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ORIGINAL PAPER

Epithelial Salivary Gland Tumors in Two Distant Geographical Locations, Finland (Helsinki and Oulu) and Israel (Tel Aviv): A 10-Year Retrospective Comparative Study of 2,218 Cases

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Abstract Salivary gland tumors (SGTs) of epithelial origin are relatively rare, and worldwide reports show considerable variations in their epidemiology. The aim of this study was to examine, for the first time, the records of SGTs from two very distant geographical locations, Finland (two medical centers) and Israel (one medical center) between 1999 and 2008, based exclusively on the 2005 WHO classification of head and neck tumors, and to compare those data to the other available (single-center) studies that used the same classification. A total of 2,218 benign and malignant tumors diagnosed in the three centers were analyzed. Differences in classification of the tumors were found between the two geographical locations as well as between the two centers from Finland. There was a higher ratio of benign-to-malignant SGTs in the Finnish centers (5.4:1 and 7:1) compared to the Israeli center (2:1), a higher frequency of tumors of minor salivary glands in the Israeli center (34%) than in the Finnish centers (4 and 11%), and a higher frequency of malignant SGTs in the minor salivary glands in Israel (64.5%) than in Finland (10.9 and 27%). The diversity of these multicenter data are compatible with reports from different parts of the world. We conclude that conducting epidemiologic surveys based on the latest WHO classification provides clinicopathologic correlations on SGTs that seem to be characteristic even in small geographical regions.

Keywords Salivary gland tumors · Finland · Israel · Epidemiology · Geographical locations

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Introduction

Salivary gland tumors (SGTs) make up about 3–10% of all head and neck tumors, with an estimated annual incidence of 0.4–13.5 new cases per 100,000 population [1, 2]. The histopathologic diversity of these tumors is not proportionate to their relatively low frequency. This is reflected by the continuously changing classifications that result from periodic re-definition of the nature of the tumors (e.g., acinic cell carcinoma and mucoepidermoid carcinoma [3]), the divergence of new histopathologic subtypes (e.g., oncocytic, oncocytic-sebaceous, apocrine, double clear subtypes of epithelial-myoepithelial carcinoma [4] and others), and the recognition of potentially new entities (e.g., mammary apocrine secreting carcinoma [5], cribriform carcinoma of the tongue [6]). It can be expected that the current classification will be further modified to adjust to updated clinicopathologic correlations as more clinical data accumulate and our molecular techniques improve.

Many epidemiologic and demographic studies on SGTs have been published in the English language literature from different parts of the world [7–11]. Although these studies have provided valuable knowledge, some of the data become contradictory and less precise as SGT classifications continue to change. As such, the actual frequency of SGTs is not known, and it is probably underestimated because benign tumors, which constitute the majority of SGTs, are often not entered into most cancer registries [12]. A comprehensive comparison of the studies reported from different parts of the world is hampered by several reasons, as summarized by Buchner et al. [7]. In general, those studies contain such variations in the incidence of tumors that questions have been raised about the influence of diverse factors, among them racial and geographic [9, 13–15].

There are few epidemiologic studies on SGTs from a number of geographic regions, among them Finland and Israel. Reports from Finland have focused mostly on the relatively rare malignancies of the salivary glands [16, 17], and they were based on the 1991 WHO classification of SGTs [3]. The age-adjusted incidence of that cancer for 2004–2008 was 0.8/100,000 person years, with no change from 1958 to the present [18]. In Israel, only one review of both malignant and benign SGTs based on the 1991 WHO classification had been published, and the findings did not differ substantially from reports emerging from some other parts of the world [19]. Another Israeli study on SGT epidemiology that was recently published focused only on malignant tumors in the parotid glands [20].

The aim of this study was to perform a comprehensive retrospective search of the clinicopathologic data on SGTs (both major and minor glands) over a period of 10 years (1999–2008) in two distant geographical locations, Finland and Israel. This is the first effort to concomitantly analyze data from Finland and Israel based on the 2005 WHO classification [1] and compare the findings with reports from other parts of the world that are also based on this classification but originate solely in single-center investigations.

