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Second Cancers Occurring After Cancers of the Mouth and Pharynx: Data From Three Population-based Registries in Australia, Scotland and Slovenia

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Data over at least 20 years from three large population-based registries in Europe and Australasia have been used to assess the risk of second primary tumours occurring after a cancer of the mouth or pharynx. These patients have previously been shown in clinical series to be at a particularly high risk of subsequent tumours, while data from cancer registries have shown conflicting results on the magnitude of the risk. In this study, patients were found to have between a 2-fold (Scotland and New South Wales) and 4-fold (Slovenia) increase in risk of a subsequent tumour over that in the population, although the actual risk in each centre was similar (between 2.8 and 3.1 per 100 person years). The risk remained for 10 years after diagnosis of the original tumour and was primarily in the upper aero-digestive tract. The most elevated risks (approximately 10-fold) were for tumours in the oral cavity and oesophagus. These data provide higher estimates of risk than previously reported from European cancer registries for second primary tumours and emphasize the need for close follow-up of patients who may represent an appropriate population in which to assess possible new chemopreventive agents.

Keywords: second primary tumours, oral cancer, pharyngeal cancer

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INTRODUCTION

THE FREQUENCY with which cancers occur in patients after the diagnosis of a tumour in the oral cavity is of particular interest. Such patients have previously been shown to be at substantial risk of developing a second primary tumour, particularly in the oral cavity but also elsewhere in the upper respiratory tract. For patients who survive the original tumour, such second tumours can represent an important source of morbidity for many years afterwards. An efficacious follow-up of this group is therefore important and the most suitable protocol is determined partly by the risk of occurrence of subsequent cancers at various sites.

Given the current interest in chemoprevention of cancers, patients in whom a primary tumour of the oral cavity has occurred represent a "high-risk" group who may be considered suitable for such intervention [1]. In these circumstances it is important to record the risk of cancers at individual sites for such patients, while in addition, the examination of the occurrence of second primary tumours can provide interesting associations which may be useful in elucidating the aetiology of certain cancers.

Much of the work in this area as been conducted by the follow-up of patients treated at clinical centres [2–4]. In order to avoid possible bias associated with such series we have chosen instead to examine data from population-based cancer registries. Previous studies using cancer registry data have shown dissimilar results with high risks of subsequent cancer diagnosis reported from the United States [5, 6] and lower rates from a European population [7]. The present study uses data from two national population-based cancer registries in Europe and a large population-based registry in Australia which together provide information on over 10 000 males diagnosed with oral cavity cancer.

Slovenia has the second highest national rate of such tumours in Europe (after France) with an age-standardised rate (ASR), (standardised to the world population) of 19.4 per 100 000 man years in 1982–1987, while New South Wales (NSW), Australia represents an area of intermediate risk (ASR

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8.8 per 100 000 male years in 1983–1987), and Scotland a country with relatively low risk (ASR 5.7 per 100 000 in 1983–1987) [8, 9]. Trends in incidence have been upward in each of the three areas [10–13].

MATERIALS AND METHODS

The registries included in this study were the New South Wales Central Cancer Registry (average male population (1983–1984), 2 727 256), the Central Scottish Cancer Registry (average male population (1983–1987), 2 478 922) and the Slovenian Cancer Registry (average male population (1982–1987), 949 768) [9].

Each registry provided a data file with details of all cases of oral cavity cancer occurring in the following sites: tongue, gum, floor of mouth, other areas of the mouth, hypopharynx, oropharynx and oral cavity unspecified (ICD-9 141, 143–146, 148 and 149) [14]. Henceforth, the term "oral cavity" when used in relation to the present study will refer to this group of sites. These were chosen because these sites are believed to have similar aetiologies. The vast majority of cancers in "other and ill-defined sites within the lip, oral cavity and pharynx" (ICD-9 149) are likely to have occurred in one of these sites and are included in this study. The actual time-period over which the cases were diagnosed varied between registries: New South Wales (NSW) (1972–1991), Slovenia (1965–1990), Scotland (1968–1991). Data were abstracted for any primary malignant cancer (excluding non-melanoma skin cancer) diagnosed subsequent to the registration of oral cavity cancer in these persons (i.e. second primary cancers). In all centres, an internal linkage was carried out to determine second primary tumours after the occurrence of oral cavity cancer. The analysis has been restricted to men, since such tumours are relatively uncommon in women, providing too few cases for a meaningful analysis of second primary tumours. Also, since the relative importance of the main risk factors known for oral cavity tumours (i.e. tobacco and alcohol) is lower in women, and it is estimated that the aetiology is unknown in approximately half of the cases in women, it has been decided not to combine the data for men and women [15].

