The Relation between Cancer Incidence among Relatives and the Occurrence of Multiple Primary Carcinomas following Head and Neck Cancer

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Abstract

Despite improvement in therapeutic modalities in head and neck squamous cell carcinoma (HNSCC) the overall survival rate has only marginally improved during the last decades. The occurrence of second primary tumors (SPTs) in the respiratory and upper digestive tract (RUDT) is the main cause of treatment failure in early stage HNSCC. Identification of risk factors for the development of SPT by epidemiological analysis may lead to better risk assessment in individual cases. Ninety-seven HNSCC patients who ultimately developed SPTs and 100 HNSCC patients who remained free of other carcinomas after treatment of the first for a minimal period of 6 years were interviewed about the incidence of RUDT carcinomas within parents and siblings. All questioned patients were smokers. Among the SPT-positive patients, 50 (8.9%) of the 562 family members were reported to have had cancer of the respiratory or upper digestive tract *versus* 16 (2.5%) of the 629 family members of the SPT-negative patients. This difference was statistically significant ($P < 0.0001$) with the stratified version of Fisher's exact test. All these 66 probands with RUDT cancer were smokers, and the percentages of smokers were similar in both proband groups. Neither age and sex of the patient, nor tumor stage influenced the occurrence of SPTs in this study. The percentages of probands with tumors outside the RUDTs were almost similar, 8.0 and 7.0% in the SPT-positive and -negative groups, respectively. Having one or more relatives with RUDT cancer was established as a risk factor (odds ratio, 3.8; 95% confidence interval, 2.0–7.6) for patients with initial HNSCC to develop an SPT. These findings suggest that, in addition to external carcinogens, an intrinsic susceptibility may influence the risk for the development of SPTs in HNSCC patients.

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Introduction

Individual differences in susceptibility to chemically induced carcinomas are thought to be based on, at least in part, genetic variability in metabolic activation and detoxification of environmental procarcinogens (1, 2). For instance, tobacco and alcohol metabolites are identified as potential exogenous etiological factors in the induction and/or progression of HNSCC[2] (3, 4). An intrinsic susceptibility with a possibly genetic basis could explain why only a few persons of the many who have been exposed to these external carcinogens develop HNSCC. In addition, the question arises of why some HNSCC patients ultimately develop two or more primary malignant tumors in the RUDT, whereas others do not. This is an important question, because SPTs are known to be a major cause of treatment failure in patients cured for early stage HNSCC. The great majority of SPTs occur more than half a year after the first, so-called index tumors and are designated metachronously. The constant annual rate for the first 5 years is estimated to be nearly 3% (5). The incidence of second primary tumors varies from 10 to as high as 40%, depending on the site of the index tumor (6). Second cancers in patients previously treated for HNSCC have enhanced morbidity and mortality, because of their appearance at notoriously bad sites, such as the lungs and the esophagus, or at previously irradiated or operated areas. This clinical scenario has lead to the focus on early detection and (chemo)prevention strategies to reduce the morbidity and mortality rates. Taking into account, as has been said above, that SPTs occur with a constant rate over the years, intense follow-up should be continued for long periods, if not lifelong. One of the problems with such intense follow-up of cancer patients is the enormous workload for a medical team. Passive prevention (*e.g.*, smoking cessation) has a doubtful contribution to the reduction of the risk of SPTs. Because HNSCC is in principal a disease of people in the sixth decade of their lives, who have already been smoking and drinking for approximately 30 years, it is clear that much injury has already been caused before prevention can be started (7). Chemoprevention by 13-*cis*-retinoic acid has been demonstrated to be successful but has a high level of side effects (8). In this context, it should be a logical approach to tailor the application of screening and chemoprevention procedures to the estimated risk in each individual case. Until now, some insight has been gained about which kinds of patients are at high risk of developing SPTs, but this knowledge is still fragmentary. Two recent epidemiological studies have confirmed familial aggregation with HNSCC, suggesting that genetic predisposition may be an important risk factor (9, 10). A Dutch study revealed that having a brother or

[2] The abbreviations used are: HNSCC, head and neck squamous cell carcinoma; SPT, second primary tumor; RUDT, respiratory and upper digestive tract.

sister with cancer in the RUDT results in a relative risk of developing HNSCC of 14.6 (9). In a Brazilian population, an elevated risk of developing HNSCC with a factor of 8.6 was found with siblings having HNSCC (10). Familial aggregation has also been reported for lung cancer. These data may be relevant for HNSCC, because etiological factors are similar (2), and SPTs following HNSCC can develop in the lung (6, 7). Some studies have reported a familial clustering for lung (11–13), in particular, squamous lung, cancer (14). Having a relative with lung cancer is found to be a risk factor for HNSCC (9). In addition, having a proband with laryngeal cancer is a risk factor for lung cancer (11). Because RUDT cancer occurs mostly in smokers, the prevalence of smoking has a profound influence on the identification of a clear genetic hereditary pattern. Using families with probands born before and after World War I, it was shown by Sellers *et al.* (13) that a genetic predisposition for lung cancer exists. These authors have hypothesized that virtually all lung cancers occur among susceptibility gene carriers, and that a moderate smoker older than 80 years is a noncarrier. It is conceivable that the lung cancer susceptibility gene is the same as the gene that accounts for HNSCC.