Patients and Methods

This study was carried out in two geographic locations and included three university hospitals: Helsinki University and Oulu University in Finland, and Tel Aviv University (TAU) in Israel. Helsinki University Hospital is the largest tertiary hospital in Finland serving the districts of Uusimaa and Southern Karelia, with a total population of approximately 1.4 million people. It is also the area with the largest concentration of immigrants and people of non-Finnish descent. The immigrant population size is otherwise very low throughout the country. The records of patients diagnosed as having SGT were retrieved from the archives of the Department of Pathology. During the 10-year period between 1999 and 2008, 1,444 cases of SGTs of epithelial origin were managed at this center.

The Oulu cases were retrieved from the files of the Department of Pathology, University of Oulu, which serves an area comprising the two most northern provinces of Finland and is made up of 43 municipalities with a population of about 700,000. Northern Finland is much less cosmopolitan and has a much lower immigrant population than the Helsinki area. A total of 444 SGTs of epithelial origin were diagnosed and treated in this center during the study period.

The Chaim Sheba Medical Center, affiliated with TAU, is the largest tertiary medical center in the country and serves about one million people who live in central Israel. The population in this area, as in the rest of Israel, is a mixture of the immigrants who originated mainly from Europe, North African and Middle East countries and their second- and third-generation Israeli-born offspring. The non-Jewish population in the center of the country is less than 7%. A total of 330 cases of SGTs were retrieved from the Department of Oral Pathology at the TAU Dental School and from the Institute of Pathology at the Chaim Sheba Medical Center during the study period, and they comprise the TAU collection.

The case files containing the clinical records of all patients with epithelial SGTs were retrieved. All the pathologists who reviewed the material (MV, DD, IL, TS, IOB) strictly followed the protocol of the 2005 WHO classification [1]. All non-epithelial tumors were excluded, with further exclusion of some epithelial tumors whose origin from salivary glands was doubtful (e.g., squamous

cell carcinomas and small cell carcinomas). Re-classification of cases included the following: "adenoma" revised to basal cell adenoma ($n = 2$) and canalicular adenoma ($n = 1$); "carcinoma" revised to mucoepidermoid carcinoma, adenocarcinoma NOS, and salivary duct carcinoma ($n = 1$, each); polymorphous low-grade adenocarcinoma revised to adenocarcinoma NOS ($n = 1$); and pleomorphic adenoma revised to polymorphous low-grade adenocarcinoma ($n = 1$). Notably, however, those re-classified cases were too few to influence the relative percentage of the corresponding types of SGTs.

Data analysis was performed to identify the incidence of the tumor types and to compile the data on the age and gender of the patient as well as the distribution of the site of each tumor. The analyses were done separately for each of the three centers using IBM® SPSS® Statistics (version 19).

Results

During the 10-year study period, 1,444 cases of SGTs of epithelial origin were managed in the Helsinki center, 444 in Oulu and 330 in TAU. The estimated annual incidence of SGTs was 10.3 per 100,000 population in Helsinki, 5.7 in Oulu, and 3.3 in TAU. In Helsinki, the benign tumors accounted for 1,217 cases and the malignant tumors for 227, yielding a benign-to-malignant ratio of 5.4:1. In Oulu, 389 cases were benign and 55 cases were malignant, yielding a ratio of 7.1:1. In TAU, 220 of the 330 SGTs were benign and the rest were malignant, yielding a ratio of 2:1. Pleomorphic adenoma (PA) and adenoid cystic carcinoma (ACC) were the most common benign and malignant tumors, respectively, in all the three centers. Warthin tumor and mucoepidermoid carcinoma were the second most common benign and malignant tumors, respectively. The distribution of benign and malignant tumors in the three centers is shown in Table 1 (further details in Supplementary Tables 1a–c).

