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Second Respiratory and Upper Digestive Tract Cancer Following Oral Squamous Cell Carcinoma

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727 patients with squamous cell carcinoma (SCC) of the lip and oral cavity have been followed for the occurrence of second primary tumours (SPTs) in the respiratory and upper digestive tract (RUDT). 74 patients (10%) developed at least one SPT in the RUDT. The incidence of SPTs was expressed per 1000 person-years of follow-up. In our study about 28 SPTs per 1000 person-years of follow-up were seen in the RUDT. Patients were at risk for a second primary tumour, at a steady rate of approximately 2.8% per year during at least 10 years. Furthermore, patients with an index tumour in the lower part of the mouth (floor of mouth, retromolar area and lower alveolar process), which is more related to tobacco and/or alcohol, seem to be more at risk for SPTs than patients with an index tumour in the other (sub)sites of the mouth.
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INTRODUCTION

To REDUCE the mortality of patients with oral squamous cell carcinoma (SCC), emphasis is put on prevention, early detection and improvement in treatment. Although the cure rates of primary oral tumours have improved, the overall survival rates have hardly increased. To a large extent this lack of progress is due to the occurrence of second primary tumours (SPTs) [1–3]. The awareness of SPTs among patients suffering from oral SCC has been paid substantial attention in the literature. It has been stated that the most precancerous condition in oral cancer is oral cancer itself [4].

The percentages of second primary tumours after oral SCC vary from 10 to 27% [2, 3, 5–8]. Most likely, due to risk factors such as the use of tobacco and alcohol, a great majority of the second primary tumours occur in the respiratory and upper digestive tract (RUDT) [7].

The aim of this study was to investigate whether the incidence of an SPT in the RUDT following oral SCC is related to (1) the anatomical site of the index tumour, and (2) the use of tobacco and alcohol.

PATIENTS AND METHODS

The population of study consisted of 740 consecutive, previously untreated patients with SCC of the lip and the oral cavity. The SCC had been diagnosed at the Free University Hospital, Amsterdam, the Netherlands in the period from 1 January 1971 to 1 January 1991. Age, gender, use of tobacco and alcohol were registered at the time of diagnosis of the index tumour. Concerning the use of tobacco a division of non-smokers, moderate smokers (1–20 cigarettes per day) and heavy smokers (more than 20 cigarettes per day) was made. One cigar and one pipeful were assumed to be equal to 4 and 2 cigarette equivalents, respectively. None of the patients had a history of using smokeless tobacco. Intake of alcoholic beverages was expressed in units of alcohol per day, assuming that the amount of alcohol in a consumption of hard liquor, wine and beer is equal (approximately 10 g of alcohol per unit) [9]. Patients were divided into non- or incidental drinkers, moderate drinkers (one to four units per day) and heavy drinkers (more than four units per day).

The oral (sub)sites of the index tumour were specified according to the International Union Against Cancer (UICC) [10]. Patients with a history of another malignancy, a total of 13 cases, were excluded from this study. The remaining 727 cases were included in the analysis. The population of study comprised 464 male and 263 female patients. The median age was 62 and 69 years, respectively. Details of the patients' data have been described elsewhere [11]. All additional tumours

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following SCC of the lip and oral cavity located in and outside the RUDT are presented in Fig. 1(a) and (b), respectively.

For the analysis of this study, only tumours in the RUDT were regarded as eligible SPTs. As the study was focused on the incidence of additional primary tumours in patients related to the site of the index tumour or tobacco and alcohol habits, the inclusion of third and fourth primary tumours would introduce a bias [12]. Therefore, additional tumours following the SPT were excluded in this analysis. The RUDT is specified as being the lip, oral cavity, pharynx, larynx, oesophagus and lung and is defined according to the classification of the UICC [10].

The follow-up has been performed until the date of diagnosis of the second primary, until 1 January 1992, the patient's death or the date of the last follow-up visit, whichever occurred first. The follow-up has been described in person-years of follow-up. The incidence of SPTs is defined as the total number of second tumours that developed, divided by person-years of follow-up at risk, and expressed per 1000 person-years of follow-up [12].

The SPTs were identified by using the criteria provided by Warren and Gates [13]. These criteria require that both tumours are histologically malignant, that they are separated by normal healthy mucosa, and that one tumour is not a metastasis of the other. The cell types, the degree of differentiation and the presence of regional spread were also taken into account to distinguish between a metastasis and an SPT. Any subsequent SCC at the same site or direct vicinity (<2 cm) of the index tumour, regardless of the time since diagnosis and treatment of the index tumour, was considered to be a recurrence and subsequently excluded.

