J Oncol Sci 5 (2019) 23–30

Contents lists available at ScienceDirect

J Oncol Sci

journal homepage: www.journalofoncology.org

Review

Nasopharyngeal cancer in Saudi Arabia: Epidemiology and possible risk factors

Abdullah Dakheel Alotaibi [a], Hussain Gadelkarim Ahmed [a, *], Abdelbaset Mohamed Elasbali [b]

[a] College of Medicine, University of Hail, Saudi Arabia
[b] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Qurayyat, Saudi Arabia

ARTICLE INFO

Article history:
Received 16 May 2018
Received in revised form
19 January 2019
Accepted 25 January 2019
Available online 2 February 2019

Keywords:
Nasopharyngeal carcinoma
Saudi Arabia
Epidemiology
Risk factors

ABSTRACT

Although, Nasopharyngeal Carcinoma (NPC) is uncommon in Arab countries, but its incidence is raising due to increased exposure to diverse risk factors. Many of the NPC-related risk factors are becoming more and more apparent in Saudi Arabia. Risk factors such as, higher antibody titers against the EBV, intake of preserved foods, tobacco smoking with alcohol consumption, family history of NPC, certain human leukocyte antigen class I genotypes, history of chronic respiratory tract conditions, exposure to different inhalants, herbal medicines, and occupational exposures are frequently encountered in Saudi population. In spite of the importance of this subject in Saudi Arabia, there is still a paucity of literature on the features and outcome of NPC in the Middle East and most Arab countries. Therefore, the objective of this review was to provide an overview of NPC and recent advances in the multidimensional understanding of this disease focusing in the available literature in epidemiology and risk factors with especial emphasis in Saudi Arabia. The previous literature was retrieved through electronic search in Medline, PubMed, Cochrane, ScienceDirect, and other electronic data base, as shown in the citation.

1. Introduction

Nasopharyngeal cancer (NPC) is one of the most frequent head and neck cancers with elevated prevalence rates in Asia.[1–3] Several epidemiological studies suggest that, though the incidence rates of NPC are gradually declining, death from NPC has decreased substantially. This decreasing might be due to a combination of life style amendment, population screening and developments in the treatment.[4]

The etiology of NPC is exceptional and multifarious, which is not entirely understood. NPC is considered as a rare cancer in several populations worldwide, though it is relatively increased in some populations including Southeast Asia, the Middle East, and North Africa and with the peak in Southern China. This characteristic racial/ethnic and global geographical dissemination of NPC proposes that both genetic and environmental factors play a major role in its etiology.[5] Regardless of incidence and geographical distribution, the development of NPC has been linked to interaction of multiple environmental and genetic factors comprising: Epstein Barr Virus (EBV),[6,7] chromosomal disorders, aberrant promoter hyper methylation and other genetic related factors.[8]

NPC has a high survival rate if diagnosed at stages I or II (approximately 95%), hence it has poor survival rates if diagnosed at stages III or IV (just above 50%).[9]

Because of a greater cure frequency for early-stage NPC, the perception of screening for the disease has an instinctive application. Further improvement of treatment is essential but insufficient to improve the survival of patients with NPC.[10] The development of reliable, non-invasive, and cost-effective early-detection approaches for NPC is a great urgency. Application of tumor markers thus delivers an applicable method to attain early detection of NPC. The prompt achievement of completely sequenced cancer genomes will be one influential mean to detect biomarker candidates for early detection, subtyping, and cancer screening.[11]

In spite of the importance of this subject in Saudi Arabia, there still a paucity of literature on the features and outcome of NPC in the Middle East and most Arab countries. The available studies from Saudi Arabia in this context have focused in narrow areas.[12–18] Consequently, the focus of this review was to make available an overview of NPC in Saudi Arabia, mainly the recent insights regarding epidemiology and risk factors.

