salivary gland malignancy (sSGM) in patients with primary thyroid cancer has, however, not been evaluated before. In the present study, we used the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database of well-differentiated thyroid cancer (WTC) patients to determine the risk of sSGM compared to general population.

Methods

We identified all cases of WTC diagnosed between 1973 - 2014 from the SEER 18 registry using the following International Classification of Disease for Oncology, 3rd edition (ICD-O-3) codes: 8330/3, 8331/3, 8332/3, 8335/3, 8340/3, 8341/3, 8342/3, 8343/3 and 8344/3. We excluded cases diagnosed at autopsy and those lost to follow-up. Using the Warren and Gates criteria as modified by National Cancer Institute, sSGM was defined as a metachronous salivary gland malignancy developing at least 6 months after the diagnosis of WTC [6, 7]. Patients were followed up from the time of diagnosis of WTC to the date of last known vital status, death or the last point of data collection. We used multiple primary standardized inci-
dence ratio session of the SEER*Stat software (version 8.3.4 - March 23, 2017) to calculate standardized incidence ratio (SIR) and excess risk (ER) of sSGM for WTC patients. Confidence intervals and P-values were calculated using Poisson exact methods for the ratio of observed to expected events. Separately, all cases of primary salivary gland malignancy (pSGM) diagnosed between 1973 - 2014 were extracted from the SEER 18 registry using the following International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) codes: C07.9, C08.0, C08.1, C08.8 and C08.9. The different characteristics between pSGM and sSGM were compared using independent samples t-test for continuous variables and Chi-square tests for categorical variables.

Results

There were a total of 68,339 patients with primary WTC in SEER 18 registries. Of these, 18 patients developed sSGM with the observed to expected ratio (O/E) being 3.58 (95% CI: 2.12 to 5.65; P < 0.05) and excess risk (ER) being 0.48 per 10,000 population (Table 1). The median age at diagnosis for sSGM was 55 years (range 22 - 81 years) with a median latency period of 39.5 months (range 5 - 97 months) from the time of diagnosis of thyroid cancer. The incidence of sSGM remained higher between 6 months to 10 years from the time of diagnosis of thyroid cancer.

The risk of developing sSGM in those with primary thyroid carcinoma as compared to those without primary thyroid carcinoma was significantly higher among the patients below 60 years of age with an O/E of 4.51 (95% CI: 2.33 - 7.88; P < 0.05) and ER of 0.44 per 10,000 population. Similarly, the risk was higher among females (O/E: 4.91; 95% CI: 2.80 - 7.97; P < 0.05) and whites (O/E: 3.04; 95% CI: 1.62 - 5.19; P < 0.05). Furthermore, among the patients with well-differentiated thyroid carcinoma or among those treated with radioactive iodine (RAI), the incidence of sSGM was higher as compared to those

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**Table 1. Secondary Salivary Gland Malignancy in Patients With Thyroid Cancer**

|                          | Secondary salivary malignancy |          |          |          |
|--------------------------|-------------------------------|----------|----------|----------|
|                          | Observed | O/E          | 95% CI of O/E | Excess risk |
| Total Cases              | 18       | 3.58         | 2.12 - 5.65 | 0.48       |
| Age                      |          |              |          |          |
| < 60 years               | 12       | 4.51         | 2.33 - 7.88 | 0.44       |
| ≥ 60 years               | 6        | 2.53         | 0.93 - 5.50 | 0.64       |
| Gender                   |          |              |          |          |
| Male                     | 2        | 1.13         | 0.14 - 4.07 | 0.04       |
| Female                   | 16       | 4.91         | 2.80 - 7.97 | 0.59       |
| Race                     |          |              |          |          |
| White                    | 13       | 3.04         | 1.62 - 5.19 | 0.39       |
| Black                    | 2        | 5.20         | 0.63 - 18.79| 0.70       |
| Asian or Pacific Islander| 3        | 9.38         | 1.93 - 27.41| 1.18       |
| Grade of thyroid malignancy |          |              |          |          |
| I - well differentiated   | 7        | 9.70         | 3.90 - 19.98| 1.56       |
| II - moderately differentiated | 0       | 0.00         | 0.00 - 19.54| -0.20      |
| III - poorly differentiated| 1      | 14.52        | 0.37 - 80.88 | 3.56      |
| IV - undifferentiated     | 0        | 0.00         | 0.00 - 636.06| -0.24     |
| Unknown                  | 10       | 2.47         | 1.18 - 4.54 | 0.27       |
| Radioactive iodine therapy |          |              |          |          |
| No RAI                   | 6        | 2.18         | 0.80 - 4.74 | 0.23       |
| RAI                      | 12       | 5.26         | 2.72 - 9.19 | 0.76       |
| Latency period           |          |              |          |          |
| 2 - 5 months             | 1        | 3.94         | 0.10 - 21.97| 0.49       |
| 6 - 11 months            | 3        | 8.25         | 1.70 - 24.10| 1.21       |
| 12 - 59 months           | 9        | 3.82         | 1.75 - 7.25 | 0.50       |
| 60 - 119 months          | 5        | 3.11         | 1.01 - 7.25 | 0.42       |
| 120+ months              | 0        | 0.00         | 0.00 - 8.18 | -0.22      |

CI: confidence interval; O/E: observed to expected ratio; RAI: radioactive iodine.
without primary thyroid carcinoma with O/E of 9.70 (95% CI: 3.90 - 19.98; P < 0.05) and 5.26 (95% CI: 2.72 - 9.19; P < 0.05) respectively.

