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Second Primaries after Major Salivary Gland Cancer

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Abstract

Objectives. To evaluate the risk of second primary cancers in patients with major salivary gland cancer using a large population database and to examine the effects of sex, salivary gland cancer histology, and radiation therapy on the risk of second primaries.

Study Design. Population-based study using the Surveillance, Epidemiology, and End Result (SEER) cancer database.

Subject and Methods. The subjects were 15,572 men and women ages 15 and above, diagnosed with cancer of the major salivary glands from 1973 to 2006.

Results. There was an increased risk of oral cavity (standardized incidence ratio [SIR] = 3.48, $P < .05$), salivary (SIR = 9.97, $P < .05$), lung and bronchus (SIR = 1.60, $P < .05$), kidney (SIR = 1.68, $P < .05$), and thyroid (SIR = 2.66, $P < .05$) cancers. Men had an increased risk of developing kidney cancer (SIR = 1.70, $P < .05$) compared with women (SIR = 1.64, $P > .05$). Patients with mucoepidermoid carcinoma had an increased risk of a second salivary gland cancer (SIR = 8.97, $P < .05$) and thyroid cancer (SIR = 3.97, $P < .05$). Patients with adenoid cystic carcinoma had an increased risk of oral cavity (SIR = 3.76, $P < .05$) and nasopharyngeal (SIR = 16.88, $P < .05$) cancers. Patients with acinar cell carcinoma had an increased risk of salivary (SIR = 31.36, $P < .05$), kidney (SIR = 2.98, $P < .05$), and thyroid (SIR = 3.85, $P < .05$) cancers. Patients who received radiation therapy had a higher incidence of lung and bronchus (SIR = 2.11, $P < .05$), laryngeal (SIR = 3.08, $P < .05$), and thyroid (SIR = 2.95, $P < .05$) cancers compared with patients who did not receive radiation therapy (SIR = 1.18, 0.48, and 2.39, respectively; $P > .05$). Patients had an increased risk of developing second primaries, even 10 years after diagnosis of primary salivary gland cancer.

Conclusions. Patients with major salivary gland cancers are at a risk for certain second primary cancers. This highlights the need for long-term surveillance in these patients, not only for recurrence but also for second primary cancers.

Keywords

salivary gland cancer, second primaries, SEER database, population study

Salivary gland cancers are relatively rare, with an annual age-adjusted incidence of 0.9 in 100,000.[1] They account for approximately 6% of head and neck malignancies and 0.3% of all cancers.[2] However, there is evidence that the incidence of salivary gland cancer is rising.[3,4] It is thought that several factors, such as exposure to ionizing radiation, dental x-rays, and silica dust, may play a role in the development of salivary gland cancer.[5-8] However, the cause of salivary gland cancer is not completely understood.

Surveillance after treatment of salivary gland cancer generally focuses on monitoring of locoregional and distant recurrence. There is evidence that monitoring for second primary cancers should also be considered. Several studies have examined the incidence of second primary cancers in salivary gland cancer patients with varied, sometimes conflicting, results.[9-11] Unfortunately, most of these studies had small sample sizes, and none included cases diagnosed after 1992. The purpose of our study was to evaluate the risk of second primary cancers in patients with major salivary gland cancer using a large population database and to examine the effects of sex, salivary gland cancer histology, and radiation therapy on the risk of second primaries.