* Corresponding author. College of Medicine 2440, University of Hail, Saudi Arabia.
E-mail address: hussaingad5@gmail.com (H.G. Ahmed).
Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2019.01.002

1.1. Histopathologic patterns

NPC represent a discrete form of head and neck cancers, which varies from the other cancers of the by means of cause, epidemiology, pathology, clinical feature and response to treatment.[19] NPC is histologically categorized in to three distinct groups: TypeI (Keratinizing Squamous Cell Carcinoma (KSCC)), type II (Non-Keratinizing Carcinoma (NKC)), and type III (Undifferentiated Carcinoma (UDC)). Later on World Health Organization (WHO) classified NPC into two categories: squamous cell carcinoma (KSCC, type I of the previous classification), and NKC (types II and III of the previous classification joined into a single type). NKC was extra subdivided into differentiated and undifferentiated carcinomas.[20] This classification is more valid for epidemiological research and has also been revealed to have a prognostic implication. UDC have a greater local tumor control rate with treatment and increased incidence of distant metastasis than do differentiated carcinomas.[21,22]

Irrespective of race and geographical distribution, the most common type of NPCs rises from the epithelial cells lining the nasopharynx, which constitute 75%–95% of all diagnosed cases. Non-keratinizing type (WHO III) is the most common type in Saudi Arabia, mostly among the younger age population, imitating China and South Korea in the histopathologic form and distribution.[23]

1.2. Incidence of NPC

NPC is a rare cancer with an infrequent diverged geographic distribution worldwide.[24] According to WHO, NPC mortality trends from 1970 to 2014 showed substantial. difference in numerous countries around the world. In 2012, the highest age standardized (world standard) rates were in Hong Kong (0.451/10.000 men and 0.115/10.000 women), followed by nominated Eastern European countries (EU). The lowest rates were in Northern Europe and Latin America. EU rates were 0.027/10,000 men and 0.009/10,000 women, US rates were 0.020/10,000 men and 0.008/10,000 women and Japanese rates were 0.016/10,000 men and 0.004/10,000 women.[25]

Some southeastern Asia and north America countries have witnessed a substantial decline in NPC incidence in recent years with average annual percent deviations (AAPCs) of −0.9% to −5.4% in males and −1.1% to −4.1% in females. Drops in age-standardized mortality rates (ASMRs) are even more notable and widespread. Falling trends in NPC incidence maybe because of tobacco control, alterations in diets and economic growth. Drops in death rates are the consequences of advancements in diagnostic and radiotherapy techniques, as well as dropped incidence rates.[24]

According to the International Agency for Research on Cancer report in 2008, more than 80% of patients with NPC are in Asia, and only 5% of these cancers are reported in Europe. Specifically, 71% of new NPC cases are recorded in East and Southeast Asia, and 29% are diagnosed in South and Central Asia and North and East Africa.[26]

NPC represent 33% of head and neck cancers that diagnosed annually in Saudi Araba with an annual age-standardized incidence of 0.25 per 10,000 for males and 0.08 per 10.000 for females. Notably, HNCs represent 6% of all malignancies diagnosed annually in Saudi Arabia.[27,28] The overall incidence of NPC in all ages is 0.1–0.13 per 10,000. The Crude rate and Age-world standardized Incidence rate (ASR (W)) of NPC in Some Arab countries was described in Table 1, Fig. 1.[29]

The distribution of NPC in different regions of Saudi Arabia was previously described[30] The highest rate was from Riyadh (36%) followed Medina Almowarah (18%). Jeddah (15%), Dammam (12%), Gizan (8%), Tabuk (6%) and4% reported from non-Saudi patients, as shown in Fig. 2.

