

Background

- Exposure to ionizing radiation is a well known risk factor for salivary gland carcinoma (SGC).
- Children seem more susceptible than older individuals.
- Little quantitative information is available for SGC risk following radiation exposures early in life.
- Few data are available concerning SGC following chemotherapy (CT).
- The role of cigarette smoking is still controversial.

Objectives

- To assess therapy-related risk for SGC and the role of cigarette smoking.

Population

- The current study includes 14,135 5-year survivors of childhood cancer.
- Diagnosed with cancer < 21 years between 1970 and 1986 at 25 institutions in the US and Canada.
- Followed up with self-administered questionnaires from 1994 through 2004.

Exposure assessment

- Information on radiotherapy (RT) and CT (25 agents) abstracted from medical records.
- RT records photocopied.
- Medical physicists used RT data to estimate doses to salivary glands.
- Information on cigarette smoking obtained from questionnaires.

Statistical analysis

- Person years at risk (PYR) beginning 5 years after initial diagnosis and continuing to the earliest of: date of SGC diagnosis, date of death, date of last known follow-up or close of study date (January 1st 2005).
- Standardized Incidence Ratios (SIRs) and associated 95% confidence intervals (CIs) calculated based on age-, sex-, and calendar year- specific incidence rates for US general population (SEER*).
- Relative risks (RRs) within the cohort based on Poisson regression, incorporating incidence rates for general population.

Results

Table 1 : Characteristics of the study population

Characteristics	No of patients	%	Person years of follow-up
All patients	14,135	100	228,439
Gender			
Male	7,585	53.7	120,303
Female	6,550	46.3	108,136
Age of diagnosis of first cancer			
≤4	5,658	32.3	91,524
5-9	3,138	30.1	50,668
10-14	2,869	20.3	46,460
15-20	2,470	17.3	39,787
Original diagnosis			
Leukemia	4,741	33.6	74,003
HL	1,902	13.4	32,414
CNS cancer	1,853	13.1	28,227
Kidney cancer	1,240	8.8	20,794
Soft tissue cancer	1,226	8.7	20,763
Bone cancer	1,175	8.3	18,961
NHL	1,059	7.5	17,316
Neuroblastoma	939	6.7	15,961
Calendar year of diagnosis			
1970-1974	2,544	17.7	55,447
1975-1979	4,070	28.3	73,918
1980-1986	7,748	54.0	99,074
No of patients entering follow-up			
5-9	14,135	100	68,458
10-14	13,279	93.9	63,811
15-19	12,152	86.0	52,677
≥20	8,173	57.8	29,683
Treatment modalities			
No RT, No CT	911	6.4	15,438
CT only	3,022	21.4	46,863
RT only	1,501	10.6	26,915
RT and CT combined	6,934	49.1	112,239
Missing treatment data	1,767	12.5	26,984

Abbreviations: SGC: Salivary gland carcinoma; HL: Hodgkin lymphoma; CNS: Central nervous system; NHL: Non-Hodgkin lymphoma; CT: Chemotherapy; RT: Radiotherapy.