Cytogenetic studies, measuring the bleomycin-induced damage in cultured lymphocytes, also support the existence of constitutional risk factors for head and neck carcinogenesis (15, 16). Moreover, sensitivity to bleomycin-induced chromosomal damage was significantly highest in HNSCC patients who had ultimately developed SPTs (16).

To optimize treatment strategies and reduce mortality rates in HNSCC patients, knowledge of events involved in cancer development are of great need to identify patients at high risk of developing SPTs. Therefore, the objective of the current study is to evaluate whether the family history for cancer of the RUDT is related to the development of an SPT.

Patients and Methods

Study Population. 97 HNSCC patients who ultimately developed SPTs (SPT+) and 100 HNSCC patients who remained free of other carcinomas after treatment for the first for a minimal period of 6 years (SPT−) were asked to participate in this study. All patients have had histopathologically proven squamous cell carcinomas. Details on the patient groups are shown in Table 1. Patients from both study groups were interviewed during the regular follow-up. The median follow-up times were 8 and 6 years from the diagnosis of the first carcinoma for the SPT− and SPT+ groups, respectively. The median time difference between the occurrence of the first and second primary tumor was 2 years. All patients were in good mental health, did not consume an excessive amount of alcoholic beverages (less than five drinks per day) and had intact families. We classified SPTs according to the original criteria of Warren and Gates (17), as later modified by Hong *et al.* (8). In short, an SPT has to be separate from the first tumor by at least 2 cm of normal, nonneoplastic mucosa. Each tumor has to be malignant at histological examination and, in any case, the possibility that the second one is a metastasis from the first has to be eliminated.

Data Collection. A standard questionnaire was filled in with the following data: year of birth; year of occurrence of the first tumor; smoking habits; and incidence and sites of cancer in parents and siblings. For the relatives, smoking was recorded as positive or negative. Alcohol consumption was not part of the questionnaire because of the unreliability of the reports by family members.

Table 1 Patient and primary tumor characteristics of SPT+ and SPT− groups

Characteristic[a]	SPT+	SPT−
Total *n*	97	100
Age		
Mean	57	59
>60 yr (%)	62	52
≤60 yr (%)	38	48
Sex		
Female (%)	26	18
Male (%)	74	82
No. of smokers (%)	100	100
Site of tumor		
Larynx (%)	40	71
Oral cavity (%)	60	29
Tumor stage[b]		
T_1 (%)	36	33
T_2 (%)	32	28
T_3 (%)	15	27
T_4 (%)	16	12
Node stage[b]		
N_0 (%)	69	73
N_1 (%)	21	22
N_2 (%)	8	4
N_3 (%)	2	1

[a] Characteristics are for the first tumor at the time it was diagnosed.
[b] According to the TNM classification (18).

Statistical Analysis. Differences in occurrence of carcinomas in the RUDT in parents and siblings between both groups were tested for statistical significance using the stratified version of Fisher's exact test. For the measurement of cancer risk, the Mantel-Haenszel estimator was used.

Results

Of the 562 probands of the 97 SPT+ patients, 50 (8.9%) were reported to have had cancer of the RUDT. This is in contrast to 16 (2.5%) of the 629 family members of the SPT− patients (Table 2). Stratification by family size was used to avoid bias by the number of family members. As shown in Table 3, a statistically highly significant difference in family related tumors between the SPT+ and SPT− groups existed (stratified Fisher's exact test, $P < 0.0001$). The Mantel-Haenszel estimate of the odds ratio for the development of SPTs in HNSCC patients with an affected parent or sibling was established at 3.8 (95% confidence interval, 2.0–7.6). Among the 97 SPT+ patients were 5 families with 2 affected family members, whereas 1 family had 5 lung or HNSCC cases among the 7 siblings. Among the 100 SPT− patients, only 1 family had 2 affected family members. The characteristics of the patients of both groups showed minor differences (Table 1), but oral cavity carcinoma was more frequently represented among the SPT+ group, whereas laryngeal carcinoma was the prevalent carcinoma in the other group. All 197 patients were smokers (Table 1). The mean age of the patients who developed SPTs was 57 ± 9 (SD) years, whereas the mean age of the SPT− patients was 59 ± 10 years. Therefore, these factors were not considered important confounders.

