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Epidemiology and Trends of Oropharyngeal Cancer Between 1970-2013

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Abstract

Objective: In order to expand the knowledge about Oropharyngeal Cancer (OPC), we analyzed in detail its epidemiological characteristics in Israel.

Methods: Data regarding 1,179 cases of OPC between 1970-2013, including patient age, sex, tumor site, type and stage, were provided by the national cancer registry. Statistical analysis was performed by IBM SPSS, WinPepi, and Joinpoint Regression Program.

Results: Mean age at diagnosis did not change. Males were diagnosed more often and were younger than females. Base of tongue was more common in older individuals. The SCC/lymphoma ratio increased from 1.1 to 3.5 in males, and from 0.6 to 1.5 in females. Lymphoma diagnosis decreased 2-fold in the tonsils, with differences in trends between the sexes. SCC rose steeply among individuals 50 Y to 59 Y and 60 Y to 69 Y, and increased more in the oropharynx site than the tonsils and base of tongue.

Conclusion: Compared to global data, it seems that OPC in Israel is characterized by lower SCC rates and no change in mean age at diagnosis and base of tongue malignancy. The relationship between the oropharyngeal tumor types and sites became apparent. Health care providers should be aware of the common tumor sites and types regarding specific age groups and sexes.

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Introduction

Oropharyngeal Cancer (OPC) constitutes 19.0% of all lip, oral and pharyngeal cancers globally [1]. Its proportion ranges from 8.2% in North Africa and Western Asia to 34.2% in North America and males are more diagnosed than females [1]. Pathologically, the majority of OPC is Squamous Cell Carcinoma (SCC) [2], which has recently been reported to be on the rise, mostly in younger individuals [3], and associated with Human Papillomavirus (HPV) [4]. In the USA, Oropharyngeal SCC (OPSCC) rates had been increasing since 1999, and OPSCC became the most common HPV-associated cancer in 2015 [5].

The epidemiology of oral and pharyngeal cancer in Israel were investigated between 1970 and 2006 [6,7], when the rates of oral cavity SCC were reported to decrease [7]. The epidemiology of HPV in OPSCC had been examined in a cohort study, 1999 to 2011 and a low incidence of HPV was detected [8].

Most of the epidemiological literature about OPC refers to SCC, especially in the tonsils and Base of Tongue (BOT). Other OPC neoplasms, such as lymphoma, and other OPC sites, like the lateral and posterior pharyngeal walls, have rarely been described or analyzed in detail. This study aims to address this gap. In light of the global increase in OPSCC, this work also aims to update and expand the knowledge about OPC by analyzing its epidemiology and trends in Israel between 1970 to 2013.

Methods

Patients and data

OPC patients were identified according to the Israeli National Cancer Registry (INCR) data, from the beginning of January 1970 to the end of December 2013. The data was received directly from the INCR. The INCR was established in 1960 and records all tumor diagnoses among Israeli citizens. Documentation in the registry is based on a primary tumor diagnosis, and reporting is

mandatory by the Ministry of Health.

Prior to receiving the data, the research was approved by the Institutional Review Board of the Hadassah Hospital in Jerusalem, Israel (protocol code: 0191-16-HMO) and by the INCR. The data included demographic variables (age, sex) and clinical variables (tumor site, type, and stage).

Five groups of age at diagnosis were created according to the age distribution of the data: 0 to 29 years of age (0 Y to 29 Y), 30 Y to 49 Y, 50 Y to 59 Y, 60 Y to 69 Y and 70 Y and above (70+ Y). For statistical purposes, and based on median diagnoses by years, the total period was subdivided into two periods, 1970 to 1996 and 1997 to 2013.

Tumor sites were categorized according to their distribution and the International Classification of diseases and Related Health Problems 10th Revision (ICD-10), as determined by the World Health Organization [9]. The tumor site categories include: BOT (ICD-10 code: C01.9), tonsils (C02.4, C09.0 to C09.9, C14.2) and oropharynx (C10.0 to C10.9). The term "oropharynx" refers to the specific tumor site category, and the term "oropharyngeal" refers to all three tumor site categories. Data only included malignant tumors, sorted by characteristics and distribution and according to the International Classification of Diseases for Oncology (ICD-O-3) [10]. The tumor type categories include: Unspecified malignant tumors (ICD-O-3 codes: 80003, 85613), SCC (80523 to 80763, 80833), carcinoma subtypes (80103 to 80333, 80823, 80903, 81203), salivary gland origin (81403 to 85503) sarcoma (88003 to 91403, 97583), and lymphoma (95903 to 97343, 98233).

The three tumor stage categories include localized, regional, and distant, and were categorized according to the Middle East cancer consortium classification of staging [11].

Diagnosis rate was calculated for each year, and it is defined as the number of diagnoses in a year divided by the mid-year population of the same year, multiplied by 100,000. Therefore, to calculate diagnosis rates, Israeli mid-year population data between 1970 to 2013, were provided by the INCR, based on data from the Israel Central Bureau of Statistics.

