Characterization of Yemeni patients treated for oral and pharyngeal cancers in Saudi Arabia

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ABSTRACT

الأهداف: تقدير التكرار النسبي و ترتيب كل من سرطاني الفم و البلعوم لدى مرضى السرطان اليمنيين الذين تمت معالجتهم وتسجيلهم في المملكة العربية السعودية خلال 14 عاماً، وكذلك توصيف هؤلاء المرضى وفق العوامل الديموغرافية والورمية المختلفة.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في عيادات طب أمراض الفم وذوي الاحتياجات الخاصة والبحث العلمي، قسم الأسنان، مستشفى الرياض العسكري، الرياض، المملكة العربية السعودية خلال الفترة من يناير إلى أبريل 2011م. لقد قدم السجل السعودي للأورام بالرياض وفقاً لطلب رسمي بيانات جميع مرضى السرطان اليمنيين المسجلين لديه خلال الفترة من 1994م إلى 2007م. تمت إعادة تصنيف هذه البيانات وتحليلها وفق مواقع الإصابة الرئيسة المعتمدة في برنامج غلوبوكان 2008، فيما تم توصيف وتحليل بيانات مرضى سرطاني الفم والبلعوم إحصائيا وفقاً للمتغيرات الديموغرافية وتفاصيل الورم.

النتائج: لقد بلغ عدد المرضى اليمنيين المصابين بأورام خبيثة 5862 مريضاً. وكان سرطان الفم ثامن الأورام الخبيثة ترتيباً (215، 3.7%)، وبلغت نسبة إصابة الذكور إلى الإناث 1.65:1. بينما حل سرطان البلعوم المرتبة السابعة (245، 4.2%) وبلغت نسبة إصابة الذكور إلى الإناث 2.06:1. كان اللسان أكثر المواقع الفموية تعرضاً للإصابة (91، 42.3%) بينما كان البلعوم الأنفي مسئولاً عن 79% (194) من أورام البلعوم. وكان مرضى سرطان البلعوم أصغر سناً من مرضى سرطان الفم (45.88±16.72 مقابل 55.6±15.75). وكان سرطان حرشفية الخلايا أكثر الأنماط تكرراً من ناحية التركيب الشكلي (289، 63.5%)، ولكنه كان أكثر تكرراً لدى مرضى سرطان الفم. ولقد تم تشخيص 255 (56%) من مرضى سرطاني الفم والبلعوم في مراحل متقدمة إلا أن أكثرهم كانوا مصابين بسرطان البلعوم (155، 64.6%).

خاتمة: أثبتت هذه الدراسة بأن التكرار النسبي لسرطاني الفم والبلعوم يعد مرتفعاً نسبياً في اليمن. ومن الواضح أيضاً اختلاف ميزات مرضى سرطان الفم عن مرضى سرطان البلعوم.

Objectives: To determine the relative frequency and rank of oral cancer (OC) and pharyngeal cancer (PC) among Yemeni cancer patients who were treated and registered in the Kingdom of Saudi Arabia (KSA) over 14 years, and to characterize these patients by different grouping factors.

Methods: In this retrospective study, the Saudi Cancer Registry, Riyadh, KSA officially provided the data regarding all Yemeni patients registered between 1994 and 2007. These data were reclassified and analyzed to present the cancer distribution by the main sites adopted by Globocan 2008. The OC and PC patients were statistically described and analyzed according to the demographic data and tumor details. This study was conducted at the Oral Medicine, Medically Compromised and Research Clinic, Department of Dentistry, Riyadh Military Hospital, Saudi Arabia between January and April 2011.

Results: There were 5862 Yemenis registered with malignancies. The OC ranked the eighth most common malignancy (215, 3.7%) with 1.65:1 male to female ratio, whereas PC ranked the seventh (245, 4.2%) with 2.06:1 male to female ratio. The most affected oral subsite was the tongue (91, 42.3%) while the nasopharynx accounted for 79% (194) of PC. The PC patients were significantly younger than those with OC (45.88±16.72 versus 55.6±15.75). The squamous cell carcinoma was the most frequent morphological type (289, 63.5%) but significantly more frequent in OC. Approximately 56% (255 patients) were diagnosed at advanced stage, however, significantly more frequent in PC (155, 64.6%).

