



## Radiotherapy for oral cancer as a risk factor for second primary cancers

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### Abstract

Radiation exposure, known to cause DNA damage, may be a potential source of field cancerization of the upper aerodigestive tract. Radiotherapy for head and neck cancers has been examined as a possible risk factor for second primary cancers, but the results have been equivocal. We evaluated the impact of therapeutic radiation for oral cancer on the risk of second primary cancers with data from the Surveillance, Epidemiology, and End Results (SEER) program for 1973–1999. Among 30,221 first primary oral squamous cell carcinoma patients, 6163 (20.4%) patients developed a second primary cancer, 5042 of which were metachronous. Patients treated with radiation only (RR = 1.64, 95%CI = 1.18–2.29) or radiation with surgery (RR = 1.49, 95%CI = 1.07, 2.06) had elevated risks of developing a second primary tumor, whereas patients treated with surgery only did not appear to be at increased risk (RR = 1.28, 95%CI = 0.93, 1.76). Consistent with an expected latent period between radiation exposure and tumor occurrence, radiation became a risk factor after 10 years of follow-up for solid cancers of the oral cavity (RR = 2.8, 95%CI = 1.5, 5.2), pharynx (RR = 5.9, 95%CI = 1.7, 20.7), esophagus (RR = 3.9, 95%CI = 1.1, 13.4) and lung (RR = 1.5, 95%CI = 1.0, 2.4), and after 1–5 years of follow-up for second primary leukemia (RR = 2.5, 95%CI = 1.0, 6.7). Radiotherapy for oral cancer appears to be a risk factor for second primary tumors. Further studies that account for chemotherapy and examine frequency and duration of radiotherapy would be of interest in confirming the observed association. © 2004 Elsevier Ireland Ltd. All rights reserved.

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### 1. Introduction

The most frequent type of radiotherapy treatment for oral cancer patients, external beam radiation, delivers X-radiation and gamma radiation, which

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have been classified as human carcinogens [1]. Radiation exposure causes DNA strand breakage, chromosomal aberrations, mutations, and overall genetic instability [2]. In this context, radiation therapy is a potential source of field cancerization of the upper aerodigestive tract. Field cancerization is a proposed mechanism for the development of independent multiple premalignant lesions and tumors in the head and neck suggesting that the upper aerodigestive tract epithelium undergoes simultaneous genetic changes due to common carcinogenic exposures [3].

The effects of radiation exposure are dependent upon the tissue type exposed [1]. Proliferating cells such as those of the hematopoietic system and intestinal epithelium are most sensitive to radiation. Leukemia tends to develop a few years after radiation exposure, with the risk declining after 10 years, whereas the proposed latent period for the initiation of solid cancers is generally 10 years and the risk may persist over a long period, though the quality of the data beyond 25 years of follow-up after radiation exposure may be limited.

The typical mode of treatment for early stage oral cancers is radiation therapy or surgery alone whereas advanced oral cancer is often resected by surgery, followed by administration of postoperative external beam radiotherapy or brachytherapy [4,5]. External beam radiation involves radiation delivery via radiation therapy ports to the tumor as well as overlapping normal structures by linear accelerators, which are placed outside of the patient [6]. Brachytherapy, also referred to as interstitial radiation therapy, allows the delivery of high doses of radiation to the tumor, with minimal doses to the surrounding normal tissues, by placing a radiation source such as interstitial or intracavitary implants in the tumor target. A variety of radioactive isotopes are available, but the most commonly used isotopes are Iridium-192 and Iodine-125 [7,8]. Chemotherapy may be administered as adjuvant treatment, as a follow-up treatment after the primary treatment. Patients with unresectable head and neck tumors or questionable tumor margins and positive nodal involvement postsurgically are usually treated with radiotherapy alone, or a combination of chemotherapy and radiotherapy [9], provided that the patient can withstand the toxicity of concurrent therapy, as radiotherapy and chemotherapeutic agents may possibly interact with one another [10].

Studies examining the association between radiotherapy for a first primary head and neck cancer and the risk of developing second primary cancers have been conflicting [11]. Standardized incidence ratios (SIRs) for second primary tumors within the head and neck were elevated for both Caucasian men and women who had received radiation therapy for the first primary (including all histologies) according to a study using US SEER (Surveillance, Epidemiology, and End Results) data (1973–1989) [12]. This study showed an excess incidence of second primary head and neck cancer cases among subjects who received radiation therapy and subjects who did not. However, the excess may not be specifically attributed to radiotherapy because the SIRs for the two groups cannot be compared as they were standardized to different distributions of person-years. In a retrospective cohort study conducted in the UK, a difference was not observed between the proportion of subjects who received radiotherapy as the primary treatment in subjects who had one HNSCC (squamous cell carcinoma of the head and neck) primary and subjects who had a second primary in the head and neck following a HNSCC [13]. Another study conducted with SEER data from 1973 to 1984 observed lower survival among second primary head and neck cases who had received radiotherapy for the first primary squamous cell carcinoma of the head and neck (median survival=20 months) compared to cases that were treated by surgery (median survival=35 months) [14]. The authors proposed that radiation-induced DNA damage might have caused the tumors developing after radiotherapy exposure to be more aggressive, thus leading to higher (or possibly earlier) mortality. A study on first primary laryngeal cancer cases with SEER data (1973–1996) reported that radiotherapy conferred an age-adjusted RR (relative risk) of 1.68 (95%CI=1.16, 2.43) for developing second primary head and neck cancers, among patients who survived more than 5 years [15].

