Salivary Gland Cancer in the United States

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Abstract
The risk of salivary gland cancer (SGC) is increased in atomic bomb survivors and after radiotherapy, but other risk factors are not well established. Some studies have suggested an association of SGC with breast cancer and with exposure to various viruses or UVB radiation. Corroborating evidence of these associations was sought by using population-based registries to examine the demographic distribution of SGC, patterns of secondary primary cancers after SGC, and risk of SGC with AIDS. SGC incidence per 100,000 persons did not change between 1973 and 1992, averaging 1.2 in males and 0.8 in females, with a steep age gradient. To examine the relationship between UVB exposure and SGC, population-based, age-adjusted incidence rates of SGC were plotted against the UVB insolation of each registry site. Regression analysis suggested no correlation between SGC incidence and increasing UVB insolation ($\beta = 0.10$, $R^2 = 0.08$). SGC also did not appear to be associated with second cancers that have been linked to herpes or papilloma viruses or with AIDS [observed/expected (O/E) ratio, $<2.8$], but all of these conditions are so uncommon that only very large relative risks would have been statistically significant. Women with SGC before age 35 had a statistically nonsignificant elevation in breast cancer risk [O/E, 3.30; 95% confidence interval (CI), 0.66–9.65], and older women had no increased risk of breast cancer. SGC patients were at increased risk for nonsalivary, second-primary oropharyngeal cancers (O/E, 3.27; 95% CI, 2.00–5.05), thyroid cancer (O/E, 3.31; 95% CI, 1.07–7.73), and lung cancer (O/E, 1.86; 95% CI, 1.45–2.35), particularly in patients whose SGC was treated with radiotherapy (O/E, 2.83; 95% CI, 2.06–3.80). In summary, SGC remains rare and does not appear to be associated with AIDS, virally related malignancies, or UVB. Patients who have had SGC, however, should be monitored for subsequent oropharyngeal, thyroid, and lung cancers.

Introduction
SGC is a rare disease, with an incidence rate of approximately 0.9 per 100,000 in the United States (1). In contrast to other malignancies, there is relatively little international variation in the incidence of SGC (2). The etiology of SGC is not well known, although correlations of varying strengths between SGC and possible risk factors have been found. One of the most well-established risk factors of SGC is exposure to radiation. High-dose radiation has been conclusively linked to excess SGC in studies of atomic bomb survivors, with a strong dose-response seen for mucoepidermoid carcinomas (3).

Therapeutic radiation has been linked to an increased risk of SGC. Schneider et al. (4) found an increased incidence of SGC among patients who had been exposed to head, face, or neck radiation that was used as a treatment for benign tumors, and Preston-Martin et al. (5–7) determined that exposure to radiation during dental radiography led to an increased risk of SGC. Hall et al. (8) found an increased risk of SGC among patients who had been treated with $^{131}$I for hyperthyroidism, as did Hoffman et al. (9), although the latter association was not statistically significant. Using 1973–1981 data from the SEER program, Spitz et al. (10) noted an increased incidence of SGC in the southern registries, suggesting an association between SGC and UVB exposure.

Several viruses have been implicated in the etiology of SGC. EBV has been found in lymphoepithelioma-like carcinomas of the salivary gland (11), although only among Asian patients (12). Human papillomavirus types 16 and 18 have been found in SGCs (1), in addition to their known or potential roles in anal (13), cervical (14), vulvar (15, 16), esophageal (17, 18), and oral (19, 20) squamous cell cancers. Polyomavirus can induce SGC if it is injected into mice on the first day of life (1, 21). If injected after the first day of life, the incidence of SGC drops dramatically, suggesting that polyomavirus may play a role in SGC only when the immune system is immature. Cytomegalovirus can induce salivary gland tumors in mice (22), and human immunodeficiency virus type 1 has been found in cystic lymphoepithelial lesions of the salivary gland (23).

Workers in various occupations experience an increased incidence of SGC, including rubber manufacturing (1), plumbing (1), and woodworking in the automobile industry (24). Graham et al. (25) found an increased risk of SGC among people living in asbestos-mining counties in Quebec, with the risk inversely related to the distance from the asbestos mines.

