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Familial Predisposition for Salivary Gland Cancer in Finland

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ABSTRACT

BACKGROUND: Salivary gland cancer (SGC) accounts for 3–5% of head and neck malignancies, and register-based studies estimate the familial proportion to be 0.15%.

OBJECTIVE: We studied familial predisposition for SGC in the genetically distinct Finnish population.

PATIENTS AND METHODS: We sent a patient questionnaire to 161 Finnish SGC patients, 86 of whom responded.

RESULTS: A total of 76% of the patients reported having one or more relatives with cancer, 30% two or more, and 9% three or more but only one patient reported having a relative with SGC. Tracing the birthplaces of the SGC patients' grandparents showed no regional clustering suggestive of a founder effect.

CONCLUSIONS: Lack of familial SGC patients and the absence of a founder effect strongly suggest that familial predisposition for SGC is insignificant in the Finnish population. Various histological subtypes and the rarity of these neoplasms make it impossible to draw conclusions about site-specific association between SGC and other malignancies.

KEYWORDS: cancer risk, familial, head and neck, salivary gland

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Introduction

Salivary gland carcinomas (SGCs) account for 3–5% of all head and neck malignancies. The variety of subtypes and the relative rarity of SGC pose difficulties in diagnostics, treatment, and prognostication, and complicate studies evaluating potential predisposing factors or heritable etiology.

The etiology of SGC may be related to a number of potential risk factors, such as environmental and dietary factors, as well as unhealthy lifestyles.[1] Individuals may also show variable intrinsic susceptibilities to environmental factors or abilities to detoxify carcinogens.[2,3] Tobacco and excessive alcohol consumption increase the risk for head and neck cancer,[1,4] but tobacco is not a known risk factor for SGC.[5] Salivary gland tumors associate with ionizing radiation. Malignant tumors predominate in patients with a history of radiotherapy, the most common subgroup of which is mucoepidermoid carcinoma (MEC).

In addition to environmental and lifetime factors, familial predisposition is well recognized for many cancers. Based on a Swedish Family-Cancer database, Hemminki and Vaittinen[6] reported that maternal or paternal colorectal cancer increases the risk for SGC in offspring 2.4- to 3.6-fold. If both parents had any cancer, the risk for cancer in offspring was 1.3- to 1.4-fold. Parental SGC can increase the risk for medulloblastoma in offspring.[7] Another study also indicated a higher risk for developing SGC in individuals having a sibling with Hodgkin lymphoma or a brain tumor.[8]

Reported familial cases of salivary gland neoplasms are few and include pleomorphic adenoma, Warthin tumor, submandibular gland carcinoma, MALT lymphoma, and acinic cell carcinoma (ACC).[9–13] In addition, two studies report familial clustering of ACC.[9,10] Five siblings in two families among Inuit in Greenland had familial SGC.[14]

Several factors suggest a possible genetic predisposition for SGC. Inuit in Greenland show a 4.5- to 9-fold higher incidence of SGC than the representative incidence in Europe.[15] Epstein–Barr virus (a known risk factor for endemic nasopharyngeal carcinoma) is highly associated with lymphoepithelial carcinoma of the salivary glands, the most common SGC subtype among Inuit.[16] During an 11-year period, 15 SGCs were diagnosed in Greenland, and five patients (33%) were members of familial clusters.[15] In these families, first-degree relatives are at high risk for virally associated SGC and cervical cancer.[17] This higher risk for SGC among Inuit is unique and suggests the influence of genetic and environmental risk factors.[18]

Finland is one of the best-studied genetic isolates. The small number of original founders followed by their geographic isolation restricted the Finnish gene pool; the small number of founders resulted in consanguineous marriages.[19] Random inbreeding increased the local incidence of inherited disorders, and in many diseases, regional clustering is still evident.[20] Strategies utilizing these unique features have proved effective in disease gene mapping. Tracing the birthplaces of patients' grandparents has revealed a founder effect in several diseases of the Finnish disease heritage.[21] The aim of our study was to (1) identify potential cancer pedigrees with SGC, (2) identify a possible founder effect for SGC by tracing the birthplaces of patients' grandparents, and (3) respond to SGC patients' question, "Can this disease be heritable?"

Patients and Methods

We collected the files of patients diagnosed with SGC between 1974 and 2009 from the records of the Department of Pathology, Haartman Institute, Helsinki University Central Hospital (HUCH), Helsinki, Finland. This tertiary care academic center currently covers an area with approximately 1.5 million inhabitants, and the management of SGC is centralized in the university hospitals in Finland. Because patients with SGC are in average older, the overall survival rate for SGC is relatively poor, and because the retrieval period was long, many of the 437 patients had died. Consequently, we were able to identify and reach 161 SGC patients. These patients received a detailed questionnaire inquiring about their physical health, relatives with SGC or other site-specific malignancies, birthplaces of grandparents, and numbers of siblings as well as maternal and paternal aunts and uncles. The questionnaire was sent twice if necessary in a prepaid and preaddressed envelope. If needed, we also contacted the 86 respondents (53%; 86/161) by phone or email to obtain more information after they had provided their written informed consent in the questionnaire.

