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Second Cancers Following Oral and Pharyngeal Cancer: Patients' Characteristics and Survival Patterns

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A survey was made of second primary cancers among patients who were enrolled in a large case–control investigation of oral and pharyngeal cancer, hereafter called oral cancer, during 1984–1985 in four areas of the United States. Among the original 1090 patients with oral cancer (nearly all squamous cell carcinomas), 107 developed a second cancer (one-half of them squamous cell) by the end of follow-up in June 1989 (average follow-up 2.6 years), with 69% occurring in the oral cavity, pharynx, oesophagus, larynx or lung. Rates of second tumours varied by age and socioeconomic status, but not sex or race, and were higher among those whose initial cancer was localised, even after adjusting for their longer survival. Long-term survival was lower among those with second cancers. Conditional on surviving for 2 years, the survival at 5 years was under 50% and nearly 70%, respectively, for those with versus those without a second cancer in the first 2 years. These findings confirm the exceptionally high rate of second cancers (especially of the aerodigestive tract) following oral cancer, describe the clinical and pathological features of patients with multiple cancers and indicate the importance of preventive measures.

Keywords: second primary tumours, oral cancer, pharyngeal cancer, population-based, demographics, survival

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INTRODUCTION

ALTHOUGH PATIENTS with oral cancer are known to be at high risk of developing new primary cancers, there is limited understanding of aetiological mechanisms and means of identifying and monitoring high-risk patients. Second primary cancers following an index oral cancer occur nationally at a rate of nearly 4% per year in the United States [1], with rates of 3–7% reported in Connecticut [2] and from several hospital-based studies [3–6]. As identified recently in our study population, the major determinants of new primaries following oral cancer are high levels of tobacco smoking and alcohol drinking [7]. Although the majority of oral cancers are squamous cell carcinomas, little is known about the spectrum of cancer sites and histological types of second cancers. Herein we describe patients' characteristics, patterns of second cancers and the survival experience of a large population-based cohort of oral cancer patients identified by cancer registries in four areas of the United States [8]. Such information should be helpful in the follow-up and surveillance of oral cancer patients, and in the development of cancer prevention and control strategies aimed at high-risk individuals.

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PATIENTS AND METHODS

A follow-up study of 1090 patients with oral cancer (International Classification of Disease, 9th revision, codes 141, 143–6, and 148–9), excluding cancers of the lip (140), salivary gland (142), and nasopharynx (147) diagnosed between January 1984 and March 1985 was undertaken so that risk factors and other characteristics of second primary cancers (excluding non-melanoma skin cancers) following oral cancer

could be determined. The patient cohort, previously enrolled in a population-based case–control study of oral cancer [8], was followed up through June 1989, with population-based registry files utilised to ascertain second cancers and to obtain information on patient survival, including date of death or the patient's disease status at the end of the study. A copy of the death certificate was obtained for deceased subjects. The medical records of each patient in whom second primary cancers developed during the study period were reviewed for details on the index tumour classification and staging, the treatment modality used for the index tumour, and site and histological diagnosis of second primary tumours. Second cancers identified by death certificate were excluded. Information on race/ethnicity, education, occupation and other sociodemographic variables, as well as risk factors, were collected for each oral cancer patient at the time of the baseline survey in 1984–1985 through in-person interviews using a standardised questionnaire.

Second primary cancers were defined according to the standard Warren–Gates criteria [9]: (1) each tumour was clearly malignant on histological examination; (2) the tumours were anatomically separated by normal-appearing mucosa; and (3) the possibility that the second tumour represents a metastasis of the original oral cancer was excluded. Multiple primary cancers were classified also by their temporal sequence; a second tumour was considered to be simultaneous (and *not* a second primary) if found at the same time or within 2 months of the index oral cancer, consistent with guidelines of the Surveillance, Epidemiology and End Results (SEER) program [10].

Frequency distributions for demographic and other characteristics of the patients with second cancers (cases) were compared with the rest of the underlying cohort of patients with a single tumour (non-cases) using likelihood ratio χ^2 tests [11]. Survival curves estimating the proportion of cases and non-cases surviving to a particular time following the index diagnosis (time = 0) were obtained by the Kaplan–Meier method [12]. To evaluate the effect on survival of having a second primary cancer, the survival distributions of patients who did vs. those who did not develop second cancers were compared using generalised rank statistics for censored data [13].