Considering that the survival rate of subjects with multiple primary tumors is worse than subjects with only one primary tumor [13], preventing the second primary tumor is crucial for the patient. It is of interest to determine whether therapeutic radiation causes cancers in the field of radiation and beyond. In this study, our aim was to evaluate the impact of therapeutic radiation for oral cancer, on the risk of

subsequent second primary cancers of various sites, not limited to the head and neck. Previous studies often focused only on head and neck sites for second primaries, had not estimated RRs for radiotherapy, or had not adjusted for various potential confounders. We used the SEER data for 1973–1999 to estimate the risk of second primary tumors due to radiotherapy, adjusting for potential confounders such as age at diagnosis, sex, and tumor grade and stage. We focused on squamous cell carcinomas, the predominant histological type of first primary oral cancers, since etiology may differ by histology.

## 2. Methods

### 2.1. Study population

The SEER program identified 35,015 first primary oral cancer cases (ICD-9 140–145) from 1973 to 1999. As outlined in Fig. 1, a total of 4794 subjects were excluded from our analysis, due to one or more of the following reasons: (1) histology was not SCC ( $n=3467$ ), (2) data was missing on the second cancer ( $n=466$ ) or survival time for patients with the first cancer ( $n=155$ ), (3) the second primary tumor was in situ ( $n=394$ ), or (4) the date of the second primary was earlier than the first cancer ( $n=496$ ). Of the 30,221 subjects with a first primary oral SCC included in the analysis, 6163 (20.4%) subjects developed a second primary cancer of various sites and 11,498 were treated with radiation, primarily with beam radiation. The SEER program rules for determining second primary tumors are based on histology and site. Two cancers of the same histology at different sites and two cancers of the same histology and same site diagnosed after 2 months are considered second primaries. Cancers that have different histology are always considered independent primaries whether they occur simultaneously or at different times. To minimize the possibility of including subjects with metastases or recurrence, we censored synchronous cases, which are cases diagnosed with the second primary cancer within 6 months after the diagnosis of the first primary cancer ( $n=1121$ ). Thus, for our analysis 5042 cases with a metachronous second primary cancer, defined as second primaries diagnosed after 6 months, remained in this study.

The definition for the different types of radiation therapy in the SEER data are as follows [16]: (1) *Beam radiation*. ‘Beam radiation directed to cancer tissue regardless of source of radiation, included is treatment via X-ray, Cobalt, Linear accelerator, Neutron beam, Betatron, Spray radiation, Stereotactic radiosurgery such as gamma knife and proton beam’. (2) *Radioactive implants*. ‘Interstitial implants, molds, seeds, needles, or intracavitary applicators of radioactive material such as cesium, radium, radon, or radioactive gold’. (3) *Radioisotopes*. ‘Internal use of radioisotopes, such as Iodine-131 or Phosphorus-32, when given orally, intracavitarily, or by intravenous injection’.

### 2.2. Statistical analysis

Proportional hazards analysis comparing subjects exposed to radiation treatment and subjects not exposed to radiation treatment was used to obtain maximum likelihood estimates of relative risks (RRs) and 95% confidence intervals (95%CI) to assess the association of radiation therapy with second primary tumors. Age at first diagnosis, race/ethnicity, sex, tumor grade, SEER stage, surgery and decade of diagnosis were considered potential confounders since they were associated with radiotherapy status (Table 1) and were also risk factors for second primary cancers (Table 3). Thus, covariates included in the adjusted

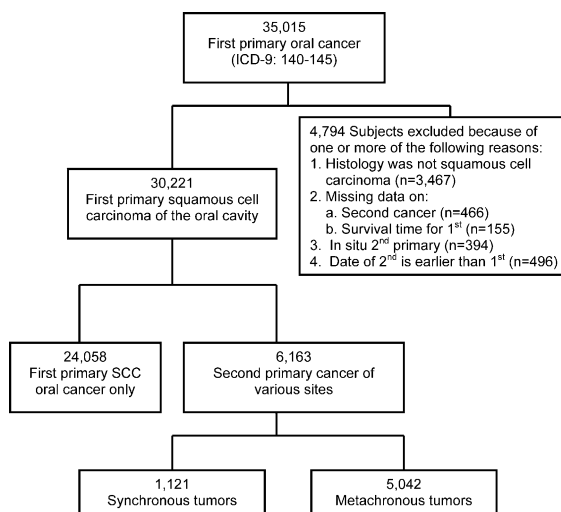


Fig. 1. Exclusion criteria for first primary oral cancer and subsequent second primaries in SEER data, 1973–1999.

