

Studies on Nasopharyngeal Carcinoma in the Sudan—I. Epidemiology and Aetiology*

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Abstract—Three hundred and seventy-four cases of nasopharyngeal carcinoma (NPC) recorded in the Sudan Cancer Registry (SCR) and 512 cases seen at the Radiation and Isotope Centre, Khartoum (RICK) were analysed. NPC formed 5.8% of all cancer cases in the SCR and 7.2% at the RICK; this is the highest frequency so far reported outside the Chinese. The male/female ratio was 3:1; NPC was the commonest tumour in males at the RICK (12.1%) and second commonest in the SCR (9.2%). It tended to occur in younger patients (youngest, 3 yr), with 14 and 12.1% of cases in children 14 yr or under in the SCR and RICK respectively; it is the commonest childhood malignancy in the Sudan. The ethnic and geographical distribution of the cases showed that racial susceptibility played a significant role in the aetiology of NPC in the Sudan whereas environmental factors could be excluded; however, Epstein-Barr virus might be an exciting factor.

INTRODUCTION

THE SUDAN, a vast country stretching from the Sahara Desert to the equatorial swamps and forests, and the home of divergent ethnic groups ranging from the Caucasoid Arabs to the Negroid Africans, offers a favourable setting for observations on the epidemiology and geographical pathology of cancer. This is particularly so with tumours such as nasopharyngeal carcinoma (NPC) in which ethnic and/or geographical factors have been aetiologically incriminated.

Although NPC in the Sudan is currently assuming great importance as an epidemiological, clinico-pathological and therapeutic problem, only two reports dealing with it have so far been published—Saad [1], reporting on 17 cases, and Milosev *et al.* [2], on 73 cases. Consequently, a detailed study of this cancer problem was deemed necessary. The present communication deals only with the epidemio-

logical and aetiological aspects of NPC in the Sudan; other facets of the condition will be dealt with separately.

Geography and ethnography (see Figs 1 and 2)

The Sudan, covering an area of one million square miles and inhabited by some 16 million people, is the largest country in Africa and has common borders with 8 countries (Egypt in the north; Libya, Chad and Central African Republic in the west; Kenya, Uganda and Zaire to the south; Ethiopia in the east). It is centrally traversed throughout its length by the River Nile and its tributaries. It lies wholly within the Tropics but can be conveniently divided into two fairly distinct regions—North and South.

Northern Sudan

This extends between latitude 12 and 22° north. It is largely desert or semi-desert, merging southwards into savannah, and is hot and dry for most of the year. Its 12 million inhabitants form a heterogeneous mixture of Arabs and Africans but constitute 3 main tribal groups:

(a) *Arab tribes.* These form the majority. A few are pure Arabs of Semitic stock but most have some admixture of African blood. They have an essentially Arab-Muslim culture. They are either town dwellers and cultivators along the Nile

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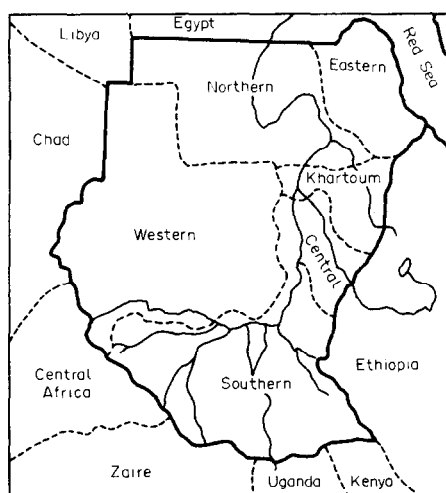


Fig. 1. Map of Sudan showing regional boundaries.

