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Salivary Gland Tumors after Childhood Radiation Treatment for Benign Conditions of the Head and Neck: Dose–Response Relationships

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We have investigated the dose–response relationships for the incidence of salivary gland tumors in a cohort of 2945 individuals who were irradiated as children between 1939–1962. Most of the patients were treated to reduce the size of their tonsils and adenoids. The mean dose to the salivary glands (±SD) was 4.2 ± 1.7 Gy. Eighty-nine patients developed 91 salivary gland neoplasms; 22 had single malignancies, 64 had single benign neoplasms, 2 developed two separate benign neoplasms, and 1 developed a single neoplasm but did not have surgery. The majority (81 of 89) of the patients developed neoplasms in the parotid glands. Mucoepidermoid carcinomas were the most common malignancy and mixed (pleomorphic) adenomas were the most common benign neoplasm. For all salivary gland tumors, the excess relative risk per gray (ERR/Gy) was 0.82; however, the 95% confidence interval was wide (0.04, upper bound indeterminate). The trend was determined principally by benign tumors, as there was no dose–response relationship for salivary gland cancer, although there were too few cases to draw definitive conclusions. Overall, our study provides support for an association between salivary gland tumors and radiation exposure. Although most salivary gland tumors are benign and are usually readily detected, they may cause morbidity, and people who have been irradiated in the area should be monitored for their occurrence.

INTRODUCTION

An association between radiation exposure and salivary gland tumors was suggested initially by reports of cases in radiation-exposed cohorts and by sporadic case reports (*1–19*). Only recently, however, have the dose–response relationships between radiation and salivary tumors and the effects of other risk factors been investigated (*18*, *20–22*). Studies of salivary gland tumors have been limited because they are rare and usually asymptomatic.

We have been studying a cohort of irradiated patients (*14*, *23*, *24*) and have reported on the dose–response relationships for benign and malignant thyroid tumors and benign parathyroid tumors (*25–27*). We also have described an increased frequency of salivary gland and neural tumors in this cohort (*10*, *15*) and have suggested that there were variations in susceptibility to radiation-induced tumors in the exposed population (*16*, *28*). In this paper, we describe the dose–response relationships for benign and malignant salivary gland tumors.

MATERIALS AND METHODS

Population at Risk

The cohort consisted of 4296 patients who received conventional radiation therapy before their 16th birthday for benign conditions in the head and neck area between 1939 and 1962. An effort was begun in 1974 to locate and examine as many of the members of this cohort as possible. In this study, 2947 (68.6%) individuals with adequate follow-up information and estimated radiation dose to the salivary glands are included (*25*). There was absent or insufficient follow-up information for 1232 patients and insufficient treatment information to perform dosimetry for 117 patients. Of the 2947, the radiation treatment was designed to reduce the size of the tonsils and adenoids in 2691 (91%). The next two most common indications were enlarged thymus (67 patients) and enlarged cervical lymph nodes (61 patients). Two patients with salivary gland tumors with unknown dates of diagnosis (one with a parotid gland cancer and the other with a parotid gland tumor of unknown histology) were excluded, leaving 2945 patients for the analysis. Follow-up efforts occurred uniformly without regard to the dose estimates. Time to event was defined as the date of the first radiation treatment until surgery for a salivary gland tumor, the date of last contact or August 1, 1993, whichever came first. The presence of salivary gland tumors and their characteristics were confirmed by a review of the operative reports, pathology reports and the original pathology slides.

Dosimetry

Patients were treated with 200 keV peak orthovoltage X rays, 1.2 mm Cu half-value layer (filter of 0.5 mm Cu + 0.5 mm Al) and 50 cm focal–skin distance. A typical treatment consisted of right and left lateral fields directed to the posterior pharynx. The fields were either square or rectangular, with rectangular fields used more commonly. The field size varied but was typically 8 × 10 cm. The patient usually received three treatments of 125 R in air to each lateral field, for a total of 375 R to each field. Approximately 12% of the study population received more than one course of treatment.

Radiation doses to the parotid, sublingual and submandibular glands were estimated. Individual treatment parameters (machine, field description, configuration and size, dose delivered, number of courses of therapy) were abstracted from each patient's radiotherapy record to estimate that patient's specific doses. Organ doses were estimated from measurements made in a water phantom in conjunction with a three-dimensional mathematical phantom. The data for the water phantom were compared with measurements in an anthropomorphic phantom of a 6-year-old and showed good agreement. The mathematical phantom was sized according to the age of the patient to provide distances and depths to sites of interest with respect to the treatment fields.