Statistics

Significance level was set at $\alpha<0.05$ and all tests are two-sided. IBM SPSS (version 27) was used to perform the following analyses: Comparing between means by two independent samples Student's t-test [12], one-way analysis of variance and Scheffe's method. The mean and its standard deviation are presented as: Mean (standard deviation). Pearson's Chi Squared test χ^2). Cochran-Mantel-Haenszel χ^2 test and Mantel-Haenszel common odds ratio. WinPepi (version 11.65) was used to perform the following: rate ratio and its 95% Confidence Interval (CI) [13], difference between proportions and its 95% CI, Sidak-adjusted correction. Joinpoint Regression Program (version 4.6.0.0) was used to examine trends of single series of diagnosis rates by the annual percent change (APC) and its 95% CI [14], and for pairwise comparison between two single series of diagnosis rates [15]. For more details about the statistical methods, please see Supplementary 1.

Results

A total of 1,179 cases were diagnosed between 1970-2013. The distribution of tumor type categories by period, sex, age at diagnosis groups, and tumor sites, is presented in Table 1. The age at diagnosis ranged from 0 Y (number of cases (N) =2) to 102 Y (N=1). Mean age at diagnosis was 62.2 Y (16.7) and median age was 63.6 Y. Frequency of diagnosis increased with age (Table 1). The male to female ratio was 1.8, the main tumor site category was the tonsils, and the main tumor type categories were SCC and lymphoma (Table 1).

Between 1997-2013, SCC was the most common in 50 Y to 59 Y (32.1%, N=125) followed by 60 Y to 69 Y (27.4%, N=107) and 70+ Y (27.4%, N=107). Lymphoma was frequent in 70+ Y (33.6%, N=50) followed by 50 Y-59 Y (23.5%, N=35) and 60 Y-69 Y (22.1%, N=33) (χ^2 exact test (20) =46.2, P=0.001).

The most frequent tumor type category in males was SCC, whereas in females it was lymphoma (Table 1). This proportional contradiction between the sexes was also found to be significant by the Sidak-adjusted correction ($\chi^2(5)$ =34.9, P<0.001).

There were no significant changes regarding mean age at diagnosis for any variable between the sub-periods and throughout the whole period. Males were diagnosed younger (61.0 Y (16.6)) than females (64.4 Y (15.4)) (t(1177) =3.5, P=0.004). Mean age for BOT (65.0 Y (14.6)) was higher than the tonsils (61.0 Y (16.7)) and the oropharynx site (61.4 Y (16.7), F(2) =6.9, P=0.001). Specifically, between 1997-2013 the mean age for BOT (65.3 Y (14.2)) was higher than the tonsils (61.1 Y (15.3)) (Scheffe's method, P=0.015) (F(2) =4.2, P=0.015). The mean age at diagnosis was similar for all tumor type categories, and no differences were noted in the sub periods for each tumor type category. Mean ages for SCC, lymphoma and malignancies of salivary gland origin were 62.7 Y (12.4), 61.5 Y (19.8) and 61.1 Y (17.0), respectively. Despite this, between 1997-2013 the mean age at diagnosis for SCC was the highest for the BOT (66.3 Y (12.5)) (F(2) =8.1, P<0.001), and specifically higher than the mean age for the tonsils (61.3 Y (12.4)) and the oropharynx site (60.2 Y (10.9)) (Scheffe's method, P=0.003 and P=0.002; respectively).

The data for tumor stage at diagnosis was only available for 384 cases (less than 40% of all cases), and distributed as follows: localized (N=53, 13.8%), regional (N=242, 63.0%) and distant (N=89, 23.2%). Regarding the sub-periods, there were data about tumor stage for 31.2% between 1970-1996 and for 33.8% between 1997-2013.

Comparison of sub-periods

A 1.2-fold increase in males and a 0.9-fold decrease in females were observed between the sub- periods of 1997-2013 and 1970-1996 ($\chi^2(1)$ =6.9, P=0.009). This association was not clearly explained after stratifying by age at diagnosis, tumor type, and tumor site (the Cochran-Mantel- Haenszel χ^2 test and Mantel-Haenszel Common Odds Ratio were significant across each stratification, and the association in each stratum was not significant).

Accordingly, between 1970-2013 general diagnosis rates increased in males from 0.3/100.000 in 1970 to 1.0/100,000 in 2013 (APC=1.09, [0.3, 1.8)], but decreased non-significantly in females (APC= -0.4, [-1.2, 0.3]). OPC diagnosis rates in total did not change during the study period.

Between 1970-1996, more cases of lymphoma than SCC were diagnosed, but between 1997-2013, the pattern was reversed (Table 2). Between 1997-2013 a decrease of 0.9-fold in the tonsils was observed. By contrast, in the oropharynx site the diagnosis increased 2.6-fold ($\chi^2(2)$ =35.1, P<0.001).