The patients were asked about the birthplace of their parents and grandparents to identify regional clustering and a possible founder effect. If the grandparents' birthplaces were unknown, we used parents' birthplaces.

For site-specific associations between SGC and other malignancies, we excluded the grandparents of the patients from the analysis of cancer history because grandparents often have poor documentation and/or memory of their medical history. We did, however, include children, parents, siblings, aunts, and uncles.

The Research Ethics Board of the HUCH approved the study proposal.

Results

Women comprised 54% of the total patient population and 64% of the respondents. Among all 437 SGC patients, the median age for MEC was 66 years (range, 15–87), for ACC 62 years (range, 11–84), and for adenoid cystic carcinoma (AdCC) 55 years (range, 27–88). The median age of MEC patients who completed the questionnaire was 57 years (range, 27–85), for patients with ACC 50 years (range, 19–77), and for patients with AdCC 59 years (range, 26–81).

The study population of 86 patients included 64 carcinomas of the parotid glands, 14 carcinomas of the submandibular glands, 6 carcinomas of the minor salivary glands, and 2 carcinomas of unspecified salivary gland origin. The most frequent SGCs were ACC (25%), MEC (24%), and AdCC (20%). The number of patients with ACC, MEC, and AdCC was comparable to the number of patients with similar histologies in the total database patient population of 437 (data not shown). The distribution of the histological subtypes of SGC and relatives with cancer history appears in Table 1.

Most (93%; 80/86) of the respondents reported their own birthplaces, and 66% (57/86) reported their grandparents' birthplaces. We used parents' birthplaces in 27% (23/86) of cases. We found no regional clustering suggestive of a genetic founder effect (Fig. 1). The distribution of birthplaces reflects the distribution of the Finnish population given the HUCH localization in Southern Finland.

A total of 86 patients reported 127 sisters, 125 brothers, 134 maternal aunts, 141 maternal uncles, 114 paternal aunts, and 123 paternal uncles. Of these patients, 9% (12/127) of sisters, 13% (16/125) of brothers, 20% (17/86) of mothers, 20% (17/86) of fathers, 5% (7/134) of maternal aunts, 8% (11/141) of maternal uncles, 9% (8/86) of maternal grandmothers, 10% (9/86) of maternal grandfathers, 8% (9/114) of paternal aunts, 3% (4/123) of paternal uncles, 3% (3/86) of paternal grandmothers, and 7% (6/86) of paternal grandfathers reported a history of cancer. Of the 1284 relatives reported, 49% were women (635/1284; men 649/1284). Altogether 10% (97/960) of first-degree relatives, maternal or paternal aunts, and uncles, had a history of cancer (10% (48/474) women, 10% (49/486) men).

As much as 76% of patients reported one or more relatives with cancer, 30% reported two or more, and 9% three or more (Table 1, Fig. 2). Patients with MEC had more cancers among their relatives (14%) than did patients with ACC

Table 1. Distribution of SGC histology and family history of cancer in first-degree relatives, aunts and uncles.

HISTOLOGY	PATIENTS (n)	PATIENTS WITH A FAMILY HISTORY OF CANCER		
		1 OR MORE RELATIVES WITH CANCER % (n)	2 OR MORE RELATIVES WITH CANCER % (n)	3 OR MORE RELATIVES WITH CANCER % (n)
ACC	22	**82 (18/22)**	18 (4/22)	5 (1/22)
MEC	21	76 (16/21)	29 (6/21)	14 (3/21)
AdCC	18	72 (13/18)	39 (7/18)	6 (1/18)
Adenocarcinoma	10	**80 (8/10)**	50 (5/10)	10 (1/10)
Salivary duct carcinoma	4	50 (2/4)	25 (1/4)	0 (0/4)
Squamous cell carcinoma	4	75 (3/4)	0 (0/4)	0 (0/4)
Carcinoma ex pleomorphic adenoma	3	67 (2/3)	67 (2/3)	33 (1/3)
Epithelial-myoepithelial carcinoma	2	100 (2/2)	0 (0/2)	0 (0/2)
Myoepithelial carcinoma	1	100 (1/1)	100 (1/1)	100 (1/1)
Lymphoepithelial carcinoma	1	100 (1/1)	0 (0/1)	0 (0/1)
Total	**86**	**76 (65/86)**	**30 (26/86)**	**9 (8/86)**

Abbreviations: SGC, salivary gland cancer; n, number; AdCC, adenoid cystic carcinoma; ACC, acinic cell carcinoma; MEC, mucoepidermoid carcinoma.