The placement of the pharynx field on the mathematical phantom was based on diagrams found in some of the treatment records. The records were ambiguous about the orientation of the axes of the rectangular field. For the parotid glands, the orientation did not change the dose estimates because the glands were completely within the field in either orientation. For the sublingual and submandibular glands, doses were estimated with the long axis of the field placed both vertically and horizontally. For the analyses, the doses were the mean of these estimates. On average, the ratio of dose estimates from the two different orientations of the field (vertical/horizontal) was 0.82 for the sublingual glands and 1.28 for the submandibular glands. In the 87 patients (3.0% of the cohort) for whom the doses administered to the left and right sides differed, the mean dose to the right and left gland was used for analysis. For analyses that combined the three salivary glands, weighted mean doses were calculated, with weights proportional to the relative sizes of the salivary glands (parotid = 2/3, submandibular = 1/6, and sublingual = 1/6).

Statistics

Data were analyzed using Cox proportional hazards regression methods, as implemented by the Epicure computer programs (*29*), with age at event or age at end of follow-up as the time variable and age at treatment as the entry time. All analyses were adjusted for sex. Dose categories for relative risks (RR) were defined as <4, 4.0–4.4, 4.5–4.9, 5.0–5.4 and ≥5.5 Gy. The referent category was specified as <4.0 Gy, because all members of the study were irradiated. For dose–response analyses, we fitted a linear excess RR (ERR) model, i.e., $RR = 1 + \beta \times \text{dose}$, where β is the ERR/Gy. Confidence intervals for the estimated β were computed using likelihood-based methods (*30*). We evaluated variations in the dose–response relationship within categories of age at first radiation exposure, years since first radiation exposure, attained age and calendar year. The Kaplan-Meier method was used to plot tumor-free survival (*31*).

RESULTS

During follow-up, 89 of the 2945 individuals developed salivary gland tumors. One individual did not have surgery and 2 individuals had 2 independent salivary tumors. The demographic and treatment characteristics of these 89 individuals are shown in Table I. No differences were observed, comparing the patients who developed salivary gland tumors with those who did not, with respect to the proportion of males (57.3% compared to 59.8%) and the other characteristics shown in the table.

The distribution of radiation doses to the individual salivary glands is shown in Fig. 1. The parotid glands were generally within the primary treatment field and therefore received higher doses of radiation than the submandibular and sublingual glands (Fig. 1). The majority of individuals (65.9%) received 4.5–5.5 Gy to their parotid glands, and these doses did not vary with the age of the individual. For the submandibular glands, the range of doses was larger because, with increasing age, the separation

TABLE I
Demographic Characteristics of the Individuals Included in this Study and those Who Developed Salivary Gland Tumors

	Cohort	Salivary gland tumors
Number of subjects	2,945	89
Female (%)	1,187 (42.7)	38 (40.2)
Males (%)	1,758 (57.3)	51 (59.8)
Mean year of birth (±SD)	1942.6 (±5.1)	1941.4 (±5.0)
Date at first treatment (±SD)	1946.9 (±3.7)	1946.2 (±3.5)
Age at first treatment (±SD)	4.3 (±3.1)	4.9 (±3.2)
Mean dose[a] in Gy (±SD)	4.2 (±1.7)	4.6 (±1.5)
Dose range in Gy	0.01–15.8	0.008–9.7
Dose interquartile range in Gy	3.8–4.6	3.9–4.7

[a] For all of the salivary glands weighted as described in the Materials and Methods.

between the treatment field and these glands increased. The weighted mean dose for all salivary glands was 4.2 Gy and for the parotid glands alone it was 5.0 Gy. For the weighted average doses, the interquartile range was between 3.8 and 4.7 Gy (Table I).

Of the 90 salivary gland tumors (in 88 individuals) for which surgical pathology materials and reports were available, 80 occurred in parotid glands, 9 in submandibular glands and 1 in a sublingual gland. Sixty-eight of them were benign (Table II). The first benign salivary gland tumor was removed 13.3 years after exposure (Fig. 2). The majority