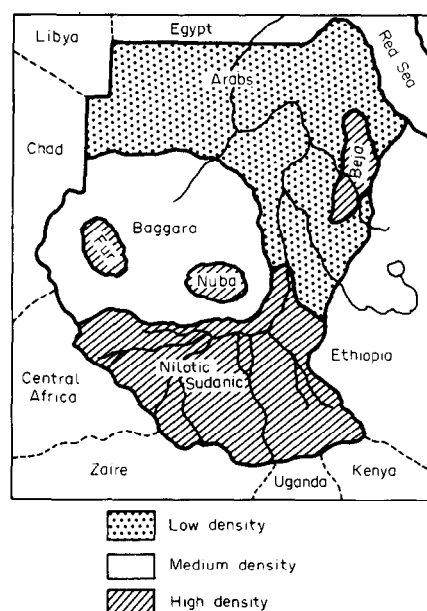


Fig. 2. Map of Sudan showing ethnic distribution of NPC.

Valley (Arab-Nile tribes) or nomadic camel and sheep breeders on the surrounding plains (Arab-nomadic tribes). Their standard of living and education is on the whole the highest in the country and they have greater access to the larger medical centres.

(b) *Baggara tribes*. These are Muslim tribes with an Arab background but with a more uniform admixture of African blood than those mentioned above. In many respects, including skin colour, they form an intermediate group between the Arabs and Africans. They are cattle breeders (the word Baggara is derived from Bagar, Arabic for cattle).

(c) *'Indigenous' African tribes*. These are isolated groups of tribes in the northern Sudan, surrounded by the Arabs and Baggara, many of whom still keep their local tribal customs and

non-Arabic dialects. They include (i) Fur tribes, originally Sudanic, are Muslims living in the highlands of Jabal Marra in the western region of the country. They are terrace cultivators; (ii) Nuba tribes, who were also originally Sudanic, live on the Nuba Hills, also in the western region, and are mainly pagans, though a few are Muslims or Christians. They are cattle breeders; (iii) Beja tribes, originally Hamitic, who live on the Red Sea Hills in the eastern region. They include the Hadandawa or 'Fuzzy-wuzzy' of Rudyard-Kipling fame. They are Muslims and are mainly nomadic camel breeders.

Southern Sudan

This extends between latitudes 3 and 12° north and is hot, humid and green for most of the year. It is inhabited by 4 million people, most of whom are pagans, the rest being Christians or Muslims. They form a complex mixture of African tribes. The majority are Nilotics (Dinka, Shuluk and Nuer) living in the northern swampy reaches of the region; they are cattle breeders. The remainder are Sudanic (e.g. Zande) or Nilo-Hamitic (e.g. Baria) and who live in the tropical equatorial forests further south; they are largely game-hunters or small cultivators.

Administratively, the Sudan is divided into six local government regions in addition to the national capital Khartoum, which has its own municipality. For the purpose of the present study we have followed the same regional administration in four regions, i.e. (a) northern, (b) eastern, (c) central and (d) southern, but have combined the two regions of Kordofan and Darfur into one region designated as (e) the western region.

Medical and health facilities are not evenly distributed amongst these regions [3] but the histopathology and radiotherapy services and cancer registration are at present centralized in Khartoum.

The primary sources of population studies in the Sudan are, unfortunately, few and unreliable, and census material is neither accurate nor comprehensive. However, according to the best information [4], about 45% of the population is 14 yr of age or under and the sex distribution is about equal. More than 80% of the population live in rural areas and is engaged in nomadism or cultivation. Light industry is found on a limited scale in towns. On the whole, men are the bread-winners, although women help in the field in villages and take up office jobs in towns.

MATERIALS AND METHODS

The material in this communication is based on two sources: (a) a study of 374 histologically

proven cases of NPC included in the Sudan Cancer Registry (SCR) during the period 1970–1975 inclusive; and (b) a study of 513 cases of histologically proven NPC cases included in the records of the Radiation and Isotope Centre, Khartoum (RICK) during the period 1967–1980 inclusive; they also include most of the cases in source (a).