After stratifying the tumor site categories by SCC and lymphoma, the diagnosis of SCC between 1997-2013 increased 2.0-fold in the tonsils, and 3.9-fold in the oropharynx site (Table 3). However,

Table 1: Distribution of oropharyngeal tumor types by period, sex, age at diagnosis groups, tumor sites.

Tumor types										
Variable Period		UMT	Carcinoma subtypes	SCC	SGO	Sarcoma	Lymphoma	Total	c^2 (df)	*P*
1970-1996	N	17	30	226	25	1	268	567	83.5 (5)	<0.001
	%	3	5.3	39.9	4.4	0.2	47.3	48.1		
1997-2013	N	12	22	390	32	7	149	612		
	%	2	3.6	63.7	5.2	1.1	24.3	51.9		
Age at diagnosis(Y)										
0-29	N	2	4	3	1	2	35	47	90.0 (20)	<0.001
	%	4.3	8.5	6.4	2.1	4.3	74.5	4		
30-49	N	2	6	83	15	1	49	156		
	%	1.3	3.8	53.2	9.6	0.6	31.4	13.2		
50-59	N	4	10	179	12	0	76	281		
	%	1.4	3.6	63.7	4.3	0	27	23.8		
60-69	N	7	13	171	8	1	98	298		
	%	2.3	4.4	57.4	2.7	0.3	32.9	25.3		
70+	N	14	19	180	21	4	159	397		
	%	3.5	4.8	45.3	5.3	1	40.1	33.7		
Sex										
Males	N	17	30	447	27	5	228	754	43.4 (5)	<0.001
	%	2.3	4	59.3	3.6	0.7	30.2	64		
Females	N	12	22	169	30	3	189	425		
	%	2.8	5.2	39.8	7.1	0.7	44.5	36		
Tumor sites										
BOT	N	6	11	219	39	2	45	322	227.1 (10)	<0.001
	%	1.9	3.4	68	12.1	0.6	14	27.3		
Tonsils	N	10	31	281	10	2	346	680		
	%	1.5	4.6	41.3	1.5	0.3	50.9	57.7		
Oropharynx	N	13	10	116	8	4	26	177		
	%	7.3	5.6	65.5	4.5	2.3	14.7	15		
Total	N	29	52	616	57	8	417	1179		
	%	2.5	4.4	52.2	4.8	0.7	35.4	100		

df: Degrees of Freedom; BOT: Base of Tongue; N: Number of Cases; SCC: Squamous Cell Carcinoma; SGO: Salivary Gland Origin Tumors; UMT: Unspecified Malignant Tumors; Y: Years of Age; *P*: p-value

In 0 Y-29 Y the leading specific type was Burkitt's lymphoma (45.7%, N=16). In the rest of age groups SSC was followed by lymphoma. The main SCC type was SCC (66.7%, N=411), and the main lymphoma type was diffuse large b-cell lymphoma (48.7%, N=203). Lymphoma was the main tumor type in the tonsils. SCC was the most diagnosed in the BOT and the oropharynx site. SGO was the third most diagnosed in BOT as it was mainly diagnosed in the BOT. The main SGO types in BOT were mucoepidermoid carcinoma (38.5%, N=15) and adenoid cystic carcinoma (38.5%, N=15).

SCC in the BOT remained unchanged. The diagnosis of lymphoma decreased 2.0-fold in the tonsils (Table 3).

Trends of rates

SCC and lymphoma: Table 4 presents the APC values for the various trends of SCC and lymphoma. SCC rates increased significantly between 1970-2013, both in general and in males specifically (Table 4, Figure 1A). Lymphoma rates increased significantly between 1997-2013 (Table 4, Figure 1B). SCC rates were significantly higher than lymphoma in most years during 1997-2013, but no significant differences were found between the two malignancies in most years between 1970-1996 (Supplementary Table 1). Lymphoma rates decreased in males between 2001-2013, and that trend occurred for a longer time in 70+ Y males between 1977-2013 (Table 4). Oppositely, in females, the lymphoma rates increased between 1997-2013 (Table 4), including in 70+ Y (Table 4). No significant difference was found in comparing the trends and rates between the sexes, concerning SCC and lymphoma.

Trends of SCC by age at diagnosis groups: In 30 Y to 49 Y the SCC rates increased in general and in males between 1970-2013 (Table 4). In 50 Y to 59Y the rates increased between 1970-2013 (Table 4, Figure 1C), including a steep increase from 1982 (0.0/100,000) to 2013 (1.43/100,000) (APC=17.5, [4.1, 32.7]). This finding was observed in males as well (Table 4), including a steep increase from 1982 (0.0/100,000) to 2013 (2.70/100,000) in 2013 (APC=19.5, [0.5, 42.0]), and also in females from 1983 to 2013 (Table 4).