Table 1

Factors that may affect radiotherapy administration among primary oral cancer patients ( $n=30,221$ )

	No radiation		Beam radiation		Other types of radiation		Missing	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
<i>Age at first diagnosis</i>								
< 60	6081	52.5	4628	41.0	577	5.0	288	2.5
60–69	4934	54.6	3483	38.5	445	4.9	182	2.0
70–79	3867	60.3	2201	34.3	223	3.5	122	1.9
≥ 80	2046	64.1	972	30.5	100	3.1	72	2.3
Missing	0		0		0		0	
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Sex</i>								
Male	12,267	57.2	7782	36.3	900	4.2	484	2.3
Female	4661	53.0	3502	39.9	445	5.1	180	2.1
Missing	0		0		0		0	
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Race</i>								
White	15,400	58.1	9401	35.5	1176	4.4	538	2.0
Black	851	34.4	1429	57.8	87	3.5	104	4.2
Other	470	47.3	432	43.5	79	8.0	13	1.3
Missing	207	85.9	22	9.1	3	1.2	9	3.7
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Grade</i>								
I	5528	70.3	1947	24.8	253	3.2	138	1.8
II	4862	48.8	4434	44.5	471	4.7	193	1.9
III	1374	34.2	2313	57.5	233	5.8	100	2.5
IV	60	34.7	98	56.7	10	5.8	5	2.9
Missing	5104	62.2	2492	30.4	378	4.6	228	34.3
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Stage</i>								
Local	10,785	77.8	2448	17.7	512	3.7	126	0.9
Regional	4040	35.1	6571	57.0	627	5.4	287	2.5
Distant	583	28.2	1337	64.6	75	3.6	76	3.7
Missing	1520	55.2	928	33.7	131	4.8	175	6.4
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Surgery</i>								
None	2073	24.5	5100	60.4	924	10.9	352	4.2
Yes	14,804	68.5	6101	28.2	414	1.9	291	1.4
Missing	51	31.5	83	51.2	7	4.3	21	13.0
$\chi^2$ <i>P</i> -value	<0.0001							
<i>Year of diagnosis</i>								
1973–1979	4387	55.5	2824	35.8	417	5.3	272	3.4
1980–1989	6765	58.2	4108	35.4	508	4.4	240	2.1
1990–1999	5776	54.0	4352	40.7	420	3.9	152	1.4
Missing	0		0		0		0	
$\chi^2$ <i>P</i> -value	<0.0001							

The  $\chi^2$  test was used to test differences in the three groups of no radiation, beam radiation, and other types of radiation.

models were: age at first diagnosis (years), race/ethnicity (white, black, others), sex, tumor grade (I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated/anaplastic), SEER stage (in situ, localized, regional, distant,

localized/regional, unstaged), surgery (none, yes) and decade of diagnosis (1970s, 1980s, 1990s). Information on chemotherapy is not available in the SEER public use data because it has become more difficult and costly to collect this information as chemotherapy

administration is conducted more frequently in the oncologist or physician's office instead of the hospital. SEER has conducted a substudy to examine patterns of cancer care and confirmed an underreporting of chemotherapy [17]. Information on cigarette smoking and alcohol drinking is also not available in the SEER data.

### 3. Results

Approximately, 41.8% ( $n=12,629$ ) of the 30,221 first primary oral SCC patients received radiation

therapy, with the majority (84.9%) receiving beam radiation. A combination of beam radiation with radioactive implants or radioisotopes was the second most common type of radiotherapy administered. A higher proportion of patients diagnosed with oral cancer at a younger age received radiotherapy (Table 1). Women and African-Americans were also treated with radiotherapy treatment at a higher proportion. As expected, cancer patients who had higher grade or stage were more likely to have radiotherapy. Among all primary oral cancer patients, 20.0% ( $n=6024$ ) were treated with radiation only, 49.0% ( $n=14,804$ ) were treated with surgery only