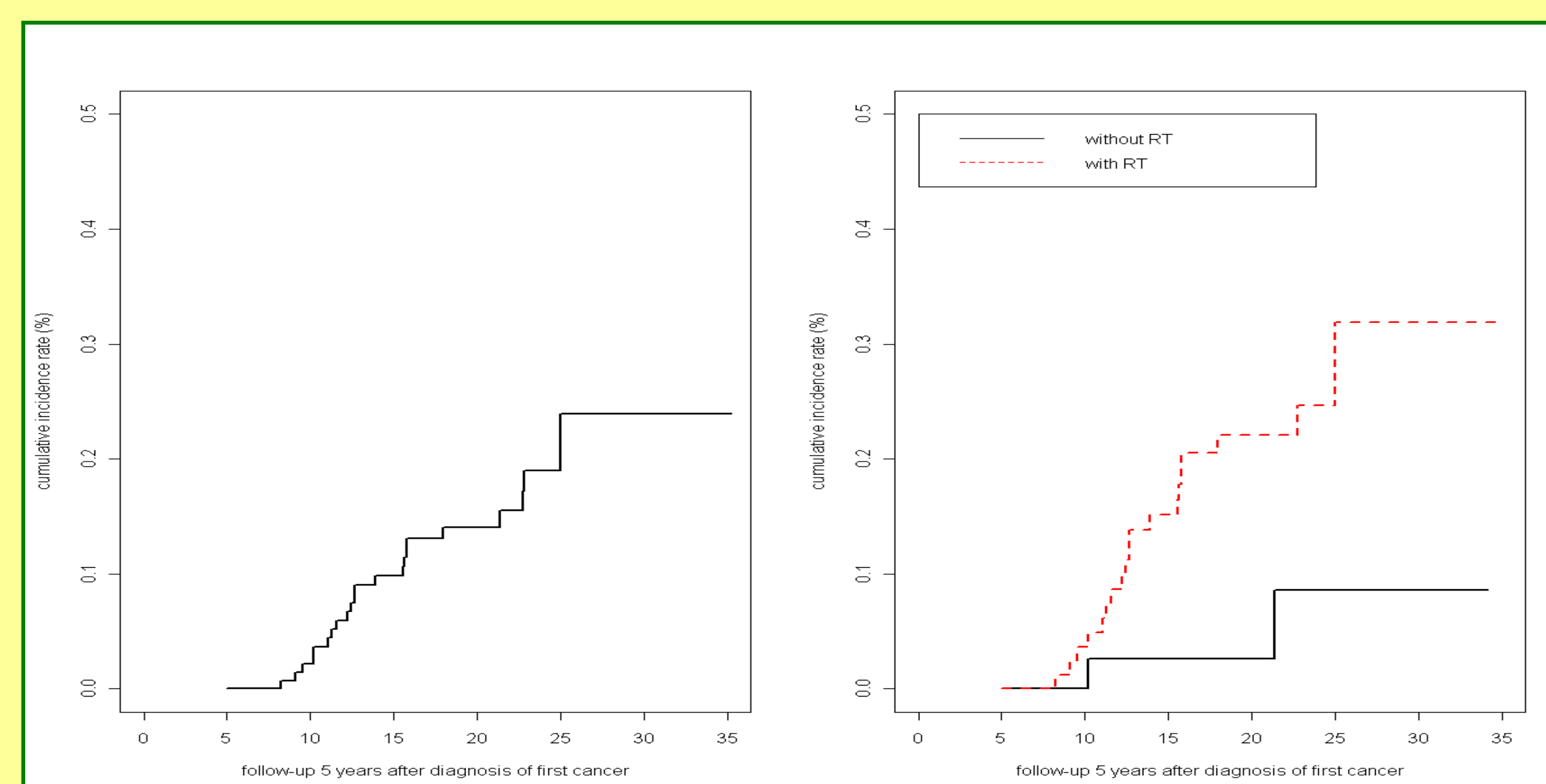


Figure 1: Cumulative incidence of SGC starting 5 years after diagnosis of the first cancer.

Table 2: Risk of subsequent with respect to initial characteristics.

Characteristics	O	SIR	95% CI	RR*	95% CI	P†
All patients	23	39.4	25.0-59.1	~		
Gender						
Male	13	48.7	25.9-83.3	1.0		
Female	10	31.6	15.1-58.1	0.7	0.3-1.6	0.42
Calendar year of diagnosis						
1975-1980	6	28.5	10.5-62.1	1.0		
1981-2005	17	45.5	26.5-72.9	1.6	0.6-4.0	0.41
Age at diagnosis of the primary cancer, yrs						
≤4	9	54.2	24.8-103.0	1.0		
5-9	3	24.2	5.0-70.8	0.5	0.1-1.9	
10-14	3	21.5	4.4-62.8	0.6	0.1-2.7	
15-20	8	51.9	22.4-102.3	2.1	0.5-8.7	0.16‡
Original diagnosis						
Leukemia	10	59.3	28.4-109.0	1.0		
CNS cancer	1	14.3	0.4-79.6	0.2	0.0-1.7	
HL	6	54.0	19.8-117.5	0.8	0.3-3.1	
NHL	4	85.1	23.2-218.0	1.8	0.5-6.5	
Soft tissue cancer	1	17.7	0.5-98.9	0.4	0.1-3.8	
Neuroblastoma	1	35.5	0.9-197.6	0.9	0.1-7.7	0.30
Kidney cancer	0	(E=0.04)	~	~		
Bone cancer	0	(E=0.04)	~	~		
Attained age, yrs						
5-14	6	138.6	50.9-301.7	1.0		
15-19	3	29.4	6.1-86.0	0.2	0.1-0.8	
20-29	7	31.5	12.7-65.0	0.2	0.1-0.6	
≥30	7	32.4	15.4-67.9	0.2	0.1-0.6	0.04‡
Latency, yrs						
5-9	3	31.8	6.6-92.9	1.0		
10-14	10	73.1	35.0-134.4	3.5	0.9-13.0	
15-20	5	32.3	10.5-75.4	2.5	0.5-12.2	
>20	5	32.3	8.2-59.1	2.8	0.5-17.2	0.36‡
Histologic subtype						
Mucoepidermoid carcinoma	14	57.7	31.6-96.8	1.0		
Adenocarcinoma	3	171.1	35.3-499.9	2.78	0.79-9.73	
Acinar cell carcinoma	3	16.9	3.5-49.5	0.30	0.1-1.04	
Other¶	3	13.8	2.9-40.3	0.23	0.1-0.80	0.004
Pack years smoked						
Never smoked	17	41.4	24.1-66.2	1.0		
0.05-4	0	(E=0.03)	~	~		
4.2-9.6	2	60.6	7.3-218.8	1.49	0.3-6.5	
>9.6	2	47.2	5.7-170.4	1.09	0.2-4.8	
Unknown	2	88.0	10.7-317.8	2.34	0.5-10.2	>0.5‡

