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HIGH CONSTANT INCIDENCE RATES OF SECOND PRIMARY CANCERS OF THE HEAD AND NECK: A POOLED ANALYSIS OF 13 CANCER REGISTRIES

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Abstract

Scanty data are available on the incidence (i.e., the absolute risk) of second cancers of the head and neck (HN) and its pattern with age. We investigated this issue using data from a multicentric study of 13 population-based cancer registries from Europe, Canada, Australia and Singapore for the years 1943-2000. A total of 99,257 patients had a first primary HN cancer (15,985 tongue,

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22,378 mouth, 20,758 pharyngeal, and 40,190 laryngeal cancer), contributing to 489,855 person-years of follow-up. 1294 of the patients (1.3%) were diagnosed with second HN cancers (342 tongue, 345 mouth, 418 pharynx, and 189 larynx). Male incidence rates of first HN cancer steeply increased from 0.68/100,000 at age 30-34 to 46.2/100,000 at age 70-74, and leveled off at higher age; female incidence increased from 0.50/100,000 at age 30-34 to 16.5/100,000 at age 80-84. However, age-specific incidence of second HN cancers after a first HN cancer in men was around 200-300/100,000 between age 40-44 and age 70-74, and tended to decline at subsequent ages (150/100,000 at age 80-84); in women, incidence of second HN cancers was around 200-300/100,000 between age 45-49 and 80-84. The patterns of age-specific incidence were consistent for different subsites of second HN cancer and sexes; moreover, they were similar for age-specific incidence of first primary HN cancer in patients who subsequently developed a second HN cancer. The incidence of second HN cancers does not increase with age, but remains constant, or if anything, decreases with advancing age.

Impact statement—While the incidence of first primary cancers of the head and neck increases with advancing age that of second primary cancers is stable between age 40 and 70 and, if anything, declines thereafter.

Keywords

second neoplasms; head and neck cancer; incidence; age

INTRODUCTION

Patients who had a cancer in one of the organs of the head and neck (HN) have a substantial excess risk of a second primary cancer in the same or another HN organ, and this is a major reason for their poor prognosis [1-3]. Moreover, it has been shown that relative risks (RR) of second HN cancers are higher at younger age, and decline with advancing age [4, 5].

Population-based information on the incidence of second cancers of the HN, and on its relation with age are available only from a series of about 3,000 cancers of the oral cavity and pharynx registered between 1974 and 2003 in the Swiss Cantons of Vaud and Neuchatel, including 233 second cancers [4]. The incidence of second oral and pharyngeal cancers showed no increase with age, and indeed declined from 30.3/1000 at age 40-49 to 12.5/1000 at age 70-79 years, in sharp contrast with the incidence of the first primary cancer, which increased 20-fold between age 30-39 and 70-89 [4]. Thus, those data suggested that the incidence of second primary cancers of the HN follows the same pattern observed for breast and a few other neoplasms, indicating no increasing incidence of second neoplasms with age [5-13].

In order to further investigate the age-relation of the incidence of second HN cancers, overall and within subsites, we analyzed data from a multicentric study including 13 population-based cancer registries from Europe, Canada, Australia and Singapore. A previous report on the same dataset analyzed the standardized incidence rates (SIR) of second HN cancers, and their relation with age at and time since diagnosis of the first HN cancer, as well as the cumulative risk of second HN cancers [14].

MATERIALS AND METHODS

Data were derived from an international multicenter study of cancer registries that have been in operation for at least 25 years to conduct a systematic analysis of second primary cancers [14, 15]. Briefly, the registries include New South Wales in Australia, British Columbia, Manitoba and Saskatchewan in Canada, Denmark, Finland, Iceland, Norway, Scotland, Singapore, Slovenia, Sweden, and Zaragoza in Spain. These registries had cancer data

covering different time periods within 1943 2000. A high degree of completeness of ascertainment by the registry is suggested by an appropriate level of microscopically verified cases, a low proportion of cases registered from death certificates only, and their consistent inclusion in the "Cancer Incidence in Five Continents" series [16].

Data were provided from each cancer registry on all first primary cancers, including age and sex of the patient, diagnosis and date of the first primary, follow-up for mortality and diagnosis and date of the second primary, if any. In this study, registries used different cancer codes, which were systematically converted into those of the International Classification of Disease, Ninth Revision (ICD-9).