Age and Gender

The peak incidence for benign tumors in all three centers was the sixth decade, within a range between the third and eighth decades (Table 2). In patients with malignant SGTs, the peak incidence was in the sixth decade in Helsinki, in the seventh decade in TAU, and in the eight decade in Oulu (Table 2; Supplementary Tables 1a–c). In general, benign SGTs outnumbered the malignant tumors in every decade of life and in each of the Finnish centers, while malignant tumors were more commonly found than benign tumors in TAU patients aged 71–90 years (Table 2).

The mean age of patients presenting with benign tumors was in the sixth decade and it was similar for both genders in the Finnish centers. This was about 5 years older than in the TAU center. The mean age for patients presenting with malignant tumors was at the end of the sixth decade to the beginning of the seventh decades for all three centers, with only minor differences between genders (Supplementary Tables 1a–c).

There was a total of 761 females and 683 males (an F:M ratio of 1.1:1) in the Helsinki cases, 248 females versus 196 males (an F:M ratio of 1.3:1) in the Oulu cases and 165 females versus 165 males (an F:M ratio of 1:1) in the TAU cases. Except for Warthin tumor, which had a strong predilection for males, most benign tumors were more commonly found in females in all the centers. PA was strongly associated with female gender in all 3 centers. Among the carcinomas, ACC had strong affinity for female gender in all centers. There was a strong male predominance for mucoepidermoid carcinoma in the TAU patients in contrast to a slight female predominance in the two Finnish centers (Table 1).

Tumor Site

The vast majority of the tumors diagnosed during the study period occurred in the parotid gland, accounting for 85% (378/444) of the Oulu cases, 79% (1,146/1,444) of the Helsinki cases and 63% (205/330) of the TAU cases (Supplementary Tables 2a–c). The second most common site in both Helsinki and TAU was the minor salivary glands, while it was the submandibular glands in Oulu. SGTs in minor salivary glands accounted for 34% (111/330) in TAU, 11% (158/1,444) in Helsinki, but just slightly over 4% (19/444) in Oulu.

The most common benign tumor within the parotid gland was PA followed by Warthin tumor in all three centers. PA was also the most common benign tumor in the minor salivary glands in all three centers (Table 3; Supplementary Tables 2a–c, 3a–c).

Malignant SGTs in the major salivary glands accounted for 76% of Oulu cases, 71% of Helsinki cases, and only 35% of TAU cases. Most malignant tumors commonly occurred in the parotid gland in the Finnish centers; however, among the TAU cases, malignant tumors were more commonly seen in the minor salivary glands rather than the parotid gland. The most commonly diagnosed malignant tumors were ACC, mucoepidermoid carcinoma, and acinic cell carcinoma in all three centers. Although very rarely diagnosed, lymphoepithelial carcinoma was mostly found in the submandibular gland (Supplementary Tables 2a–c). The malignant tumors most commonly found in the minor salivary glands were ACC and mucoepidermoid carcinoma (Table 3). The palate was by far the most commonly

Table 1 Distribution of benign and malignant salivary gland tumors in patients from Helsinki and Oulu (Finland) and Tel Aviv (Israel)