Entry into the study cohort occurred 2 months after the date of diagnosis of the original oral cavity tumour. It was, therefore, restricted to those who survived 2 months after the date of diagnosis and did not have a second tumour diagnosed within this 2-month period (or simultaneously with the primary oral cavity tumour). Cohort members contributed person years of risk to the cohort from the date of entry into the cohort until either the date of diagnosis of a second primary tumour, date of death, or date of censoring if still alive, whichever occurred earliest. The date of censoring was taken as 31 December 1991 (31 December 1992 in Scotland) for all subjects who were not known to be dead and who did not have a record of a second primary tumour. Again, the methods of follow-up varied between registries although in each an external linkage between the cancer database and death records was made to determine whether subjects had died, and if so, the date of death.

Person years of risk were classified by 5 year age-group, by time-period of diagnosis of the original tumour and by time since entry into the cohort. The expected number of cancers (overall or at a specific site) was computed by applying the age-specific rate for the appropriate time-period to the person years of risk in that age-group/time period accumulated by the cohort, and summing over all age-group/time periods. The observed number of cancer cases (O) was divided by the expected number (E) to obtain a Standardised Incidence Ratio (SIR: O/E) and the statistical significance of the SIR determined by assuming that the observed number of cases followed a Poisson distribution with a mean (O). The SIR was calculated for all cancer sites (excluding non-melanoma skin cancer) and selected individual sites, for the complete period of follow-up and for sub-periods since entry into the cohort of less than 1 year, 1–4 years, 5–9 years, 10 years and over. This method of analysis ensured compatibility with a previously published NCI monograph on second primary tumours occurring in Connecticut and Denmark [16].

RESULTS

The total number of men diagnosed with oral cavity cancer in the three areas in the given time-periods was 10 839, with a total follow-up period of 31 542 person-years (Table 1). The

Table 1. *Number of subjects in each centre by oral cavity site; number of second primary tumours and total person years (py) of follow-up*

Site Code (ICD-9)	Site description	New South Wales	Scotland	Slovenia	Total
141, 143–146, 148, 149	All sites included	4311	3130	3398	10 839
141	Tongue	1159 (27%)	792 (25%)	723 (21%)	2674 (25%)
143	Gum	151 (4%)	183 (6%)	107 (3%)	441 (4%)
144	Floor of mouth	689 (16%)	624 (20%)	561 (17%)	1874 (17%)
145	Other mouth	623 (14%)	517 (17%)	255 (8%)	1395 (13%)
146	Oropharynx	853 (20%)	460 (15%)	1126 (33%)	2439 (23%)
148	Hypopharynx	702 (16%)	390 (12%)	621 (18%)	1713 (16%)
149	Unspecified	134 (3%)	164 (5%)	5 (0%)	303 (3%)
	No. of secondary primary tumours	376	299	244	919
	Person-years of follow-up	13 612	10 137	7793	31 542
	Rate of second tumour occurrence	2.8 per 100 py	2.9 per 100 py	3.1 per 100 py	2.9 per 100 py

difference in sub-site distribution of cancers within the oral cavity is marked: while in Scotland, cancers of the oropharynx and hypopharynx account for 27% of all tumours, this rises to 36% in NSW and 51% in Slovenia (Table 1). A second notable difference is in the average period of follow-up per person: in NSW and Scotland it is 3.2 years, but in Slovenia it is only 2.3 years. Given that in the majority of cases the period of follow-up represents the time from diagnosis to death this indicates a lower survival from such oral cavity tumours in Slovenia in comparison with other centres. The number of second primary tumours was 7% of the total number of cases in Slovenia, 9% in NSW and 10% in Scotland.