Conclusion: The relative frequencies of oral and pharyngeal cancers in Yemen are quite high. The demographic and tumor characteristics of these cancers are obviously different.

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Oral cancer (OC) and pharyngeal cancer (PC) were estimated globally to affect more than 482,000 people in 2008, and more than half of them (273,000) die of the disease.[1] Unfortunately, two-thirds of these cases occurred in developing countries.[2] The prevalence of OC and PC shows a wide disparity by gender and geographic areas.[1,3] While nasopharyngeal cancer is prevalent in South East Asia,[4] OC has been known to be prevalent in South Asian countries, such as India[5] and Pakistan[6]. The widespread habit of betel quid chewing within these populations has been closely associated with extremely high incidences of the disease.[7] In addition to chewing betel quid, smoking tobacco, alcohol consumption, and poor oral hygiene are well established risk factors for these cancers.[8] Other assumed risk factors include human immunodeficiency virus (HIV) infection[8], chronic illnesses, poverty, and malnutrition.[9] The previously mentioned risk factors are quite prevalent in Yemen except HIV infection, betel quid chewing, and alcohol consumption. Moreover, khat chewing and smokeless tobacco use (locally known as shammah) are highly prevalent. Both habits have been linked with OC in Yemen[10] and Saudi Arabia[11]. Hospital-based studies furthermore revealed very high relative frequencies and ranks of OC,[12] and head and neck cancer[13,14] in Yemen. Nonetheless, there has been no well-documented national population-based cancer registry in Yemen as yet. As many Yemeni cancer patients had access to be treated in the Kingdom of Saudi Arabia (KSA), and they were well-documented, the objectives of this study were to determine the relative frequencies and ranks of OC and PC among those who were treated and registered in KSA over a period of 14 years (1994-2007), and to characterize these patients by different grouping factors.

Methods. The present descriptive epidemiological study was carried out on retrospective data provided upon official request by the Saudi Cancer Registry (SCR), Riyadh, KSA. The SCR provided a soft copy of the data regarding all registered Yemeni patients over 14 years (1994-2007). These data included demographic (gender and age), and tumor details (diagnosis date, primary site, histology, behavior, grade, stage, and basis of diagnosis). The primary site (topography) and histology (morphology) of the neoplasms were already identified and coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).[15] Tumor staging was already coded according to SEER Summary Stage Manual 2000.[16] Patients with benign tumors, carcinoma in situ, or with any missing datum were excluded. The main morphology of the malignant tumors were reclassified as: neoplasm; carcinoma, not otherwise specified (NOS); carcinoma, undifferentiated, NOS; and squamous cell carcinoma. The less frequent morphological types were reclassified as others. To allow for comparison with other published data and proper presentation of the relative frequencies and rankings of site-specific cancers, the primary sites (ICD-O-3) were reclassified as adopted by GLOBOCAN 2008.[1]

This study was conducted at the Oral Medicine, Medically Compromised and Research Clinic, Department of Dentistry, Riyadh Military Hospital, Saudi Arabia between January and April 2011.

The statistical description and analyses were carried out using PASW software computer program version 18. The descriptive statistics were presented as means with standard deviations and relative frequencies with 95% confidence interval (CI). The differences in age, by gender and site were analyzed by independent t-test while the associations of the cancer distribution (OC versus PC) with the different grouping factors were analyzed using Chi-square test. All analyses were performed at 0.05 significance value.