Here, we analyzed the occurrence of second HN cancers in patients who survived from first primary HN cancer (ICD-9 codes: tongue: 141; mouth: 143 145; oropharynx: 146; hypopharynx: 148; pharynx unspecified: 149 and larynx: 161), who have already been included in a previous report [14]. Lip (ICD-9: 140), salivary glands (ICD-9: 142) and nasopharyngeal cancer (ICD-9: 147) were not included in the analysis.

Coding of multiple primaries in the cancer registries has followed a common set of rules proposed by the International Association of Cancer Registries and the International Agency for Research on Cancer [17]. According to the rules, a primary cancer is one that originates in a primary site or tissue and is thus neither an extension, nor a recurrence, nor a metastasis. Second HN cancers from the same site (defined as tongue, other parts of the mouth, oropharynx, hypopharynx, pharynx unspecified, and larynx) as the first primary cancer were excluded from registration in most cancer registration areas, and are therefore not considered in the present report.

All cases of first primary HN cancers were followed up for second HN cancers from the date of HN cancer diagnosis (1943–2000) to the date of second HN cancers (1943–2000), the date of death or end of follow-up (1992–2000), depending on the coverage of each registry when the study closed.

Expected numbers of second HN cancers were calculated from the accumulated person-years and the age-, sex-, calendar period-specific first primary HN cancer incidence rates in each of the cancer registries [18]. By comparing the observed and expected number of second HN cancers, we computed the SIR of HN cancer, and the corresponding 95% confidence intervals (CIs), based on the Poisson distribution.

We computed age-specific incidence rates/100,000 of first HN cancer in the populations covered by the cancer registries, and those of second HN cancer in the cohort of patients with a first HN cancer. For Denmark, Norway, Scotland, Slovenia, Sweden, Spain and Manitoba, the registries provided the population covered by sex, age and calendar year. For other registries, population data were derived from the "Cancer Incidence in Five Continents" volumes [16].

RESULTS

A total of 99,257 patients (74,988 men; 24,269 women; median age 63) had a first primary HN cancer (15,985 tongue, 22,378 mouth, 20,758 pharyngeal, and 40,190 laryngeal cancer) who contributed 489,855 person-years of follow-up (mean follow-up time: 4.9 years). During the follow-up period, 1294 of these patients (1.3%) were diagnosed with second HN cancers at a different site (342 of the tongue, 345 of the mouth, 418 of the pharynx, and 189 of the larynx), versus 115.75 expected, corresponding to a SIR of 11.2 (95% CI 10.6-11.8) (Table 1). The SIR was 9.5 in men (based on 995 cases), and 28.3 in women (based on 299 cases). The SIR was 16.4 under age 50, and decreased to 8.8 at age 70 or more. A similar

pattern was observed in both sexes, although the decrease in the SIR with increasing age at diagnosis was smaller in women (SIR=36.8 at age <50 and 24.5 at age ≥70) than in men (SIR=14.6 at age <50 and 6.2 at age ≥70). With reference to subsite at first HN cancer, the SIRs were 16.7 when the site of the first cancer was the tongue, 14.1 when it was the mouth, 14.0 when it was the pharynx, and 7.1 when it was the larynx. Corresponding figures were 13.2, 11.3, 12.0 and 6.7 in men, and 36.6, 32.4, 31.8 and 13.8 in women. Considering subsites at second HN cancer, the SIRs were 16.0 when the site of the second cancer was the tongue, 12.5 when it was the mouth, 11.7 when it was the pharynx, and 6.1 when it was the larynx. Corresponding figures were 12.6, 10.1, 10.6 and 5.6 in men, and 40.9, 30.9, 24.9 and 12.9 in women.

Figure 1 shows the age-specific incidence of first HN cancer (overall and by subsite) in men and women separately. In men, incidence rates steeply increased from 0.68/100,000 at age 30-34 to 46.2/100,000 at age 70-74, and leveled off at higher age; in women, incidence increased from 0.50/100,000 at age 30-34 to 16.5/100,000 at age 80-84. Similar patterns were observed for various subsites of HN.