In 60 Y to 69 Y the rates increased between 1972-2013 (Table 4, Figure 1D), including a steep increase from 1989 (0.0/100,000) to 2013 (1.90/100,000) (APC=22.5, [0.9, 48.7]). The increase between 1972-

Table 2: Oropharyngeal SCC and lymphoma distribution by period, stratified by sex, between 1970-1996 and 1997-2013.

		Period							
		1970-1996		1997-2013					
Sex	Tumor type category	N	%	N	%	Total	Ratio [a]	χ^2 (df)	*P*
Total	SCC	226	39.9	390	63.7	616	1.7	76.0 (2)	<0.001
	Lymphoma	268	47.3	149	24.3	417	0.6		
	Rest of categories	73	12.9	73	11.9	146	1		
	Total	567	100	612	100	1179	1.1		
	Ratio [b]	0.8		2.6		1.5			
Males	SCC	157	46	290	70.2	447	1.8	51.2 (2)	<0.001
	Lymphoma	146	42.8	82	19.9	228	0.6		
	Rest of categories	38	11.1	41	1	79	1.1		
	Total	341	100	413	100	754	1.2		
	Ratio [b]	1.1		3.5		2			
Females	SCC	69	30.5	100	50.3	169	1.4	20.2 (2)	<0.001
	Lymphoma	122	54	67	33.7	189	0.5		
	Rest of categories	35	15.5	32	16.1	67	0.9		
	Total	226	100	199	100	425	0.9		
	Ratio [b]	0.6		1.5		0.9			

df: Degrees of Freedom; N: Number of Cases; *P*: p-value; SCC: Squamous Cell Carcinoma
χ^2 Pearson's chi-square test, two sided significance
[a] Ratio between 1997-2013 and 1970-1996. [b] Ratio between SCC and lymphoma
Rest of categories - a unified category that includes unspecified malignant tumors, carcinoma subtypes, salivary gland origin tumors and sarcoma. The association between tumor type categories and period was significant even without this unified category in general (χ^2 (5) =83.5, P<0.001), for males (χ^2 (5) =56.1, *P*<0.001), and for females (χ^2 (5) =24.6, *P*<0.001).

Table 3: Oropharyngeal tumor sites distribution, stratified by SCC and lymphoma, between 1970-1996 and 1997-2013.

		Period							
Tumor type	Tumor site	1970-1996		1997-2013					
category	category	N	%	N	%	Total	Ratio	c^2 (df)	*P*
SCC	BOT	109	48.2	110	28.2	219	1	30.5 (2)	<0.001
	Tonsils	93	41.2	188	48.2	281	2		
	Oropharynx	24	10.6	92	23.6	116	3.8		
	Total	226	100	390	100	616	1.7		
Lymphoma	BOT	27	10.1	18	12.1	45	0.7	14.5 (2)	0.001
	Tonsils	233	86.9	113	75.8	346	0.5		
	Oropharynx	8	3	18	12.1	26	2.3		
	Total	268	100	149	100	417	0.6		

BOT: Base of Tongue; N: Number of Cases; *P*: p-value; SCC: Squamous Cell Carcinoma
χ^2 Pearson's chi-square test

2013 was noted in both males and females (Table 4). No significant trends were found in 0 Y to 29 Y and 70+ Y.

Trends of SCC by tumor site categories: Regarding BOT, no significant trends in SCC were found (Table 4, Figure 2A). In the tonsils, SCC rates increased significantly between 1970-2013 (Table 4, Figure 2B). This was noted in males and in females (Table 4). The increase in tonsillar SCC was noted in the four adult age groups (Table 4): 30 Y to 49 Y, 50 Y to 59 Y including a steep increase from 1983 (0.0/100,000) to 2013 (0.7/100,000) (APC=44.9, [16.4, 80.3]), in 60 Y to 69 Y, and in 70+ Y - including a steep increase from 1984 (0.0/100,000) to 2013 (0.5/100,000) (APC=32.2, [4.7, 67.0]). In the oropharynx site, the SCC rates significantly increased between 1970-2013, both in general and in males (Table 4, Figure 2C).

Between 1970-2013 the increasing trend of SCC in the oropharynx site was higher than the BOT (P<0.001) and the tonsils (*P*=0.001). No significant difference was found in the trends between the BOT and tonsils. This finding was noted in 50 Y to 59 Y (oropharynx and BOT (*P*=0.007), oropharynx and tonsils (*P*=0.027)).

Discussion

Recent publications about OPC have focused on the increase in SCC diagnoses at younger ages [3] and its associations with HPV [4]. Here, we outline some of the broader epidemiological aspects of OPC.

Overall OPC rates remained steady, but changed when segmented by the different variables. OPC rates increased in other regions [16-18], while tumor types were not examined in these reports. In England, the rise was assumed to be associated with HPV infection [16], and was related to the increased proportion of HPV-16 positive

Table 4: Annual percent change values of oropharyngeal SCC and lymphoma rates, stratified by sex, age at diagnosis groups, tumor sites, between 1970-2013.