Results. There were 5938 Yemenis registered with neoplasms at SCR within the study period. Of them, 5862 had malignancies (averaging 419 patients each year). There were 460 (7.8%, 95% CI=6.6-9.1) patients with OC and PC. After reclassification based on GLOBOCAN (**Table 1**), OC was the eighth most common malignancy among both genders (215, 3.7%; 95% CI=3.2-4.2) and among women (81, 3.2%; 95% CI=2.5-3.9), but it unexpectedly ranked the eleventh among men (134, 4%; 95% CI=3.4-4.7). The male to female ratio was 1.65:1. On the other hand, the PC ranked the seventh most common malignancy among both genders (245, 4.2%; 95% CI=3.4-4.9), the sixth among men (165, 4.9%; 95% CI=4-5.9), and the ninth among women (80, 3.1%; 95% CI=2.3-4.2). The male to female ratio was 2.06:1. The most affected oral sub-site was the tongue, and it accounted for more than 42% of the OC (91 patients; 95% CI=34.5-51.7) with insignificant difference by gender (**Table 2**). The nasopharyngeal cancer accounted for more than 79% of the PC (194 patients; 95% CI=73.9-84.5), however, it was significantly more frequent among men compared to women. **Table 3** presents the characteristics of OC and PC patients. The overall mean age of both cancer patients was 50.62 ± 16.87 years. However, patients with OC were significantly older. Furthermore, 127 patients (27.9%) were 40 years old or less, though most of them were significantly involved by PC. More than half of OC and PC (289, 63.5%) were squamous cell carcinoma but significantly more frequent among OC. The well and moderately differentiated cancers were significantly more frequent in OC (127, 59.1%) compared to PC (40, 16.6%). Unfortunately, high

Table 1 - The GLOBOCAN 2008 distribution of Yemeni patients with malignancies who were treated in the Kingdom of Saudi Arabia between 1994 and 2007 by gender.

Cancer sites	Men			Women			Both genders		
	n	(%)	95% CI	n	(%)	95% CI	n	(%)	95% CI
Lip, oral cavity C00-08	134	(4.0)	3.4-4.7	81	(3.2)	2.5-3.9	215	(3.7)	3.2-4.2
Nasopharynx C11	140	(4.2)	3.5-4.9	54	(2.1)	1.6-2.7	194	(3.3)	2.8-3.8
Other pharynx C09-10, C12-14	25	(0.7)	0.5-1.0	26	(1.0)	0.7-1.5	51	(0.9)	0.6-1.1
Esophagus C15	79	(2.4)	1.9-2.9	49	(1.9)	1.4-2.5	128	(2.2)	1.8-2.6
Stomach C16	155	(4.6)	3.9-5.4	56	(2.2)	1.7-2.8	211	(3.6)	3.1-4.1
Colorectum C18-21	294	(8.8)	7.8-9.8	164	(6.5)	5.6-7.5	458	(7.8)	7.1-8.5
Liver C22	225	(6.7)	5.9-7.7	60	(2.4)	1.8-3.0	285	(4.9)	4.3-5.4
Gallbladder C23-24	14	(0.4)	0.2-0.7	12	(0.5)	0.2-0.8	26	(0.4)	0.3-0.6
Pancreas C25	56	(1.7)	1.3-2.1	28	(1.1)	0.7-1.6	84	(1.4)	1.1-1.8
Larynx C32	73	(2.2)	1.7-2.7	8	(0.3)	0.1-0.6	81	(1.4)	1.1-1.7
Trachea, bronchus and lung C33-34	152	(4.5)	3.8-5.2	46	(1.8)	1.3-2.3	198	(3.4)	2.9-3.8
Melanoma of skin C43	8	(0.2)	0.1-0.4	9	(0.4)	0.2-0.6	17	(0.3)	0.2-0.4
Kaposi sarcoma C46	19	(0.6)	0.3-0.8	3	(0.1)	0-0.3	22	(0.4)	0.2-0.5
Breast C50	22	(0.7)	0.4-1.0	618	(24.5)	22.8-26.2	640	(10.9)	10.1-11.7
Cervix uteri C53				143	(5.7)	4.8-6.5	143	(2.4)	2.0-2.8
Corpus uteri C54				54	(2.1)	1.6-2.7	54	(0.9)	0.7-1.2
Ovary C56				106	(4.2)	3.5-5.0	106	(1.8)	1.5-2.2
Prostate C61	118	(3.5)	2.9-4.2				118	(2.0)	1.7-2.4
Testis C62	36	(1.1)	0.7-1.5				36	(0.6)	0.4-0.8
Kidney C64-66	87	(2.6)	2.1-3.1	39	(1.5)	1.1-2.1	126	(2.1)	1.8-2.5
Bladder C67	231	(6.9)	6.0-7.8	47	(1.9)	1.3-2.4	278	(4.7)	4.2-5.3
Brain, nervous system C70-72	145	(4.3)	3.7-5.1	61	(2.4)	1.9-3.0	206	(3.5)	3.1-4.0
Thyroid C73	55	(1.6)	1.2-2.1	131	(5.2)	4.4-6.1	186	(3.2)	2.7-3.6
Hodgkin lymphoma C81	136	(4.1)	3.4-4.8	61	(2.4)	1.8-3.1	197	(3.4)	2.9-3.8
Non-Hodgkin lymphoma C82-85, C96	311	(9.3)	8.4-10.4	128	(5.1)	4.2-6.0	439	(7.5)	6.8-8.2
Multiple myeloma C88, C90	42	(1.3)	0.9-1.6	9	(0.4)	0.2-0.6	51	(0.9)	0.6-1.1
Leukemia C91-95	242	(7.2)	6.3-8.2	150	(6.0)	5.0-6.8	392	(6.7)	6.0-7.3
Others	543	(16.2)	15.1-17.5	377	(15.0)	13.5-16.4	920	(15.7)	14.7-16.7
Total	**3342**	**(100.0)**		**2520**	**(100.0)**		**5862**	**(100.0)**	