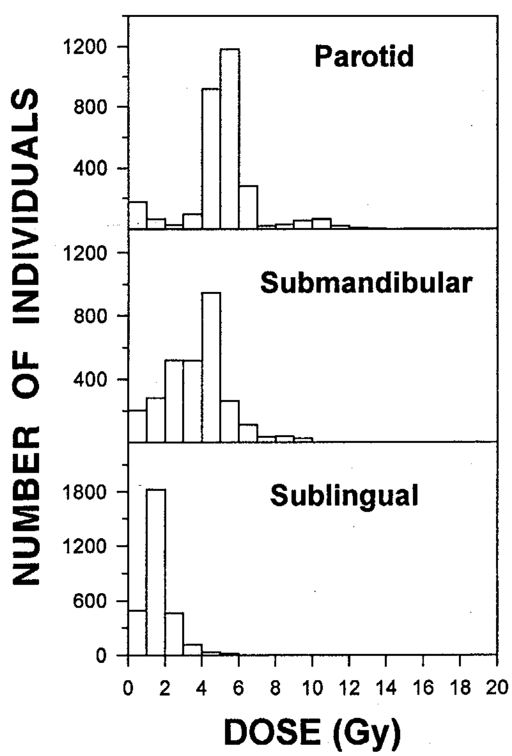

FIG. 1. Distribution of estimated doses for the parotid, submandibular and sublingual salivary glands for the 2945 individuals included in this study.

TABLE II
Distribution of 90 Salivary Gland Tumors in 88 Individuals by Histological Type[a]

	Number
Benign tumors	
Mixed (pleomorphic) adenoma	59
Myoepithelial adenoma	2
Warthin's	2
Acinic cell	1
Cyst	1
Cystadenoma	1
Ductal adenoma	1
Unknown, benign	1
Malignant tumors	
Mucoepidermoid	9
Adenocarcinoma	3
Mixed carcinoma	3
Acinic cell	2
Anaplastic/poorly differentiated	2
Adenoid cystic carcinoma	1
Papillary	1
Unknown, malignant	1

[a]One individual with a parotid tumor did not have surgery and is not included in this table. Two patients developed two separate benign mixed (pleomorphic) tumors and both are included.

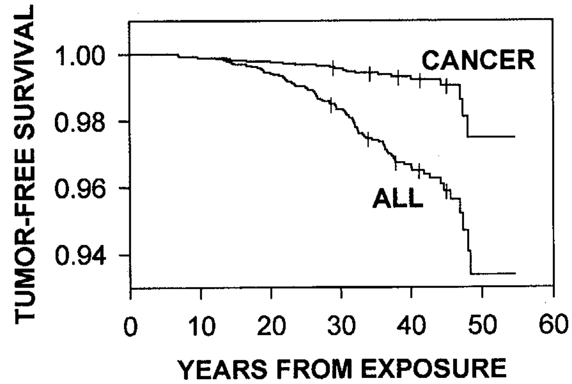

FIG. 2. Kaplan-Meier plot of salivary gland tumor-free survival from the time of radiation exposure. The intersecting vertical lines indicate the times at which the population at risk decreases by 500 individuals.

(86.8%) of these tumors were mixed (pleomorphic) adenomas. Twenty-two malignant salivary gland tumors were observed (14 in males and 8 in females). The first malignancy occurred 7 years after exposure. Nine (40.1%) of the malignant tumors were mucoepidermoid cancers.

There was a statistically significant trend with dose ($P = 0.02$) for all salivary gland tumors ($N = 89$, ERR/Gy = 0.82, 95% CI = 0.04, ∞); however, this was due entirely to a strong dose response ($P = 0.01$) for benign tumors ($N = 66$, ERR = 19.6, 95% CI = 0.16, ∞) (Table III). There was no evidence for a dose response for malignant tumors ($N = 22$, ERR = −0.06, 95% CI = −∞, 4.0). The dose response for all tumors and for benign tumors was well described by a linear relationship (Fig. 3).

None of the covariates tested changed the magnitude of the dose–response relationship for all salivary tumors significantly (Table IV). Of note, age at radiation treatment, a strong modifier of the dose–response relationship for thyroid tumors in this cohort, did not affect the relationship between radiation treatment and salivary gland tumors. In addition, the increased risk for salivary gland tumors after radiation treatment did not vary significantly with time since treatment. The onset of widespread thyroid screening in 1974 resulted in an increase in the incidence of salivary gland tumors from 5.4 cases/10^4 person-years before 1974 to 16.6 cases/10^4 person-years from 1974 onward. The dose–response relationship, however, did not change substantially.