Tumor type	First stratum	Second stratum	From	Rate	To	Rate	APC	95% CI
SCC	Total		1970	2.02	2013	3.67	2.5	1.8, 3.3
	Males		1970	0.34	2013	0.7	3.3	2.3, 4.4
	Females		1970	0.07	2013	0.15	4.4	(-1.7, 1.8)
	0-29Y		1970	0	2013	0	(-13.44)	(-27.9), 4.0
	30-49Y		1970	0	2013	0.1	12.8	0.7, 26.3
		Males	1970	0	2013	0	16.3	0.8, 34.1
		Females	1970	0	2013	0.2	6.5	(-7.9), 23.2
	50-59Y		1970	1.14	2013	1.43	11.7	2.0, 22.2
		Males	1970	1.55	2013	2.7	23.4	9.8, 38.7
		Females	1983	0	2013	0.25	62.6	28.2, 106.2
	60-69Y		1970	0.5	2013	1.9	10.6	0.3, 21.9
		Males	1970	0.97	2013	3.35	19.21	6.0, 34.1
		Females	1970	0	2013	0.6	19.8	2.8, 39.6
	70+Y		1970	1.77	2013	1.57	4.5	(-0.7), 9.9
	BOT		1970	0.07	2013	0.12	2.6	(-1.7), 1.7
	Tonsils		1970	0.13	2013	0.16	6.1	1.8, 10.4
		Males	1970	0.05	2013	0.23	13.6	5.3, 22.5
		Females	1970	0.07	2013	0.1	12.9	2.4, 24.6
		0-29Y	1970	0	2013	0	2.09	(-6.6, 11.7)
		30-49Y	1970	0	2013	0.05	29.4	15.2, 45.3
		50-59Y	1970	0.38	2013	0.65	21.3	6.5, 38.0
		60-69Y	1970	0.5	2013	0.63	20.6	5.2, 38.2
		70+Y	1970	1.77	2013	0.52	18.4	3.2, 35.7
	Oropharynx		1970	0	2013	0.14	29.9	19.3, 41.5
		Males	1970	0	2013	0.28	36.5	24.5, 49.8
		Females	1970	0	2013	0	10.6	(-2.4), 25.3
Lymphoma	Total		1970	3.7	1994	1.48	2.4	(-0.4), 5.2
	Total		1994	1.48	1997	0	(-70.5)	(-92.2, 11.2)
	Total		1997	0	2013	2.23	28.6	22.3, 35.3
	Males		1970	0.47	1995	0.25	(-0.3)	(-3.2), 2.7
	Males		1995	0.25	2001	0.16	(-96.7)	(-99.3), 85.1
	Males		2001	0.16	2013	0.18	(-15.5)	(-22.7), (-7.6)
	Males	70+Y	1970	1.84	1974	0	(-97.6)	(-99.9), 1.9
		70+Y	1974	0	1977	3.63	442.4	(-100.0), 616.6
		70+Y	1977	3.63	2013	0	(-14.1)	(-24.8), (-6.8)
	Females		1970	0.27	1978	0.22	(-78.9)	(-94.3), 22.1
	Females		1978	0.22	1997	0	56.2	(-98.0), 22.9
	Females		1997	0	2013	0.27	24.8	18.0, 31.9
	Females	70+Y	1970	0	1994	1.53	53.6	12.7, 109.4
		70+Y	1994	1.53	1997	0	(-98.6)	(-100.0), 38.1
		70+Y	1970	0	2013	0.91	111.9	19.9, 274.5

APC: Annual Percent Change; CI: Confidence Interval; SCC: Squamous Cell Carcinoma; Y: Years of Age
Rate – diagnoses per 100,000 people

OPSCC [19].

OPSCC rates were on the rise throughout the study period, but oral cavity SCC rates declined in Israel from 1990 to 2006 [7]. The possible explanations for the decrease were the low alcohol consumption rates and decreasing smoking rates in Israel [7]. The global increase in OPSC was related to HPV infection [20-24], as in the Netherlands, the proportion of HPV-positive head and neck SCC increased between 1990-2010 [25].