CI - confidence interval, C stands for malignant neoplasms in the International Classification of Diseases-10

Table 2 - The International Classification of Diseases-10 sub-sites distribution of oral and pharyngeal cancers (C00-C14) among Yemeni patients who were treated in the Kingdom of Saudi Arabia between 1994 and 2007 by gender.

Subsites of oral and pharyngeal cancer	Men			Women			Both genders		
	n	(%)	95% CI	n	(%)	95% CI	n	(%)	95% CI
Oral cancer	134	(62.3)	55.8-68.4	81	(37.7)	31.6-44.2	215	(100.0)	
Lip C00	11	(8.2)	3.7-13.4	10	(12.3)	6.2-19.8	21	(9.8)	6.0-13.5
Base of the tongue C01	1	(0.7)	0.0-2.2	4	(4.9)	1.2-9.9	5	(2.3)	0.5-4.7
Other and unspecified parts of tongue C02	54	(40.3)	31.3-48.5	32	(39.5)	28.4-49.4	86	(40.0)	34.0-47.0
Gum C03	8	(6.0)	2.2-10.4	6	(7.4)	2.5-13.6	14	(6.5)	3.3-10.2
Floor of the mouth C04	8	(6.0)	2.2-9.7	2	(2.5)	0.0-6.2	10	(4.7)	2.3-7.4
Palate C05	3	(2.2)	0.0-5.2	1	(1.2)	0.0-3.7	4	(1.9)	0.5-3.7
Other and unspecified parts of the mouth C06	31	(23.1)	16.4-29.9	16	(19.8)	11.1-28.4	47	(21.9)	16.7-27.4
Parotid gland C07	12	(9.0)	4.5-14.2	8	(9.9)	3.7-17.3	20	(9.3)	5.6-13
Other and unspecified major salivary gland C08	6	(4.5)	1.5-8.2	2	(2.5)	0.0-6.2	8	(3.7)	1.4-6.5
Pharyngeal cancer	165	(67.3)	61.6-73.1	80	(32.7)	26.9-38.4	245	(100.0)	
Tonsil C09	3	(1.8)	0.0-4.2	4	(5.0)	1.3-10	7	(2.9)	1.2-5.3
Oropharynx C10	3	(1.8)	0.0-4.2	2	(2.5)	0.0-6.3	5	(2.0)	0.4-4.1
Nasopharynx C11	140	(84.8)	79.4-89.7	54	(67.5)	57.5-77.5	194	(79.2)	73.9-84.5
Piriform sinus C12	2	(1.2)	0.0-3.6	1	(1.3)	0.0-3.8	3	(1.2)	0.0-2.9
Hypopharynx C13	14	(8.5)	4.2-12.7	17	(21.3)	12.5-30	31	(12.7)	8.6-17.1
Other and ill-defined sites in the lip, oral cavity, and pharynx C14	3	(1.8)	0.0-4.2	2	(2.5)	0.0-6.3	5	(2.0)	0.4-4.1

CI - confidence interval, C stands for malignant neoplasms in the International Classification of Diseases-10

Table 3 - Characteristics of Yemeni patients with oral and pharyngeal cancers, who were treated in Saudi Arabia (1994-2007).