1.3. Mortality of NPC

In 2012, age-standardized rates (ASR) world for NPC mortality among males and females were 0.1 per 10,000 and 0.04 per10, 000, respectively. The areas with the highest mortality were Southeast Asia (0.38/10,000 for males and 0.14 per10, 000 for females), East Asia (0.15 per10, 000 and 0.06 per10, 000), East Africa (0.14 per10, 000 and 0.09 per10, 000), North Africa (0.14 per10, 000 and 0.06 per10, 000), and Micronesia (0.13 per10, 000 and 0.1 per10, 000). The countries with the highest mortality were Indonesia (0.5 per10, 000 and 0.16 per10, 000), Vietnam (0.48 per10, 000 and 0.2 per10, 000), Singapore (0.44 per10, 000 and 0.13 per10, 000), Malaysia (0.39 per10, 000 and 0.12 per10, 000), and Brunei (0.34 per10, 000 and 0.05/10,000).[31]

The annual mortality rate per 10,000 persons with NPC in Saudi Arabia has declined by 65.9% since 1990, an average of 2.9% a year. Mortality rate for NPC has transformed over time for men and women of specific age groups in Saudi Arabia. For men, the deathliness of NPC in Saudi Arabia heights at age 80+. It executes men at the lowest rate, at age 25–29. At 0.68 deaths per 10,000 men in 2013, the highest mortality rate for men was higher than that of women, which was 0.33 per 10,000 women. Women are executed at the highest rate from NPC in Saudi Arabia at age 80+. It was least lethal to women at age 25–29. The three most deadly cancers in Saudi Arabia during 2013 were liver cancer, “tracheal, bronchus and lung cancer”, and colon and rectum cancer respectively. Though this was the trend in Saudi Arabia inclusive, diverse demographic groups are affected differently and is likely much different between men and women at different ages in life. The crude rate and Age-world standardized Mortality Incidence rate (ASR (W)) per 100,000 of NPC in Some Arab countries, as indicated in Table 2, Fig. 3.[29,32]

1.4. Survival patterns of NPC

NPC has very good response to radiation and cure is promise, especially if early detected. Radiotherapy is the backbone treatment strategy for NPC. But about 70% of the patients with NPC present with stages III or IV are at risk to suffer from local or/and regional recurrence or distant metastases after radiotherapy.[33–35] However, the treatment of advanced NPC often require a combination of chemotherapy and radiation therapy. It was found that adjuvant chemotherapy together with conventional radiotherapy botched to improve NPC comprehensive survival.[36] The outcomes of these trials were confirmed by a number of subsequent studies.[37] Though the neoadjuvant chemotherapy has verified better loco-regional control and event-free survival, its benefit on general survival has not yet to be well-known.[38] This mean that, it lacks potential indications to confirm overall survival advantages from chemotherapy,[39] even though randomized trials of simultaneous chemo-radiation therapy for advanced NPC have showed a progression-free survival.[40–42]

The intensity modulated radiotherapy (IMRT) has been demonstrated often to produce greater dose distributions in terms of improved tumor exposure and lower doses to normal tissues for a variety of cancers originating in the NPC region.[43] However, many factors are associated with the NPC prognosis, including age, gender, anemia, TNM stage, histopathology, radiation dose, radiation field, and combined manner of chemotherapy.[44–46]

1.5. Risk factors of NPC

NPC has a unique and complicated etiology that is incompletely stated. Although NPC is rare in most populations, it is a leading form of cancer in a few well-defined populations. The wide

Table 1
Crude rate and Age-world standardized Incidence rate (ASR (W)) per 100,000 of NPC of NPC in Some Arab countries.

Country	Both sex (all ages)		Males (All ages)		Females (all ages)	
	Crude rate	ASR (W)	Crude rate	ASR (W)	Crude rate	ASR (W)
Yemen	0.8	1.5	0.9	1.8	0.8	1.1
Saudi Arabia	1.0	1.3	1.3	1.7	0.6	0.9
Jordan	0.8	1.1	1.0	1.3	0.6	0.8
Syrian	0.7	0.8	0.8	1.1	0.5	0.6
Emirates	0.4	0.8	0.5	0.9	0.4	0.4
Iraq	0.4	0.7	0.5	0.9	0.3	0.5
Qatar	0.5	0.7	0.6	0.8	0.2	0.3
Lebanon	0.7	0.7	1.1	1.1	0.4	0.3
Kuwait	0.4	0.5	0.4	0.4	0	0
Palestine	0.3	0.5	0.5	0.8	0.2	0.2
Oman	0.3	0.4	0.4	0.5	0.2	0.2
Bahrain	0.3	0.2	0.4	0.2	0.2	0.2

