

RESEARCH ARTICLE

Head and Neck Cancer in Saudi Arabia: a Systematic Review

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Abstract

Background: Head and neck cancer (HNC) is the ninth most common cancer worldwide, and has a poor 5-year survival rate averaging 50%, which has not changed for decades. A high prevalence of HNC has been reported in the southwestern region of Saudi Arabia, as compared to other areas of the country. However, data in regards to HNC are scattered and not well documented. Thus, the aim of this systematic review was to gather all available and updated important information regarding HNC in Saudi Arabia, and highlight the gaps of knowledge in our country with regard to this disease. In addition, suggestions of solutions to overcome the current status and improve our future standard of care to fight HNC are also highlighted. **Materials and Methods:** The electronic databases PubMed and Google Scholar using English-language literature were used for this systematic review, using specific inclusion and exclusion criteria and keywords. The search was performed in April 2016 and updated in June 2016. **Results:** Our search revealed twenty-one studies that fulfilled our inclusion and exclusion criteria and that were conducted in Saudi Arabia. These studies investigated different aspects of HNC, including prevalence, risk factors, biomarkers, and assessed knowledge and awareness of both public and practitioners with regard to HNC. **Conclusions:** This review uncovered a big gap in our epidemiological data in cancer information in general, and head and neck cancer in particular. In addition, a lack of knowledge and awareness of both the public and health care practitioners hinders the early diagnosis of disease and negatively impact the prognosis, treatment and outcome. The Ministry of Health in Saudi Arabia should develop a more systematic way and adapt policies to gather cancer information in general, and head and neck cancer in particular, from all governmental and private sectors from all over the kingdom, and develop educational programs to raise the knowledge and awareness of HNC in the country.

Keywords: Head and neck cancer - oral cancer, squamous cell carcinoma - SCC - Saudi Arabia - review

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Introduction

Head and neck cancer (HNC) is the ninth most common cancer worldwide, and this term used to describe a number of different malignancies that develop in or around the throat, larynx, nose, sinuses, and mouth (Ferlay et al., 2013). Studies have estimated the global incidence of all head and neck cancers to be between 400,000 and 600,000 new cases per year and the mortality rate to be between 223,000 and 300,000 deaths per year (Chaturvedi et al., 2013).

HNC has a poor 5-year survival rate averaging 50%, and this has not changed for decades (American Cancer Society, 2015). The most common risk factors associated with HNC are tobacco and alcohol use, with a large interaction observed between them (Blot et al., 1988). In addition, in Asian countries, using different kinds of smokeless tobacco has increased the incidence of HNC,

especially the hypopharynx and larynx cancers (Krishna Rao et al., 2013). HNC and, specifically, oral cancer is reported to be a prevalent malignancy in Saudi Arabia (Tandon et al., 1995). The high prevalence of oral cancer was reported in the southwestern region of Saudi Arabia compared to others (Allard et al., 1999). However, few reports have looked into the prevalence and risk factors of HNC in Saudi Arabia. In addition, few studies have assessed the knowledge and awareness of HNC in both the medical/scientific and general populations in Saudi Arabia (Jaber et al., 2011; Quadri, 2014; Al-Maweri et al., 2015).

Thus, the aim of this review was to gather all available and updated important information regarding HNC in Saudi Arabia, and highlights the gaps of knowledge in our country in different aspect in regards to this disease. In addition, suggestions of solutions to overcome the current inadequate status and improve our future standard of care

to fight HNC will be also highlighted.

Materials and Methods

The electronic databases PubMed and Google Scholar using English-language literature were used for this systematic review. The search was done in April 2016 and updated in June 2016. The keywords used were combinations of the following: “head and neck cancer”, “HNSCC”, “Squamous Cell Carcinoma”, “oral cancer”, “awareness”, “knowledge”, “epidemiology”, “risk factor”, “prevalence”, “incidence” and “Saudi Arabia”. The following inclusion and exclusion criteria were applied to the search results as follows:

Inclusion criteria: *i)*. English language text, *ii)*. Human subjects, *iii)*. Epidemiological studies, *iv)*. Original research articles, *v)*. Published head and neck cancer reports from Saudi Arabia, *vi)*. Studies conducted in Saudi Arabia.