Abbreviations: O: Observed number of cases; E: Expected number of cases; O/E: Observed-to-expected ratio; CI: confidence interval; RR: Relative risk; HL: Hodgkin lymphoma; CNS: central nervous system; NHL: non-Hodgkin lymphoma ~: not applicable.
 *All risks were adjusted for radiation dose, tobacco smoking and attained age
 † PHET: P for heterogeneity (refer to text for details).
 ‡ P trend P for trend (refer to text for details).
 ¶ Patients were included in the study and followed-up if they survived at least 5 years after diagnosis of the primary
 § Patients were included in the study if they survived at least 5 years after diagnosis of their first cancer.
 Other histologic subtypes included carcinoma, NOS (M-8010), epithelial-myoepithelial carcinoma (M-8562), and mixed tumor, NOS (M-8940).

Table 3: Risk of subsequent SGC with respect to treatment for initial cancer.

Characteristics	O	SIR	95% CI	RR*	95% CI	P†
Radiation dose, Gy						
0	2	13.1	1.6-47.5	1.0		
>0-1.2	0	(E=0.09)	~			
1.3-2.9	5	54.5	17.7-127.1	4.1	0.8-21.0	
3-1.14	5	73.5	23.9-171.5	6.1	1.2-30.8	
1.15-8.0	8	73.5	31.7-144.7	7.7	1.6-38.1	
Unknown	3	39.9	12.9-123.6	3.1	0.5-18.7	0.002‡
Anthracyclines, mg/m²						
None	11	32.8	16.4-58.7	1.0		
0.12-174	2	56.1	6.8-202.7	1.6	0.4-7.5	
175-290	2	48.1	5.8-173.6	1.5	0.3-6.9	
291-390	3	70.1	14.5-204.8	2.4	0.7-8.6	
391-8370	2	40.7	4.9-147.0	1.6	0.3-7.3	
Missing	3	37.9	7.8-110.8	0.4	0.09-1.7	0.46‡
Alkylating agent dose, mg/m²						
None	5	19.5	6.3-45.4	1.0		
0-3280	5	102.2	33.2-238.4	4.3	1.2-15.0	
3281-6825	4	65.4	17.8-167.4	3.1	0.8-11.5	
6826-12500	3	53.1	11.0-155.3	2.4	0.6-10.2	
>12500	3	53.8	11.1-157.3	2.7	0.6-11.2	
Missing	3	28.8	5.9-84.2	1.8	0.4-8.9	0.28‡

Conclusions

- Largest study to date to assess risk of SGC after childhood cancer and the first to investigate the effects of cigarette smoking.
- Risk positively associated with high dose RT and CT.
 - Dose response for RT but not for CT.
- The first study to suggest an increased risk of radiation-related adenocarcinoma compared with mucoepidermoid; however this observation is based on only 3 cases of adenocarcinoma.
- No statistical evidence of cigarette smoking effect.
- Because of the limited number of SGC cases, a pooled investigation including various cohorts would provide a reasonable number of SGC cases and will improve estimates.