Histological type	Helsinki				Oulu				Tel Aviv			
	Total	% of tumor group	% of all tumors	Total of females (%)	Total	% of tumor group	% of all tumors	Total of females (%)	Total	% of tumor group	% of all tumors	Total of females (%)
Benign salivary gland tumors												
Pleomorphic adenoma	690	56.7	47.8	431 (62.5)	254	65.3	57.2	156 (61.4)	155	70.5	46.9	83 (53.5)
Warthin tumor	391	32.1	27.1	126 (32.2)	112	28.8	25.2	44 (39.3)	44	20	13.3	12 (27.3)
Myoepithelioma	43	3.5	3.0	21 (48.8)	5	1.3	1.1	5 (100)	7	3.2	2.1	4 (57)
Basal cell adenoma	26	2.2	1.8	14 (53.8)	6	1.5	1.5	5 (83.3)	5	2.3	1.5	4 (80)
Oncocytoma	37	3.0	2.6	17 (45.9)	7	1.8	1.6	4 (57.1)	4	1.8	1.2	3 (75)
Cystadenoma	22	1.9	1.5	14 (63.6)	5	1.3	1.1	2 (40)	3	1.3	0.9	2 (66.7)
Canalicular adenoma	5	0.4	0.3	3 (60)	–	–	–	–	2	0.9	0.6	1 (50)
Intraductal papilloma	3	0.2	0.2	3 (100)	–	–	–	–	–	–	–	–
Total	1,217	100.0	84.3	629 (51.7)	389	100	87.6	216 (55.5)	220	100	66.4	109 (49.5)
Malignant salivary gland tumors												
Adenoid cystic carcinoma	54	23.8	3.7	31 (57.4)	13	23.6	2.9	11 (86.4)	35	31.8	10.6	23 (65.7)
Mucoepidermoid carcinoma	48	21.1	3.3	33 (68.8)	12	21.8	2.7	7 (58.3)	31	28.2	9.4	6 (19.4)
Acinic cell carcinoma	43	18.9	3.0	26 (60.5)	4	7.3	0.9	3 (75)	12	10.9	3.6	6 (50)
Basal cell adenocarcinoma	7	3.1	0.5	3 (42.9)	1	1.8	0.2	0 (0)	–	–	–	–
Adenocarcinoma, NOS	4	1.8	0.3	2 (50)	7	12.7	1.6	2 (28.6)	11	10.0	3.2	7 (63.6)
Myoepithelial carcinoma	12	5.3	0.8	7 (58.3)	–	–	–	–	–	–	–	–
Polymorphous low-grade adenocarcinoma	9	4.0	0.6	8 (88.9)	3	5.5	0.7	2 (66.7)	8	7.3	2.4	5 (62.5)
Salivary duct carcinoma	16	7.0	1.1	7 (43.8)	5	9.1	1.1	2 (40)	5	4.5	1.5	3 (60)
Carcinoma in pleomorphic adenoma	17	7.5	1.2	5 (29.4)	4	7.3	0.9	3 (75)	3	2.3	0.9	2 (66.7)
Clear cell carcinoma	4	1.8	0.3	2 (50)	–	–	–	–	1	0.9	0.3	1 (100)
Cystadenocarcinoma	4	1.8	0.3	2 (50)	–	–	–	–	1	0.9	0.3	1 (100)
Lymphoepithelial carcinoma	1	0.4	0.1	1 (100)	3	5.5	0.7	1 (33.3)	1	0.9	0.9	0 (0)
Epithelial-myoepithelial carcinoma	3	1.3	0.2	1 (33.3)	2	3.6	0.5	1 (50)	–	–	–	–
Hybrid carcinoma (low-grade)	1	0.4	0.1	1 (100)	–	–	–	–	–	–	–	–
Undifferentiated carcinoma	4	1.8	0.3	3 (75)	–	–	–	–	–	–	–	–
Large-cell carcinoma	–	–	–	–	–	–	–	–	2	1.8	0.6	1 (50)
Oncocytic carcinoma	–	–	–	–	1	1.8	0.2	0 (0)	–	–	–	–
Total	227	100	15.8	132 (58.1)	55	100	12.4	32 (58.2)	110	100	33.7	56 (50.9)
Total number of tumors	1,444		100	761 (52.7)	444		100	248 (55.9)	330		100	165 (50)

Table 2 Age distribution of benign and malignant salivary gland tumors in patients from Helsinki and Oulu (Finland) and Tel Aviv (Israel)

Range, years	Helsinki			Oulu			Tel Aviv		
	Benign	Malignant	Total	Benign	Malignant	Total	Benign	Malignant	Total
0–10	0	1	1	0	1	1	1	0	1
11–20	14	3	17	7	2	9	12	6	18
21–30	81	12	93	22	3	25	31	5	36
31–40	142	20	162	48	2	50	29	6	35
41–50	205	22	227	76	3	79	45	19	64
51–60	346	66	412	104	12	116	46	21	67
61–70	244	50	294	81	10	91	33	24	57
71–80	151	32	183	43	18	61	16	21	37
81–90	31	21	52	8	3	11	4	7	11
91–100	3	0	3	0	1	1	3	1	4
Total	1,217	227	1,444	389	55	444	220	110	330

affected minor salivary gland site in all three centers irrespective of whether the tumor was benign or malignant (Supplementary Tables 3a–c).