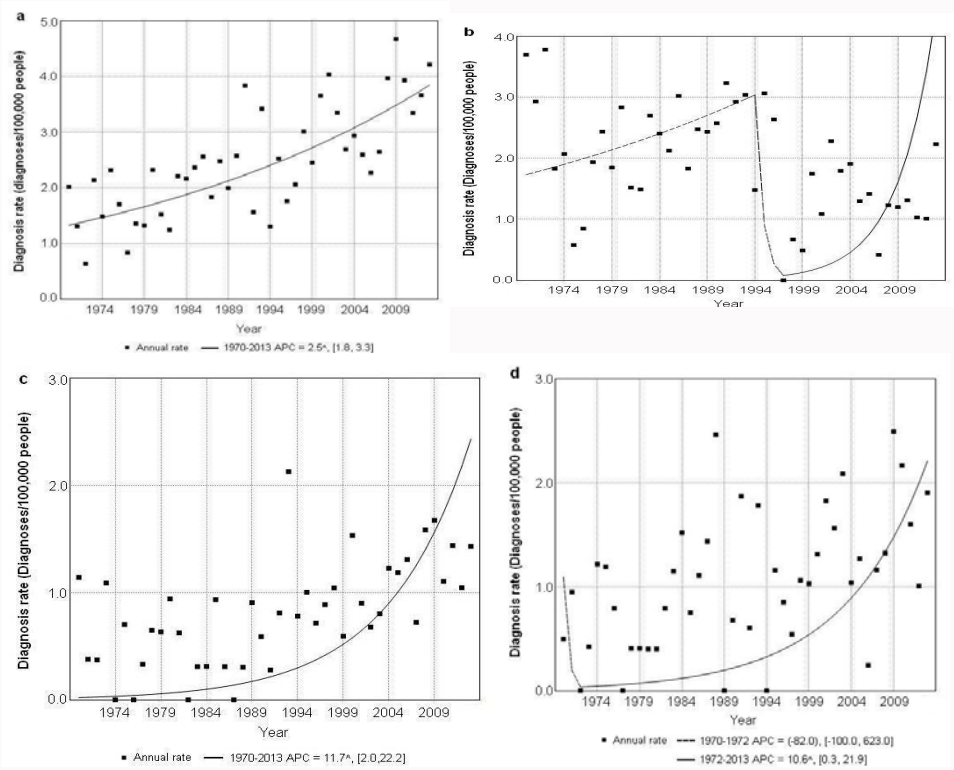

Figure 1: Diagnosis rates of oropharyngeal SCC and lymphoma, 1970-2013. Diagnosis rates of general oropharyngeal SCC (A) and lymphoma (B), and oropharyngeal SCC in 50 Y-59Y (C) and 60 Y-69Y (D).
SCC: Squamous Cell Carcinoma; APC: Annual Percent Change
^ The APC is significantly different than zero at α=0.05 (based on t distribution).

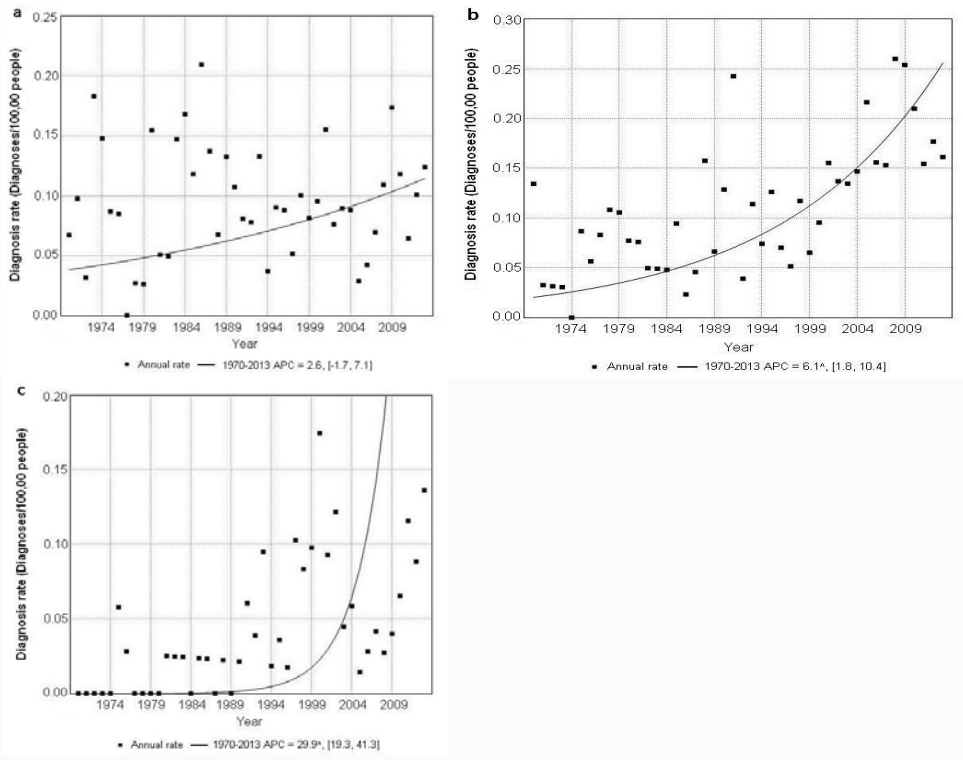

Figure 2: Diagnosis rates of oropharyngeal SCC by tumor sites, 1970-2013. Diagnosis rates of oropharyngeal SCC in the base of tongue (A) the tonsils (B) and the oropharynx site (C).
^ The Annual Percent Change (APC) is significantly different than zero at α=0.05 (based on t distribution).