Table 2  
Sites for second primary cancers following a first primary oral cancer

	Male		Female		Total	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
<i>Major sites</i>						
Oral cavity and pharynx	612	16.4	298	22.6	910	18.1
Digestive system	599	16.1	203	15.4	802	15.9
Pancreas	54		18		72	
Stomach	69		16		85	
Colon	241		69		310	
Liver and intrahepatic bile duct	108	2.9	41	3.1	149	3.0
Respiratory	1146	30.8	345	26.2	1491	29.6
Lung	971		315		1286	
Skin excluding basal and squamous	83	2.2	12	0.9	95	1.9
Breast	4	0.1	195	14.8	199	4.0
Female genital system	0	0.0	79	6.0	79	1.6
Male genital system	629	16.9	0	0.0	629	12.5
Prostate	621		0		621	
Urinary	253	6.8	40	3.0	293	5.8
Bladder	195		25		220	
Brain and nervous system	14	0.4	6	0.5	20	0.4
Endocrine	10	0.3	3	0.2	13	0.3
Lymphoma	114	3.1	38	2.9	152	3.0
Leukemia	56	1.5	17	1.3	73	1.5
Other	97	2.6	40	3.0	137	2.7
Total	3725	100.0	1317	100.0	5042	100.0
<i>Head &amp; neck sites</i>						
Oral	430	50.4	226	60.6	656	53.5
Lip	77		13		90	
Tongue	128		75		203	
Salivary gland	22		6		29	
Floor of mouth	63		36		99	
Gum and other mouth	140		96		236	
Nasopharynx	6	0.7	3	0.8	9	0.7
Pharynx	118	13.8	41	11.0	159	13.0
Larynx	133	15.6	26	7.0	159	13.0
Esophagus	167	19.6	77	20.6	244	19.9
Total	832	100.0	367	100.0	1199	100.0

and 21.6% ( $n=6515$ ) were treated with both surgery and radiation. There appears to be a steady increase in the percentage of patients who get treated with both surgery and radiation from the 1970s (16.3%) through the 1980s (20.3%) to the 1990s (26.7%; not shown in table).

The distribution of second primary sites following a first primary oral cancer are shown in Table 2. The most prominent sites for second primaries include the oral cavity and pharynx, as well as the respiratory tract, for both men and women. Second primaries were also common at the breast for women and the prostate for men. Within upper aerodigestive tract sites, oral cancer was the most common second primary site followed by the esophagus.

Beam radiation for the first primary oral cancer appeared to be a moderate risk factor for any type of second primary cancer (RR of 1.2; 95%CI=1.1, 1.4), after adjustment for age at diagnosis, sex, race, grade, stage, surgery and decade of diagnosis (Table 3). Higher grade and stage at diagnosis of the first primary oral cancer and older age at first diagnosis were related to increased risk for second primary tumors.

Patients who received radiotherapy only had a slightly higher risk of second primary cancers compared to patients who received radiotherapy with surgery, but patients who were treated with surgery only did not have an elevated risk of second primaries (Table 4). In the analysis stratified by stage, these associations were observed only in patients who were diagnosed with a first primary oral cancer at local stage. When we further stratified by grade, we observed increased risks only for patients whose tumors were local stage and grade I; the RRs were 2.35 (95%CI=1.19, 4.62) for treatment by radiation therapy only, 1.71 (95%CI=0.92, 3.19) for surgery only and 2.11 (1.09, 4.11) for radiation therapy and surgery (not shown).

Site-specific estimates indicated that risks due to radiotherapy for second primary cancers were elevated in head and neck sites such as the tongue, floor of mouth and esophagus (Table 5). Radiotherapy was also associated with an increased risk for second primary cancers at other major sites, specifically the lung, colon, and liver in both genders and the breast in women. The strongest overall associations were observed for second primary brain cancer

(RR=4.8, 95%CI=1.0, 22.8) and leukemia (RR=2.3, 95%CI=0.9, 5.5) in men. While the point estimates of effect for women at these sites were close to the null value of one, the confidence intervals

Table 3

Characteristics of first primary oral cancers as possible risk factors for a second primary cancer

	Second primary	First primary oral	Adjusted RR <sup>a</sup> (95%CI)
Total	5042	30,221	
<i>Radiation</i>			
None	3247	16,928	1.0
Beam	1501	11,284	1.2 (1.1, 1.4)
Other	211	1345	1.1 (0.9, 1.4)
Missing	83	664	
<i>Age at first diagnosis</i>			
<60	1865	11,574	1.0
60–69	1813	9044	1.6 (1.5, 1.7)
70–79	1065	6413	1.7 (1.6, 1.9)
≥80	299	3190	1.5 (1.2, 1.7)
<i>P for trend</i>			<0.0001
<i>Sex</i>			
Male	3725	21,433	1.0
Female	1317	8788	0.8 (0.8, 0.9)
<i>Race</i>			
White	4564	26,515	1.0
Black	366	2471	1.7 (1.5, 1.9)
Other	106	994	0.7 (0.5, 0.8)
Missing	6	241	
<i>Grade</i>			
I	1368	7866	1.0
II	1583	9960	1.3 (1.2, 1.4)
III	529	4020	1.3 (1.1, 1.4)
IV	22	173	1.4 (0.9, 2.1)
Missing	1540	8202	
<i>P for trend</i>			<0.0001
<i>Stage</i>			
Local	2821	13,871	1.0
Regional	1642	11,525	1.1 (1.0, 1.2)
Distant	161	2071	1.1 (0.9, 1.4)
Missing	418	2754	
<i>P for trend</i>			0.0582
<i>Surgery</i>			
None	968	8449	1.0
Yes	4054	21,610	1.0 (0.9, 1.1)
Missing	20	162	
<i>Year of diagnosis</i>			
1973–1979	1787	7900	1.0
1980–1989	2248	11,621	1.0 (0.9, 1.0)
1990–1999	1007	10,700	0.9 (0.8, 1.0)
<i>P for trend</i>			0.1959

<sup>a</sup> Adjusted for all other covariates in table.