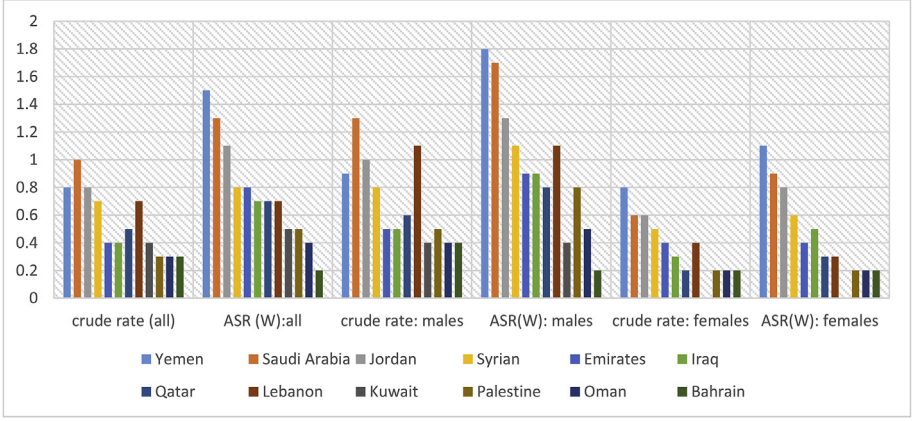

Fig. 1. Crude rate and Age-world standardized Incidence rate (ASR (W)) per 100,000 of NPC of NPC in Some Arab countries.

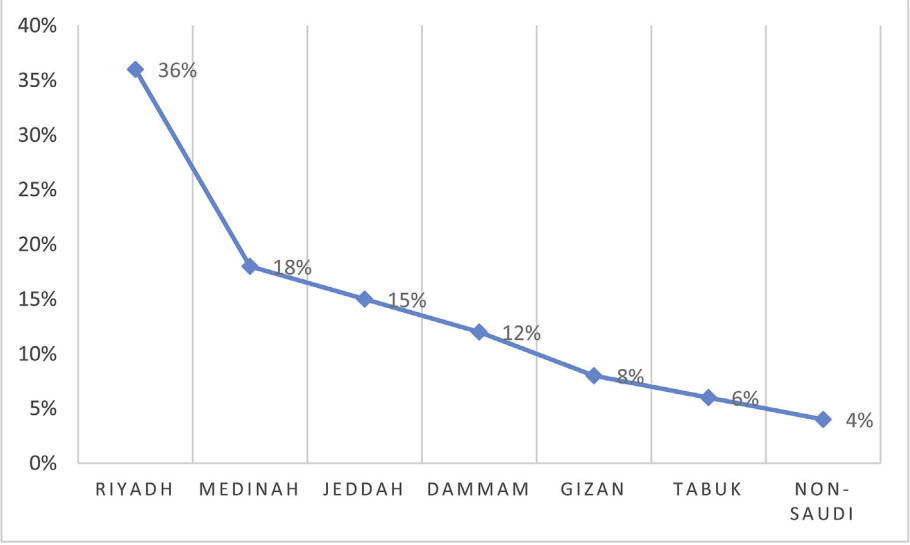

Fig. 2. Proportions of NPC in different geographical Regions in Saudi Arabia.

geographical and racial distribution of NPC indicates the multiplicity variability of risk factors. Well-known risk factors for NPC include higher antibody titers against the EBV, intake of salt-preserved fish, a family history of NPC, and certain human leukocyte antigen class I genotypes. Intake of other preserved foods, tobacco smoking, and a history of chronic respiratory tract conditions may be linked to raised NPC risk, while intake of fresh fruits and vegetables and other human leukocyte antigen genotypes may be linked to reduced risk. Indication for a contributory role of different inhalants, herbal medicines, and occupational exposures is varying. Other than dietary modification, no real preventive measures for NPC exist. Assumed the unsettled gaps in

Table 2
Crude rate and Age-world standardized Mortality Incidence rate (ASR (W)) per 100,000 of NPC in Some Arab countries.