(5%) or those with AdCC (6%). Patients with AdCC (22%) and ACC (18%) had more relatives with breast cancer than did patients with MEC (5%). Liver (14%) and prostate (14%) carcinomas occurred more often in MEC patients' relatives (Table 2). These differences, however, showed no statistical significance (Kruskal–Wallis one-way ANOVA test, data not shown).

Discussion

Family history of cancer may reveal a heritable etiology. Hemminki and colleagues[22] reported the proportion of familial SGC to be 0.15% in Sweden. For comparison, the proportion of familial breast cancer was 14%. We hoped to identify SGC pedigrees suitable for genetic analyses or to recognize a possible genetic predisposition caused by a founder effect.

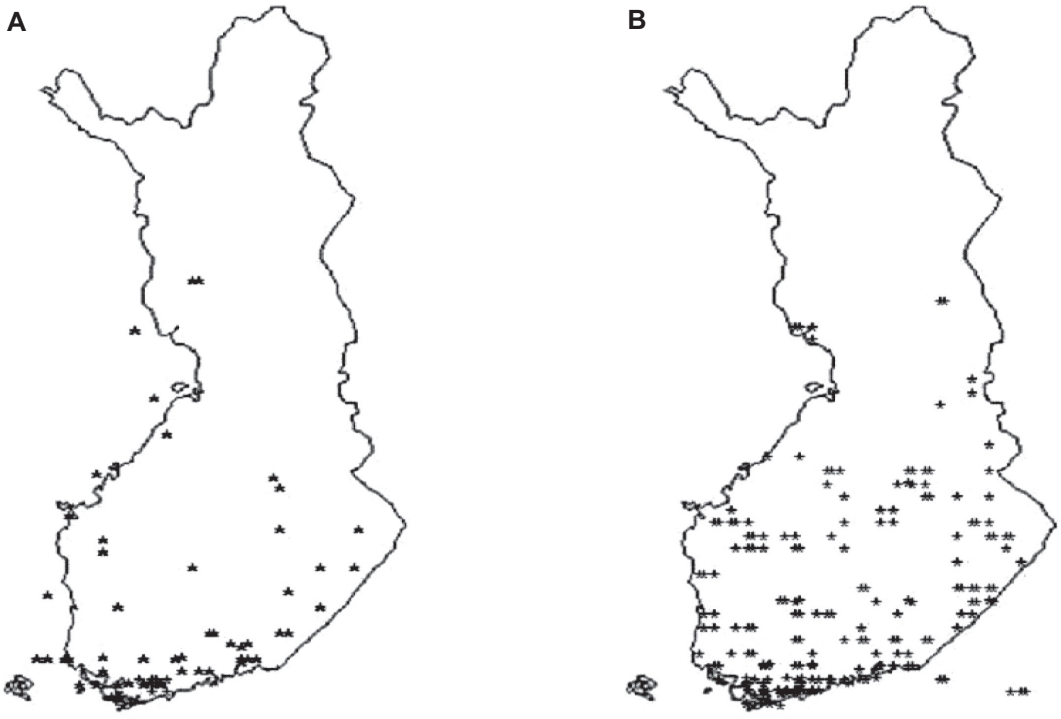

Figure 1. The birthplaces of SGC patients (**A**) and their parents or grandparents (**B**).