The characteristics of the parents and siblings of the HNSCC patients with and without SPTs are reported in Table 2. The increased frequency of SCC among relatives of SPT+ patients was observed both in parents and in siblings. A positive family history for RUDT carcinoma was slightly less frequent in patients with laryngeal carcinoma than in patients with oral

Table 2 Characteristics of probands of head and neck squamous cell carcinoma patients with and without a second primary tumor

Proband	No.		% ever smoked		No. with tumors of the RUDT (%)		No. with tumors outside the RUDT (%)	
	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−
Total	562	629	71	66	50 (8.9)	16 (2.5)	45 (8.0)	44 (7.0)
Father	97	100	91	89	19 (19.5)	6 (6.0)	8 (8.2)	10 (10.0)
Mother	97	100	27	31	4 (4.1)	1 (1.0)	13 (13.4)	14 (14.0)
Brother	188	236	89	82	19 (10.1)	6 (2.5)	13 (6.9)	7 (10.6)
Sister	180	193	65	51	8 (4.4)	3 (2.2)	11 (6.1)	13 (7.2)

Table 3 Frequency of cancer of the respiratory and upper digestive tract in probands, divided according to family size

Families[a]	No. of probands/family											
	2–3		4		5		6–7		8–10		>10	
	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−	SPT+	SPT−
Affected	7	2	13	3	4	2	5	3	8	3	4	3
Not affected	11	18	14	16	10	10	9	16	5	15	7	9

[a] The numbers of families are shown that have or have not had family members affected by RUDT carcinoma. Taking family size into account, a highly significant difference in family related tumors between both groups existed ($P \leq 0.0001$, stratified Fisher's exact test).

cavity carcinoma (26 *versus* 30%). Relatives of this study population did not differ with respect to the other types of tumors. These were equally represented in both patient groups (Table 2).

All the 66 relatives with cancer of the RUDT were smokers, and the percentage of smokers of all probands did differ minimally between the groups, being 71 and 66% in the probands of the SPT+ and SPT− patients, respectively.

Discussion

The development of SPTs is one of the major causes of treatment failure in patients suffering from early stage HNSCC. Causative factors in HNSCC are undoubtedly multiple and complex. However, for strategies of early detection and chemoprevention to be successful, identification of high-risk individuals is essential. The selection of patients who will benefit most from preventive strategies justifies possible side effects.

Tobacco and alcohol consumption are known risk factors for the development of SPTs in the RUDT (7, 19, 20). The results of the present study, in addition, show that a positive family history is associated with the occurrence of an SPT. We estimated an odds ratio of 3.8 for the development of SPTs in individuals with parents or siblings who suffered from carcinoma of the RUDT.

As for HNSCC, familial aggregation has previously been reported for Dutch and Brazilian populations (9, 10). Moreover, a strong familial aggregation in the occurrence of lung (11–14) and multiple esophageal cancer (20) has been found by others. To explain this increase in cancer risk, two possibilities may be considered. First, a factor with a hereditary basis determines the cancer risk. The genetically controlled metabolism of tobacco (and perhaps alcohol) is a possible explanation why only some heavy smokers and drinkers develop HNSCC and why only some of the HNSCC patients develop SPTs. Variability in genetically determined detoxification pathways of procarcinogenic components of cigarette smoke by specific enzyme systems (*e.g.*, glutathione *S*-transferase μ and cytochrome P-450 enzymes) has been described and may form the basis of cancer susceptibility (1, 2). Moreover, the results of increased mutagen sensitivity, as recently shown for HNSCC patients, especially those who develop SPTs (15, 16), are in line with this intrinsic cancer susceptibility.

A second explanation is that the same risk habits such as smoking and drinking may be aggregated within the same family, leading to the observation of a close relationship between family history and the multiplicity of cancer. It was not possible to test this hypothesis. The exact amount of tobacco and alcohol consumption was not recorded in the present study. It must be emphasized that patients in both groups were all smokers, and the percentages of patients who ever smoked were nearly identical in the groups with relatives with respect to parents and siblings (Table 2). All individuals who were interviewed were in good mental health and were not abusers of alcohol; therefore, recall bias about family characteristics can be excluded.

Our data suggest that the relative degree of risk in an individual for developing an SPT in the RUDT also depends on an intrinsic factor. Combination of other identified risk factors, such as exposure to tobacco and alcohol, mutagen sensitivity, and expression of specific enzyme systems in the mucosa of HNSCC patients (21), could lead to further target opportunities for cancer prevention and control.

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