Country	Both sex (all ages)		Males (All ages)		Females (all ages)	
	Crude rate	ASR (W)	Crude rate	ASR (W)	Crude rate	ASR (W)
Yemen	0.6	1.2	0.7	1.5	0.5	0.9
Saudi Arabia	0.5	0.7	0.6	0.9	0.3	0.5
Jordan	0.3	0.6	0.4	0.7	0.3	0.5
Syrian	0.4	0.5	0.4	0.7	0.3	0.4
Emirates	0.2	0.4	0.2	0.4	0.1	0.2
Iraq	0.2	0.5	0.3	0.6	0.2	0.3
Qatar	0.2	0.4	0.3	0.6	0.0	0.0
Lebanon	0.3	0.3	0.6	0.5	0.1	0.1
Kuwait	0.1	0.1	0.1	0.1	0.0	0.0
Palestine	0.2	0.3	0.3	0.5	0.1	0.1
Oman	0.1	0.2	0.2	0.3	0.1	0.1
Bahrain	0.1	0.1	0.1	0.1	0.0	0.0

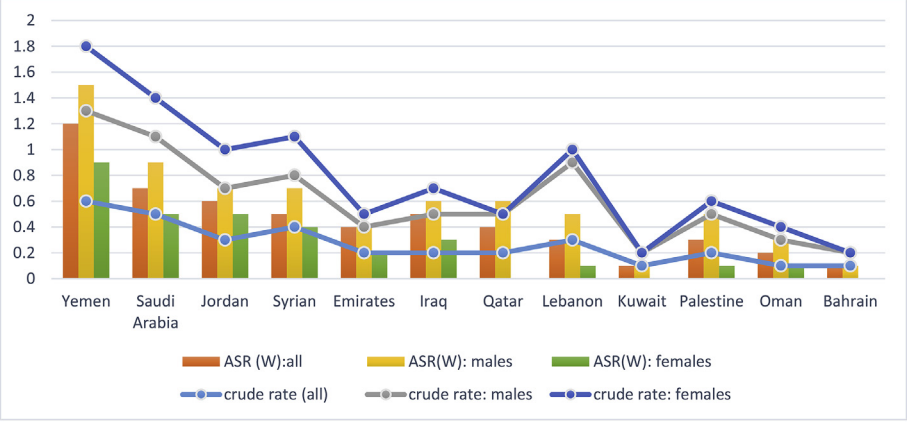

Fig. 3. Crude rate and Age-world standardized Mortality Incidence rate (ASR (W)) per 100,000 of NPC in Some Arab countries.

understanding of NPC, there is a strong need for large-scale, population-based molecular epidemiologic studies to clarify in what way environmental, viral, and genetic factors interact in both the progress and the prevention of NPC.[47]

1.6. Epstein-barr virus

NPC is well recognized as EBV-associated malignancy, yet, EBV infection is very common in general population. These lead to a hypothesis that there might be an NPC specific EBV subtype contributing to the increased incidence of NPC in the endemic areas. Several studies have been done to ascertain the NPC-associated EBV subtype.[48,49] One study detected a polymorphism at EBV encoded gene, *RPMS1* (locus 155,391 G > A), to be significantly related to NPC in southern and northern Chinese (OR = 5.27, 95% CI = 4.31–6.44, P < 0.001); furthermore, the rates of the EBV variant are significantly associated with the global incidence rates; moreover, the variant is possibly related to NPC but not other EBV-associated condition.[50] These bring powerful proof of the presence of NPC-specific EBV subtype. What is more, the threshold model indicated that the EBV polymorphism (155391G > A) can explained 5.5% of the variance, two times more than that by the genetic loci as stated before. These propose that the involvement of EBV to NPC prevalence or proneness should be given more attentions.