Bilateral and Multiple (Synchronous or Metachronous) Tumors

Data were available only for the Helsinki cases and totaled 26 patients, who presented with bilateral synchronous tumors (Warthin, $n = 15$; PA, $n = 1$; and basal cell adenocarcinoma, $n = 1$), different synchronous tumors (PA and Warthin, $n = 4$; PA and acinic cell carcinoma, $n = 1$; and Warthin and oncocytoma, $n = 1$), and different metachronous tumors (Wartin and PA, Warthin and oncocytoma, and PA and myoepithelial carcinoma, $n = 1$, each).

Discussion

This study reviewed a total of 2,218 SGTs diagnosed in three large urban university hospitals in Finland and Israel over a 10-year period (1999–2008). This was the first study that compared the data on SGTs from two remote geographic locations by examiners who collated data strictly according to the 2005 WHO classification [1]. Other studies similarly reporting epidemiologic data on SGTs provided data accumulated within individual centers and described their results in comparison with studies carried out according to earlier WHO classification systems [9, 21–24].

The main findings of this research were the differences in the annual incidence of the SGTs (highest in Helsinki, lower in Oulu, and lowest in TAU), in the frequency of the malignant forms of SGT (two- to three-fold higher in TAU than in the Finnish centers), and in the frequency of malignant SGTs in the minor glands versus the parotid gland (higher in TAU compared to the Finnish centers). There were considerable similarities between the Israeli and the Finnish centers regarding the other clinicopathologic findings. PA and Warthin tumor were the most common benign tumors, while ACC and mucoepidermoid carcinoma were the most common malignant tumors. Another interesting finding was a higher predilection of SGTs in female Finnish patients that was not seen in patients from Israel, irrespective of whether or not the tumor was malignant.

The variations in the annual incidence of SGTs among the geographically distant study centers (Finland and Israel) and between the two Finnish centers may reflect the impact that the composition of the population may have on the epidemiology of SGTs. Specifically, the center in Helsinki serves a mixed Finnish and immigrant population, while the center in Oulu serves a largely native Finnish population and it was found to have an annual incidence of SGTs almost half that of Helsinki. In contrast, TAU serves a completely different population in terms of origins and ethnicities, and the annual SGT incidence was found to be about one-third that of Helsinki and about one-half that of Oulu. A definitive breakdown in the ethnicities of the heterogenic Helsinki and Israeli populations is beyond the scope of the current work.

The 2:1 ratio of benign-to-malignant SGTs in TAU was within the range reported in studies from other regions of the world based on the 2005 WHO classification, including Sri Lanka, 1:1 [9], the UK and China, 2:1 each, [23, 24, respectively], Iran (South), 2.19:1 [21], and Turkey, 3:1 [22]. The results from the Finnish centers were remarkably different, with a benign-to-malignant ratio of 5.4:1 in Helsinki and 7.1:1 in Oulu. Similar to the data on the annual incidence of SGTs, this variation in ratios further emphasizes that geographic location, even within the same country and inevitably across continents, may have an impact on the distribution of benign and malignant SGTs.