The age curve was totally different for second HN cancers, as shown in Figure 2. The age-specific incidence of second HN cancers after a first HN cancer in men was around 200-300/100,000 between age 40-44 and age 70-74, and tended to decline at subsequent ages (150/100,000 at age 80-84). Though the patterns were less stable in women due to the lower number of female HN cancer patients, the incidence of second HN cancers was similar to that in men around 200-300/100,000 between age 45-49 and 80-84. The patterns of age-specific incidence were consistent for different subsites of second HN cancer, both in men and in women.

Analyses of incidence of second HN cancers by subsite of first HN cancer showed similar age patterns – although less stable – to those observed in the overall analysis (Figure 3).

DISCUSSION

Our data confirm the existence of a substantial excess risk of HN cancer in patients who had a previous HN cancer as compared to the general population. At every age, incidence rate of second HN cancers was greater than the rate of first primary cancers, with particularly high relative risk at younger ages. This is due to the fact that – as observed for breast cancer and for a few other cancer sites for which it was possible to analyze the incidence of second primary tumors [5-13] – the incidence of second HN cancers does not increase with age, but remains constant, or if anything, decreases with advancing age. The higher relative risk of HN cancers in younger observed in this as in a few other studies [4, 5, 19], well reflects the age-specific incidence curves of second HN cancers. Likewise, the incidence of primary HN cancers in patients who eventually developed a second HN cancer does not rise with a power of age. Rates for all HN sites at age 50 to 75 ranged around 0.40-0.50/100,000 in men and around 0.1 in women (data not shown in Figure).

Consistent age-specific incidence patterns were observed for various organs within the HN (i.e., tongue, other parts of the mouth, pharynx and larynx), as well as HN cancers after a first cancer at the same organs, although the incidence of second HN cancer was generally lower when the first HN cancer originated in the larynx.

The observed age-specific incidence patterns were also consistent in men and women, although in women the rates were less stable, due to lower number of female patients. Interestingly, we observed that, while the incidence of first HN cancer is lower in women than in men, the incidence of second cancer is similar in the two sexes, and consequently the SIRs of second cancer are higher in women than in men [19, 20]. This has not been reported

previously, probably because the small sample size of previous studies has precluded separate analyses for women.

The present findings confirm the age- specific incidence patterns of second primary cancers reported in a previous analysis on oral and pharyngeal cancer in two Swiss cancer registries [4]. The estimates of the absolute, as well as the relative, risk of second HN cancers in our data are, however, lower than those reported in those cancer registries. This can be due to various factors, including the higher baseline incidence of oral and pharyngeal cancers in Switzerland as compared to most countries included in this pooled analysis [16] and the different registration and exclusion criteria of second tumors in those Swiss registries, as compared to most of those included in our analyses. The Swiss registries have an active follow-up of cancer, in particular HN, patients, as also indicated by the high proportion of patients with a second primary cancer of the oral cavity and pharynx (7.5%) observed in that cohort, as compared to that reported in our as well as in other studies [19, 21]. Our SIR estimates are, however, comparable with those observed in a nationwide database from Sweden [21], and higher that those from a few other studies from northern Europe [19, 22].

The interpretation of the age-specific incidence curves for second HN cancers is not simple. Subjects with a primary cancer of the HN differ from the general population in several aspects, which can affect their risk of a new primary tumor. They constitute a group of susceptible subjects, probably characterized by a high genetic predisposition. Moreover, the exposure to the agents which caused the primary tumors may also have triggered the development of multiple primary cancers at other HN sites, originated by the same field as proposed within the “field cancerization” theory [23, 24] or originated from multiple independent lesions [25]. The treatments for their first cancer may also affect their risk of developing a subsequent primary cancer.

The power relation with age of the incidence of first primary HN cancer has been interpreted within the multistage model of carcinogenesis, as an indication that tumors arise from the accumulation of several essentially random genetic changes [26]. On the other hand, the constant age patterns of second HN cancers are not compatible with the occurrence of a number (5 to 8) of subsequent mutational events or clones of cells [27, 28], but indicate that this population of susceptible individuals may need a single additional mutational event to develop a second cancer [29, 30]. This is also supported by the similar age pattern for primary HN cancers in patients who had second HN cancers, observed also for other neoplasms [5, 8, 13].