During the search for data regarding the relationship between EBV and NPC in Saudi Arabia, only two studies were found. Tumor biopsies obtained from 25 Saudi patients with NPC were examined for the presence of EBV. About 92% of the tumor specimens were found to carry EBV DNA.[51] The incidence of Hodgkin's lymphoma (EBV related cancer) is markedly higher in Saudi Arabia than in the USA, and accounts for 10.5% of all neoplasias in children aged 15 years or older in Saudi Arabia. In a study investigated the role of EBV for the high frequency of Hodgkin's lymphoma (HL) in Saudi Arabia, about 169 cases of HLs from Saudi Arabia and 30 HLs from Europe were analysed for EBV infection by in situ hybridization with fluorescence in-conjugated EBV on tissue microarray sections. All Saudi Arabian and European HLs were analysed in one experiment under identical conditions. Unexpectedly, the data show only minor, insignificant differences in EBV infection rates between Saudi Arabian (42 out of 147 informative cases 28.6%) and European HL (nine out of 30 informative cases; 30%; P = 0.8752).[52]

1.7. Genetic susceptibility

Linage analysis and association study are two main approaches to recognize genes leading to NPC risk. Four linkage investigations have been reported, where susceptibility loci containing 6p21[53], 4p15.1–q12,[54] 3p21.31–21.2,[55] and 5p13[56] have been involved in NPC families of Chinese origins.

Genome-wide association study or GWAS is a hypothesis-free approach, applying association tests at genome-wide level.[57] For NPC, four GWASs have been done in Chinese populations in Malaysia, Taiwan, and southern China,[58–61] which detected susceptibility loci of *ITGA9* at chromosome 3p22.2, *HLA-A* and *GABBR1* at 6p22.1, *HLA-B/C*, and *MICA* at 6p21.33, *HLA-DQ/DR* at 6p21.32, *MECOM* at 3q26.2, *CDKN2A/2B* at 9q21.3, and *TNFRSF19* at 13q12.12, in that order. In depth information has been summarized in this source.[62]

Since NPC has been associated with EBV, association of immune-associated genes particularly *HLA* and NPC have been extensively investigated. The relationship of *HLA* loci with NPC risk is the most reliable outcome on the full. This comprises the first linkage study including 30 sib ships of NPC families from southern China, Singapore and Malaysia, which discovered a recessive susceptibility gene deliberating an augmented risk of 20.9 (95% CI = 5.1 to infinite) for NPC.[53]

TERT/CLPTM1L has been reported as susceptibility locus for several cancers.[63,64] Differences at the locus have been linked to NPC risk, comprising rs401681 in Hong Kong Chinese (OR = 0.77; $P = 1 \times 10^{-4}$) with candidate gene approach.[65]

Several association studies have been continuously done between candidate genes and NPC risk, such as those associated with DNA damage repair and oxidative stress pathways. Alleles in nitric oxide synthase (*NOS*; *NOS3*−786C, *NOS3*+894T, and *NOS2*−277G) and glutathione-S transferases (*GSTs*; *GSTT1* del/del genotype) were dominant in Tunisians NPC patients.[66] However, the association of *GSTT1* gene and NPC risk was not significant in a large-scale meta-analysis included 1295 cases and 1967 controls.[67]

A common characteristic of NPC incidence is the male dominance, other than geographic and ethnic proneness. In most populations, the incidence rate is 2- to 3-fold greater in males than females.[68,69] The sexual dissimilarity may be somewhat attributed to the imbalanced exposures of environmental risk factors between males and females, like smoking, diet habit, and so on. At genetic feature, the involvement of X-chromosome disparities in NPC progress has been hypothesized.[70,71]