There were also 19,008 cases of pSGM in the registry. There was no difference in the mean age at diagnosis (59.80 ± 18.361 vs. 53.28 ± 16.634; P = 0.132) or the proportion of patients below 60 years of age (45.3% vs. 66.7%; P = 0.07) in the pSGM and sSGM groups (Table 2). There were a greater proportion of females developing sSGM than pSGM (88.9% vs. 46.1%; P < 0.05). There was, however, no difference in the proportion of different races developing pSGM and sSGM. There was also no difference between the primary and secondary salivary gland malignancies (SGM) in either the proportion of the salivary gland involved or the grading of the tumor.

### Discussion

Thyroid cancer is the most common endocrine malignancy with an increasing incidence over the last few decades [8, 9]. It is a malignancy of the relatively young, the median age at diagnosis being 46 years [10]. More than 90% of thyroid cancers are of well-differentiated variety consisting of papillary carcinoma and follicular carcinoma, and the 10-year survival rate is estimated to be more than 90% with appropriate treatment [11-13]. This combination of young age at diagnosis and favorable prognosis leads to an increased incidence of subsequent secondary malignancies. Several studies have estimated the incidence of second primary malignancy in thyroid cancer to be 7-8% [14, 15]. This has been attributed to the genetic predisposition to malignancy and associated treatments like RAI or radiation therapy [16-18].

Malignant salivary gland tumors are rare, and comprise less than 1% of all cancers of head and neck [1]. The annual incidence of malignant tumors of major salivary glands varies between slightly greater than 0.05 and less than 2 per 100,000 [19]. The incidence, however, has been increasing in recent years in United States [20]. They tend to vary considerably in their anatomic site of origin and histology. Most of the SGM are adenocarcinomas of the parotid gland [1].

### Table 2. Characteristics of Primary and Secondary Salivary Gland Malignancy

| Primary Salivary Malignancy | Secondary Salivary Malignancy |
|----------------------------|-----------------------------|
| n | % | n | % |
|---|---|---|---|
| Total cases | 19,008 | - | 18 | |
| Age at diagnosis | 59.80 ± 18.361 | 53.28 ± 16.634 | P = 0.132 |
| Age group |  |  |  |  |
| < 60 years | 8,615 | 45.3% | 12 | 66.7% |
| ≥ 60 years | 10,393 | 54.7% | 6 | 33.3% |
| Gender |  |  |  |  |
| Male | 10,240 | 53.9% | 2 | 11.1% |
| Female | 8,768 | 46.1% | 16 | 88.9% |
| Race |  |  |  |  |
| White | 15,630 | 82.2% | 13 | 72.2% |
| Black | 1,656 | 8.7% | 2 | 11.1% |
| Other | 1,486 | 7.8% | 3 | 16.7% |
| Unknown | 236 | 1.2% | 0 | 0% |
| Primary site |  |  |  |  |
| C07.9 - parotid gland | 15,134 | 79.6% | 17 | 94.4% |
| C08.0 - submandibular gland | 2,845 | 15% | 0 | 0% |
| C08.1 - sublingual gland | 184 | 1.0% | 0 | 0% |
| C08.8 - overlapping lesion of major salivary glands | 20 | 0.1% | 0 | 0% |
| C08.9 - major salivary gland, NOS | 825 | 4.3% | 1 | 5.6% |
| Grade of salivary cancer |  |  |  |  |
| I - well differentiated | 1,733 | 9.1% | 4 | 22.2% |
| II - moderately differentiated | 3,337 | 17.5% | 5 | 27.8% |
| III - poorly differentiated | 3,322 | 17.5% | 1 | 5.6% |
| IV - undifferentiated | 1,487 | 7.9% | 0 | 0% |
| Unknown | 9,129 | 48% | 8 | 44.4% |

It is a malignancy of the relatively young, the median age at diagnosis being 46 years [10]. More than 90% of thyroid cancers are of well-differentiated variety consisting of papillary carcinoma and follicular carcinoma, and the 10-year survival rate is estimated to be more than 90% with appropriate treatment [11-13]. This combination of young age at diagnosis and favorable prognosis leads to an increased incidence of subsequent secondary malignancies. Several studies have estimated the incidence of second primary malignancy in thyroid cancer to be 7-8% [14, 15]. This has been attributed to the genetic predisposition to malignancy and associated treatments like RAI or radiation therapy [16-18].

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**Table 2. Characteristics of Primary and Secondary Salivary Gland Malignancy**

- **Total cases**: 19,008, 18
- **Age at diagnosis**: 59.80 ± 18.361 vs. 53.28 ± 16.634; P = 0.132
- **Age group**: < 60 years (8,615, 45.3%) vs. ≥ 60 years (10,393, 54.7%); P = 0.07
- **Gender**: Male (10,240, 53.9%) vs. Female (8,768, 46.1%); P < 0.05
- **Race**: White (15,630, 82.2%), Black (1,656, 8.7%), Other (1,486, 7.8%), Unknown (236, 1.2%); P = 0.51
- **Primary site**: C07.9 - parotid gland (15,134, 79.6%), C08.0 - submandibular gland (2,845, 15%), C08.1 - sublingual gland (184, 1.0%), C08.8 - overlapping lesion of major salivary glands (20, 0.1%), C08.9 - major salivary gland, NOS (825, 4.3%); P = 0.48
- **Grade of salivary cancer**: I - well differentiated (1,733, 9.1%), II - moderately differentiated (3,337, 17.5%), III - poorly differentiated (3,322, 17.5%), IV - undifferentiated (1,487, 7.9%), Unknown (9,129, 48%); P = 0.08

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This study utilized the SEER 18 database. The interpretation of this data is the sole responsibility of the authors. The authors acknowledge the efforts of Surveillance Research Program, National Cancer Institute and the SEER program tumor registries in the creation of the SEER database.

Conflict of Interest

None.

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