Exclusion criteria: *i)*. Articles that focused and investigated treatment modalities and their outcomes for HNC in Saudi Arabia, *ii)*. Review article, *iii)*. Studies conducted in neighboring countries of Saudi Arabia, such as Yemen, *iv)*. Articles that focused on other types of cancer such as thyroid cancer in Saudi Arabia, *v)*. Studies conducted in Saudi but using samples other than the residents of Saudi Arabia, *vi)*. Studies that focused on risk factors such as types of smoking but did not look into

Table 1. Summary of All Included Studies in the Systematic Review

vb	Author	Year	Main Conclusions
1	Alhazzazi T	2016	Knowledge and awareness of HNC in low among both general public and dental health practitioners.
2	Quadri MF et al.	2015	Smokeless tobacco (shamma) is a major risk factor for oral cancer in the Jazan region of Saudi Arabia.
3	Quadri MF et al.	2014	Intervention programs are effective approach to increase knowledge among Saudis against oral cancer.
4	Kujan et al.	2014	It is warranted to implement oral cancer screening, prevention, and diagnostic aspects in undergraduate dental curriculum to improve our future health care system.
5	Al-Zahrani et al.	2014	85.5% of the examined HNC patients had suffered from pain, and 82% had metastasis.
6	Jabar L	2012	There is an inadequate role of health care practitioners in screening and obtaining enough knowledge and understanding about HNC. Continuing education courses about HNC are needed.
7	Al-Hadyan KS	2012	The genetic biomarkers, p21 C31A, Ku80 A2790G, and MDM2 T309G SNPs could be used to screen high risk patients for HNC.
8	Saudi Cancer Registry Report	2011	HNC represents only 0.8% of all newly diagnosed cases.
9	KFSH&RC	2011	Oral cancer accounts for 4.2% of all reported cancer types.
10	Halboub ES et al.	2011	The relative frequencies of oral and pharyngeal cancers in Yemeni patients, living in Saudi Arabia, are quite high. The tongue is the most affected site (42%).
11	Jabar L	2011	About 50% of health practitioners had low level of knowledge and training about HNC.
12	Al-Herabi AZ.	2009	All oncological services of head and neck cancer patients should be provided in one oncology center to achieve standard patient care, adequate follow up, and surveillance.
13	Brown A et al.	2006	Overall the burden and risk of oral cancer in Saudi Arabia is not large. However, cancer of the oral cavity is a significant public health problem for the residents of Jizan and the women of Najran. Saudi females in both these regions have a higher burden of oral cancer.
14	Andejani AA et al.	2004	There is a sharp increase in the incidence of nasopharyngeal cancer in young people in both males & females in Saudi Arabia. This may suggest a possible underlying genetic factor in Saudis.
15	Al-Balawi et al.	2002	An association between tobacco chewing and oral cancer was documented. Patients that had a history of shamma usage did not show deep invasion even in large tumors, and demonstrated better prognosis after treatment.
16	Allaerd et al.	1999	About 35.4% of all referred oral cancer cases to KFSH&RC (in period from 1976 to 1995) were referred from one province -Jizan. An association was found between shamma and oral cancer.
17	Tandon et al.	1995	Some malignancies are more common in Gizan Province compared to elsewhere in Saudi Arabia. Oral cancer was the most common cancer in females, whereas liver cancer was the most common in males.
18	Al-Ghamdi et al.	1994	Oral and pharyngeal cancers were the second most common skin cancer among males and the third in females. Study conducted in the southwest region of Saudi Arabia (Asir Region).
19	Al-Idrissi	1990	Nasopharyngeal carcinoma was the most common site (43.1%) for HNC is the studied samples. 41.5% of patients were smokers and 26.2% used chewable tobacco.
20	Hannan AM et al.	1986	Analysis of shamma using high-performance liquid chromatography (HPLC), revealed three major extracts, of which two were found to be mutagenic.
21	Ibrahem Em et al.	1986	Study conducted in the southern region of Saudi Arabia. 81% used shamma, whereas 42% were alqat users. The majority (59%) had oral cancer, while the rest had pharyngeal and laryngeal cancer.