1.8. Tobacco smoking and alcohol consumption

Tobacco smoking accounts for 5% of cancer cases globally.[72] Over the years, many studies have tried to institute an association between tobacco smoking and an increased risk of NPC, but their outcomes have been inconsistent. The findings revealed that ever smokers had a 60% more risk of developing NPC than never smokers (95% confidence interval: 1.38, 1.87); this was a vigorous dose-dependent association. More significantly, robust links were detected in low-risk populations and among persons with the largest histological type of differentiated NPC than in high-risk populations and persons with an undifferentiated type; the odds ratios were 1.76 and 2.20, respectively, versus 1.29 and 1.27. In this wide-ranging meta-analysis, well-known statistical confirmation was delivered about the role of tobacco smoking in the etiology of NPC.[73] Although alcohol drinking was not, per se, considerably associated with NPC risk, the combination of tobacco smoking and alcohol consumption accounted for 57% of differentiated NPCs, while it accounted for only 14% of undifferentiated carcinomas. It was found that, in western populations, NPC comprises two distinct things: the differentiated NPC, related to tobacco smoking like other cancers of head and neck, and the undifferentiated NPC, upon which tobacco smoking has diminutive or no impact.[74]

With undetermined burden of alcohol beverages use in Saudi Arabia due to social barriers, tobacco smoking is dramatically increasing in recent years. Many studies have reported that cigarette smoking is a major public health issue in Saudi Arabia in recent years, particularly among adolescents.[75]

1.9. Family history

A clear evidence was previously provided that the risk of NPC was associated with a first-degree family history of cancers, including NPC and cancers of the head and neck, lung and breast.[76] However, the association of family history and NPC survival has not been well confirm up to now.[77] The geographic and familial clustering of this specific malignancy proposes that a heritable factor may play an imperative role in its etiology. It also proposed that the clinical characteristics of NPC may vary between the familial and sporadic types. Former studies on familial clustering of NPC mostly focus on variances in epidemiological and overall clinical characteristics between the familial and sporadic types.,[78,79] and petite is known about the clinical features of familial NPC. It was proposed that both family history of NPC and anti-EBV sero-positivity are significant factors of subsequent NPC risk and that the influence of family history on NPC risk cannot be completely clarified by mediation via EBV serologic reactions.[80] There is a lack of literature regarding the relationship between NPC and family history of NPC reported from Saudi Arabia.

1.10. Salt-preserved fish and preserved foods

It was reported that the Chinese people, who intake Chinese-style salted fish in their daily diet, had twice the incidence of NPC compared with the other Chinese who intake lower amount of salted fish.[81] Many studies reported that consumption of Chinese salted fish was associated with higher risk for NPC. There was a dose-dependent association between frequency and duration of intake and NPC risk. The relationship was stronger for consumption of salted fish during childhood up to 10 years of age compared with consumption at older ages.[82] The non-viral exposure most dependably and powerfully connected with risk of NPC is intake of salt-preserved fish, a traditional staple food in numerous NPC-endemic areas. In studies of Chinese populations, the relative risk of NPC associated with weekly intake, compared with no or occasional intake, usually fluctuated from 1.4 to 3.2, whereas that for daily intake extended from 1.8 to 7.5.[83,84] The risk of NPC is also raised in overtone with other preserved food substances, comprising meats, eggs, fruits, and vegetables, in southern Chinese, Southeast Asians, North Africans/Middle Easterners, and Arctic natives.[85,86] Salt-preserved foods are a dietary staple in all NPC-endemic populations,[87,88]; hence, this dietary form may describe portion of the international distribution of NPC incidence. Although there is a wide spectrum of preserved foods usage in Saudi Arabia, but studies in this regard.

1.11. History of chronic respiratory tract conditions

Head and neck tumors develop on mucosa of the aero-digestive tract and are the tumors that happen: oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands, thyroid, parathyroid, bone, soft tissue, neural structures -vascular and skin that part of the human body.[89,90] Head and neck cancers are fatal tumors that has been verified since the origin of the human race and continues to be a challenge for patients, especially for ENT specialists and oncologists, with major health difficulties that undertake this complaint.[89] It was suggested that benign inflammation and infection of the respiratory tract may render the nasopharyngeal mucosa more vulnerable to growth of NPC. Moreover, some bacteria can reduce nitrate to nitrite, which can then form carcinogenic *N*-nitroso composites.[91] Most studies investigating prior chronic ear, nose, throat, and lower respiratory tract disorders discovered that they almost doubled up the risk of NPC.[92,93] These results propose that benign inflammation and infection of the respiratory tract may render the nasopharyngeal mucosa more likely to progress NPC.[94] In Saudi Arabia, outbreaks of infectious diseases that spread through respiratory route, such as influenza, are highly frequent among Hajj (an annual Islamic pilgrimage to Mecca) worshipers in Mecca City in KSA.[95]