All cancer cases at the RICK are well documented as regards age, sex, geographical locality, tribal origin, social status, occupation, habits etc. This information is thus more accurate than that of the SCR, where some of these criteria are deficient. However, the RICK material, being built on cases referred for radiotherapy, naturally suffers from selectivity bias. It was therefore decided to combine the two sources in an effort to minimize possible epidemiological errors.

All the cases were histologically verified by qualified pathologists and one of the authors (M.O.A.M.) had the opportunity to report personally on most of the 374 cases in source (a) and to review the others (all these were again reviewed jointly by two of the authors, M.O.A.M. and M.S.R.H.).

Blood group serology (A,B,O,Rh) was carried out in the Haematology Dept., National Health Laboratory, Khartoum, while studies on Epstein-Barr virus (EBV) antibody titres were carried out in the Virology Dept., St. Thomas's Hospital Medical School, London.

RESULTS

General frequency

The 374 NPC cases formed 5.8% of the 6367 histologically verified cases of malignant neoplasms reported in the SCR during the same 6-yr period—9.2% in males and 2.7% in females.

The 512 NPC cases formed 7.2% of the 7212 cancer cases seen at the RICK during the same 11-yr period—12.1% in males and 3.1% in females.

Sex distribution

Of the 374 NPC cases, 283 were males and 91 females, giving an M/F ratio of 3/1. In the age groups 0–14, 15–39 and 40 and over, the M/F ratios were 1.4/1, 4.1/1 and 3.2/1 respectively.

Of the 512 NPC cases, 392 were males and 120 females, giving an M/F ratio of 3.3/1. In the age groups 0–14, 15–39 and 40 and over, the M/F ratios were 2.3/1, 4/1 and 3/1 respectively.

Age distribution

Of the 374 cases, 14% occurred in children 14 or under, 33.7% in adults 30 or under and 54.6% in adults 40 or under. The youngest patient was 3 yr old and the eldest 78 yr. The average age was

37.4 yr (males, 39.8 and females, 34.4). The maximum incidence was in the 4th decade.

Of the 512 cases, 12.1% occurred in children 14 yr or under, 37.3% in adults 30 or under and 54.8% in adults 40 or under. The youngest patient was 5 yr old and the eldest 86 yr. The average age was 38 yr (males, 37.2 and females, 39.3). The maximum incidence was in the 2nd followed by the 4th decade.

Geographical distribution

The frequency ratio of NPC to all cancer cases at the SCR was 9.6% in the western region and 8.5% in the southern region, while it ranged from 2.8 to 5.8% in Khartoum and the central and northern regions.

The frequency ratio of NPC to all cancer cases at the RICK was 12.9% in the western region and 11.9% in the southern region, while ranging from 4.7 to 7.7% in Khartoum and the central and northern regions.

Ethnic distribution

The frequency ratio of NPC to all cancer cases at the SCR was 12.7% in the Nuba and Fur tribes (western region), 11.4% in the Nilotics (southern region) and 10.4% in the Beja tribe (eastern region). This ratio was intermediate (7.4%) in the Baggara tribes (western region) and lowest (2.3–5.9%) in the Arab tribes (Khartoum and the central and northern regions).

The frequency ratio of NPC to all cancer cases at the RICK was 19.5% in the Nuba and Fur, 13.6% in the Nilotics and 11% in the Beja tribes. It was intermediate (9.4%) in the Baggara and lowest (2.9–5.9%) in the Arab tribes.

EBV antibody titres

Using 1F techniques, EBV-VCA antibody titres were determined in sera from 226 subjects (41 NPC patients; 79 with other head and neck cancers; 21 with malignant lymphomata; 63 with other cancers; 6 with specific granulomata; 18 normal controls). The results have been published elsewhere [5]. In summary, of the NPC patients 87.8% had titres of ≥ 320 and 43.9% of ≥ 2560 , whilst none had a titre of < 40 ; their GMT level was 1855. By contrast, the other patients and normal controls showed significantly more percentages of cases with low titres and fewer percentages of cases with high titres than the NPC cases, and their GMT level was 4–16 times lesser. The high NPC titres were independent of age, sex, tribe or locality of the patients.