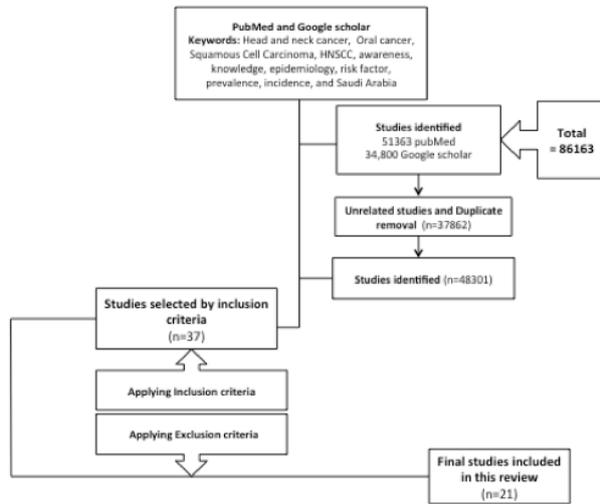


Figure 1. Flow Chart of the Search Strategy Used in this Systematic Review

their association with HNC.

A summary of the systematic review search strategy is given in Figure 1.

Results

Our search revealed twenty-one studies that fulfilled our inclusion and exclusion criteria and which were conducted in Saudi Arabia. These studies investigated different aspects of HNC in Saudi Arabia, including: prevalence, risk factors, biomarkers, and assessed knowledge and awareness of both the public and medical practitioners in regards to HNC. A summary of all included studies is presented in Table 1.

Discussion

Head and neck cancer is a public health problem in both developing and developed countries (Ferlay et al., 2010). Despite that, HNC represents only about 3% of all malignant tumors in the United States (American Cancer Society, 2015) and Europe (Ferlay et al., 2010), but in many other parts of the world such as India and Southeast Asia, they are more prevalent, and are in the top ten most common malignancies (Reichart and Way, 2006; Jemal et al., 2011; Krishna et al., 2013). HNC ranks as the sixth most common malignancy in Asia (Krishna Rao et al., 2013). Thus, high incidence rates are reported from developing nations situated in the south-central and south-east regions of Asia (Krishna et al., 2013), which clearly shows the importance of geographic factors in the incidence of HNC. In Saudi Arabia, Brown et al. in 2006 published a study using the National Cancer Registry of Saudi Arabia. Their study included cases of oral cancer that were reported between 1996 and 1998. Oral cancer ranked as the 15th most common cancer in males and the 11th most common cancer in females, with a male/female ratio of 1:1 and a median age at diagnosis of 62 years (Brown et al., 2006). Interestingly, very wide regional disparities in the incidence of oral cancer was found, with about a 30-fold difference in age-standardized rate (ASR)

between the highest and lowest rates among the regions of Saudi Arabia (Brown et al., 2006). The highest incidence of oral cancer was reported from Jazan (Gizan) province. Here, oral cancer ranked the second most common cancer in males and the most common in females. Jazan had the highest ASR (6.2/100,000 for males and 9.82/100,000 for females) among Saudi Arabia's regions (Brown et al., 2006). Moreover, the highest ASR (4.48/100,000) was found in females in the neighboring Najran province. Both regions are located in the south and are considered developing areas in Saudi Arabia. The fact that oral cancer was on top of the list in the southern regions of Saudi Arabia, has not changed for decades. Allard et al. (1999) also reported that 35.4% of the referred oral cancer cases in their study were from the province of Jazan. In addition, Tandon et al. in 1995 reported that oral cancer was the most common cancer found in females, whereas liver cancer was the most common type in males (Tandon et al., 1995). This implicates that oral cancer is a significant public health problem in south of Saudi Arabia and specifically, for the residents of Jazan and Najran.

