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Risk of Salivary Gland Cancer After Childhood Cancer: A Report From the Childhood Cancer Survivor Study

Houda Boukheris, MD,* Marilyn Stovall, PhD,† Ethel S. Gilbert, PhD,* Kayla L. Stratton, MS,‡ Susan A. Smith, MPH,† Rita Weathers, MS,† Sue Hammond, MD,§ Ann C. Mertens, PhD,‖ Sarah S. Donaldson, MD,¶ Gregory T. Armstrong, MD, Leslie L. Robison, PhD,** Joseph P. Neglia, MD,†† and Peter D. Inskip, ScD***

**Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; †Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, Texas; ‡Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; §Department of Pathology, Ohio State University School of Medicine, Columbus, Ohio; ‖Department of Pediatrics, Emory University, Atlanta, Georgia; ¶Department of Radiation Oncology, Stanford University Medical Center, Stanford, California; **Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee; and ††Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota*

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Summary

Little is known about risk of salivary gland cancer (SGC) after exposure to ionizing radiation during childhood. In a retrospective cohort study of 14,135 ≥5-year survivors of childhood cancer, we evaluated risk of SGC with respect to radiation dose to the salivary

Purpose: To evaluate effects of radiation therapy, chemotherapy, cigarette smoking, and alcohol consumption on the risk of second primary salivary gland cancer (SGC) in the Childhood Cancer Survivor Study (CCSS).

Methods and Materials: Standardized incidence ratios (SIR) and excess absolute risks (EAR) of SGC in the CCSS were calculated using incidence rates from Surveillance, Epidemiology, and End Results population-based cancer registries. Radiation dose to the salivary glands was estimated based on medical records. Poisson regression was used to assess risks with respect to radiation dose, chemotherapy, smoking, and alcohol consumption.

Results: During the time period of the study, 23 cases of SGC were diagnosed among 14,135 childhood cancer survivors. The mean age at diagnosis of the first primary cancer was 8.3 years, and the mean age at SGC diagnosis was 24.8 years. The incidence of SGC was 39-fold higher in the cohort than in the general population (SIR = 39.4; 95% CI = 25.4-57.8). The EAR was 9.8

Reprint requests to: Peter D. Inskip, ScD, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Boulevard, Room 7052, Bethesda, MD 20892. Tel: (301) 594-7515; Fax: (301) 402-0207; E-mail: inskippe@mail.nih.gov

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Conflict of interest: none.

Acknowledgments—The Childhood Cancer Survivor Study (CCSS) is a collaborative, multi-institutional project, funded as a resource by the National Cancer Institute, of individuals who survived 5 or more years after diagnosis of childhood cancer. The CCSS study population is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed before age 21 between 1970 and 1986 and approximately 4000 siblings of survivors, who serve as a control group. The cohort was assembled through the efforts of 26 participating clinical research centers in the United States and Canada. Information on how to access and use the CCSS resource is available at www.stjude.org/ccss.

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glands. Risk increased linearly with dose, and excess risk persisted for more than 20 years. Results underscore the importance of long-term follow up of childhood cancer survivors for the development of new malignancies.

per 100,000 person-years. Risk increased linearly with radiation dose (excess relative risk = 0.36/Gy; 95% CI = 0.06-2.5) and remained elevated after 20 years. There was no significant trend of increasing risk with increasing dose of chemotherapeutic agents, pack-years of cigarette smoking, or alcohol intake.

Conclusion: Although the cumulative incidence of SGC was low, childhood cancer survivors treated with radiation experienced significantly increased risk for at least 2 decades after exposure, and risk was positively associated with radiation dose. Results underscore the importance of long-term follow up of childhood cancer survivors for the development of new malignancies.

Introduction

Exposure to ionizing radiation is a widely accepted risk factor for salivary gland carcinoma (SGC). Supportive evidence has accumulated from cohort studies of patients treated with head-and-neck irradiation for benign childhood conditions (1, 2), patients irradiated for the treatment of malignancies (3-6), and from studies of atomic bomb survivors (7, 8); however, the magnitude of radiation-related risk for SGC is uncertain. Some studies have suggested that young children are more susceptible to radiation-related salivary gland tumors than older individuals (1, 4, 9), but relatively little quantitative information is available concerning risks after 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 radiation therapy for Hodgkin lymphoma, can result in appreciable scatter doses to the salivary glands. With respect to possible risk factors other than ionizing radiation, few data are available concerning risk of SGC following chemotherapy, and the evidence concerning cigarette smoking and alcohol consumption is mixed (10-16). We undertook a cohort analysis of second primary SGC using the unique resource of a large cohort of childhood cancer survivors that provides the opportunity to improve knowledge about therapy-related risk factors for SGC and the role of cigarette smoking and alcohol consumption.

Methods and Materials

Study population

The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort study of childhood cancer survivors that was established in 1994. Eligibility criteria included the following: diagnosis before age 21 years with leukemia, central nervous system (CNS) cancer, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), renal tumor, neuroblastoma, soft-tissue sarcoma, or bone sarcoma between January 1, 1970, and December 31, 1986, at 1 of 26 collaborating institutions in the United States and Canada, and survival for at least 5 years after diagnosis. The CCSS study protocol and contact documents were approved by institutional review boards at each participating medical institution. The study design for constructing the cohort and collecting treatment, risk factor, and outcome information has been described in detail previously (17, 18). A baseline, self-administered questionnaire sent in 1994 obtained data for demographic characteristics, education, income, employment history, marital status, height, weight, personal health habits, family history of cancer, use of medications, reproductive history, new malignant disorders, and other health outcomes. Among the 20,346 eligible participants, 14,135 (69.5%) were located, agreed to participate, and completed a questionnaire. Information on the cohort was updated in periodic follow-up mail surveys, which elicited further, although less extensive, information. Each survey inquired about the occurrence of new cancers. Copies of questionnaires are available at http://ccss.stjude.org.

Copies of radiation therapy (RT) records for the first cancer diagnosis and treatment were obtained from the treating institution and forwarded to the collaborating radiation dosimetry center. Chemotherapy (CT) data were abstracted from medical records using uniform data abstraction procedures across institutions. Abstraction of CT information included the beginning and ending dates of all chemotherapy agents and cumulative doses (mg/m^2) and routes of administration for 22 specific agents (abstract forms are available at http://ccss.stjude.org). An alkylating agent score was calculated according to the method of Tucker et al (19).

Pathology reports were obtained and reviewed by the study pathologist to verify self-reported cancers. Questionnaires administered through the year 2004 identified 24 pathologically verified subsequent primary salivary gland carcinomas in the cohort. One case was subsequently excluded because the diagnosis occurred less than 5 years after the diagnosis of the first primary malignancy, leaving 23 cases for analysis.

Radiation dosimetry

Dose to the salivary glands (average of parotid, submandibular, and submaxillary regions) was estimated for each patient who received radiation therapy for their initial cancer. Dose calculations were based on 26 points located in the 3 salivary gland regions. If the salivary glands were outside the beam, doses were estimated using measurements in a water phantom (20). If the salivary glands were in the beam, dose was derived using standard radiation therapy techniques (20). Each patient's dosimetry was assigned a quality score on the basis of the completeness of the records received and the proximity of the salivary glands to the treatment beam. Of the patients who received RT, 91% had records adequate for dosimetry.

Statistical analysis

We calculated standardized incidence ratios (SIR) as the ratio of observed (O) to expected (E) numbers of SGC (O/E). Expected numbers of cases were based on incidence rates from the