Table 4  
Treatment and the risk of second primary cancers following a primary oral cancer, stratified by stage

	Second primary	First primary oral	Adjusted RR <sup>a</sup> (95%CI)
<i>Overall</i>			
None	187	2073	1.00
Radiation only	738	6024	1.64 (1.18, 2.29)
Surgery only	3050	14,804	1.28 (0.93, 1.76)
Radiation+ surgery	965	6515	1.49 (1.07, 2.06)
Missing	102	703	
<i>Local stage</i>			
None	62	423	1.00
Radiation only	245	1343	1.74 (1.13, 2.69)
Surgery only	2205	10,350	1.29 (0.85, 1.95)
Radiation+ surgery	283	1604	1.51 (0.98, 2.32)
Missing	26	125	
<i>Regional stage</i>			
None	23	565	1.00
Radiation only	348	3205	1.36 (0.79, 2.33)
Surgery only	665	3458	1.12 (0.66, 1.90)
Radiation+ surgery	569	3941	1.30 (0.76, 2.21)
Missing	37	319	
<i>Distant stage</i>			
None	3	280	1.00
Radiation only	55	777	4.10 (0.55, 30.58)
Surgery only	31	297	2.62 (0.35, 19.72)
Radiation+ surgery	66	621	3.61 (0.49, 26.52)
Missing	6	90	

<sup>a</sup> Adjusted for age, sex, race, grade, surgery and year of diagnosis.

for women were wide and included the point estimates of the men, suggesting that the smaller sample size in women resulted in low statistical power limiting the estimation of risks for women at these sites.

Further stratification by follow-up time revealed that radiotherapy seemed protective in the first year of follow-up (RR=0.6, 95%CI=0.5, 0.8), but the risks of all second primary cancers were elevated after 10 or more years of follow-up (RR=1.5, 95%CI=1.2, 1.9; Table 6) and specifically for oral, pharynx and lung second primaries. The increased risk for lung cancer seems to start after 1 year of follow-up, though the confidence interval included the null. Five to 10 years after the first primary diagnosis, the RRs for liver, esophageal and digestive tract cancers were elevated in relation to radiation. The risk of leukemia increased in years 1–5 of follow-up

(RR=2.5, 95%CI=1.0, 6.7), and subsequently declined during later follow-up periods.

When we stratified by age at diagnosis (results not shown in tables), the RR of developing a second primary at any site after a first primary oral cancer did not seem to be elevated (RR=1.21, 95%CI=0.56, 2.63) due to radiotherapy for subjects under 40 years of age. However, the sample size was limited relative to the other strata, with 49 patients developing second primaries among 705 first primary oral cancers. Subjects diagnosed at 40–49 years of age had the highest RR for radiation therapy (358 second primaries/2616 first primary oral cancers, RR=1.5, 95%CI=1.2, 2.0), while the risk in subjects who were 50–59 years (842/4751, RR=1.22, 95%CI=1.03, 1.46), 60–69 years (1188/5973, RR=1.22, 95%CI=1.06, 1.42) and ≥70 years (878/6257, RR=1.19, 95%CI=0.99, 1.44) were more moderately elevated.

#### 4. Discussion

According to our results, radiation therapy for a first primary oral cancer was a risk factor for various types of second primary cancers. Consistent with an expected latent period between radiation exposure and the initiation of a solid second primary tumor, radiotherapy became a risk factor after 10 or more years of follow-up for solid cancers. Curiously, radiation was protective against a second primary cancer within the first year of follow-up. Perhaps, radiotherapy leads to destruction of all cancer cells in the irradiated area, or patients treated with radiotherapy might have higher mortality so that the second primary tumors might not have enough time to develop. The suggestion of an increased risk for lung cancer after 1 year of follow-up may point to a cancer promoting effect, not just an initiating effect for this site. The observed increased risk of second primary leukemia during 1–5 years of follow-up was consistent with the latent period expected for hematopoietic cancers.