Studied variable	Lip and oral cavity cancer	Pharyngeal cancer‡	*P*-value
Age (mean ± standard deviation)			
Men	55.58 ± 15.75	45.81 ± 16.13	<0.000*
Women	55.64 ± 15.38	46.04 ± 18.05	0.001*
Both genders	55.6 ± 15.75	45.88 ± 16.72	<0.000*
Age categories, n (%)			<0.000†
≤40 years	38 (17.7)	89 (37.1)	
>40 years	177 (82.3)	151 (62.9)	
Gender, n (%)			0.248
Men	134 (62.3)	162 (67.5)	
Women	81 (37.7)	78 (32.5)	
Main morphology, n (%)			<0.000†
Squamous cell carcinoma, NOS	167 (77.7)	122 (50.8)	
Neoplasm	5 (2.3)	3 (1.3)	
Carcinoma, NOS	6 (2.8)	29 (12.1)	
Carcinoma, undifferentiated, NOS	3 (1.4)	77 (32.1)	
Others	34 (15.8)	9 (3.8)	
Grade, n (%)			<0.000†
Well differentiated	54 (25.1)	10 (4.2)	
Moderately differentiated	73 (34.0)	30 (12.5)	
Poorly differentiated	32 (14.9)	38 (15.8)	
Undifferentiated	5 (2.3)	108 (45.0)	
Unknown	51 (23.7)	54 (22.5)	
Tumor extension, n (%)			<0.000†
Localized	73 (34.0)	33 (13.8)	
Regional	68 (31.6)	104 (43.3)	
Distant metastasis	32 (14.9)	51 (21.3)	
Unknown	42 (19.5)	52 (21.7)	

*independent t-test, †Chi-square test, ‡other and ill-defined sites in the lip, oral cavity, and pharynx (C14) were excluded, NOS - not otherwise specified

proportion of OC and PC patients (255, 56%) were diagnosed at advanced stages; however, the PC patients were significantly more frequent (155, 64.6%). Almost all cases were histologically verified.

Discussion. Since no oncology center had been available in Yemen before 2005, a high proportion of cancer patients were going abroad for reasonable therapy. In an ascending order, Jordan, Egypt, Iraq (before 2003), and KSA are the main destinations for these patients. Although the health resources for cancer therapy have improved since 2005, some patients still preferred to be treated outside Yemen. The available data regarding Yemeni patients who were registered in SCR are considerable, and based on such, the magnitude of site-specific cancer in Yemen could be reflected. The data are well-documented and collected over a period of 14 years with minute differences in distribution by year of registration, thus, they can be relied on for accurate estimations.

Comparing the burden of a site-specific cancer between different countries is more reliable when using the Age Standardized Incidence Rate rather than the relative frequency. However, the former parameter requires population-based data to which the present study lacks.

The present analysis obviously contradicts 2 different hospital-based studies,[12,14] which reported higher relative frequencies (18%[12] and 8.7%[14]), and ranks (the first[12] and the fifth[14]) of OC in the Central and Northern regions of Yemen. However, the figures in this study slightly exceed those reported from the southern region of Yemen, where the relative frequency of OC was 2.9% and it ranked the thirteenth.[17] Such a regional disparity was reported in Yemen[18] and KSA[11]."

In support of GLOBOCAN estimations[19] and other reports,[3,20-22] OC in Yemen appears to have higher relative frequency, and a higher rank compared with other Arab and most Western countries. However, the figures obtained from Myanmar,[23] Pakistan,[6] and India[24] were higher. This worldwide variety in OC distribution reflects different prevalence and patterns of different risk habits. In light of the present finding, the assumed etiological role of the indigenous habits of khat chewing and shammah use in Yemen should be considered seriously.