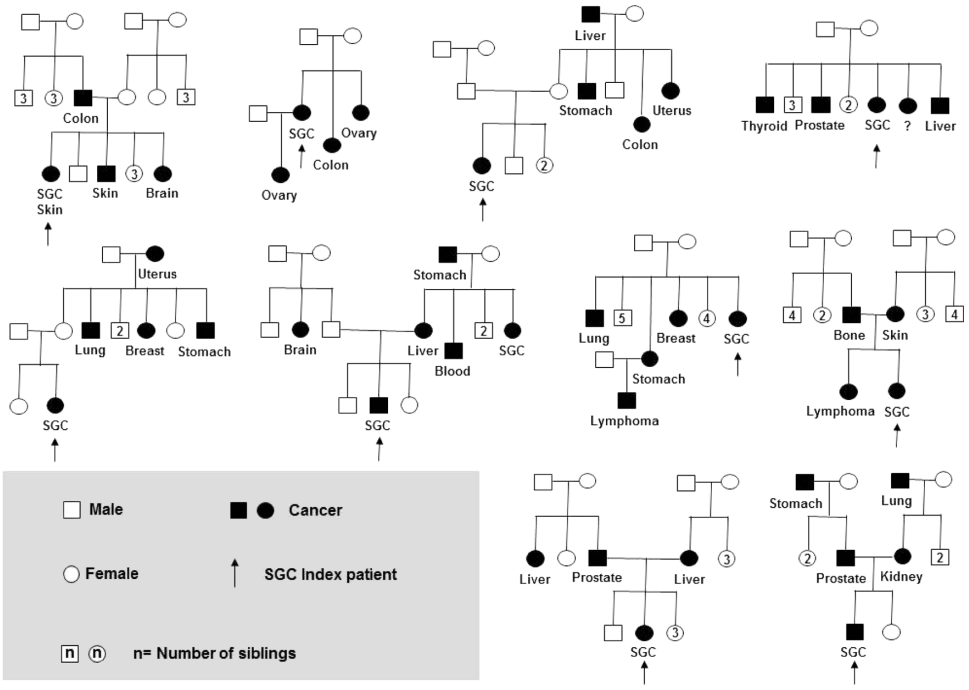

Figure 2. Pedigrees with salivary gland cancer (SGC) and three or more affected relatives with malignancy. The cancer site is defined according to the index patient's description in the questionnaire. Siblings do not appear in age-order.

However, we found neither. Only 1 of our 86 patients reported a relative with SGC (Fig. 2). Analysis of the birthplaces of the grandparents of Finnish SGC patients revealed no founder effect: the birthplaces were relatively evenly distributed given the HUCH localization in Southern Finland (Fig. 1). MEC (19%), ACC (17%), and AdCC (27%) are the most frequent types of SGC in Finland.[23] Therefore, in the present study we focused on these types of SGC because other types were infrequent.

For additional confirmation of our findings, we asked the Finnish Centre of Excellence in Cancer Genetics Research (http://www.helsinki.fi/coe/cancer-genetics/index.html) to screen their patient material for familial predisposition for SGC. This center has approximately one million cancer cases available for familial cluster studies. These cancer cases have been registered by the Finnish Cancer Registry throughout its nearly 60 years of existence. This screening revealed that SGCs do not seem to cluster in the Finnish population in any particular fashion, unlike other tumor types. This tendency further supports the findings of our present study.

Despite the negative findings, we feel that the study design was suitable: our study cohort represents a full population-based sample of treated SGCs in the HUCH area, including all patients alive and reachable by questionnaire. Of the 161 patients, only 86 (53%) responded. Fortunately, this low response rate does not skew the aims or conclusions of this study. Given good documentation of the patients' clinical findings and the centralized management of SGC in the five university hospitals in Finland according to national treatment

Table 2. Number of relatives with a specific cancer, presented according to the study patient's SGC histology.

HISTOLOGY	LUNG n = 9 *♂30; ♀12	BREAST n = 9 *♀95	GASTRIC n = 6 *♂7; ♀4	BRAIN n = 3 *♂12; ♀14	LIVER n = 4 *♂5; ♀2	PROSTATE n = 4 *89	SGC n = 1 *♂0.7; ♀0.6	LEUKEMIA n = 4 *♂8; ♀6
ACC n = 22	3	4	2	1	1	1	1	3
MEC n = 21	2	1	2		3	3		1
AdCC n = 18	4	4	2	2		1		

*Age-adjusted incidence for SGC per 100 000 person years in Finland.[24]
Abbreviations: ♂, men; ♀, women; other abbreviations as in Table 1.

guidelines, the present patient cohort seems well defined. Our data on patients with SGC are based on hospital records, but the index patient with SGC provided the information on the affected relatives. Although the latter is inarguably a limitation in this study, our aim was to identify any relative with SGC (high sensitivity with low specificity). More importantly, possible familial SGC patients would all have been verified through hospital records in the centralized cancer care system.

The age-adjusted incidence rate for SGC per 100,000 person years in Finland is approximately 0.7,[24] which is markedly less than in some other Western populations (2.5–3 cases per 100,000 person years, www.cancer.gov). Although the incidence of SGC in Finland resembles the global annual incidence, the reason for this low incidence in Finland is unknown or, to our knowledge, has not been discussed before.

Conclusion

The lack of familial SGC patients and the absence of regional clustering suggest that familial predisposition for SGC is insignificant in the Finnish population. Whether this explains the low incidence of SGC in Finland remains speculative. Owing to a large number of different histological subtypes and the rarity of these diseases, drawing conclusions on site-specific associations between SGC and other malignancies is impossible.

Author Contributions

Conceived and designed the experiments: KA, TK, AM. Analyzed the data: KA, TK. Wrote the first draft of the manuscript: KA. Contributed to the writing of the manuscript: KA, TK, IL, AM. Agree with manuscript results and conclusions: KA, TK, IL, AM. Jointly developed the structure and arguments for the paper: KA, TK, AM. Made critical revisions and approved final version: KA, TK, IL, AM. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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