Table 3 Distribution of tumors in the major and minor salivary glands of patients in Helsinki and Oulu (Finland) and Tel Aviv (Israel)

Salivary gland tumors	Helsinki				Oulu				Tel Aviv			
	Major glands (%)	Minor glands (%)	Unclassified (%)	Total (%)	Major glands (%)	Minor glands (%)	Unclassified (%)	Total (%)	Major glands (%)	Minor glands (%)	Unclassified (%)	Total (%)
Benign												
Pleomorphic adenoma	630 (56.6)	58 (60.4)	2 (25%)	690 (56.7)	244 (64.9)	10 (76.9)	(0)	254 (65.3)	22 (67.8)	33 (82.5)	0 (0)	155 (70.5)
Warthin Tumor	379 (34.1)	6 (6.3)	6 (75%)	391 (32.1)	110 (29.3)	2 (15.4)	0 (0)	112 (28.8)	44 (24.4)	0 (0)	0 (0)	44 (20)
Myoepithelioma	35 (3.1)	8 (8.3)	0 (0)	43 (3.5)	5 (1.3)	0 (0)	0 (0)	5 (1.3)	5 (2.8)	2 (5)	0 (0)	7 (3.2)
Oncocytoma	37 (3.3)	0 (0)	0 (0)	37 (3)	7 (1.9)	0 (0)	0 (0)	7 (1.8)	4 (2.2)	0 (0)	0 (0)	4 (1.8)
Others (benign)	32 (2.9)	24 (25)	0 (0)	56 (4.6)	10 (2.7)	1 (7.7)	0 (0)	11 (2.8)	5 (2.8)	5 (12.5)	0 (0)	10 (4.5)
Total	1,113 (100)	96 (100)	8 (100)	1,217 (100)	376 (100)	13 (100)	0 (0)	389 (100)	180 (100)	40 (100)	0 (0)	220 (100)
Malignant												
Adenoid cystic carcinoma	34 (21)	19 (30.6)	1 (33.3)	54 (23.8)	11 (22.4)	2 (33.3)	0 (0)	13 (23.6)	6 (15.4)	29 (40.8)	0 (0)	35 (31.8)
Mucoepidermoid carcinoma	20 (17.3)	28 (33.2)	0 (0)	48 (21.1)	10 (20.4)	2 (33.3)	0 (0)	12 (21.8)	10 (25.6)	21 (29.6)	0 (0)	31 (28.2)
Acinic cell carcinoma	38 (23.5)	3 (4.8)	2 (66.7)	43 (18.9)	4 (8.4)	0 (0)	0 (0)	4 (7.3)	8 (20.5)	4 (5.6)	0 (0)	12 (10.9)
Polymorphous low grade adenocarcinoma	0 (0)	9 (14.5)	0 (0)	9 (4)	1 (2)	2 (33.3)	0 (0)	3 (5.5)	0 (0)	8 (11.3)	0 (0)	8 (7.3)
Others (malignant)	62 (38.3)	11 (17.7)	0 (0)	73 (32.2)	23 (46.9)	0 (0)	0 (0)	23 (41.8)	15 (38.5)	9 (12.7)	0 (0)	24 (21.8)
Total	162 (100)	62 (100)	3 (100	227 (100)	49 (100)	6 (100)	0 (0)	55 (100)	39 (100)	71 (100)	0 (0)	110 (100)

Only the major tumors have been shown while others tumors were grouped into "others"

We are aware that the present results closely reflect the registries of the participating medical centers and that SGTs, especially the benign types, are also diagnosed in private laboratories in each of the locations. We contend that the remarkable difference in the incidence of benign and malignant tumors found between Israel and Finland is not likely to change had these "missed" cases of SGTs been accounted for.

Another speculated risk factor for the emergence of SGTs, especially in the parotid glands, is the use of cellular phones [25, 26]. This seems to suggest an explanation for the overlap in intensive use of cellular phones and the increased incidence of malignant tumors in the parotid glands, in particular in the Israeli population, which is an extreme user of cellular phones [20]. However, there is still contradictory evidence to support a link between the two. A Finnish study performed about 10 years ago failed to support any connection between the use of cell phones with SGTs [27]; however, that study focused only on cases of SGTs registered during 1 year (1996), at a time that cell phone use was not as widespread as today.