The risk of second primary cancers was increased among patients who had received radiotherapy alone or with surgery, but not among patients who received surgery only. The specific second primary sites for which radiation therapy was a risk factor included cancers of the oral cavity, pharynx, esophagus, lung,

Table 5  
Radiation for the first primary oral cancer and the risk of specific second primary cancers, stratified by sex

	Women		Men		Overall	
	<i>n</i>	RR <sup>a</sup> (95%CI)	<i>n</i>	RR <sup>a</sup> (95%CI)	<i>n</i>	RR <sup>b</sup> (95%CI)
<i>Head neck second primary sites</i>						
Oral	153	0.9 (0.6, 1.4)	275	1.7 (1.2, 2.3)	428	1.4 (1.1, 1.7)
Lip	6	0.5 (0.1, 4.9)	48	0.6 (0.2, 1.5)	54	0.5 (0.2, 1.4)
Tongue	56	1.1 (0.6, 2.2)	85	2.3 (1.4, 4.0)	141	1.7 (1.1, 2.6)
Salivary gland	3	–	11	1.5 (0.3, 8.4)	14	0.7 (0.1, 3.6)
Floor of mouth	27	0.8 (0.3, 2.2)	50	3.0 (1.5, 6.2)	77	1.8 (1.0, 3.3)
Gum and other mouth	64	1.0 (0.5, 1.8)	92	1.5 (0.9, 2.6)	156	1.3 (0.8, 1.9)
Nasopharynx	1	–	5	1.0 (0.1, 9.6)	6	1.0 (0.1, 8.2)
Pharynx	28	1.2 (0.5, 3.3)	78	1.1 (0.6, 1.9)	106	1.2 (0.7, 1.9)
Larynx	20	1.1 (0.4, 3.3)	76	1.1 (0.6, 2.1)	96	1.1 (0.7, 1.9)
Esophagus	53	1.8 (1.0, 3.4)	108	2.0 (1.2, 3.2)	161	1.9 (1.3, 2.8)
<i>Other major sites</i>						
Digestive system	132	1.3 (0.8, 1.9)	382	1.4 (1.1, 1.9)	514	1.4 (1.1, 1.8)
Pancreas	9	1.3 (0.2, 8.6)	31	1.2 (0.5, 3.2)	40	1.3 (0.6, 3.1)
Stomach	11	0.3 (0.1, 1.8)	39	1.5 (0.6, 3.5)	50	1.0 (0.5, 2.2)
Colon	45	1.5 (0.7, 3.0)	155	1.5 (1.0, 2.3)	200	1.5 (1.0, 2.2)
Liver and intrahepatic bile duct	24	1.7 (0.6, 4.6)	66	1.5 (0.8, 2.8)	90	1.6 (0.9, 2.7)
Respiratory	239	1.5 (1.1, 2.0)	764	1.4 (1.2, 1.7)	1003	1.4 (1.2, 1.7)
Lung	215	1.5 (1.1, 2.1)	662	1.5 (1.2, 1.8)	877	1.5 (1.3, 1.8)
Skin excluding basal and squamous	8	1.0 (0.2, 6.4)	47	1.5 (0.7, 3.5)	55	1.4 (0.7, 3.0)
Breast	127	1.4 (0.9, 2.1)	4	2.8 (0.2, 32.6)	131	1.4 (0.9, 2.2)
Female genital system	49	1.1 (0.5, 2.2)	–	–	–	–
Male genital system	–	–	384	0.8 (0.6, 1.1)	–	–
Prostate	–	–	381	0.9 (0.7, 1.2)	–	–
Urinary	28	1.7 (0.7, 4.2)	145	0.8 (0.6, 1.1)	173	0.9 (0.6, 1.4)
Bladder	20	1.5 (0.5, 4.4)	106	0.7 (0.4, 1.4)	126	0.9 (0.5, 1.5)
Brain and nervous system	3	1.1 (0.0, 38.7)	10	4.8 (1.0, 22.8)	13	3.6 (0.8, 15.3)
Endocrine	2	0.4 (0.0, 24.3)	5	1.2 (0.1, 11.7)	7	1.0 (0.1, 6.8)
Lymphoma	22	1.5 (0.6, 4.0)	73	0.9 (0.5, 1.8)	95	1.1 (0.6, 1.8)
Leukemia	12	1.2 (0.3, 5.2)	33	2.3 (0.9, 5.5)	45	1.8 (0.9, 3.9)

*n* = observed number of second primaries, reference group is subjects who did not receive radiotherapy for the first primary oral cancer.

<sup>a</sup> Adjusted for age, race, grade, stage, surgery and year of diagnosis.