In the last published cancer report from the Saudi Health Council, Saudi Cancer Registry in 2011, the total reported number of cancer incidence cases was 14,776 (Saudi Cancer Registry, 2011). Interestingly, the overall number of cancer cases was greater in females than in males. Thus, cancer affected 6,459 (46.1%) males and 7,552 (53.9%) females with a male to female ratio of 86:100. This is in contrast to the recently published American Cancer Society 2015 report, where the incidence in cancer was greater in males compared to females (American Cancer Society, 2015). In regards to oral cancer, the 2011 report, surprisingly, documented that only 0.8% of all cancer cases were oral cancer (Saudi Cancer Registry, 2011). This percentage is much lower than other reports around the region such as those from India and Pakistan where the incidence ranges between 8-10% (Sunny et al., 2004; Bhurgri, 2005). Thus, in Karachi/Pakistan, oral cancer rates the second among all reported cancer types in both males and females (Franceschi et al., 2000; Bhurgri, 2005). This may be due to the presence of different risk factors and lifestyles. In addition, the 0.8% reported by the 2011 Saudi cancer registry, seems to be significantly underestimating the actual numbers of HNC in Saudi Arabia and does not match the fact that HNC is on the top of the list of malignancies in southern region of Saudi Arabia.

Tobacco smoking and chewing, and alcohol consumption are the main risk factors for HNC and these have been estimated to account for the vast majority of the disease burden worldwide (Blot et al., 1988; Blot et al., 1996). Tobacco use of all kinds seems to be common and widespread in Asian countries. Thus, counts as a major risk factor among HNC patients, including Saudi Arabia (Al-Idrissi, 1990; Al-Balawi and Nwoku, 2002; Balaram et al., 2002; Madani et al., 2010; Quadri et al., 2015). Rates of smoking are high within the Middle East, although alcohol consumption is a restricted factor due to religion and cultural reasons (Mackay, 2002; El Awa, 2008). This is especially true for Saudi Arabia, where smoking rates are increasing for both cigarettes and Shisha

use (Abdel Rahim et al., 2014; Moradi-Lakeh et al., 2015). Nevertheless, there were few studies that investigated the etiological factors of HNC in both the Middle East and Saudi Arabia. In addition, it seems that there are special types of smokeless tobacco that are specifically used in Saudi Arabia and neighboring countries, and these are considered to be a major risk factor for HNC. Sawair et al. investigated the association of khat (algalat) chewing and tobacco consumption with the occurrence of oral cancer in Sana'a, Yemen (Sawair et al., 2007). They found that squamous cell carcinoma (SCC) was the most frequent oral cancer (84%) and that higher relative frequency of oral SCC likely to be related to the habits of chewing tobacco and khat (Sawair et al., 2007). Khat (algalat) and shamma are smokeless kinds of tobacco that are rarely used in other countries around the world but are commonly used in Yemen and the southern region of Saudi Arabia. In agreement with the Sawair et al. study, others also found that algalat and shamma are both frequently used among oral cancer patients in the southern region of Saudi Arabia (Ibrahim et al., 1986; Allard et al., 1999; Quadri et al., 2015). Unfortunately, Khat was found to be among the most commonly used types of tobacco use among undergraduate students of the Jazan region (Mahfouz et al., 2014). The Khat chewing habit was also found to be associated with lower socioeconomic status and low health perception compared to non-users (Sheikh et al., 2014). Additionally, shamma was found to increase the incidence of oral cancer 29-fold followed by cigarette use as risk factors (Quadri et al., 2015). Shamma, with its high association as a risk factor with HNC, seems to be used in a greater percentage than is reported, especially in the southern regions of Saudi Arabia, such as Jazan (Alsanosy, 2014; Quadri et al., 2015).