Methods

Data were obtained from the Surveillance, Epidemiology, and End Result (SEER) program of the National Cancer Institute, which includes data from 9 population-based registries: 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 4 standard metropolitan areas (Atlanta, Georgia; Detroit, Michigan; San Francisco–Oakland, California; and Seattle–

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Table 1. Risk of Second Primary Cancers by Site

	Men and Women	Men	Women
All sites	1.24[a]	1.27[a]	1.20[a]
Oral cavity	3.48[a]	3.72[a]	2.97[a]
Salivary gland	9.97[a]	6.25[a]	16.51[a]
Oropharynx	1.62	1.62	1.61
Nasopharynx	2.5	1.82	4.01
Esophagus	0.89	0.58	1.88
Stomach	0.71	0.71	0.69
Small intestine	0.68	0.6	0.78
Colon	1.14	1.09	1.2
Anorectal	0.79	0.71	0.92
Hepatobiliary	0.93	1.18	0.54
Pancreas	0.97	1.16	0.76
Larynx	1.66	1.53	2.31
Lung and bronchus	1.60[a]	1.77[a]	1.32[a]
Trachea	0	0	0
Melanoma of the skin	1.17	1.37	0.81
Bones and joints	2.65	2.4	2.96
Female breast	0.96	0	0.96
Cervix	1.28	0	1.28
Uterus	0.71	0	0.71
Ovary	1.2	0	1.2
Prostate	1.08	1.08	0
Urinary bladder	0.87	0.83	1.01
Kidney	1.68[a]	1.70[a]	1.64
Brain	0.86	1.06	0.59
Thyroid	2.66[a]	3.26[a]	2.38[a]

Values are the standardized incidence ratios expressed as observed/expected.
[a]$P < .05$.

Puget Sound, Washington).[12] The study cohort consisted of men and women ages 15 and above, who were diagnosed with cancer of the major salivary glands from 1973 to 2006. The International Classification of Diseases for Oncology (ICD-O) site codes used for major salivary gland cancer were C07.9 (parotid gland), C08.0 (submandibular gland), C08.1 (sublingual gland), C08.8 (overlapping lesion of major salivary glands), and C08.9 (major salivary gland, NOS). The ICD-O histology/behavior codes were grouped into several categories: mucoepidermoid (8430/3), adenoid cystic (8200/3), adenocarcinoma (8255/3), and acinar carcinoma (8430/3). SEER files also contain information on the initial type of therapy within broad categories but do not record subsequent therapies. Radiation therapy is recorded as: none; beam radiation; radioactive implants; radioisotopes; combination of beam with implants or isotopes; radiation, not otherwise specified (NOS); other radiation; refused; recommended, unknown if administered; and unknown. For the purposes of our study, these were grouped into 2 broad categories: radiation and no radiation. The latency exclusion period for second primaries was 6 months. The SEER computer software (SEER*Stat 6.5.2) was used for statistical analysis. Standardized incidence ratios (SIRs) were calculated to evaluate the risk of second primaries for each site. SIR was obtained by calculating the ratio of the incidence of second primary cancers in the cohort to the expected incidence in general population. The expected incidence was obtained by applying age-, sex-, and site-specific incidence rates by calendar year to person-years at risk for each respective cancer case. The SIRs are displayed in tables as observed/expected (O/E). This study was exempt from the New York Eye and Ear Infirmary Institutional Review Board review because it was conducted using public data.

Results

From 1973 to 2006, the SEER system received 15,572 reports of major salivary gland cancer in patients ages 15 and above. There were 8480 men and 7092 women. Mucoepidermoid was the most common histology (20%), followed by adenoid cystic carcinoma (11%) and acinar cell carcinoma (9%). There were only 6 cases of adenocarcinoma.

Table 1 shows the SIRs for second primary cancers among men and women after major salivary gland cancer. There was an increased risk of second primary cancer when all sites are considered. There was an increased risk of oral cavity, salivary, lung and bronchus, kidney, and thyroid cancers overall. Men had an increased risk of developing kidney cancer, whereas women did not. On examining the effect of salivary gland cancer histology on the risk of second primary sites (**Table 2**), we found that patients with mucoepidermoid carcinoma had an increased risk of a second salivary gland cancer and of thyroid cancer. Patients with adenoid cystic carcinoma had an increased risk of oral cavity and nasopharyngeal cancers. Patients with acinar cell carcinoma had an increased risk of salivary, kidney, and thyroid cancers.