In all centres, those who had been diagnosed with a cancer of the oral cavity represented a group at high risk of a subsequent primary tumour. Overall, 919 second primary tumours had occurred, representing an incidence rate of 2.9 per 100 person years; 15% of the second primary tumours were in the oral cavity and 60% in the upper respiratory and digestive tract. The risk of any tumour compared to the general population varied from 2-fold in Scotland and NSW to over 3-fold in Slovenia. In all three areas, risk was highest in the period 1–5 years after diagnosis. Thereafter, the excess risk diminished, until 10 years after diagnosis the risk was close to that of the general population (Table 2). This pattern of excess risk from the time of diagnosis was also generally consistent for individual oral cavity sites. In those diagnosed below the age of 50 years the risks were even higher: a 3-fold increase in NSW, a 4-fold in Scotland, and a 7-fold in Slovenia (data not shown).

For all ages combined, the results between the centres were consistent and particularly high risks of a second primary tumour (around 10-fold increases) were noted for the oral cavity and oesophagus, with smaller excess risks for cancers of the larynx and lung (2–4-fold increases) (Table 3).

No other site exhibited a significantly increased risk in all centres, although some other sites had a significant or borderline increased risk recorded in one centre but not others, e.g. lip, pancreas and colorectal cancers. Finally, there was no substantial difference in the risk of subsequent tumours according to the sub-site in the oral cavity of the initial cancer (data not shown).

DISCUSSION

Advantages of the present study are firstly, the large number of subjects included for analysis and secondly, the inclusion of data from three cancer registries in distinct geographical areas allowing a comparison to be made. Results obtained on one data set may be confirmed or rejected by the others. This is particularly useful for cancer sites where the increase in risk may be expected to be relatively small (e.g. less than 2-fold). It is also advantageous that the cancer registries are population-based, therefore the cases registered have arisen in a defined geographical area, and the rates then describe the burden of disease in the whole population of the area. The results obtained confirm the very high risk of subsequent cancers amongst patients with a cancer in the oral cavity.

Overall, the risk is 2–3 times that in the general population in each of the areas studied. Higher risks generally occur for those sites related to tobacco smoking and the highest risk for those related in addition to alcohol consumption. The risks are relative to the population of the areas as a whole. When comparing different registries one would expect increased risks to occur for the same general groups of sites. However, there is no expectation that the risks would be the same across different registries since this depends not only on the actual risk to the oral cancer patient, but also the risk in the general

Table 2. The relative risk (and 95% confidence interval) of a second primary tumour at any site; oral cavity cancer patients compared to the general population

	Risk relative to the general population by time since diagnosis				
	≤1 year	1–5 years	5–10 years	≥10 years	Overall
New South Wales	1.8	2.5	2.2	1.3	2.1 (1.9, 2.4)
Scotland	1.5	2.3	2.1	1.0	1.9 (1.6, 2.1)
Slovenia	2.9	4.4	4.1	1.0	3.5 (3.0, 4.0)

Table 3. Number of second primary tumours, risk (and 95% confidence interval) compared to the general population