The present study was designed to examine the demographic distribution of SGC in the United States, including potential associations with the AIDS or with second primary malignancies after SGC. Berg et al. (26) originally found an 8-fold increase in breast cancer among patients with SGC. However, Moertel and Elveback (27) found no increase in...
breast cancers. Three studies found an increase of breast cancers after SGC, but these were not statistically significant (28–30). Prior and Waterhouse (31) did find a statistically significant excess of SGC after breast cancer, although this excess was 2-fold, compared with the 8-fold excess originally found by Berg et al. (26). In a much larger study using the Danish Cancer registry, Schou et al. (32) did not find a statistically significant excess of SGCs after breast cancer. Aside from breast cancers, excesses of skin, prostate, lung, larynx, and colon cancers after SGC have been found. Reversing the temporal sequence, excesses of SGC have been found after lung cancer (33), squamous cell skin cancer (34), and squamous cell conjunctival cancer (35). Unfortunately, each of the previous studies of second primaries after SGC had limited power. Furthermore, none of these studies included cases of SGC occurring after 1982, and no investigation of a possible association between SGC and AIDS has been undertaken.

Materials and Methods
Since 1973, the National Cancer Institute has monitored cancer incidence in ~10% of the United States population through the SEER program (36), which includes data from nine population-based cancer registries covering the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, as well as the metropolitan areas of Atlanta, Seattle, San Francisco and Oakland, and Detroit. SEER files also contain information on the initial type of treatment given for each tumor, within broad categories.
provide a direct measure of UVB flux reaching the earth’s surface with a magnesium tungstate sensor. The insolation index (also known as Robertson-Berger counts) are weighted according to an action spectrum that parallels that for skin erythema. The current analysis used mean insolation indices for calendar years 1974–1985 that were recorded in the following SEER sites: San Francisco, Atlanta, Detroit, Seattle, Albuquerque (for New Mexico), Mauna Loa (for Hawaii), Des Moines (for Iowa), and Salt Lake City (for Utah). The age-adjusted SGC incidence rate at each site was plotted on a log-log scale against the UVB insolation index of that site. Only white cases were included for this analysis, because of their presumed higher susceptibility to UVB radiation. Using the Statistical Analysis System (SAS, Cary, NC), the linear regression was weighted by the number of cases at each site, giving more influence to the age-adjusted rates at sites where more cases were found. The association between UVB and SGC incidence was estimated by the slope of the regression ($\beta$), and the fit of the model was estimated by the correlation coefficient ($R^2$).

### Results

From 1973 through 1992, the SEER system received reports of 4250 cases of SGC, including 2304 among males and 1946 among females. Mucoepidermoid was the most common histology (24%), followed by adenoid cystic carcinoma (16%), squamous cell carcinoma (13%), adenocarcinoma (12%), and acinar cell carcinoma (10%), with mixed and undetermined histologies for the remainder. There were 19 cases (0.4%) of lymphohemipithelioma. Of the SEER cases, 3690 SGC patients (1972 males and 1718 females) could be evaluated for risk of second primary cancers (Table 1). In general, the females tended to develop SGC at an earlier age, and they had longer follow-up periods. These SGC cases included 3117 (84.5%) whites, 262 (7.1%) blacks, and 311 (8.4%) persons of other races.

Fig. 1 shows the SEER incidence of SGC by year between 1973 and 1992. As expected, there was a slight excess of SGC among males, and there was no pronounced trend in SGC incidence over time. Fig. 2 shows the age-specific incidence of SGC on a log scale from 1973 through 1992. The incidence of SGC increased markedly with age, as expected. As noted previously (2), the incidence of SGC was slightly higher among females than males until the age interval 40–44 years, after which males were at a higher risk. The female excess at younger ages was observed with acinar cell, adenoid cystic, adenoscarcina, and mucoepidermoid SGC (data not presented).

The most common initial treatment for SGC was surgery alone (1687 cases), followed by surgery and radiation (1547 cases), and radiation alone (166 cases). Of the 313 patients who developed second primaries, 195 were male and 118 were female; most (288) were white, 18 were black, and the rest were of other races. One hundred sixty-three patients had their original SGC treated with surgery only, 36 with radiotherapy only, 110 with surgery and radiotherapy, 2 received hormone therapy, and 2 patients were either not treated or given other or unknown treatments.

Table 1 shows the distributions of the second primary cancers among both sexes. Overall, SGC patients were at a slightly increased risk of developing a second primary cancer (O/E, 1.07; 95% CI, 0.89–1.00). Risk for a subsequent SGC was increased 7-fold. Other statistically significant excesses were 3-fold for nonsalivary oropharyngeal cancers and thyroid cancer, and nearly 2-fold for lung cancer (Table 2). Men had a statistically significant, 1.4-fold risk for prostate cancer.