The risk of second primaries was increased in patients treated with and without radiation therapy. Both groups had an increased risk of developing salivary gland and oral cavity second primaries. Patients who received radiation therapy had an increased incidence of lung and bronchus, laryngeal, and thyroid cancer. Patients who did not receive radiation therapy had an increased incidence of kidney cancer (**Table 3**). **Table 4** shows the latency period between the diagnosis of primary salivary gland cancer and development of second primary cancers. Patients with salivary gland cancer had an increased risk of developing oral cavity, salivary gland, lung, and bronchus second primaries, even 10 years after diagnosis of primary salivary gland cancer.

Discussion

The results of our studies show that patients diagnosed with major salivary gland cancer are at increased risk of developing second primary cancers, especially in the salivary gland, oral cavity, thyroid, lungs, and kidneys. Furthermore, this risk remains high even 10 years after diagnosis of the initial primary cancer, especially for cancers of oral cavity, salivary gland, and lung/bronchus. This emphasizes the importance of long-term surveillance of patients after treatment of major

Table 2. Risk of Second Primary Cancers by Site and Primary Histology

	Mucoepidermoid	Adenoid Cystic	Acinar Cell
Oral cavity	1.53	3.76[a]	1.57
Salivary gland	8.97[a]	7.61	31.36[a]
Oropharynx	0	0	0
Nasopharynx	0	16.88[a]	0
Esophagus	0.51	0	1.1
Stomach	0.82	0	0.6
Small intestine	1.52	2.49	0
Colon	1.02	1.14	1.18
Anorectal	0.43	1.69	0.85
Hepatobiliary	0.99	1.07	0
Pancreas	1.05	0.65	0
Larynx	1.11	0	1.3
Lung and bronchus	1.25	1.14	1.48
Trachea	0	0	0
Melanoma of the skin	0.36	1.26	0.34
Bones and joints	5.68	8.94	0
Female breast	0.95	1	1.11
Cervix	2.5	2.04	0
Uterus	0.84	0.99	0.31
Ovary	1.15	1.37	0.57
Prostate	1.1	1.17	1.23
Urinary bladder	0.82	0.96	0.46
Kidney	1.24	2.12	2.98[a]
Brain	1.09	0	0
Thyroid	3.97[a]	2.61	3.85[a]

Values are the standardized incidence ratios expressed as observed/expected.
[a]$P < .05$.

Table 3. Effect of Radiation Therapy on Risk of Second Primary Cancer

	Radiation	No Radiation
All sites	1.37[a]	1.14[a]
Oral cavity	3.64[a]	3.47[a]
Salivary gland	12.36[a]	8.35[a]
Oropharynx	2.7	0.76
Nasopharynx	2.76	2.37
Esophagus	1.23	0.64
Stomach	0.93	0.44
Small intestine	1.52	0
Colon	0.95	1.25
Anorectal	1.06	0.6
Hepatobiliary	0.79	1.08
Pancreas	1.12	0.89
Larynx	3.08[a]	0.48
Lung and bronchus	2.11[a]	1.18
Trachea	0	0
Melanoma of the skin	1.38	0.86
Bones and joints	6.07	0
Female breast	0.91	1.02
Cervix	1.66	1.07
Uterus	0.48	0.88
Ovary	1.54	1.01
Prostate	1.03	1.16
Urinary bladder	1	0.79
Kidney	1.48	1.90[a]
Brain	0.84	0.91
Thyroid	2.95[a]	2.39

Values are the standardized incidence ratios expressed as observed/expected.
[a]$P < .05$.

salivary gland cancer. The sites of second primary cancers varied according to the histology of the primary salivary gland cancer. The sites of second primary cancers were similar between the sexes, except for kidney cancer, which showed increased risk in men compared with women. Radiation therapy increased the risk of developing cancers of the thyroid, laryngeal, and lung/bronchus. However, there was an increased risk of developing oral cancer or a second salivary gland cancer regardless of radiation status.