The most predominant benign SGT is PA followed by Warthin tumor, usually a distant second [9, 21, 22, 24]. This is in line with the present study. However, one institution-based report has shown that basal cell adenoma and canalicular adenoma may present slightly more frequently than Warthin tumor [23]. The major reason for this may be that there was a high number of SGTs of the minor salivary glands in that series, and Warthin tumors are extremely rare in minor salivary glands.

The most common malignant SGT in all the three centers was ACC, closely followed by mucoepidermoid carcinoma. Earlier single-center studies that were also based on the 2005 WHO classification have reported these two tumors as being the most common malignant SGTs, but the order differed: one study found an equal frequency of these tumors [24], two studies found ACC to be more common [21, 22], and the other two studies, including one from the UK, found mucoepidermoid carcinoma to be more common [9, 23]. Before 2005, the frequency of mucoepidermoid carcinoma among British patients was much lower than the worldwide range [1], with a predominance of ACC [10, 28]. Again, this demonstrates the changing trends in the incidence of SGT that can be related to a variety of factors, such as institutional referral bias and changing composition of the population. As for findings suggesting a link between malignant SGTs and gender in the present study, ACC had a slight female predilection in all three centers, while mucoepidermoid carcinoma was more common in females in the Finnish centers but strongly associated with males in the TAU center.

There was a higher incidence of SGTs in the submandibular glands in the Finnish population, principally in Oulu, compared to the other centers. These differences can be partially explained by the difficulty that sometimes arises in differentiating tumors that originate from the mucosal glands of the floor of the mouth from those originating within the submandibular glands, thereby artificially inflating the number of one of the two sites [23]. The incidence of SGTs in the minor salivary glands was considerably higher in TAU (34%) compared to Helsinki (11%) and Oulu (4%). Furthermore, the incidence of patients with malignant SGTs in the minor salivary glands in TAU (64.5%) was much higher compared to their counterparts in the Finnish centers (Helsinki 27% and Oulu 10.9%). The present results on malignant SGTs in minor salivary glands in TAU is in accordance with the data reported in other 2005 WHO-based studies, in which the frequency of malignant SGTs in the minor glands ranged from about 55% (Sri Lanka and southern Iran) [9, 21] to 62% (China) [24]. In the remaining two relevant studies (from the UK and Turkey), the frequency of these tumors was about 40% [22, 23], but that figure is still higher than the values from the Finnish centers. The differences in the incidence of malignant SGTs between Israel and Finland and other geographical regions appear to strengthen the influence of geographical factors and their impact on the distribution of these tumors.

Most tumors of the minor salivary glands were found in the palate in TAU (49%), Helsinki (47.5%), and Oulu (42%), in agreement with all the comparable 2005 WHO-based studies [9, 21–24]. This finding may be linked to the presence of chronic inflammation in these glands: a histomorphometric analysis of the palatal glands revealed that they were characterized by a remarkable age-related increase in both diffuse and focal chronic inflammation and were significantly different from the labial salivary glands where SGTs are uncommon [29, 30]. Interestingly, these age-related changes are in accordance with the present epidemiologic data on SGTs in terms of both age and location [1]. The presence of long-term chronic inflammation has been recognized as a solid etiologic background for the development of adjacent epithelial malignancies in several organs [31], and this could very well apply to SGTs, particularly to those in the palatal glands.

In summary, the novelty of this study is that it is the first time an epidemiologic study on SGTs was performed on populations from two vastly different geographic locations, Finland (two medical centers) and Israel (one center). Tumor classification in all three centers was based on the 2005 WHO classification, and the resulting data were compared to published single-center studies that also used the same tumor classification. There were differences that emerged between the two geographical locations and several differences were also found between the two Finnish centers. The diversity of the present data mandates the

conducting of epidemiologic surveys based on the latest WHO classification in order to provide updated and compatible clinicopathologic correlations on SGTs that seem to be characteristic even in small geographical regions.

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Conflict of Interest The authors declare that they have no conflict of interest.

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