Men were affected by OC more than women. This is in agreement with previous studies in Yemen,[13,14,17] but in contrast to Sawair et al's study[12]. This is a worldwide tendency.[3,21-24] Cultural norms allow more men to be exposed to the assumed risk factors (for example,

smoking, khat, shammah, and so forth) compared to women.

An interesting finding was the higher relative frequency of PC as compared to OC. This contradicts other studies in Yemen.[12-14,17] The relative frequencies of OC and PC in KSA were nearly equal.[21] However, the figures obtained from Egypt,[25] Myanmar,[23] USA,[22] England,[26] Pakistan,[27] and India[24] revealed lower relative frequencies of PC. Nasopharyngeal cancer, which accounted for more than 79% of the PC in the present study is relatively common among Western North African men,[28] and among South East Asians[4]. It is not considered to be tobacco-related cancer, however, the genetic and infectious etiologies have been suggested.[29]

More men were affected by PC than women. This is in agreement with other studies in Yemen,[12-14,17] and other countries[21-25]. It is difficult at present to explain the higher frequency of PC (specially the nasopharyngeal cancer) among Yemeni men. However, wearing a face cover by women might protect them through interfering with Epstein-Barr virus infection,[29] which is considered as an etiological factor for nasopharyngeal cancer.

The tongue was the most affected oral sub-site. Reports from Yemen,[12,17,18] KSA,[21] Myanmar,[23] and most developed and developing countries[3] revealed a similar result. There are differences between regions, however. In South Central Asia, the buccal mucosa is the most affected oral sub-site where betel quid is held.[3,6,24] In Iraq, the lip is reported to be the most affected oral sub-site,[30] while the gingiva is the predominant oral sub-site in Zimbabwe[31]. Although the tongue is not the main site correspondent to where khat, shammah, or both are held, being the most affected oral site can be partly implied through the concept of field cancerization,[32] being one of the high risk areas, or both.

Patients were affected by PC at a significantly earlier age compared to OC. Moreover, more than 37% of patients with PC were 40 years old or less. The occurrence of PC in young age population was reported too in KSA.[29] This might mean that the pharyngeal tissues are more susceptible to the assumed risk factors, exposures to some still little understood risk factors, which may selectively affect the pharynx or both. The mean age of the patients with OC, on the other hand, is comparable to previous studies in Yemen[12,18] and Iraq[30]. However, it is less than reported in KSA[11] and most Western countries,[33] but more than reported in Pakistan,[6] Myanmar,[23] and Zimbabwe[31]. This disparity could be reflected partly by the onset and the intensity of practicing risk habits in different regions worldwide. On average, khat chewing habit starts at the early 20's of age, and the frequency of practicing it ranges from once a week to once a day. Shammah using, on the other hand, starts earlier and practiced more than once a day.

In agreement with other studies in Pakistan,[34] Myanmar,[23] and Zimbabwe,[31] squamous cell carcinoma was significantly the most morphologic type diagnosed in OC compared to PC. Moreover, most of the OC cases graded well to moderate differentiation, while most of PC cases graded poor to undifferentiated. In addition to the better accessibility to diagnosis, the previously mentioned findings might explain the lower proportion of OC with advanced tumor extension (regional and distant metastasis) compared to PC. Although higher than reported in Pakistan,[34] only less than 35% of OC and 13% of PC were diagnosed at localized stage. This could be explained by patients' lack of awareness and health knowledge along with poor resources of primary and secondary health care. More than 96% of the cases were histologically verified, which makes the present data highly valid and reliable.

In conclusion, the high relative frequency of the PC (especially nasopharyngeal) among Yemenis is pointed out for the first time. Overall, OC and PC in Yemen represent national health burdens. They rank the eighth (OC), and seventh (PC) most common malignancies. In light of our findings, considering khat chewing and shammah using as risk factors for OC is reasonable, and deserves large-scale matched case-control studies. However, it is unreasonable to link these habits with the nasopharyngeal cancer, which occurs with higher relative frequency, but at younger ages. The presence of a national population-based cancer registry is the cornerstone to assess the burden of each site-specific cancer, and to plan and direct the available health care resources and programs accordingly.

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