RESULTS

By the end of follow-up (30 June 1989), 64% of the 1090 cohort members were known to have died, 33.5% to be living and 2.5% lost to follow-up. The cohort provided nearly 2900 person-years of follow-up during which a total of 107 histologically-proven second primary cancers were identified. Of the 107 cases, 12 (11%) had their second tumour between 2 and 6 months after the first diagnosis and 95 (89%) were detected 6 months or more after the index cancer. The mean time to occurrence of a second cancer was 27 months (median 24 months; 25th percentile 13 months; 75th percentile 41 months).

Table 1 shows the baseline (i.e. at enrollment to the patient cohort in 1984–1985) characteristics of those oral cancer patients who did vs. those who did not develop a second primary cancer. There were no significant differences between the 107 cases and the rest of the cohort (non-cases) with respect to sex, race, geographical area, occupation or family history of cancer. However, the age distribution of non-cases was younger ($P < 0.001$) than that of cases, with 26% of non-cases vs. 10% of cases under age 55 years at the index diagnosis. Age of second cancer cases ranged from 44 to 80 years (median 64 years). Patients who developed second cancers were more often married (71 vs. 54%), more likely to have completed high school (71 vs. 61%) and to be of Protestant religion (57 vs. 47%), but the distribution of these variables fluctuated somewhat according to age and patterns of smoking and drinking. Nearly all of the patients had been tobacco smokers (93% cases, 90% non-cases) or regular (≥ 1 drink/week) consumers of alcoholic beverages (93% cases, 90% non-cases). Second tumours occurred more frequently among patients with index cancers of the mouth other than tongue and with localised disease.

Table 2 shows that the overall rate of second cancer among oral cancer patients in the four geographical areas was 3.7% per year, identical to the national rate reported from nine SEER registries based on over 61 000 person-years of follow-up [1]. The risk was highest among patients aged 60–69 years, and among those with localised disease, even with adjustment for their longer length of follow-up. When we examined second cancers by interval since diagnosis of the initial cancer, the risk increased over time, with the annual rates for 0 to 2.5 years and 2.5 to 5.0 years of follow-up being 3.4 and 4.4%, respectively.

Most second tumours (69%) arose in the aerodigestive tract (ADT), notably the oral cavity, pharynx, oesophagus and lung. Table 3 shows that among the 107 cases, development of a second ADT cancer was independent of site of the index cancer, with nearly identical percentages of second ADT cancers occurring following index tumours of the tongue (68.2%), other areas of the mouth (69.8%) or pharynx (68.8%). Lung cancer was the most common second cancer for all subsites of the index cancer. There were slight variations in patterns of non-ADT second cancers according to subsites of the index tumour, but numbers were small.

Nearly all (92%) of the index oral cancers were squamous cell carcinomas, with only 5% adenocarcinomas and 3% other types (sarcomas 2 cases and lymphoma 1 case, all of tonsillar origin). As shown in Table 4, the histology of the second tumour was often unlike that of the initial tumour, indicating that the problem of misclassified metastases was probably not substantial. Overall, one-half of the second cancers were squamous cell carcinomas (50%), followed by adenocarcinomas (30%), other carcinomas (14%) and non-epithelial second tumours [5.6%, including cases of carcinosarcoma (uterus), melanoma (ear), acute myeloid leukaemia, Hodgkin's disease and lymphoma]. Among the patients whose first oral cancers were adenocarcinomas (three floor of mouth, one soft palate, one cheek mucosa), three of the five second tumours were squamous cell carcinomas (two oesophagus, one soft palate), while two were intraductal carcinomas of the breast. For all but 4 patients who developed two squamous cell cancers, the first and second cancers occurred in different sites at the three-digit level of the ICD code. Almost all (90%) second cancers of the mouth and pharynx (19/20 cases), oesophagus (11/13), nasal cavities (1/1) and larynx (6/7)—together termed upper aerodigestive tract—were squamous cell carcinomas, while the percentage distribution of second lung cancers was squamous cell 49%, adenocarcinoma 21% and other types 30% (including small cell, large cell and unspecified carcinoma). Approximately 70% of second non-ADT cancers were adenocarcinomas.