Among females, the only statistically significant excess was a new primary SGC (O/E, 10.05; 95% CI, 1.19–7.12). The relative risk for breast cancer among women approached unity (O/E, 1.07; 95% CI, 0.72–1.53). Women with primary SGC up to age 35 appeared to have a higher risk of breast cancer (O/E, 1.45–7.73; 95% CI, 0.24–1.76), based on three cases, two of which were female; most (288) were white, 18 were black, and the rest were of other races. One hundred sixty-three patients had their original SGC treated with surgery only, 36 with radiotherapy only, 110 with surgery and radiotherapy, 2 received hormone therapy, and 2 patients were either not treated or given other or unknown treatments.

Table 2 shows the distributions of the second primary cancers among both sexes. Overall, SGC patients were at a slightly increased risk of developing a second primary cancer (O/E, 1.33; 95% CI, 1.19–1.48). Risk for a subsequent SGC was increased 7-fold. Other statistically significant excesses were 3-fold for nonsalivary oropharyngeal cancers and thyroid cancer, and nearly 2-fold for lung cancer (Table 2). Men had a statistically significant, 1.4-fold risk for prostate cancer.

Among females, the only statistically significant excess was a new primary SGC (O/E, 10.05; 95% CI, 1.19–36.30). The relative risk for breast cancer among women approached unity (O/E, 1.07; 95% CI, 0.72–1.53). Women with primary SGC up to age 35 appeared to have a higher risk of breast cancer (O/E, 1.45–7.73; 95% CI, 0.24–1.76), based on three cases, two of which occurred among 10+ year survivors. However, this risk was not statistically significantly different from the breast cancer risk among women who had SGC at >35 years [P = 0.07, 1-sided test; O/E (O) for ages 35–39, 40–54, and 55+ were 1.55 (2), 0.89 (6), and 1.00 (19), respectively].

To examine the effect of exposure to radiation given as a first course of therapy, we further stratified our data by type of treatment received for the original SGC. Table 3 shows the risk of developing a second primary cancer among women who had radiation as their first course of therapy.
of second primary cancers by treatment for SGC, surgery only or any radiation therapy. The excess of gingival cancers was statistically significant only among patients who had been treated with surgery for their SGC (O/E, 3.92; 95% CI, 1.05–10.03). Conversely, the excess of tongue (O/E, 7.81; 95% CI, 2.10–20.00) and lung cancers (O/E, 2.83; 95% CI, 2.06–3.80) existed only among patients who had been given radiotherapy for their SGC. Moreover, the relative risk for lung cancer among SGC patients who had been treated with radiotherapy was statistically significantly higher than the risk among patients who had been surgically treated for their SGC ($P < 0.01$). However, the relative risks for tongue and lung cancers did not increase with length of time since the radiotherapy had been administered for the SGC (Table 3).

In the AIDS-Cancer match registry, four salivary gland neoplasms were observed among persons with AIDS, including two acinar cell carcinomas, one adenoid carcinoma, and one undifferentiated small cell type carcinoma. From 5 years before through 2.25 years after the initial AIDS-defining disease, 2.26 cases of SGC were expected. Thus, the relative risk of being diagnosed with SGC (1.77) was not statistically significantly increased with AIDS.

With respect to UV radiation exposure, Fig. 3 shows the log-log plot of SGC incidence and UVB insolation. The regression line for log SGC incidence versus log UVB index was slightly upward sloping ($\beta = 0.10)$, but the predicted SGC incidence rate fit the observed data poorly ($R^2 = 0.08$).