The tendency for a decline in the incidence of second primary neoplasms of the HN may be partly due to selective stopping of risk factors modifiable in middle and elderly age, i.e. smoking and alcohol drinking in (elderly) patients with a first diagnosis of HN cancer, with the consequent fall in their risk of HN cancer [31]. This can, however, be caused by the progressive elimination of predisposed (very high risk) individuals at young ages, as suggested also for breast cancer [8, 10, 29, 30], together with some possible under-reporting at elderly ages, which, however, is unlikely to explain a decline in rates starting at age 55. A fall in rates in the elderly may also be due to some reduction in the ability to respond to promoters, as indicated by animal experiments on mice given initiators and promoters at different times in their life [32, 33].

Increased surveillance of patients who had a first primary HN cancer and some misclassification – due to difficulties to distinguish second primary cancers from recurrence of first tumors or metastases – may have affected our rates estimates. We have adopted strict rules to exclude recurrences of first primaries. This may have led to underestimation of the real cancer rates, but cannot account for the observed age-specific incidence curves. The

relatively long follow-up and, mostly, the large number of patients are among the strengths of this study, which allowed us to provide estimates of age-specific incidence rates of second HN cancers, not only overall, but also by sex and subsites.

In terms of individual risk assessment and clinical implications, these results indicate that young HN cancer patients, although rare, are at particularly high risk of developing another primary cancer in the HN. The rates of second HN cancers of the order of 150 to 250/100,000 in the fifth decade of age are indeed comparable or larger than the rates of all cancers in the general population at age 40 to 49 [34].

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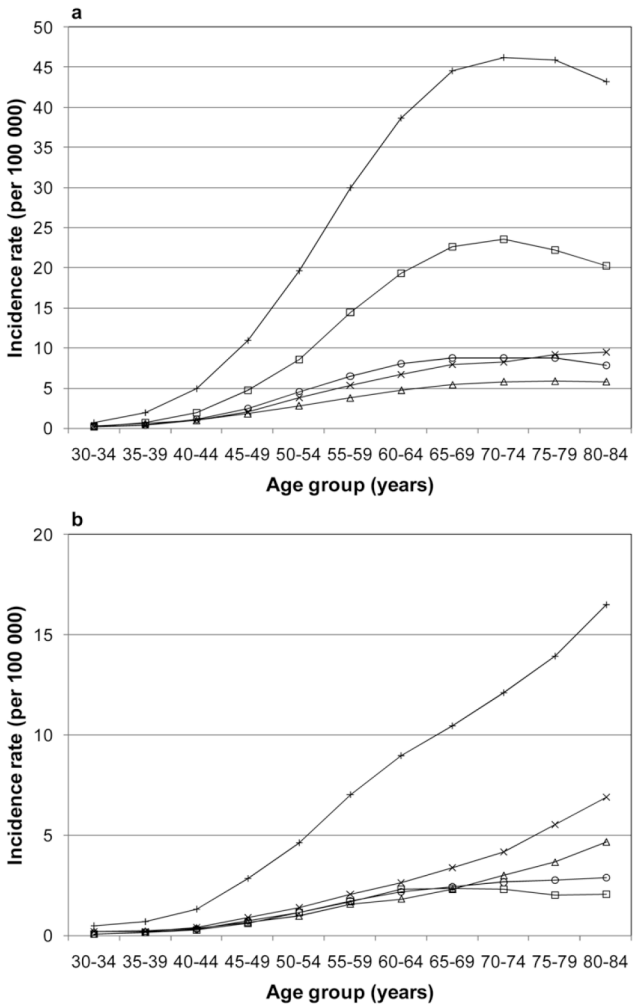

Figure 1.

Age-specific incidence rate of first cancers of the head and neck in the general population, in 74,988 male (a) and 24,269 female (b) cases.

Any head and neck; Larynx; Pharynx; Mouth; Tongue.