<sup>b</sup> Adjusted for age, sex, race, grade, stage, surgery and year of diagnosis.

colon, liver, brain, and nervous system. Development of leukemia and second primary cancers in the irradiated head and neck area is biologically plausible with potential mechanisms such as DNA damage. In contrast, the increased risk of colon, liver and lung cancers due to radiotherapy was unexpected and may be due to radiotherapy exposure beyond the intended field or reduced immune function due to radiotherapy treatment [18]. Another possible mechanism for out-of-field second primary cancer occurrence is the radiation-induced bystander effect, where cells that have not been directly exposed to radiation may

exhibit effects of having been exposed to radiation, such as chromosome instability and mutations [19,20]. One possible explanation for these associations is confounding by chemotherapy, which can be given concurrently with radiotherapy. Some chemotherapy agents used to treat oral cancer, such as cisplatin, are known animal carcinogens [21]. Although, it would be of interest to study the influence of other therapies such as chemotherapy as a combination treatment on the effect of radiation, the SEER Public use database does not include information on the first course chemo- and hormonal

Table 6  
Radiation and the risk of specific second primary cancers, stratified by years of follow-up

	RR <sup>a</sup> (95%CI) 6 months–1 year	RR <sup>a</sup> (95%CI) 1–5 years	RR <sup>a</sup> (95%CI) 5–9 years	RR <sup>a</sup> (95%CI) ≥ 10 years
Second cancer /total	417/7979	2360/11,431	1401/5616	864/5195
<i>Overall</i>				
None	1.0	1.0	1.0	1.0
Beam	0.6 (0.5, 0.8)	0.9 (0.8, 1.1)	1.1 (0.9, 1.3)	1.5 (1.2, 1.9)
Other	0.6 (0.3, 1.1)	0.9 (0.7, 1.2)	1.6 (1.1, 2.3)	1.1 (0.7, 1.8)
<i>By site</i>				
Oral cancer	0.4 (0.2, 0.8)	0.9 (0.7, 1.3)	1.1 (0.7, 1.8)	2.8 (1.5, 5.2)
Pharynx	0.3 (0.0, 1.7)	0.5 (0.3, 1.1)	1.4 (0.6, 3.4)	5.9 (1.7, 20.7)
Larynx	0.3 (0.1, 2.1)	0.6 (0.3, 1.1)	1.8 (0.7, 4.7)	4.0 (0.8, 20.6)
Esophageal	1.2 (0.3, 4.0)	0.7 (0.4, 1.2)	3.3 (1.7, 6.5)	3.9 (1.1, 13.4)
Digestive system	1.1 (0.5, 2.2)	0.9 (0.7, 1.3)	1.5 (1.0, 2.2)	1.0 (0.5, 2.0)
Pancreas	0.7 (0.1, 7.7)	0.7 (0.2, 2.1)	1.5 (0.2, 10.2)	4.0 (0.2, 87.3)
Stomach	0.4 (0.0, 7.1)	1.0 (0.4, 2.7)	0.6 (0.1, 2.8)	0.5 (0.0, 7.8)
Colon	1.9 (0.5, 6.7)	1.2 (0.7, 2.0)	1.2 (0.6, 2.3)	0.8 (0.3, 2.3)
Liver and intrahepatic bile	1.2 (0.2, 8.0)	0.8 (0.4, 1.7)	2.8 (1.0, 8.2)	1.6 (0.3, 8.3)
Respiratory	0.5 (0.3, 0.9)	1.1 (0.9, 1.3)	1.3 (0.9, 1.8)	1.6 (1.0, 2.5)
Lung	0.6 (0.4, 1.1)	1.2 (0.9, 1.4)	1.3 (0.9, 1.8)	1.5 (1.0, 2.4)
Skin excluding basal and squamous	1.4 (0.2, 9.6)	1.0 (0.4, 2.6)	0.4 (0.0, 6.7)	1.9 (0.4, 9.1)
Breast	0.8 (0.2, 3.0)	1.3 (0.7, 2.3)	0.6 (0.3, 1.5)	1.9 (0.6, 5.9)
Female genital system	1.0 (0.1, 8.5)	0.8 (0.3, 1.9)	0.6 (0.1, 2.8)	–
Male genital system	0.4 (0.1, 1.0)	0.7 (0.5, 1.1)	0.6 (0.3, 1.0)	0.7 (0.3, 1.7)
Prostate	0.4 (0.1, 1.1)	0.7 (0.5, 1.1)	0.6 (0.3, 1.0)	0.8 (0.3, 1.8)
Urinary	0.3 (0.1, 0.9)	0.8 (0.4, 1.4)	0.6 (0.2, 1.5)	1.5 (0.5, 4.8)
Bladder	0.2 (0.1, 1.0)	0.8 (0.4, 1.6)	0.6 (0.2, 1.7)	0.7 (0.1, 3.5)
Brain and nervous system	–	4.6 (0.3, 66.1)	3.7 (0.2, 56.5)	5.7 (0.4, 73.2)
Endocrine	0.2 (0.0, 3.0)	0.8 (0.1, 9.4)	–	–
Lymphoma	0.2 (0.0, 0.9)	0.9 (0.4, 1.8)	1.5 (0.5, 4.2)	0.4 (0.0, 2.8)
Leukemia	0.5 (0.0, 6.5)	2.5 (1.0, 6.7)	1.1 (0.2, 4.9)	–

Reference group is a subject who did not receive radiotherapy for the first primary oral cancer.