The product-limit method of Kaplan–Meier was used to assess the incidence of the SPTs over a period of time. Subgroups were compared by means of the log-rank test (Mantel–Haentzel test for censored survival times). Stratification was applied whenever appropriate to eliminate possible confounding.

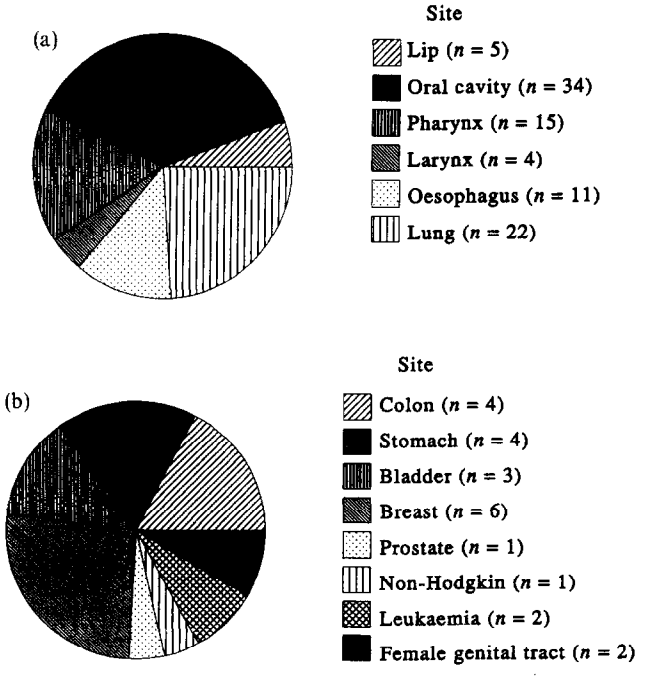

Fig. 1. (a) All additional tumours located in the respiratory and upper digestive tract (n=91). (b) All additional tumours located outside the respiratory and upper digestive tract (n=23).

Table 1. Incidence and localisation of second primary tumours in the respiratory and upper digestive tract (RUDT) in 727 cases of squamous cell carcinoma of the lip and oral cavity

Sites in RUDT	n	Incidence*
Lip	3	1.1
Oral cavity	26	9.9
Pharynx	13	4.9
Larynx	5	1.9
Lung	19	7.2
Oesophagus	8	3.0
Total	74	28.0

*Incidence per 1000 person-years of follow-up.

RESULTS

The mean follow-up of the 727 patients was 3.63 years, being a total of 2638 person-years at risk. The incidence and localisation of the SPTs are shown in Table 1. For all SPTs in the RUDT an incidence of 28.0 per 1000 person-years of follow-up was found.

In Fig. 2 the estimate of patients free of SPTs in the RUDT is presented. It appeared that during the entire follow-up period patients were continuously at risk for an SPT at a steady rate of approximately 2.8% per year. The Kaplan–Meier estimate for patients free of an SPT was not significantly different for men and women.

In Table 2 an overview is given of the incidence of SPTs by the anatomical site of the index tumour. Of the major index (sub)sites the incidence rates varied from 5.7 for the cheek mucosa to 43.9 for the lower alveolar ridge. In Fig. 3 the incidence of SPTs is related to index tumours of the lower part of the oral cavity (floor of mouth, retromolar area and lower alveolar ridge) vs. the remaining (sub)sites of the oral cavity (cheek mucosa, tongue, upper alveolar ridge and hard palate). It appeared that SPTs occurred significantly more often after SCC in the lower part of the oral cavity compared with the rest group (P=0.01). However, after controlling for the use of tobacco and/or alcohol this difference was no longer statistically significant. In Fig. 4 it is shown that a significant trend is

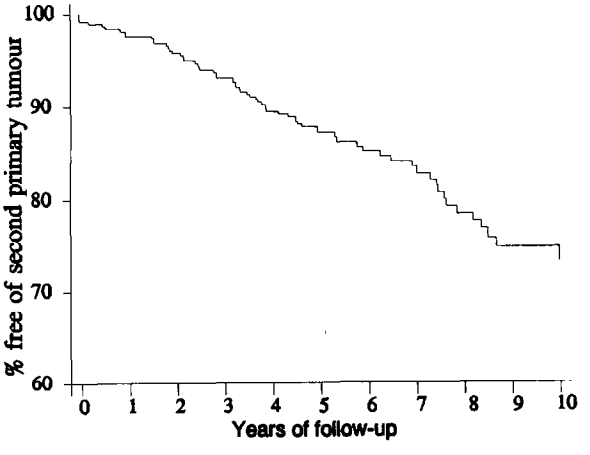

Fig. 2. Kaplan–Meier estimate of patients free of second primary tumours in the respiratory and upper digestive tract.