The median age at diagnosis in this study (63.0 Y) was higher than in New Zealand and Queensland (59.0Y) [22], but the younger mean age for OPSCC in males was similar to Australia [26]. Mean age regarding the tonsils was similar to southeast England (60.4 Y) [27]. In contrast to our findings, the mean age for BOT in Australia was higher than the tonsils but lower than other orophrayngeal sites [26].

During the study period, no significant change was noted in mean age at diagnosis. However, several indices of age significantly decreased in other countries [18,20,26]. Changes in Australia, such as earlier age at sexual debut [28] and increased numbers of oral sex partners were thought to contribute to the younger age at diagnosis [26,29], because HPV-positive OPSCC is associated with sexual behavior. The lack of significant change in this study may be due to low proportion of HPV-related tumors in Israel [8] or other factors.

Furthermore, in southeast England the mean age at diagnosis for tonsillar cancer significantly decreased [27]. That was in parallel with significant increase in rates in 40 Y to 59 Y and 60 to 79, the most common age groups at diagnosis [27]. The authors explained that this may be due to increased diagnostic scrutiny or earlier presentation [27].

In this study, age at diagnosis was positively related to OPC frequency between 1970-1996. Oral Cavity Cancer (OCC) in Israel between 1970-2006 also had this association [7]. However, between 1997-2013 the overall age groups with the most diagnoses were 50 Y to 59 Y and 60 Y to 69 Y. That was also found regarding SCC, probably because of the significant increase in SCC rates in 50 Y to 59 Y and 60 Y to 69 Y. Despite this, the increase in younger ages did not lower the mean age at diagnosis.

Similarly, in other regions OPC was also predominantly detected in younger age groups [23-30]. In England, OPC rates increased significantly in 50 Y to 59 Y and 60 Y to 69 Y [16]. In Taiwan, 40 Y to 49Y and 50 Y to 59 Y were the most frequent, with a faster increase in rates [24]. In Queensland, OPSCC increased in less than 50 Y and in 50 Y to 59 Y [22]. The higher frequency in the younger age groups was related to higher HPV levels in younger individuals [31], and changes in sexual behavior [22,24].

The general OPC male to female ratio was 1.8, which is slightly higher than the ratio for OCC in Israel (1.3) [7]. Compared with other areas, the higher ratio for OPC than OCC is similar [16,17,32]. In Scotland, the male predominance of OPC was partially explained by the greater prevalence of HPV in males [17,33]. In this study, the OPSCC male to female ratio (2.6) was higher than the oral cavity SCC ratio in Israel (2.0) [7]. Reports with similar [21-23] and contradicting data [24] were also found. The overall predominance in males may be due to increased SCC rates in general and in three age groups, 30 Y to 49 Y, 50 Y to 59 Y and 60 Y to 69 Y. In New Zealand, SCC rates increased in both sexes, but males still had higher rates, whereas in Queensland the rates only increased in males [22]. In Taiwan, SCC increased in males across all age groups, but in females it only increased in 40 Y to 49 Y and 50 Y to 59 Y [24]. In the USA, OPSCC increased primarily among males [5]. In Taiwan the higher diagnosis of HPV-related head and neck cancer in males was also related with the higher prevalence of oral HPV infection in males [24,34].

Similar distributions of tumor sites, with tonsils as the most frequent, have been reported elsewhere [16,26,30]. Overall tonsillar cancer decreased between 1997-2013, possibly due to the decrease in lymphoma, although tonsillar SCC increased throughout the period. In southeast England, the general increase in tonsillar cancer was considered to reflect the earlier presentation of tonsillar cancer [27]. Tonsillar SCC also increased in other regions [22,24,35,36], as in both Stockholm region [35] and eastern Denmark these increases were associated with HPV [36].

Diagnosis of BOT malignancy did not change during the study period. In contrast, an increase was found in England [16]. BOT SCC increased in other regions [22,35,37], as in Stockholm region, Sweden [35], and eastern Denmark the increase was related with an increase in HPV positive detection [37].

Considering tumor sites, the literature on OPC or HPV-related cancer refers mainly to the tonsils and BOT and less to the oropharynx site and its sub-sites (ICD-10: C10.0 to C10.9) [9]. In other areas, malignancy in the oropharynx site increased [16,21], but also decreased [38], and even remained unchanged [22]. The reasons for those findings were not discussed nor explained. The increase in the oropharynx site in this study, which was significantly higher than the tonsils and the BOT, may be the result of changes in anatomical classifications or may be due to biological or environmental factors.

As mentioned above, HPV detection is related to OPSCC diagnosis and increase. In addition, smoking, alcohol and other lifestyle habits are also risk factors for OPSCC, as for OCC, including oral cavity SCC [39]. In a recent cohort study in Israel, HPV was positively detected in 33.8% of the patients, mostly in those younger than 50 Y [8]. The lower OPSCC proportion was thought to be related with low exposure to HPV [8]. In contrast, the prevalence and distribution of HPV types in Israeli cervical cancer samples were similar to worldwide reports [40,41]. In addition, there has been a decrease in cigarette smoking in Israel since 1970 [42]. However, due to the sample size in that cohort study [8], and the lack of lifestyle risk factors in the current study, we cannot determine with certainty if HPV exposure or any other lifestyle risk factors, might be the reason for the increase in SCC in the current study.