1.12. Fresh fruits and vegetables

In contrast to preserved foods, regular intake of fresh fruits and/or vegetables, mainly during childhood, has been connected with a lower risk of NPC.[96,97] Some studies reported reverse relations with consumption of particular fruits or vegetables, containing carrots, Chinese flowering cabbage, green leafy vegetables, fresh soybean harvests; and citrus fruit, oranges, or tangerines or with dietary consumption of vitamin E or C, or serum levels of carotene, but there have been few in depth assessments of dietary relations with NPC risk. The obvious protecting influence of fruits and vegetables may be attributed to antioxidant properties, inhibition of nitrosamine development, and other anti-carcinogenic effects.[98]

1.13. Herbal medicines

In Asian populations, several case control studies reported a 2- to 4-fold excess risk of NPC in association with use of traditional herbal medicines,[99] although three studies in southern China found no link.[95] Any association with use of herbal drugs may be challenging to separate from other characteristics of a traditional lifestyle, such as diet. A part of Chinese herbal plants in NPC growth is, however, biologically possible because several such commonly used plants can induce viral lytic antigen expression by activating EBV *in vitro*.[100]

Herbal preparations are popular because most of peoples believe that they are natural and safe, more than others synthesized drugs. In Saudi Arabia, the traditional medicine is mainly built on herbal preparations and spiritual healing, both as a commodity and as homemade mixtures.[101]

1.14. Occupational exposures

Since precise occupational exposures have a tendency to be uncommon in the overall population, they are doubtfully to excuse for a considerable proportion of NPC, particularly in endemic areas. Occupational exposure to fumes, smokes, dusts, or chemicals overall was associated with a 2- to 6-fold higher risk of NPC in some but not all studies.[102] A few studies reported no association between solvents in general and risk of NPC,[103] and other studies detected no relations with any occupational exposures inspected.[104]

However, taken together, NPC is a multifarious cancer with multifactorial influences from genetic vulnerability, environmental exposures and EBV infection; though some advances have been addressed in recognizing genetic and viral factors to NPC risk, there is still a huge gap to entirely clarify the heritability or prevalence of NPC. Efforts are looked-for to bridge the gap, till when NPC risk prediction could be helpful for effective population screening of people with high NPC-risk. As moving onward, a genetic risk score model integrating the seven GWAS loci,[105] environmental risk factors (consumption of salted fish and preserved vegetables and cigarette smoking with alcohol consumption) and family history of NPC[106] and EBV infection[107–109] should be carefully considered in future scope for each population setting. Moreover, as around 20% of human cancers are associated with viruses. EBV contributes to gastric cancer, nasopharyngeal carcinoma, and certain lymphomas, but its role in other cancer types remains controversial.[110] Thus it is important to think about the co-effects of EBV with multifactorial outcomes when assorted with other potential conditions. Long non-coding RNAs (lncRNAs) have been wildly verified to modulate multiple tumorigeneses, especially NPC. It was indicated that LINC00319 was markedly increased in NPC tissues and cells. Silence of LINC00319 was able to suppress NPC cell growth *in vitro* while overexpression of LINC00319 inversed this process. These facts provide a novel insight for NPC tumorigenesis.[111]

2. Conclusions

The highest incidence rates of NPC in Arab countries were in Yemen followed by Saudi Arabia. It leftovers clear that, even with the new evidence on a wide range of risk factors for NPC, most important prevention for the majority of these tumors must be undertaken through control of tobacco smoking and alcoholic intake, reduction in Salted and preserved food intake, as well as reductions in carcinogen exposure in occupational settings.

Conflicts of interest

The author declare that they have no conflicts of interest for this work.

Acknowledgement

The author would like to cordially thank Prof. Hussain Gadelkarim Ahmed for his meticulous revision of the manuscript.

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