Blood groups

The A, B, O and Rh blood groups were determined in all the 226 subjects on whom the EBV-ab

titres were done. There was no significant difference from the general population pattern.

DISCUSSION

In the Sudan, as in most developing countries, there is at present no reliable statistical information on absolute cancer incidence rates; this is due to a combination of factors which have been outlined in previous reports on cancer in the Sudan [6, 7] and on mortality patterns [8]. Fortunately, the centralization of the histopathology and radiotherapy services and the establishment of a national cancer registry since 1966 have made possible the working out of relative frequency ratios; these are resorted to for purposes of comparison, despite their well-known shortcomings as epidemiological tools.

As Table 1 shows, the overall frequency ratio of NPC in the Sudan (5.8–7.2%), as recorded in this study, is much higher than that reported in Caucasian populations. In fact, this frequency is the highest so far recorded outside the Chinese. The actual incidence of NPC in the Sudan is probably much higher because (a) ENT specialist facilities mainly exist in Khartoum; general practitioners and other clinicians are unlikely to establish a diagnosis of NPC in patients presenting with neck swellings in a country where tuberculosis is rampant and such bizarre symptoms as trismus or proptosis are common; (b) some cases have presumably been lost through anatomic designation as belonging to the pharynx or oral cavity; (c) since the high-risk NPC areas have very limited access to medical facilities many patients die at home, and as no autopsies are done these cases are also lost.

Sex distribution

The male preponderance in this series (3/1) is in conformity with most published reports. However, in this study NPC was the commonest tumour in males seen at the RICK and the second commonest in the SCR. This does not conform to

the general Sudanese population structure or cancer pattern and we cannot explain it at present.

Age distribution

The tendency of NPC to occur in younger patients is reported from most sources, but in our series it seems to be more striking. Thus the average age of our patients was 5–10 yr lower than in most series and the peak incidence was in the 4th decade, which is one decade lower than reported for high-risk populations, including the Chinese and Kenyans, and two decades lower than among low-risk white races [9]. The present series includes the highest number of NPC cases in children under 14 ever reported. It is difficult to explain this trend merely on the younger age structure of the Sudanese population, as a similar age structure is found in Kenya, Uganda and Tunisia.

Geographical distribution

Generally speaking, NPC was 2–3 times more frequent in the western and southern regions than in the rest of the country. However, pockets of high frequency also occurred in the eastern region. There was no topographic or climatic factor common to these high-risk areas. Again, low-risk areas such as Khartoum and the central and northern regions differed in their geographical patterns.

Ethnic distribution

The highest frequency of NPC in the series occurred in three tribal groups: the Nuba-Fur tribes in the western region, the Nilotic-Sudanic tribes in the southern region and the Beja in the eastern region. These highly susceptible tribes live in different parts of the country under different topographic and climatic conditions, and differ in their modes of life, dietary patterns and local customs and traditions. The only factor common to these tribal groups is that they represent the original indigenous African inhabitants of the Sudan ‘country of the Sud–Arabic

Table 1. Frequency of NPC in different populations (based on information by Clifford [9])

A. Low frequency—less than 1%	White races in Europe and North America Indians Japanese
B. Moderate frequency—1–5%	Thai, Vietnamese, Phillipinos Arabs, Maltese Africans, e.g. Nigerians, Algerians
C. High frequency—more than 5%	Chinese (especially southern) Malays African tribal groups, e.g. in Kenya and Tunisia

for black' before the advent of the Arab-Muslims; even today they keep their original local customs and non-Arabic dialects and many are still non-Muslims, although Arab-Muslim influence is increasing. It was interesting to note that intermediate NPC frequencies occurred in the Baggara tribes, whose blood is about half-Arab and half-African, whilst the lowest frequency occurred in the more pure Arab tribes of the northern region.