Table 2. Incidence of second primary tumours (SPTs) by gender and (sub)site of the index tumour

Localisation of the index tumour	*n* SPT/*n* index tumour		Incidence*		Incidence*	
	Male	Female	Male	Female	Both genders	95% C.I.
Lower alveolar ridge	7/31	3/25	50.3	33.8	43.9	21.0–80.8
Retromolar area	10/57	0/20	53.0	0	36.9	17.7—67.9
Floor of mouth	16/138	6/59	32.8	29.8	31.9	20.0–48.4
Lower lip	7/50	1/6	31.6	36.9	32.2	13.9–63.5
Tongue	9/134	10/106	18.8	23.5	21.0	12.7–32.9
Cheek mucosa	0/26	1/26	0	12.5	5.7	0.1–31.7
Upper lip/commissure	0/2	0/1	0	0	0	0–174.1
Upper alveolar ridge	2/10	0/11	92.8	0	53.7	6.0–193.7
Hard palate	0/8	0/5	0	0	0	0–80.1
Simultaneous tumours in lip and oral cavity	1/8	1/4	86.6	119.7	100.5	11.3–362.9
All (sub)sites	52/464	22/263	30.9	23.0	28.0	22.0–35.2

*Incidence per 1000 person-years of follow-up. C.I. = confidence interval.

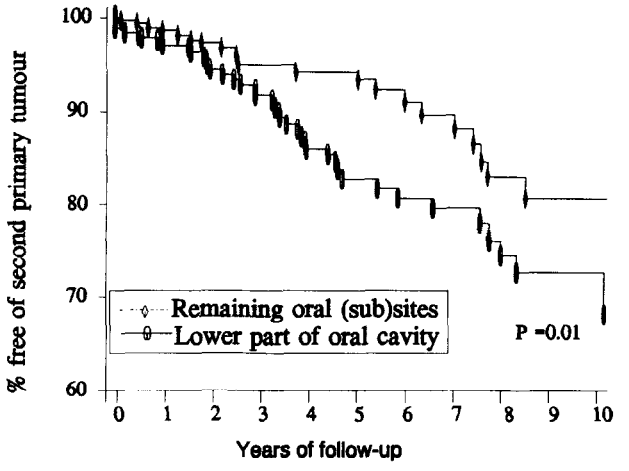

Fig. 3. Kaplan–Meier estimate of patients free of second primary tumours in the respiratory and upper digestive tract. Index tumours in lower part of oral cavity vs. index tumours in remaining oral (sub)sites. Lower part of oral cavity: floor of mouth, lower alveolar ridge and retromolar area. Remaining (sub)sites: cheek mucosa, tongue, upper alveolar ridge and hard palate.

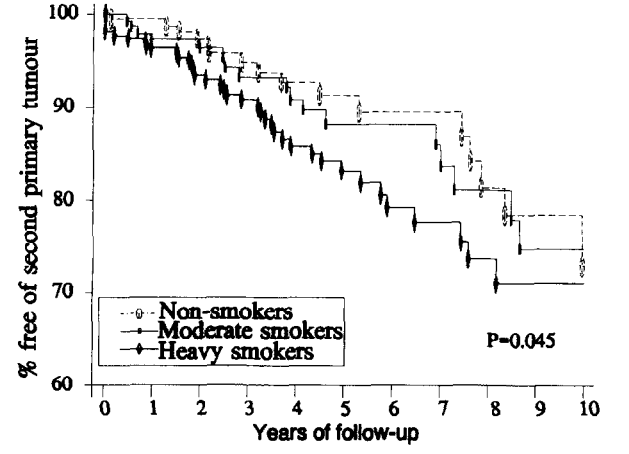

Fig. 4. Kaplan–Meier estimate of patients free of second primary tumours in the respiratory and upper digestive tract related to the use of tobacco.

observed between the use of tobacco and the incidence of SPTs ($P = 0.045$). After stratification for the use of alcohol, however, no significance was seen. The trend for alcohol drinking appeared to be not significant ($P = 0.07$).