<sup>a</sup> Adjusted for age, sex, race, grade, stage, surgery and year of diagnosis.

therapy because it was considered largely under-reported. Considering potential interactions between radiation and other therapies, specific studies need to be conducted to address these issues.

Since tobacco and alcohol are risk factors for second primary head and neck cancers [22] and patients are known to continue tobacco and alcohol habits after cancer treatment, these factors must be considered as possible confounders. In particular, patients who underwent more complex treatments reportedly were less likely to continue smoking [23–25]. Continued smoking was more prevalent in patients treated with radiotherapy alone relative to patients treated with combination therapy and patients who consumed more alcohol [25]. Replication of our results with adjustment for tobacco and alcohol will

be necessary to confirm an association between radiotherapy for oral cancer and the risk of second primary cancers.

Recently, published studies of second primary cancer occurrences after radiation treatment for first cancers supported results from the atomic bomb survivor studies concerning differences in latency by type of cancer, specifically higher risk of hematopoietic cancers in the first 10 years of follow-up compared to higher risks of solid cancers with increasing follow-up after that time, and by age at exposure, specifically higher risk for breast cancer in adolescence and during the reproductive years. It is largely undisputed that leukemia and cancers of the thyroid, breast and lung are associated with radiation and associations have been found at relatively low

doses ( $<0.2$  Gy) [1]. The risk, however, may depend to some extent on the age at exposure, for example childhood exposures increasing the risk of leukemia and exposure during reproductive age increasing the risk of breast cancer and, as some studies suggested, that lung cancer risk may be stronger for exposures later in life.

Galper et al. [26] examined second cancer occurrence in 1884 primary incident breast cancers cases who received radiation treatment to the tumor site. They observed a lung cancer excess 52% higher than expected from SEER rates and most of these lung cancers occurred more than 5 years after treatment and in women who were more than 50 years at the time of breast cancer diagnosis. Kleinerman et al. [27] examined cancer incidence at all sites after radiation treatment in 86,193 primary cervical cancer patients reported to 13 population-based cancer registries in five countries. Focusing on 3750 radiation treated patients who survived for at least 30 years after diagnosis, they observed an overall 25% increase in cancer incidence (SIR=1.25; 95%CI 1.22–1.28). Most of the excess risk found for pelvic organs was in close proximity to the field of irradiation. At lower doses, an increased risk was described for non-chronic lymphocytic leukemia in the first 10 years after radiation treatment. Travis et al. [28] studied leukemia incidence after primary testicular cancer in a case-control study nested within a cohort of 18,567 survivors of primary testicular cancer from eight population-based registries. Radiotherapy without chemotherapy resulted in a threefold elevated risk of leukemia (RR=3.1 95% CI=0.7–22 based on N=22 cases). Brenner et al. [29] examined primary prostate cancer cases from the SEER program: 51,584 men who received radiotherapy and 70,539 men who underwent surgery for prostate cancer without radiotherapy. Radiotherapy for prostate carcinoma was associated with an overall small increase in the risk of solid tumors (RR=1.06; 95% CI=1.01–1.11) relative to treatment with surgery. Among patients who survived for more than 5 years, the increased RR for all solid cancers reached 15% (RR=1.15; 95% CI=1.06–1.24), and increased further to 34% for patients surviving more than 10 years (RR=1.34; 95% CI=1.14–1.57).

Though our study supports the hypothesis that radiotherapy for primary oral cancer is a risk factor for

second primaries, there are several limitations to our study. One possible limitation is that increased surveillance for recurrence in cancer patients may lead to detection bias. The level of surveillance for the first primary and the second primary cancer will obviously differ, as cancer patients are under increased surveillance for metastases or recurrence. However, we would not expect that the surveillance for second primaries differed according to radiotherapy treatment status. Therefore, detection bias may not limit our ability to estimate the effect of radiotherapy on second primary cancers.

Another methodological limitation is that distinguishing metastases from second primary tumors and assigning the order of primaries can be difficult when the dates of diagnosis for the primaries are close together [30]. The SEER program rules for determining second primary tumors are based on histology and site, as described previously in Section 2. Despite the SEER rules, assignment of primaries is still difficult and imprecise. We attempted to address this limitation by censoring synchronous cases. Disease misclassification could lead to bias toward the null if non-differential misclassification occurred in the different radiotherapy exposure categories and the misclassification was independent of other errors. However, we would not expect the disease misclassification to differ by radiotherapy status.

In conclusion, radiation therapy for the first primary oral cancer appears to be a risk factor for solid second primary cancers 10 years after the first cancer and for leukemias 1–5 years after the first cancer. Further studies adjusting for chemotherapy treatment, tobacco and alcohol as potential confounders are necessary to confirm these results. If the association is confirmed, identifying oral cancer patients who are genetically susceptible to radiation will be important in preventing radiation-induced second primary cancers.

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