Qualitatively, OPC general rates as diagnoses per population seem to be lower in Israel than in England [16]. OPSCC rates in Israel seem to be lower than in the USA [5], the Netherlands [21], New Zealand and Queensland [22], but higher than in Taiwan, except for tonsillar SCC [24]. In comparison with other regions where the diagnosis rates were calculated as age standardized or in person years [23,35,36], the comparison is not worthwhile. Therefore, although the OPSCC increase was similar to other countries, particularly in younger age groups, the lower rates in Israel may be related to the relatively lower male: female ratio and the lack of significant change in mean age at diagnosis.

Distribution of OPC tumor types or more generally, oral and pharyngeal cancer or head and neck cancer, are sparsely reported in the literature. As in the current study, SCC has been reported by others as the most diagnosed tumor type [43-46]. Other similarities include SCC as the main tumor type in males, and lymphoma as the main tumor type in females [44,47]. In general, lymphoid malignancies are more common in males than females [48], so sex predominance may be altered when considering anatomical aspects. In addition, the SCC/lymphoma rate seemed to increase more dramatically in males than females between 1997-2013. This highlights the predominance of SSC diagnosis in males and may explain the higher male to female ratio for SCC (2.6) than lymphoma (1.2).

Most of the lymphoma cases were diagnosed in the tonsils,

which had been reported as the leading lymphoma site of all oral and pharyngeal sites in Israel [49]. Lymphoma was the most commonly diagnosed cancer in the youngest age group, and the main specific type was Burkitt's lymphoma, in accordance with the literature [50]. The demographic and clinical characteristics of lymphoma, such as the predominance of males, tonsils and the specific type diffuse large b-cell lymphoma, were similar to hospital-based reports [51-54]. Since the oropharyngeal sites are part of Waldeyer's ring [55], the majority of head and neck lymphomas are diagnosed in the Waldeyer's ring, mainly in the tonsils [56]. This might explain the higher frequency of lymphoma in the tonsils in this study.

Total diagnosis of lymphoma decreased between 1997-2013 compared to 1970-1996. However, lymphoma rates increased in females after 1997 and decreased in males. In India, the increase in lymphoma was explained by improved diagnosis and changes in classification [57]. In the USA, the proportional part of head and neck lymphoma increased between 1985-1989 and 1990-1994 [58], but decreased between 1995-1999 and 2000-2004 [59]. The increase was related to Human Immunodeficiency Virus (HIV) prevalence and other factors affecting the immune system [58]. The decrease was explained by the impact of antiretroviral therapy against HIV [59]. In contrast, head and neck lymphoma increased in South Africa between 1993-2012, and this was associated with a high prevalence of HIV [60]. In Israel, antiretroviral therapy was introduced in 1997 and became available to all citizens [61]. Among Israeli HIV patients older than 15 Y, the incidence of non-Hodgkin lymphoma decreased between 1997-2010 compared to 1981-1996, due to the improved efficacy and tolerability of antiretroviral therapy [61]. Since reporting to the INCR is mandatory by a ministerial decree, it is not possible that the total decrease in lymphoma between 1997-2013 was due to information bias. Furthermore, the relationship between HIV or antiretroviral therapy and lymphoma was not examined in this study. The associated etiology of the main lymphoma type in this study, diffuse large b-cell lymphoma, includes different biological factors [62,63], and might be associated with occupational exposures [62]. Therefore, different risk factors and environmental exposure levels may explain the diversity in lymphoma frequency and trends between the sexes in this study. But as no lifestyle data were available, no conclusions regarding risk factors can be drawn.

Malignancies of salivary gland origin were mostly diagnosed in the BOT. Similarly to this study, other reports had mucoepidermoid carcinoma as the leading type followed by adenocarcinoma [64], while in others adenoid cystic carcinoma was the leading type [65,66].

Conclusion

Although OPC rates and especially OPSCC rates in Israel seem to be lower, the increase of OPSCC, especially in the tonsils and oropharynx site, is similar to other countries. It is important to note that such comparisons are made with populations in different geographical areas. Ecologically, different populations might be exposed to different levels of environmental risk factors. That may contribute to the diversity in diagnosis rates between countries.

A limitation of this study is the lack of data regarding known OPC risk factors, which limits our ability to determine reasons for changes in OPC with certainty.

This study also noted other OPC histopathological types, and the relations between the oropharyngeal tumor types became apparent. Health care providers should be aware of the common tumor sites and types for specific age groups and sexes, in order to detect early malignant symptoms for better prognosis.

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