DISCUSSION

In many studies SPTs are expressed in percentages of patients. Therefore, the period of follow-up is not included. To include the follow-up, the incidence of SPTs is expressed per 1000 person-years of follow-up [12]. In the present study 28 SPTs per 1000 person-years of follow-up are seen in the RUDT. This means that 1 SPT develops during 1 year follow-up of 36 (1000/28) patients.

According to the literature, most cases of the SPTs occur in the RUDT [6, 14, 15] with high occurrence rates in the oral cavity itself [3, 7, 14, 15]. In our series about 40% of the SPTs in the RUDT affected the lip and oral cavity again (Table 1). Traditionally, this has been explained by the susceptibility of the epithelium of the oral cavity—"field cancerisation" [16]—to carcinogens such as tobacco and alcohol. Recently, experimental evidence for this concept has been provided [17].

Nowadays, it is well accepted that the whole RUDT is susceptible to common exogenic influences [18]. In addition, it has also been reported that the presence of oral leukoplakia among patients with oral SCC does increase the risk of additional cancers at the site of the leukoplakia [19]. The development of second malignancies remains the most obvious expression of field cancerisation.

This study confirms previous studies, which report a virtually constant risk of an SPT in the RUDT in the course of time [3, 20, 21]. In our study the patients were at continuous risk of an SPT of approximately 2.8% per year for at least 10 years. No significant difference was seen between male and female patients. In the literature, a preference for female as well as for male patients is reported [3, 22].

In view of SPTs following oral cancer, there is evidence that smokers and alcohol drinkers are more at risk than non-smokers and non-drinkers, respectively [22–25]. However, it is not entirely clear, whether the risk is decreased if the use of tobacco and alcohol is discontinued after diagnosing the first neoplasm [26]. When changes in lifestyle do not result in a decrease in risk of an SPT, the entire mucosa may be primed

for neoplasia before the first clinical cancer has occurred. On the other hand, it has been reported that among non-smokers the frequency of second tumours is similar to that among smokers [27, 28].

According to a previous study by our group, patients with index tumours in the lower part of the oral cavity (floor of mouth, lower alveolar ridge and retromolar area) had a significantly higher rate of incidence of SPTs than patients with index tumours in the remaining (sub)sites of the oral cavity (cheek mucosa, tongue, upper alveolar ridge and hard palate) [7]. After stratification for the use of tobacco and/or alcohol no significance is observed. This supports the theory that SCC of the lower part of the oral cavity is more related to the use of tobacco and alcohol than the rest of the oral cavity [29–30]. This explains a higher incidence rate of SPTs in the RUDT in index tumours of the lower part of the oral cavity. Furthermore, a significant trend of the amount of smoking could be seen in the development of SPTs. However, after the stratification for the use of alcohol no significance is observed. The trend for alcohol drinking appeared to be not significant ($P=0.07$, one-sided). Whether the use of tobacco and alcohol continued after diagnosis of the index cancer could not be reliably retrieved from our data.

The development of SCC of the oral cavity is to a large extent related to exogenous carcinogens in cigarette smoke and to alcohol abuse. Occupational and dietary factors play a role as well [31, 32], while the role of viral infections with human papilloma virus and herpes simplex remains to be elucidated [33]. The fact that only a minority of heavy smokers and drinkers develop cancer of the oral cavity points to a possibly endogenous, individual susceptibility to these carcinogens. Several of such endogenous factors that may play a role in the aetiology of oral cancer have been reported, including HLA antigens, immunoglobulin allotypes [34, 35], and increased occurrence of cancers in the RUDT in first degree relatives of oral cancer patients [36]. With regard to the endogenous factors, the mutagen sensitivity, presumably the result of a DNA repair deficiency, might be associated with an increased risk of developing malignancies [37]. Schantz *et al.* [38] reported that patients with a decreased DNA repair capacity, after controlling for the use of tobacco and alcohol indeed experienced over four times the risk of an SPT compared to patients with normal DNA repair capacity.

In conclusion, patients with an index tumour in the lower part of the mouth which is more related to the use of tobacco and/or alcohol, seem to be more at risk of an SPT than patients with an index tumour in the other (sub)sites of the mouth. Apart from factors such as the use of tobacco and alcohol, other factors such as occupation, nutrition, viral infection, genetic and as yet unknown factors may play a (major) role in the risk of developing SPTs as well.

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