**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. Proposed investigators include:


| | | |
|---|---|---|
| Houda Boukheris | boukherh@mail.nih.gov | National Cancer Institute |
| Joseph Neglia | jneglia@tc.umn.edu | University of Minnesota School of Medicine |
| Marilyn Stovall | mstovall@mail.mdanderson.org | The University of Texas M.D. Anderson Cancer Center |
| Sue Hammond | HammondS@chi.osu.edu | Ohio State University-School of Medicine |
| Ann Mertens | Ann.Mertens@choa.org | Emory University |
| Anna Meadows | meadows@email.chop.edu | Children's Hospital of Philadelphia |
| Sarah Donaldson | sarah2@stanford.edu | Stanford University Medical Center |
| Greg Armstrong | Greg.Armstrong@stjude.org | St. Jude Children's Research Hospital |
| Leslie Robison | Les.robison@stjude.org | St. Jude Children's Research Hospital |
| Peter Inskip | inskippe@mail.nih.gov | National Cancer Institute |


## 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 then 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


1. Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, Tokunaga M, Mabuchi K. Incidence of salivary gland tumors among atomic bomb survivors, 1950-1987. Evaluation of radiation-related risk. Radiat.Res. 1996 Jul;146(1):28-36.

2. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat.Res. 2007 Jul;168(1):1-64.

3. Saku T, Hayashi Y, Takahara O, Matsuura H, Tokunaga M, Tokunaga M, Tokuoka S, Soda M, Mabuchi K, Land CE. Salivary gland tumors among atomic bomb survivors, 1950-1987. Cancer 1997 Apr 15;79(8):1465-75.

4. Shore-Freedman E, Abrahams C, Recant W, Schneider AB. Neurilemomas and salivary gland tumors of the head and neck following childhood irradiation. Cancer 1983 Jun 15;51(12):2159-63.

5. Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, Shore-Freedman E, Gierlowski TC. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat.Res. 1998 Jun;149(6):625-30.

6. Preston-Martin S, White SC. Brain and salivary gland tumors related to prior dental radiography: implications for current practice. J.Am.Dent.Assoc. 1990 Feb;120(2):151-8.

7. Spitz MR, Fueger JJ, Goepfert H, Newell GR. Salivary gland cancer. A case-control investigation of risk factors. Arch.Otolaryngol.Head Neck Surg. 1990 Oct;116(10):1163-6.

8. Whatley WS, Thompson JW, Rao B. Salivary gland tumors in survivors of childhood cancer. Otolaryngol.Head Neck Surg. 2006 Mar;134(3):385-8.

9. Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: a report from the International Database on Hodgkin's Disease. Ann.Oncol. 1992 Sep;3 Suppl 4:117-28.

10. Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socie G, Travis LB, Horowitz MM, Witherspoon RP, Hoover RN, Sobocinski KA, et al. Solid cancers after bone marrow transplantation. N.Engl.J.Med. 1997 Mar 27;336(13):897-904.

11. Katz AD, Preston-Martin S. Salivary gland tumors and previous radiotherapy to the head or neck. Report of a clinical series. Am.J.Surg. 1984 Mar;147(3):345-8.

12. Beal KP, Singh B, Kraus D, Yahalom J, Portlock C, Wolden SL. Radiation-induced salivary gland tumors: a report of 18 cases and a review of the literature. Cancer J. 2003 Nov;9(6):467-71.

13. Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ, Robison LL, Miller JS, Neglia JP. Malignant neoplasms following bone marrow transplantation. Blood 1996 May 1;87(9):3633-9.

14. Inskip PD. Multiple primary tumors involving cancer of the brain and central nervous system as the first or subsequent cancer. Cancer 2003 Aug 1;98(3):562-70.

15. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J.Pathol. 1985 May;146(1):51-8.

16. Parkin DM, Muir CS, Whelan, Gao YT, Ferlay J and Powell J. Cancer Incidence in Five Continents. IARC scientifique publication N 120 ed. Lyon, France: International Agency for Research on Cancer; 1992.

17. Curtis RE, Ries LAG. Methods. Bethesda, MD: NIH Publ; 2006. Report No.: 05-5302. 9-14 p.

18. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, van Leeuwen FE, Holowaty EJ, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J.Clin.Oncol. 2002 Aug 15;20(16):3484-94.

19. Boice JD, Jr., Fraumeni JF, Jr. Second cancer following cancer of the respiratory system in Connecticut, 1935-1982. Natl.Cancer Inst.Monogr 1985 Dec;68:83-98.

20. Hayes RB, Bravo-Otero E, Kleinman DV, Brown LM, Fraumeni JF, Jr., Harty LC, Winn DM. Tobacco and alcohol use and oral cancer in Puerto Rico. Cancer Causes Control 1999 Feb;10(1):27-33.

21. Muscat JE, Wynder EL. A case/control study of risk factors for major salivary gland cancer. Otolaryngol.Head Neck Surg. 1998 Feb;118(2):195-8.

22. Zheng W, Shu XO, Ji BT, Gao YT. Diet and other risk factors for cancer of the salivary glands:a population-based case-control study. Int.J.Cancer 1996 Jul 17;67(2):194-8.

23. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. Epidemiology 1997 Jul;8(4):414-9.

24. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. Epidemiology 1997 Jul;8(4):414-9.

25. Wassberg C, Thorn M, Yuen J, Ringborg U, Hakulinen T. Second primary cancers in patients with squamous cell carcinoma of the skin: a population-based study in Sweden. Int.J.Cancer 1999 Feb 9;80(4):511-5.

26. Milan T, Pukkala E, Verkasalo PK, Kaprio J, Jansen CT, Koskenvuo M, Teppo L. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in Finland from 1953 to 1995. Int.J.Cancer 2000 Jul 15;87(2):283-8.

27. Horn-Ross PL, Morrow M, Ljung BM. Menstrual and reproductive factors for salivary gland cancer risk in women. Epidemiology 1999 Sep;10(5):528-30.

28. Berg JW, Hutter RV, Foote FW, Jr. The unique association between salivary gland cancer and breast cancer. JAMA 1968 May 27;204(9):771-4.

29. Chan JK, Yip TT, Tsang WY, Poon YF, Wong CS, Ma VW. Specific association of Epstein-Barr virus with lymphoepithelial carcinoma among tumors and tumorlike lesions of the salivary gland. Arch.Pathol.Lab Med. 1994 Oct;118(10):994-7.

30. Lanier AP, Clift SR, Bornkamm G, Henle W, Goepfert H, Raab-Traub N. Epstein-Barr virus and malignant lymphoepithelial lesions of the salivary gland. Arctic Med.Res. 1991 Apr;50(2):55-61.

31. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med.Pediatr.Oncol. 2002 Apr;38(4):229-39.

32. Fritz A PCJA. International Classification of Disease for Oncology. 3rd ed. Geneva: WHO; 2000.

33. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat.Med. 1999 Mar 30;18(6):695-706.