The dose–response pattern for the parotid glands was essentially the same as for all salivary glands. The incidence of all tumors and benign tumors increased with increasing dose ($P < 0.05$). The ERR/Gy for benign parotid gland tumors ($N = 61$) was 3.09 (95% CI = 0.10, ∞). For malignant tumors of the parotid gland ($N = 19$, ERR = −0.02, 95% CI indeterminate) no excess risk was observed. For the submandibular glands the number of cases ($N = 9$) was too small to permit separating them into benign and malignant. The rate of 0.8 cases/10^4/year was approximately 10-fold less than for the parotid glands. No trend with dose was observed.

Analysis by histological type revealed a significant trend with dose for mixed pleomorphic adenomas ($N = 57$, ERR/Gy = ∞), but none for mucoepidermoid malignancies ($N = 9$, ERR/Gy = −0.02, 95% CI indeterminate).

DISCUSSION

The main finding of this study is the existence of a linear dose–response relationship for salivary gland tumors (Fig. 3). The estimated ERR/Gy for benign salivary gland tumors is about 20 times higher than for all salivary gland tumors; however, the estimates do not differ significantly. In contrast, no association between head and neck irradiation and malignant salivary gland tumors was found, although the 22 observed cases is substantially larger than the 0.39 expected number of cases based on sex-matched rates for white U.S. residents during 1983–1987 from the SEER program (*32*). In the results reported here, the small number of observed cases and the narrow dose range resulted in an unstable risk estimate with a very broad confidence interval.

The approximately threefold increase in the incidence of salivary gland neoplasms after 1974 is due in part to the notification and screening programs that began in that year. Other factors such as attained age also explain this increase. However, the screening program did not appear to change the dose–response relationship significantly.

The most extensive analysis of radiation-related salivary gland tumors comes from the life span study (LSS) of atomic bomb survivors in Hiroshima and Nagasaki (*21, 22*). In the most recent analysis, there were 41 malignant and 94 benign confirmed cases, and a significant dose–response relationship was demonstrated for both malignant and benign tumors.

TABLE III
Numbers of Tumors of the Salivary Gland, Individuals and Person-Years, Disease Rates, Relative Risks[a] (RR) and 95% Confidence Intervals (CI) by Categories of Estimated Dose

	Dose (Gy)					
	<4	4.0–4.4	4.5–4.9	5.0–5.4	≥5.5	Total
			All tumors			
Cases	24[b]	30	17	6	12	89
Rate × 10,000	6.3	8.3	11.4	9.1	9.6	8.2
RR[c]	1	1.46	1.88	1.28	1.52	
95% CI		(0.9, 2.5)	(1.0, 3.5)	(0.5, 3.1)	(0.8, 3.0)	
			Benign tumors			
Cases	16	24	11	4	11	66
Rate × 10,000	4.2	6.6	8.1	6.1	8.8	6.2
RR[c]	1	1.71	2.04	1.31	2.08	
95% CI		(0.9, 3.2)	(1.0, 4.3)	(0.4, 3.9)	(1.0, 4.5)	
			Malignant tumors			
Cases	7	6	6	2	1	22
Rate × 10,000	1.8	1.7	3.4	3	0.8	1.9
RR[c]	1	1.04	1.79	1.41	0.45	
95% CI		(0.3, 3.1)	(0.6, 5.7)	(0.6, 5.7)	(0.1, 3.6)	
Individuals	1,071	998	396	163	317	2,945
Person-years	38,082	36,124	14,878	6,610	12,486	108,181
Mean dose[d]	2.9	4.3	4.7	5.2	7.4	4.2

[a]ERRs compared to <4 Gy dose group based on Cox regression, adjusted for gender, using age at treatment as entry time and age at event or age at end of follow-up as survival time.
[b]One subject had a parotid gland tumor, but no surgery. This case is included in "all tumors", but not in "benign tumors" or "malignant tumors" and adds an additional 40 years of follow-up.
[c]P values for test of trend for all cases, benign tumors and cancers were $P = 0.02$, $P = 0.01$ and $P = 0.66$, respectively.
[d]Weighted by person-years.