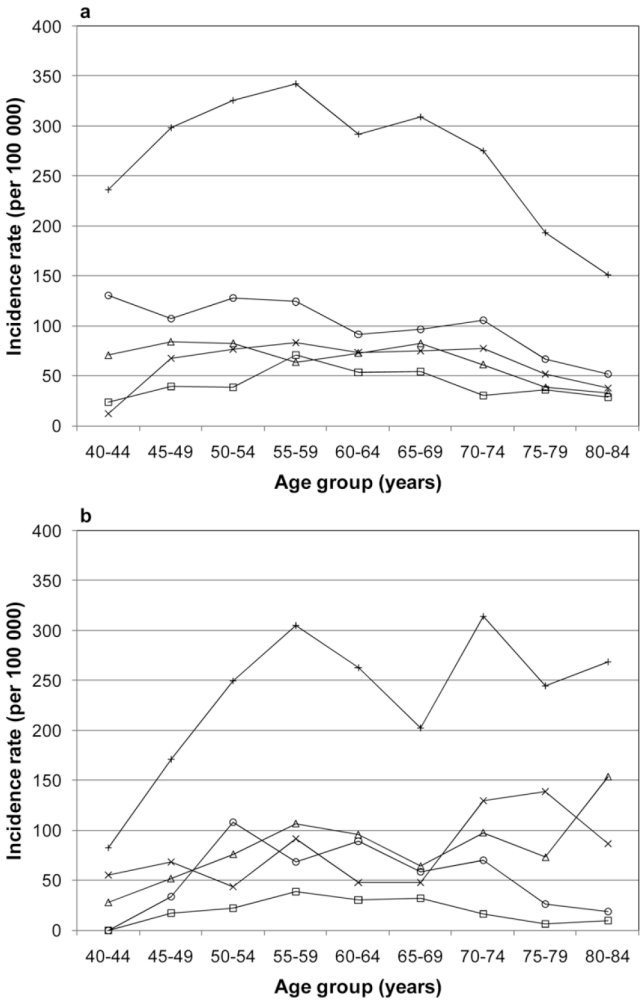

Figure 2.

Age-specific incidence rate of second cancers of the head and neck in 995 men (a) and 299 women (b) who had a first cancer of the head and neck.

Any head and neck; Larynx; Pharynx; Mouth; Tongue.

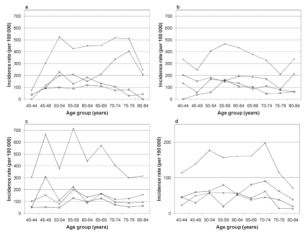

Figure 3.

Age-specific incidence rate of second cancers of the head and neck in patients who had a first cancer of the tongue (a), mouth (b), pharynx (c) and larynx (d).

Any head and neck; Larynx; Pharynx; Mouth; Tongue.

Table 1

Observed number of cases (N.) and standardized incidence ratio (SIR), and corresponding 95% confidence interval (CI), of second cancer of the head and neck in 99,257 subjects (74,988 men and 24,269 women) who had a first head and neck cancer, by age at diagnosis of first cancer and by site of first and second cancer.

	Men			Women			Total		
	N.	**SIR**	**95% CI**	**N.**	**SIR**	**95% CI**	**N.**	**SIR**	**95% CI**
Head and neck	995	9.5	8.9-10.1	299	28.3	25.2-31.7	1294	11.2	10.6-11.8
Age at diagnosis									
<50	171	14.6	12.5-17.0	34	36.8	25.9-50.7	208	16.4	14.2-18.8
50-59	367	10.9	9.8-12.0	81	35.4	28.5-43.4	458	12.6	11.5-13.8
60-69	334	8.4	7.5-9.4	81	24.4	19.6-30.1	423	9.8	8.8-10.7
≥70	123	6.2	5.1-7.3	80	24.5	19.5-30.5	205	8.8	7.6-10.1
Site of first cancer									
Tongue	191	13.2	11.4-15.3	91	36.6	29.5-44.9	282	16.7	14.8-18.7
Mouth	247	11.3	1.0-12.8	107	32.4	26.6-39.2	354	14.1	12.7-15.7
Pharynx	213	12.0	10.5-13.8	62	31.8	24.4-40.8	275	14.0	12.4-15.8
Larynx	344	6.7	6.0- 7.5	39	13.8	9.8-18.9	383	7.1	6.4-7.8
Site of second cancer									
Tongue	238	12.6	11.1-14.3	104	40.9	33.4-49.6	342	16.0	14.3-17.7
Mouth	245	10.1	8.9-11.4	100	30.9	25.2-37.6	345	12.5	11.2-13.9
Pharynx	349	10.6	9.5-11.8	69	24.9	19.4-31.5	418	11.7	10.6-12.9
Larynx	163	5.6	4.8-6.5	26	12.9	8.4-18.9	189	6.1	5.2-7.0

Tongue (ICD-9:141); Mouth (ICD-9: 143-145); Pharynx (ICD-9:146, 148-149); Larynx (ICD-9:161); Head and neck (ICD-9:141, 143-145, 146, 148-149, 161)