**Discussion**

Clues to the etiology of SGC are few and often misleading. We have examined several, refuting some previous observations, confirming and revising others. Horn-Ross et al. (41) noted an increasing SGC incidence among males in the San Francisco-Oakland area, but the current analysis revealed no secular trends either in all SEER areas combined or in San Francisco-Oakland separately (data not presented). The distribution of SGC cases by year and age that we found was consistent with data published previously. The increasing risk with age and male:female rate ratio also were consistent with that reported by Blot et al. (2). Of note, we confirmed the preponderance of female SGC cases <40 years (2).
Ours is the sixth study to estimate the relative risk of secondary breast cancer after SGC in women (Table 4). The larger number of person-years and greater area of geographical coverage make our study particularly useful. Like Moertel and Elveback (27), Dunn et al. (28), and Biggar et al. (29), we were unable to find a statistically significant increase in breast cancers after SGC, and our relative risk approached unity. Our relative risk of 1.07 was nearly identical to that of Moertel and Elveback and fell within the 95% CI of Winn and Blot. CIs were not reported for the other studies. Prior and Waterhouse (31) suggested that women at a younger age may be at an increased risk for breast cancer after SGC. We did note a statistically nonsignificant, 3-fold higher risk of breast cancer among women who had SGC before age 35, which is compatible with random chance or with early age susceptibility. Little or no elevation in breast cancer risk was seen for SGC at older ages. Studies of atomic bomb survivors have shown that radiation to the breast at a young age is an important determinant of risk (42), with most radiation-induced breast cancers observed at 10 or more years after exposure. Risk declines with increasing age, and low risks are seen for those exposed over the age of 40 years. SGC has not been noted in patients or families with known susceptibility to breast cancer.

We did find a statistically significant excess of lung cancers among both sexes combined and among males only, an observation noted previously (28, 3) and corroborated by a statistically significant excess of SGC after lung cancer. (33) This association remains unexplained. In a case-control study, Spitz et al. (43) did not find a statistically significant excess of smokers among patients with SGC. Although the statistically significant excess of lung cancer that we observed was limited to subjects whose SGC had been treated with radiotherapy, the pattern of risks over time since initial therapy appeared inconsistent with a radiation effect.

We considered but found no support for the hypothesis that a viral infection could increase the risk of SGC. Specifically, we found no excess of papillomavirus-related cancers, such as cervical cancer or anal cancer, a finding shared by previous studies (26–32). We also found that SGC patients were not at increased risk for brain cancer, which occasionally has been linked to polyomavirus. There also was no increased risk of non-Hodgkin’s lymphoma, as well as only one case of nasopharyngeal carcinoma and two cases of Hodgkin’s disease, three malignancies associated with EBV infection. Furthermore, considering both viral infections and immune deficiency, our examination of the AIDS-cancer registry match failed to demonstrate a statistically significantly increased risk of SGC among AIDS patients, suggesting that a previous finding of increasing SGC incidence among men in San Francisco, a sentinel AIDS population, was merely chance fluctuation.

Frisch et al. (34) found an excess of SGCs after squamous cell skin cancer. Because SEER does not collect data on nonmelanoma skin cancers, we can neither confirm nor refute this association. We could, however, examine the reported association between UVB exposure and SGC incidence (10). The slope of our regression line was relatively flat, and the line fit the data very poorly, suggesting a lack of an association between SGC and UVB exposure. It should be noted, however, that the UVB insolation index of a SEER registry is not an absolute indicator of UVB exposure. People can move during their lifetime, and people who are more susceptible to UVB may tend to stay indoors, especially in areas with high UVB insolation. Nonetheless, in addition to our regression findings, the geography of SGC mortality in the United States reveals no north-south gradient for SGC, nor any other pattern (shipbuilding coastal areas, agricultural areas, urban areas) that has facilitated research on other types of cancer (44, 45).

We examined a large number of associations in this study, and therefore some of the apparent excesses may have occurred by chance. In addition, errors may have occurred because of misclassification of tumors or their histologies. As mentioned previously, however, SEER data are generally considered accurate, and nearly all of our cases were histologically confirmed. The ability to detect a second primary cancer through SEER is related to the stability of the population, because later cases will be missed because of migration out of the SEER region. Thus, second-cancer associations that are detected yield conservative risk estimates.

In conclusion, our results revealed a statistically nonsignificant association between SGC and breast cancer before age 35 but no association at older ages. We detected no association of SGC with AIDS or with various virus-related malignancies, although we cannot exclude weak associations because of the small number of expected cases. We did find statistically significant associations with a few second-primary cancers after SGC, including the oropharynx, thyroid, lung, and prostate. The association with prostate cancer should be viewed cautiously, because indolent tumors such as prostate cancer can be detected incidentally during routine medical care, which is likely to be more frequent and more thorough for men who had SGC than for men in the general population. Such accelerated ascertainment could also occur in the thyroid cancer cases, but it is unlikely to account for symptomatic and aggressive cancers, as in the oropharynx and lung. Overall, these findings suggest that previous SGC is associated with an increased risk for subsequent cancer of the oropharynx, thyroid, and lung, pointing to the need for monitoring for cancer development at these sites.

References


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