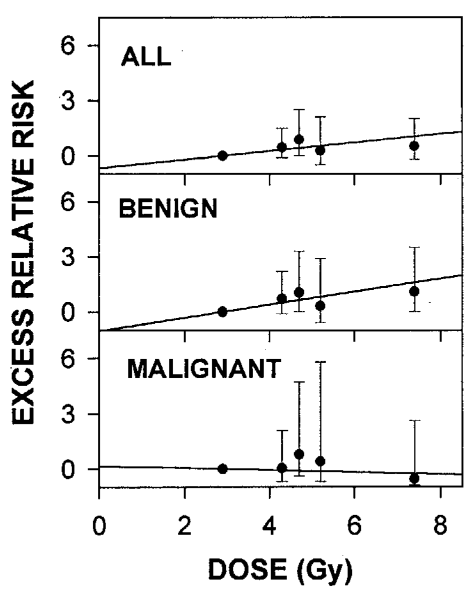

FIG. 3. Dose–response relationship for all salivary gland tumors, benign salivary gland tumors and malignant salivary gland tumors. The vertical position of each point gives the excess relative risk for the dose category, and the error bars show the 95% confidence intervals. The horizontal position of each point gives the mean dose for each interval. The dose–response line was adjusted to pass through the mean dose of the lowest dose interval, which was used for comparison. The fitted regression line for all salivary gland tumors is ERR = −0.45 + (0.19 × dose in Gy); for benign tumors it is ERR = −1.01 + (0.35 × dose in Gy), and for malignant tumors it is ERR = 0.2 − (0.07 × dose in Gy).

The relative risks at 1 Sv were 4.5 for malignant and 1.7 for benign tumors. The strongest dose responses were observed for mucoepidermoid cancers and Warthin's tumors, which accounted for 34% of all malignancies and for 19% of all benign tumors, respectively. In contrast, we found only 2 Warthin's tumors (3%), and the observed dose–response relationship for benign tumors arose from the occurrence of mixed (pleomorphic) adenomas.

The LSS results are not directly comparable to those presented here. The salivary gland doses in the present study, where 73% of the cases (64 of 89) had doses of 4.0 Gy or more, were much higher than the doses in the LSS study, where 93% of the cases (115 of 123) had doses <2.0 Sv. Also, the doses in the LSS were derived in part from neutron irradiation. Given the relatively narrow range of doses in the present study, extrapolation to lower doses may not be justified.

Data on salivary gland tumors from other studies are sparse. In the Rochester, NY, study of children whose thymus glands had been treated with radiation, 8 benign salivary gland tumors had occurred among the irradiated individuals, resulting in a relative risk of 4.4. No dose–response analysis was presented (*20*). Similar results were reported from the study of childhood irradiation for tinea capitis in Israel (*4*), based on a small number of cases (4 malignant and 3 benign salivary gland tumors in 10,902 exposed individuals). In a case-control study of 269 patients with benign

TABLE IV
Variation of the Dose–Response[a] Relationship for All Salivary Gland Tumors with Several Factors

Factor	Cases	ERR/Gy	P value[b]
Overall	89	0.82[c]	
Gender			
Male	51	0.26	
Female	38	∞	0.42
Age at treatment			
<2	14	0.65	0.94
2–3	29	0.82	
4–5	20	0.84	
≥6	26	0.87	
Attained age			
<35	48	∞	0.11
≥35	41	0.08	
Years since treatment			
<25	31	0.97	0.93
25–29	16	0.75	
30–34	20	1.02	
≥35	22	0.85	
Calendar year[d]			
<1974	39	0.81	0.62
≥1974	50	1.00	

[a] Excess relative risk per gray (ERR/Gy) based on Cox regression using age at treatment as entry time and age at event or age at end of follow-up as survival time.
[b] P value for homogeneity.
[c] 95% CI for ERR/Gy was (0.04, ∞).
[d] The ERR for the calendar period after 1974 compared to the period before 1974 was 0.21 (CI = −0.3, 1.2).

parotid gland tumors and 139 patients with malignant parotid gland tumors in Los Angeles County, Preston-Martin *et al.* (*18*) reported relative risks of 5.6 and 1.5, respectively, with exposure >0.5 Gy. The dose response was significant for malignant tumors but not for benign.

In the LSS study, benign tumors were 2.3 times more common than malignant, similar to our ratio of 3.0. This ratio is not well characterized for the general population, but it can be estimated from the case-control study of Preston-Martin (*19*). Correcting for the number of years of ascertainment (4 for benign tumors and 9 for malignant ones) and assuming no selective non-participation in the study, a ratio of 4.4 (benign/malignant) is obtained. Almost all (97%) of the benign neoplasms were mixed tumors, compared with 89% reported here and 75% in the LLS cohort (*22*).

The present study supports a dose–response relationship for benign salivary gland tumors and indicates that mixed pleomorphic adenomas, the most common benign tumor, can be induced by radiation. Because salivary gland tumors are continuing to occur, people who have been exposed to radiation as children should have a careful examination of their salivary glands and should notify their physicians promptly if they develop a mass in the area of the salivary glands.

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