	New South Wales		Scotland		Slovenia	
Site/registry	2nd tumours	Overall risk	2nd tumours	Overall risk	2nd tumours	Overall risk
Oral cavity	45	9.9 (7.1, 13.1)	26	9.7 (6.3, 14.2)	60	14.1 (11.0, 18.6)
Lip	13	6.0 (3.1, 10.1)	4	3.0 (0.8, 7.9)	1	1.1 (0.02, 6.2)
Oesophagus	30	10.9 (7.2, 15.3)	23	4.3 (2.7, 6.7)	30	13.6 (9.2, 19.5)
Stomach	13	1.6 (0.8, 2.7)	13	1.1 (0.6, 1.9)	4	0.4 (0.1, 1.0)
Colon–rectum	32	1.2 (0.8, 1.7)	32	1.5 (1.0, 2.1)	9	1.3 (0.6, 2.4)
Pancreas	11	2.2 (1.1, 3.9)	4	0.8 (0.2, 1.8)	4	1.9 (0.5, 4.9)
Larynx	15	4.4 (2.5, 7.3)	8	2.9 (1.2, 6.0)	16	6.5 (3.7, 10.4)
Lung	113	3.1 (2.6, 3.8)	111	2.1 (1.7, 2.6)	94	5.2 (4.2, 6.4)
Bladder	10	0.9 (0.4, 1.7)	18	1.5 (0.9, 2.3)	6	1.9 (0.7, 4.2)
Prostate	32	1.1 (0.7, 1.6)	24	1.2 (0.7, 1.7)	10	1.6 (0.8, 2.9)
Other cancers	62	1.3 (1.0, 1.7)	36	1.8 (1.2, 2.4)	10	0.8 (0.4, 1.4)

population of the different type of cancers. The calculated risks can also be affected by registration practices, completeness of registration and follow-up and methods for collecting information on and registering second primary tumours. However, despite all these possible influences, it is reassuring that the results across registries are consistent.

The results on the occurrence of a subsequent tumour (2.9 per 100 person years for any subsequent tumour; and 1.9 per 100 person years for cancers of the upper aero-digestive tract) are slightly lower than those reported from clinical studies [2–4]. This may be expected, since clinical groups represent a somewhat selected patient series with thorough follow-up, as opposed to data from cancer registries which should include all cases from a defined area. Compared with studies using cancer registry data, the results are closer to those from the United States by Day *et al.* [17] than the lower risks reported from Finland and Denmark [7, 18].

A second finding which is in agreement with most other studies, is that the increased risks of a subsequent tumour persist for some considerable time. This provides strong evidence that the effect of increased incidence of cancers in the oral cavity is not due to recurrent lesions being wrongly coded as new primary tumours. Increased risks were still evident up to 10 years after the initial cancer, with the highest risk between 1 and 5 years after diagnosis. Such a pattern highlights the need for close long term follow-up of these patients. Although traditional measures to reduce the incidence of oral cavity cancer focus on stopping tobacco smoking and moderating alcohol consumption, studies are conflicting as to whether such measures, after the diagnosis of an oral cavity cancer, reduce the risk of a subsequent cancer [17, 19, 20]. In these circumstances, chemopreventive agents may be considered. Such studies, which include oral cavity patients, are currently underway [21].

Finally, there was little evidence of an increase in risk at sites outside the upper aero-digestive tract. Risks of 1.5–2-fold were noted for cancers of the bladder and pancreas in two out of three centres, but were not generally statistically significant, while small increases in risk of between 1.1 and 1.5-fold were noted in all centres for cancers of the colon and rectum. The absence of a consistent increase in risk for cancers of the bladder and pancreas is somewhat surprising given that both are related to tobacco smoking; the risk of second tumours at these sites is not always reported in other studies (or no cases appear), but there is little from the published evidence available to suggest an increased risk at either of these sites. Although in the present data there was an increased risk noted for "other sites" in Scotland, one-quarter of these were recorded as liver or bone tumours and it seems likely that some of these would in fact have been metastatic tumours. No other single site had more than five cases recorded.

In summary, the present study, from registries in Europe and Australia, provide risk estimates of a second primary cancer in persons with a previous cancer of the oral cavity that are close to previous estimates reported from the United States, but higher than those reported from Finland and Denmark. The risks which are around 10-fold for the oral cavity and oesophagus and 2–4-fold for the larynx and lung persist for up to 10 years after diagnosis of the original cancer. The excess risks are confined to the upper respiratory and digestive tracts. They emphasize the need for close follow-up of such patients who may be an appropriate target for new chemopreventive agents.

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