**Title:** Subsequent salivary gland carcinomas in the Childhood Cancer Survivor Study cohort.

**Working group and investigators:** This report will be written within the Second Malignancy Working Group.

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1. **Background and Rationale**

Ionizing radiation has been shown to increase the risk of developing salivary gland neoplasms (1-7). Evidence that salivary gland tumors can be caused by ionizing radiation has accumulated from case reports, clinical series (8-12), cohort studies of patients treated with head and neck irradiation for benign childhood conditions (4;5), patients irradiated for the treatment of malignancies (9;10;13), and from studies of Atomic bomb survivors (1-3). There are few reports on salivary gland neoplasms occurring in patients treated for cancer in childhood, but some studies suggested that young children are more susceptible to radiation-related salivary tumors than older individuals (2;5;8;10;14).

Little is known about the magnitude of the radiation-related risk and the influence of features such as tumor histology or location or host factors such as age at radiation exposure. The reason lies in the fact that salivary gland tumors are relatively rare, and only one-fifth are malignant (15;16). In the United States, reported annual incidence of salivary gland carcinomas (SGC) is 1.2 per 100,000 (12 SEER sites, 1996-2000) (17). Mucoepidermoid carcinoma is the predominate histologic type reported in the literature (1;3;18), and, in a study of atomic bomb survivors, it was shown that incidence increases with the dose of radiation (1).

With respect to possible risk factors other than ionizing radiation, cigarette smoking is a strong risk factor for salivary gland cancers (19;20). One case-control study found that drinking alcohol doubled SGC risk among women, but not men (7), while another investigation reported an OR of 2.5 for heavy drinking and an associated dose-response trend for SGC among men but not women (21); however, other studies did not provide support for a link between alcohol consumption and SGC (19;20;22). Diet has received little attention in relation to SGC risk. One study found that ultraviolet (UV) light treatments to the head and neck, previously used to treat acne, were linked to an elevated risk of SGC (23). Risk of SGC was increased in patients who received UV to treat...
acne particularly for those treated before 1955 (24). SGC has also been linked to a previous history of UV-related nonmelanoma skin cancer (25;26). A possible hormonal link to SGC was supported by early reports (27;28) and some case reports suggest a strong link between Epstein-Bar virus and lymphoepithelial carcinomas of the salivary glands (29;30). Few data are available concerning risk of salivary gland tumors following chemotherapy.

In summary, other than cigarette smoking, ionizing radiation is the only clearly established environmental risk factor for salivary gland cancers. However, relatively little quantitative information is available concerning risks following radiation exposures early in life. Many childhood cancer patients are treated with substantial doses of radiation to the head and neck region, and even chest irradiation, such as from mantle radiotherapy for Hodgkin lymphoma, can result in appreciable scatter doses to the salivary glands. A cohort analysis of second primary salivary gland cancers in a large cohort of childhood cancer survivors would provide a unique opportunity to improve the knowledge on therapy-related risk factors for SGC. We propose a cohort study of second (and subsequent) salivary gland cancers based on the experience of Childhood Cancer Survivor Study (CCSS).

2. Study objectives

The aims of the study are to:

- Evaluate overall effects of radiotherapy, chemotherapy and possible joint effects of radiotherapy and chemotherapy on the risk of new primary salivary gland cancers and estimate relative and absolute excess risks.

- Quantify the risk of second salivary gland cancers among members of the CCSS in relation to a qualitative indicator of radiation dose, and evaluate the possible effect modification by factors such as gender, age at treatment, attained age, time since exposure and smoking.

- Examine the possible differential effect of radiotherapy by histologic subtype of SGC.

The intent would be to publish results of this analysis as a brief communication or short report.

Analysis framework

**Outcome of interest:** New primary salivary gland carcinomas occurring in the major salivary glands among survivors of childhood cancer (Current topography codes for malignant neoplasms of the major salivary glands (ICD-O-3) includes the parotid (C07.9), submandibular (C08.0), and sublingual (C08.1) glands as well as their associated duct). The major salivary gland sites have been chosen because carcinomas of the minor salivary glands are often attributed to sites other than the salivary glands. The study will only focus on salivary gland carcinomas, because benign tumors may be under-ascertained.
**Study population:** The CCSS cohort includes more than 14,000 five-year survivors of childhood cancer diagnosed at any of 25 institutions in the U.S. and Canada between January 1st, 1970 and December 31, 1986 (31). Eligible cases are persons with a second or subsequent carcinoma of the major salivary glands (32). To date, 23 carcinomas of the major salivary glands have been diagnosed in the CCSS. Although the number of cases is small, an analysis is nonetheless warranted, given the paucity of detailed information concerning second primary salivary gland carcinomas in the literature, particularly among childhood cancer survivors.

**Explanatory variables:** Variables to be considered include type of treatments received (surgery, radiotherapy, chemotherapy), location of radiation fields, qualitative indicator of radiation dose (see below), dose of specific chemotherapy agents, type of first cancer, year of diagnosis of the first cancer, age at the diagnosis of the first cancer, age at diagnosis of the salivary gland cancer (if applicable), year of diagnosis of the salivary gland cancer, histology and anatomic location of the salivary gland cancer, gender, cigarette smoking, and alcohol consumption. Pending approval of the concept, a detailed request will be submitted to the Statistics Center, linking this roster of variables to specific items in the medical record abstract form or baseline questionnaire. Radiation treatment information will be requested from M.D. Anderson.

**Radiation dosimetry:** Detailed individual dosimetry will not be performed for this study. Dose will be evaluated on an ordinal scale (low, medium, high), with a range of doses specified for each category. This corresponds to the so-called “second pass” dosimetry performed by M.D. Anderson and will be driven largely by the anatomic location of the initial cancer and the tumor dose. These data will be used for qualitative inference only.

**Analytic method:** Standardized incidence ratios (SIRs) and excess absolute risks (EARs) will be used to contrast salivary gland incidence in the CCSS cohort with that of the segment of the U.S. general population covered in SEER, using the SEER*STAT program. Poisson regression will be used to estimate internal relative and absolute risks among childhood cancer survivors using AMFIT. Incidence of SGC as second primary cancer, adjusted for competing risks, will be calculated according to the method of Gooley et al (33), beginning five years after diagnosis of the first cancer. The analysis would be conducted by Houda Boukheris under the direction of Peter Inskip.

**Examples of specific tables for the incidence study:**

**Table 1:** Characteristics of the CCSS cohort including survivors with a new primary salivary gland cancer, including:

- Type of first cancer
- Calendar year of diagnosis of the first cancer
- Age at diagnosis of the first cancer
- Years since first cancer
- Gender
- Race
- Type of treatment: chemotherapy, radiotherapy, combined modalities
- Part of body irradiated
- Smoking
- Alcohol consumption

Table 2:
Standardized incidence ratios (SIRs), rate ratios (RRs) based on Poisson regression and absolute excess risks (EARs), by type of first cancer, age at diagnosis of the first cancer, calendar year of diagnosis of first cancer, gender, time since first cancer, treatments received, radiation fields, and attained age.

**Figure 1.** Cumulative incidence of salivary gland cancers over time (among five-year survivors).
Reference List