Several other studies have examined the incidence of second primary cancers in salivary gland cancer patients with varied, sometimes conflicting, results. Biggar et al[10] evaluated the risk of second primary cancers following salivary gland cancer. Data were extracted from the Connecticut Tumor Registry for patients diagnosed with salivary gland cancer from 1935 to 1978. The investigators found that men had an increased risk of respiratory cancers, whereas women had an increased risk of ovarian cancer. This is in contrast to our findings, which showed no increased risk of ovarian cancer and an increased risk of lung/bronchus cancer regardless of sex. Sun et al[11] examined salivary gland cancer epidemiology in the United States. Similar to our results, they found an increased risk of second salivary gland cancer as well as tongue, gingival, lung, and thyroid cancer. Contrary to our results, they did not find an increased risk of kidney cancer. They also found an increased risk of prostate cancer in men, which we did not find. Similar to our study, Sun et al found that radiation increased the risk of lung cancer. However, they also found that radiation reduced the risk of a second salivary gland cancer and gingival/mouth cancer, which was not the case in our study. They did not examine the effect of radiation on laryngeal cancer. Their study used data from patients diagnosed from 1972 through 1992 and yielded 4250 cases in contrast to the 15,572 cases reported in our study.

Our study shows almost a 3-fold risk of thyroid cancer in patients with salivary gland cancer compared with the general population. It is well known that ionizing radiation exposure is a significant risk factor for both thyroid and salivary gland cancer.[6,7,13] Our results show that patients who received radiation as part of their treatment had an increased risk of developing second primary thyroid cancer. However, radiation therapy alone cannot account for this increased risk because the relationship between thyroid cancer and salivary gland cancer is not unidirectional. Brown et al[14] examined the risk of second

Table 4. Latency Period Between Diagnosis of First and Second Primary Cancers

	Latency Period From Diagnosis of First Primary			
	6-11 Months	12-59 Months	60-119 Months	120+ Months
All sites	1.38[a]	1.36[a]	1.27[a]	1.08
Oral cavity	4.05	3.38[a]	3.23[a]	3.68[a]
Salivary gland	16.65[a]	14.95[a]	5.79[a]	7.15[a]
Nasopharynx	0	0	4.79	3.97
Larynx	0	1.07	3.85[a]	0.81
Lung and bronchus	1.75	2.10[a]	1.3	1.33[a]
Kidney	3.98[a]	1.38	1.73	1.55
Thyroid	2.81	3.69[a]	2.27	2.01

Values are the standardized incidence ratios expressed as observed/expected.
[a]$P < .05$.

primary cancers after treatment of differentiated thyroid cancer using the SEER database and found an increased risk of salivary gland cancer in their cohort. This was confirmed by our own analysis of the SEER database. Brown et al also examined the effect of radioisotope therapy on the risk of second primaries. Radioisotope therapy did not increase the risk of developing salivary gland cancer. These findings suggest that the pathogenic mechanisms for both cancers might be related.

The risk of lung and bronchus cancer in our cohort was approximately 1½ times that of the general population. Several of the previous studies evaluating second primaries after salivary gland cancers have consistently shown an increased risk of lung and bronchus cancer.[9-11] This is interesting given that although smoking is widely recognized as a risk factor for respiratory tract cancer, it has not been shown to be a risk factor for salivary gland cancer.[15] Also, a link between salivary gland cancer and kidney cancer has not been previously reported. A review of the literature did not reveal any explanation for these findings. However, the causes and pathogenesis of salivary gland cancers are not yet fully understood, and there may be an as yet undiscovered molecular or genetic link between these cancers.