Table 1. Baseline characteristics of oral cancer patients with and without second tumours by end of follow-up

Characteristics	Patients with second tumours No.	(%)	Patients without second tumours No.	(%)
Sex				
Male	75	(70)	671	(68)
Female	32	(30)	312	(32)
Race				
White	93	(87)	806	(82)
Black	14	(13)	177	(18)
Age at index diagnosis (years)*				
<55	11	(10)	255	(26)
55–59	15	(14)	148	(15)
60–64	27	(25)	184	(19)
65–69	31	(29)	159	(16)
⩾70	23	(22)	237	(24)
Geographical area				
New Jersey	47	(44)	436	(44)
Los Angeles	44	(41)	365	(37)
Atlanta	11	(10)	121	(12)
San Francisco	5	(5)	61	(6)
Marital status				
Married	76	(71)	531	(54)
Other	31	(29)	452	(46)
Years of education				
<12	31	(29)	387	(39)
12	51	(48)	319	(33)
>12	25	(23)	277	(28)
Usual adult occupation				
Blue collar worker	59	(55)	531	(54)
White collar	43	(40)	430	(44)
Other/none	5	(5)	22	(2)
Religion				
Protestant	61	(57)	456	(47)
Catholic	23	(21)	357	(36)
Jewish	4	(4)	19	(2)
Other/none	19	(18)	151	(15)
No. of parents/siblings with cancer				
None	53	(50)	544	(55)
1	34	(31)	304	(31)
2	17	(15)	98	(10)
⩾3	3	(3)	37	(4)
Index tumour site				
Tongue	23	(22)	290	(29)
Other mouth areas	56	(52)	363	(37)
Pharynx	28	(26)	330	(34)
Index tumour stage				
Localised	71	(66)	310	(32)
Advanced	33	(31)	485	(49)
Unknown	3	(3)	188	(19)

*Mean age at index diagnosis 64.0 years for cases and 60.9 years for controls.

The impact on survival was evaluated by comparing patients with and without second cancers in a comparable time interval since the initial diagnosis. This is illustrated by the survival curves in Fig. 1, which show the probability of survival among patients with and without a second cancer at 1, 2 or 3 years after the index diagnosis, conditional on the subject surviving at least 1, 2 or 3 years, respectively, following the first cancer. Initially survival was higher among cases, but eventually fell below the curve for non-cases. Among 1-year survivors, absence of a second tumour appeared to slightly improve survival, although the difference between cases and non-cases was not statistically significant. However, among 2-year survivors, there were marked survival differences between patients who developed a second primary within 2 years of the

Table 2. Annual rates of second primary cancers by age at index diagnosis and stage of disease

Age (years)	Stage	Subjects (*n*)	Total person-years	Average follow-up (years)	Cases (*n*)	Annual rate
<60	Localised	140	509.5	3.6	16	0.031
	Advanced	212	490.8	2.3	10	0.020
	Unknown	77	220.8	2.9	0	0.000
60–69	Localised	143	434.1	3.0	37	0.085
	Advanced	190	417.6	2.2	19	0.045
	Unknown	68	167.7	2.5	2	0.012
70+	Localised	98	305.4	3.1	18	0.059
	Advanced	116	207.9	1.8	4	0.019
	Unknown	46	114.9	2.5	1	0.009
Total		1090	2868.6	2.6	107	0.037

Table 3. Distribution of second primary cancers by index tumour site

	Site of index cancer					
	Tongue		Other mouth area		Pharynx	
Site of second cancer	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Aerodigestive*	15	(68.2)	37	(69.8)	22	(68.8)
Oral (140–9)	2		10		8	
Oesophagus (150)	1		9		3	
Larynx (161)	1		4		2	
Lung (162)	10		14		9	
Other digestive (151–9)	2	(9.1)	6	(11.3)	4	(12.5)
Genitourinary (179–89)	4	(18.2)	3	(5.7)	3	(9.4)
Other†	1	(4.5)	7	(13.2)	3	(9.3)
All cancers	22	(100.0)	53	(100.0)	32	(100.0)

*Aerodigestive tumours include oral cavity and pharynx (ICD 140–9), oesophagus (150), nasal cavities (160), larynx (161) and lung (162).
†"Other" tumours include breast cancer (6 cases), lymphoma (3 cases), leukemia (1 case) and melanoma (1 case).