One other emerging risk factor for HNC is Human papilloma virus (HPV). Evidence supports the view that HPV is a major reason for the increased incidence of a subset of head and neck squamous cell carcinoma in several geographic areas around the world (Boscolo-Rizzo Pet et al., 2013; Gillison et al., 2015). HPV can cause cancers at the pharynxes, base of the tongue, and tonsils, in an area known as the "oropharynx". Kreimer et al. found that HPV is prevalent in 35.6% of oropharyngeal, 23.5% in oral and 24% in laryngeal cancers, respectively (Kreimer et al., 2005). HPV-16 was the most common subtype found in all HPV-positive cancers (Kreimer et al., 2005). In Saudi Arabia, religion and cultural boundaries may hinder the investigation of the real impact of HPV infection as a risk factor in cancer in general, and HNC in particular. To our knowledge, there is no published data about the real prevalence of HPV in HNC cases in Saudi Arabia. From the few reported studies, there is an estimated association between HPV and cervical cancer that can reach up to 95%, and speculation of an association of ~ 30% with HNC (Alsbeih, 2014). Nevertheless, these studies are still not decisive, and their results are only based on few numbers of examined samples.

In a sample of 124 adult patients interviewed in a major tertiary hospital in Saudi Arabia, the most common cancer was breast cancer (27.4%) and HNC was (15.3%) (Al-Zahrani et al., 2014). The majority (85.5%) reported pain

with a median intensity score of 5 (Al-Zahrani et al., 2014). This study demonstrates that pain seems to be a major characteristic of HNC patients in Saudi Arabia, keeping in mind that 82.3% of these patients had metastases. In a study conducted at Riyadh, Saudi Arabia, it was reported that a majority (58%) of HNC patients were tobacco users. In addition, shamma users seem to have a better prognosis but more resistance to radiotherapy than those of non-shamma users (Al-Balawi and Nwoku, 2002). One of the first papers that investigated the prevalence of HNC in Saudi, Asir region, reported that oral cancer and pharyngeal cancers were the second most common cancers after skin cancer in males, however, it was the third most common in females after thyroid and skin cancers (Al-Ghamdi et al., 1994). Furthermore, at the King Faisal Specialist Hospital & Research Center Tumor Registry in Riyadh (KFSH&RC), oral cancer accounts for 4.2% of all cancer types (total reported cases = 2,292). In their data, oral cancer ranked the 12th most common cancer among males and 6th among females (Tumor Registry Annual Report, 2011). This data is in contrast to the results from the Saudi Health Council, Cancer incident report of Saudi Arabia 2011, where oral cancer was not in the list of top common cancers in Saudi Arabia (total reported cases=14,776) (Saudi Cancer Registry, 2011). It is worth saying that KFSH&RC is one of the main participating registry offices, and has a well organized system to report their cases. This clearly shows the gap in our statistical data in Saudi Arabia. Thus, the incidence percentage varies depending on the region and reporting centers. The Saudi Health Council must implement easy but well-developed guidelines and emphasize the importance of all sectors to accurately document and regularly report electronically all cases to them, as these numbers and incidences are underestimated and masks the reality of head and neck cancer as a common burden disease in our society. Revealing real numbers will help in educating our community about the threat of that disease and aid in increasing the knowledge and awareness for protecting against HNC. These steps will hopefully help in the early diagnosis of HNC and improving prognosis and treatment outcome.

The knowledge and awareness about HNC in both the general public and health care practitioners had been investigated in Saudi Arabia in several studies. All agreed that there is a lack of knowledge and that health care practitioners feel inadequately trained to screen and diagnose HNC (Jaber et al., 2011; Jaber et al., 2012; Kujan et al., 2013; Kujan et al., 2014; Al-Maweri et al., 2015). We recently investigated the knowledge and screening status in one of the Saudi Cancer well-developed cities in Saudi Arabia, Jeddah (Alhazzazi, 2016). Unfortunately, 68% had no knowledge about the key information in regards to HNC. Eighty-two percent had never been screened for HNC. Interestingly, social media was the major source of HNC information for the examined sample (39%) (Alhazzazi, 2016). This implicates the need to utilize social media as an important tool to improve the knowledge and awareness toward HNC in our community. In addition, the development and support of intervention educational programs have been proven to increase the

knowledge against HNC in Saudi Arabia (Quadri MF, 2014).