None of the previous studies evaluating second primaries after salivary gland cancer examined the effect of histology on the risk of second primaries. Our results show that the sites of second primary cancers vary according to the histology of the primary salivary gland cancer. Patients with mucoepidermoid carcinoma had a 9-fold increase in the risk of a second salivary gland cancer and a 4-fold increase in the risk of thyroid cancer. Patients with adenoid cystic carcinoma had a 4-fold increased risk of oral cavity and a 17-fold increased risk of nasopharyngeal cancers. Patients with acinar cell carcinoma had a 31-fold increased risk of salivary gland cancer, a 3-fold increased risk of kidney cancer, and a 4-fold increased risk of thyroid cancers. The link between adenoid cystic histology and nasopharyngeal cancer is interesting. Epstein Barr-virus is a well-recognized risk factor for nasopharyngeal carcinoma.[16] Several studies have shown that this may also be a risk factor for salivary gland cancer.[17,18] There have also been reports in the literature of nasopharyngeal adenoid cystic carcinoma.[19,20] Although it is possible that nasopharyngeal adenoid cystic carcinoma accounts for the increased risk of nasopharyngeal carcinoma observed, it is improbable given the rarity of that disease. Another possible explanation is that these nasopharyngeal "second primaries" are in fact discontinuous areas of local spread or recurrence.

We excluded patients younger than 15 years of age because pediatric salivary gland malignancies are relatively rare and have not been as well studied as adult salivary gland malignancies.[21] Therefore, it is unclear whether these malignancies behave differently from their adult counterparts. Adenocarcinoma was not included in our analysis because of the very small sample size. The SEER database groups the codes for mucoepidermoid (8430/3), adenoid cystic (8200/3), adenocarcinoma with mixed subtypes (8255/3), and acinar carcinoma (8430/3) under adenocarcinoma, NOS (8140).[22] We chose to define adenocarcinoma as histology code 8255 to distinguish it from the other 3 histology groups. This may explain the lower frequency of adenocarcinoma in our study compared with other studies.[7,11,23]

There are several limitations in our study. Our study assumes that the second primaries reported in the SEER database are in fact second primaries, as opposed to recurrences or metastases. This is particularly concerning for salivary gland and lung second primaries, which may in fact be recurrences and metastases, respectively. However, the SEER Program Coding and Staging Manual has specific instructions and criteria for coding second primary cancers.[22] These include, but are not limited to, separate noncontiguous sites, different histology, time between diagnoses of multiple tumors, and laterality of paired organs. Also, the SEER*Stat program uses a default latency exclusion period of 2 months when calculating incidence of second primaries. To further reduce the risk of unintentionally including recurrences, we used a latency exclusion period of 6 months. This risk could be further reduced by extending the latency period. However, this would preclude the analysis of synchronous second primaries. The SEER database only records initial therapy. Consequently, it is difficult to know whether our no-radiation cohort received radiation after the initial therapy was reported. The strengths of our study lie in its large sample size and the diverse

inclusion population. The catchment areas used in the SEER database were selected for their ability to maintain a high-quality cancer reporting system and for demographic characteristics that are representative of the US population as a whole.

In conclusion, our results revealed a statistically significant risk of second primary salivary gland, oral cavity, thyroid, lung, and kidney cancer in patients with major salivary gland cancer. The second primary sites were affected by the histology of the salivary gland cancer. Radiation therapy may increase the risk of second primary cancers of the thyroid, lung, and bronchus. Our study highlights the importance of surveillance in patients with major salivary gland malignancy, not only for locoregional and distant recurrences but also for second primary cancers. Our results show that the risk of second primary cancers persists even 10 years after diagnosis of the initial cancer. This suggests the need for long-term surveillance, probably throughout the patient's lifetime. It is interesting to note that a majority of the sites at increased risk for second primary cancers are located in the head and neck. Thus, frequent and thorough head and neck exams, along with judicious use of imaging studies, may aid in the early detection of these cancers.

Author Contributions

Uchechukwu C. Megwalu, conception and design, acquisition of data, analysis and interpretation of data, drafting and revision of manuscript, final approval of the version to be published; **Edward J. Shin**, conception and design, analysis and interpretation of data, revision of manuscript, final approval of the version to be published.