Table 4. Distribution of histological types of 107 *second primary malignancies by index primary diagnosis (ICD-0 morphology)*

Index oral cancer	Second primary cancer	No. of cases
Squamous cell carcinoma (*n*=98)	Squamous cell carcinoma	51
	Adenocarcinoma	28
	Other carcinoma†	13
	Other malignancies‡	6
Adenocarcinoma (*n*=5)	Squamous cell carcinoma	3
	Adenocarcinoma (intraductal)	2
Carcinoma, NOS (*n*=1)	Oat cell carcinoma	1
Other malignancies* (*n*=3)	Adenocarcinoma	2
	Transitional cell carcinoma	1

*Includes immunoblastic sarcoma, reticulosarcoma and lymphoma. †Includes small (oat) cell, large cell, transitional cell and unspecified. ‡Includes carcinosarcoma, melanoma, acute myeloid leukaemia, Hodgkin's disease and lymphoma, nodular.

initial cancer and those who did not. Both the log-rank test [14] and the Gehan–Wilcoxon statistic [15] (which provides greater sensitivity to survival differences occurring earlier in time) were significant at the $P<0.001$ level. Conditional on surviving for at least 2 years, survival at 5 years following the index diagnosis was much worse for cases (46.2%) than non-cases (69.1%). Likewise, conditional on survival for at least 3 years, survival at 5 years was significantly (Gehan–Wilcoxon test:

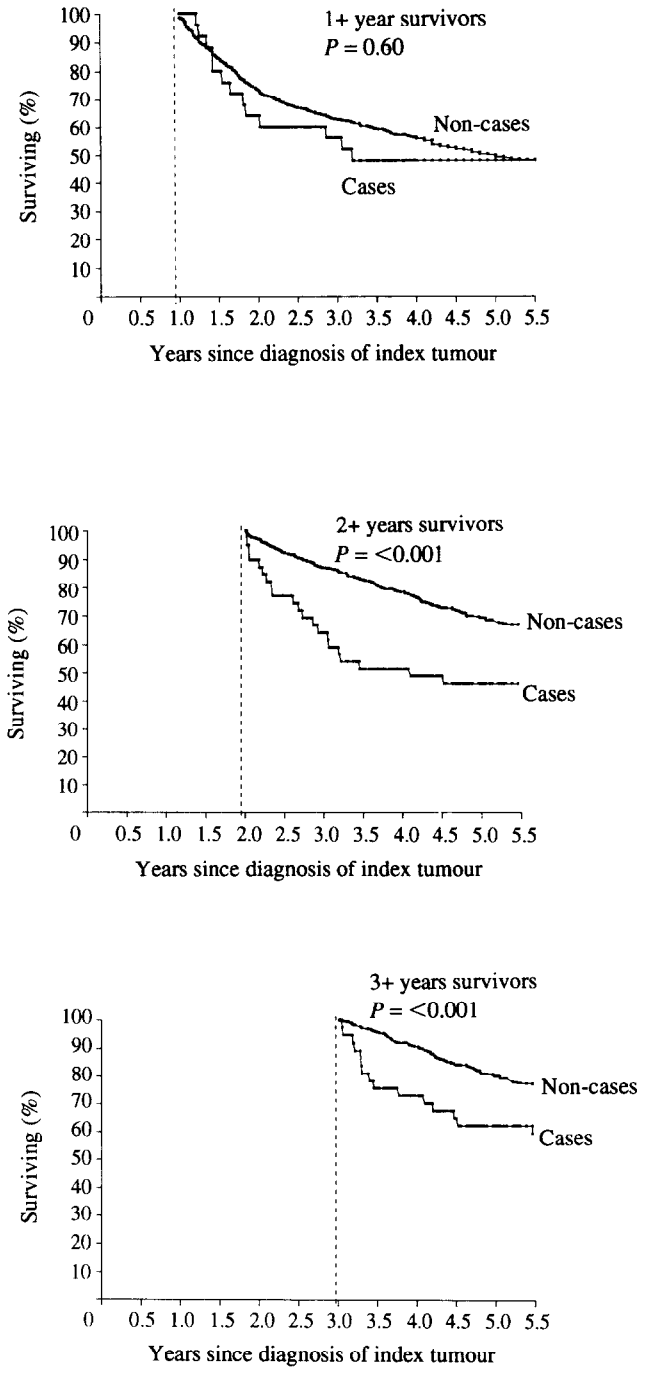

Fig. 1. Conditional probabilities of surviving $t+s$ years after diagnosis among patients with second tumours (cases) and those known to be free of a second tumour (non-cases) s years after diagnosis. The time s is indicated by a vertical dashed line.