Biomarkers seem to be one of the important factors that can help in screening and early diagnosis of HNC. Al-Hadyan et al. found that the single-nucleotide polymorphisms (SNPs) p21 C31A, Ku80 A2790G, and MDM2 T309G could be employed as useful genetic biomarkers to screen HNC patients in Saudi Arabia (Al-Hadyan et al., 2012). In addition, characterization of bacteria species using next-generation sequencing (NGS) seems to be a novel method for detecting special bacterial species that could be associated with HNC. In a pilot study, Proteobacteria were the most commonly detected species in oral squamous cell carcinoma (OSCC) samples from a Yemeni population (Al-Hebshi et al., 2015). It will be interesting to investigate this observation using samples from the Saudi population to see if there is a trend of similarities. Our group also identified sirtuins-3 (SIRT3), NAD-dependent deacetylases, as a biomarker that is overexpressed in more than 50% of OSCC samples from the US population. This overexpression seems to play a role in OSCC aggressiveness and resistance to radio- and chemotherapy treatments (Alhazzazi et al., 2011; Kamarajan et al., 2012). Similarly, we recently examined the expression of SIRT3 in HNC samples from the Saudi population. Our results also demonstrated that SIRT3 is overexpressed in HNC samples from the Saudi population compared to normal tissues (Alhazzazi et al., 2016). Early diagnosis of HNC is still the key for prognosis and survival. Studies in Saudi Arabia reported a survival rate of about 60% for diagnosis in the early stages of HNC, whereas a lower than 30% survival rate was reported for stage IV oral cancer (Al-Rajhi et al., 2002a; Al-Rajhi et al., 2002b). Oral cancer located at the alveolus had a better outcome than in other parts of the oral cavity such as the tongue and floor of the mouth (Al-Rajhi et al., 2002a). In addition, elective neck dissection seems to be advantageous and is associated with a better 5-year survival rate, especially when the tumor thickness is greater than 10 mm (Al-Rajhi et al., 2002b). More research is needed to come up with a protocol for a personalized HNC treatment options, depending on well-defined and studied parameters.

In conclusions, This review uncovered a big gap in our epidemiological data in cancer information in general, and head and neck cancer in particular. In addition, a lack of knowledge and awareness of both the public and health care practitioners will hinder the early diagnosis of that disease and negatively impact the prognosis and treatment outcome. Nonetheless, HNC is a major public health problem in Saudi Arabia. There are some common risk factors like cigarette smoking, Shisha, smokeless tobacco, betel nuts and Khat, among the provinces of Saudi Arabia. In addition, because of religion and cultural tradition, some of the major well-known risk factors are still unrevealed in Saudi Arabia. Smokeless tobacco, along with smoking and Shisha use, are the main reasons for the raised incidence rates of HNC in Saudi Arabia. There is a need for further studies to determine other causes and risk factors of local characteristics of the disease in our country to determine the importance of changing trends at different levels.

Further clinical and epidemiological research is needed to determine successful strategies for increasing awareness, screening, early detection, diagnosis and management of HNC in Saudi Arabia with its unique cultural, racial and ethnic makeup as compared to the Western countries. The Ministry of health in Saudi Arabia, should develop a more systematic way of operation and adapt policies to gather cancer information in general, and head and neck cancer in particular, from all governmental and private sectors from all over the kingdom. In addition, reports should be published every two years to enable us to track trends and secure data in regular bases. This should happen soon, to improve our health care system, and hopefully decrease the prevalence of HNC in Saudi Arabia, thus, improving the survival rate and treatment outcome in our country.

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