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References

1. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg*. 1999;120(6):834-840.
2. Ries LAG, Hankey BF, Miller BA, et al. *Cancer Statistics Review 1973-88*. Bethesda, MD: National Cancer Institute; 1991. NIH Publication No. 91-2789.
3. Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. *Otolaryngol Head Neck Surg*. 2006;135:451-457.
4. Zheng T, Holford TR, Chen Y, et al. Are cancers of the salivary gland increasing? Experience from Connecticut, USA. *Int J Epidemiol*. 1997;26(2):264-271.
5. Preston-Martin S, Thomas DC, White SC, et al. Prior exposure to medical and dental x-rays related to tumors of the parotid gland. *J Natl Cancer Inst*. 1988;80(12):943-949.
6. Spitz MR, Fueger JJ, Goepfert H, et al. Salivary gland cancer: a case-control investigation of risk factors. *Arch Otolaryngol Head Neck Surg*. 1990;116(10):1163-1166.
7. Spitz MR, Tilley BC, Batsakis JG, Newell GR, et al. Risk factors for major salivary gland carcinoma: a case-comparison study. *Cancer*. 1984;54(9):1854-1859.
8. Zheng W, Shu XO, Ji BT, et al. Diet and other risk factors for cancer of the salivary glands: a population-based case-control study. *Int J Cancer*. 1996;67(2):194-198.
9. Prior P, Waterhouse JA. Second primary cancers in patients with tumours of the salivary glands. *Br J Cancer*. 1977;36(3):362-368.
10. Biggar RJ, Curtis RE, Hoffman DA, et al. Second primary malignancies following salivary gland cancers. *Br J Cancer*. 1983;47(3):383-386.
11. Sun EC, Curtis R, Melbye M, et al. Salivary gland cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 1999;8:1095-1100.
12. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence—SEER 9 Regs Limited-Use, Nov 2008 Sub (1973-2006) <Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969-2006 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2009, based on the November 2008 submission. http://www.seer.cancer.gov. Accessed November 5, 2009.
13. Becker FO, Economou SG, Southwick HW, et al. Adult thyroid cancer after head and neck irradiation in infancy and childhood. *Ann Intern Med*. 1975;83(3):347-351.
14. Brown AP, Chen J, Hitchcock YJ, et al. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2008;93(2):504-515.
15. Muscat JE, Wynder EL. A case/control study of risk factors for major salivary gland cancer. *Otolaryngol Head Neck Surg*. 1998;118:195-198.
16. Lin JC, Chen KY, Wang WY, et al. Detection of Epstein-Barr virus DNA in the peripheral-blood cells of patients with nasopharyngeal carcinoma: relationship to distant metastasis and survival. *J Clin Oncol*. 2001;19(10):2607-2615.
17. Tsai C, Chen C, Hsu H. Expression of Epstein-Barr virus in carcinomas of major salivary glands: a strong association with lymphoepithelioma-like carcinoma. *Hum Pathol*. 1996;27(3):258-262.
18. Jen KY, Cheng J, Li J, et al. Mutational events in LMP1 gene of Epstein-Barr virus in salivary gland lymphoepithelial carcinomas. *Int J Cancer*. 2003;105(5):654-660.
19. Liu T, Yang A, Guo X, et al. Adenoid cystic carcinoma of the nasopharynx: 27-year experience. *Laryngoscope*. 2008;118:1981-1988.
20. Schramm VL, Imola MJ. Management of nasopharyngeal salivary gland malignancy. *Laryngoscope*. 2001;111:1533-1544.
21. Shapiro NL, Battacharyya N. Clinical characteristics and survival for major salivary gland malignancies in children. *Otolaryngol Head Neck Surg*. 2006;134:631-634.
22. SEER Program Coding and Staging Manual 2008. http://seer.cancer.gov/tools/codingmanuals/index.html. Accessed November 5, 2009.
23. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg*. 1986;8(3):177-184.