$P<0.001$) poorer for cases (62.2%) than non-cases (80.2%). Similar findings were observed among 4-year survivors (data not shown).

DISCUSSION

Data from a large consecutive series of oral cancer patients were used to describe demographic, medical and survival characteristics associated with development of a second primary tumour. The inclusion of subjects identified by population-based cancer registries, and the essentially complete second cancer ascertainment assured a greater degree of representativeness compared with previous hospital-based surveys. In addition, review of histology reports for each case increased the likelihood that a second neoplasm was actually a new primary cancer.

Since the incidence of cancer generally rises with age, it was not surprising that age at initial diagnosis was an important determinant of whether a second cancer developed. The average age at index diagnosis for the patients with a single tumour (60.9) was significantly lower than that of patients who subsequently developed second cancers (64.0). Rates of second cancer, however, did not increase monotonically with age, but were highest among those aged 60–69 years at the time the first cancer was diagnosed. Among other characteristics that were considered, sociodemographic factors such as marital status, level of education and religion had a greater influence on risk than did race, sex and family history of cancer.

Staging of the initial oral cancer was also an important factor influencing the risk of second cancer. The higher prevalence of second cancers among patients with localised disease was not due simply to their longer survival, since rates of second cancer took into account length of follow-up and censoring due to death, but may be due partly to heightened medical surveillance. Patients who delayed seeking medical attention for the index cancer (thus presenting with advanced stage) may also be less likely to seek follow-up care.

The second cancers occurred throughout the body, but most often affected the upper digestive tract (mainly the oral cavity, pharynx and oesophagus) and the lung. Although nearly all the index oral cancers were squamous cell carcinomas, close to one-third of the second cancers were adenocarcinomas, followed by 14% other carcinomas and 6% non-epithelial tumours. While squamous cell carcinomas constitute approximately 12% of all cancers diagnosed in the United States [16], the proportion of second primary squamous cell carcinomas among our study population was 50% overall, reaching 90% for cancers of the upper aerodigestive tract and close to one-half for second lung cancers. Having oral cancer entails a substantial excess risk of second cancers, primarily squamous, of the aerodigestive system. In a previous report, we showed that the markedly elevated risk of second aerodigestive tract cancers was linked mainly to longstanding heavy consumption of tobacco and/or alcohol consumption by the patients [7].

Relative survival rates for oral cancer are among the lowest of the major cancers, and have not improved appreciably during the last two decades. Population-based data from cancer registries participating in the SEER program indicate that patients diagnosed with oral and pharyngeal cancer (excluding lip, salivary gland and nasopharynx cancers) between 1983 and 1988 have a overall relative 5-year survival rate of approximately 43%, which may vary depending on sex, race and anatomic site [17]. Females (50%) have a better prognosis than males (39%), and whites (45%) than blacks (29%), which can be correlated with the gender and racial differences in the proportion of oral and pharyngeal cancers that are localised at diagnosis. Likewise, survival is lower for pharyngeal tumours (29%) than for tumours of the oral cavity (50%), which are generally discovered at earlier stages.

Our calculations further indicate that relative survival was significantly lower among those with a second cancer. Among patients who survived 2 or more years without a second cancer, 5-year survival was nearly 70%, compared to 50% among those developing a second cancer in the first 2 years. Thus,

survival of oral cancer patients depends only partly on risk of death from the initial cancer (or the success or failure of its treatment). Another impact results from the elevated risk of second cancers, particularly among early-stage cases and long-term survivors. A large proportion of these subjects develop new primary tumours of the aerodigestive system, at sites with even higher case fatality rates than oral cancer. Our findings are consistent with an earlier study indicating that survival is poorest among head and neck cancer patients who develop a second primary cancer [18].

In this study population, tobacco smoking and alcohol consumption were found to be the major determinants of second cancers [7] as they were for the first [8]. Therefore, primary prevention by cessation of smoking and drinking is the best approach not only to prevent oral and pharyngeal cancer, but also to reduce the risk of second cancers. Nevertheless, additional preventive measures are needed including increased intake of fruits and vegetables [19]. A promising strategy for the prevention of second cancers is chemoprevention, as with certain retinoids [20], and possibly vitamin E [21], although further research on such agents is needed. By identifying the patterns and behaviour of multiple cancers, and the underlying risk factors, it may be possible to further target opportunities for cancer prevention and control.

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