Possible aetiological factors

The knowledge that NPC showed predilection for certain populations has naturally focused attention on the possible role played by genetic and/or environmental factors. In certain high-risk areas, e.g. Kenya, environmental factors have been blamed, while in others, e.g. China, racial factors were deemed more crucial. A great deal of literature has been forthcoming about this and the following pertains to the situation in the Sudan.

(a) *Environmental factors*. 1. Household fumes. Clifford and Beecher [10] thought that the inhalation of certain wood-fuel fumes was aetiologically important in the causation of NPC in Kenya. Saad [1] also attributed the high frequency of NPC among the Nuba tribes in the Sudan to the effect of household fumes in the ill-ventilated huts of the generally humid and cool Nuba hills. However, our results show that high NPC frequencies also occurred among the Fur and Beja tribes. In these tribal areas the weather is hot and dry and life is mainly out-of-doors; buildings here are usually well-ventilated and cooking is done in a shed 'varandah' during the day and in open air in the evenings. Furthermore, the local Sudanese bread 'kisra' is made in a special kitchen 'tukul' where wood or dry grass is used as fuel. This results in heavy smoke and, since women who make the 'kisra' are exclusively exposed, one would expect NPC to be commoner in females if smoke indeed was an aetiological factor; NPC is, however, much commoner in Sudanese men.

2. Climate. Milosev *et al.* [2] thought that the irritating effect of hot and dry atmospheric conditions was probably aetiologically important in relation to NPC in 73 patients on whom they reported. Our studies, however, have shown high-risk areas in colder places, e.g. over the Nuba hills, Jabal Marra and Red-Sea hills, and in moist places, e.g. the southern region. On the other hand, some of the lowest frequencies were met within the northern region, where the climate is generally hot, dry and often dusty (incidentally, nasal polyposis and chronic sinusitis are common in this region).

3. Tobacco. Among 281 NPC patients seen at the RICK and surveyed during the period of study, 29 smoked cigarettes, 25 used local pipes and 22 were snuff-dippers. These tobacco habits were not different from those of the general Sudanese population. Furthermore, some high-risk NPC tribes such as the Fur in the western region are non-tobacco users, whereas some low-risk tribes, for instance, the Shaigia of the northern region, are heavy snuff-dippers. The low-risk population of the capital Khartoum has the highest smoking-habit incidence in the country.

4. Other factors. Most of our NPC patients came from the lower socio-economic strata (as is most of the Sudanese population), but cases were seen in well-to-do and highly educated people. The majority of the patients were from rural farming and grazing communities (as is most of the population), but cases occurred in town sedentary and factory workers. Nutritional deficiencies and diseases that might depress immunity, e.g. malaria, abound in all parts of the country.

There is a great variation in Sudanese dietary patterns due to social and cultural as well as environmental influences. Dura (sorghum) is the main staple diet in northern Sudan as a whole, whereas root crops, e.g. cassava and yam, are of considerable importance in the south. Dukhun (millet) is restricted to the sandy western regions, while maize production and consumption is limited to the Nile valleys in the northern region. Wheat is consumed largely by the more affluent town-dwellers, especially in Khartoum and the central regions. Primitive cooking methods are used all over the country. No relationship between dietary background and the distribution of NPC cases could be established.

Incense is not used by the Sudanese except on special occasions, e.g. weddings, circumcision and faith-healing ceremonies. Opium-smoking is not practiced, while hashish-smoking is limited to groups of young people in certain towns, e.g. Khartoum, Medani and Atbara—all in low-risk NPC areas. No relevant herbal medicine could be delineated. Most of the patients did not consume alcohol.

(b) *Ethnic factors*. Remarkable differences in the incidence of NPC among populations of different ethnic origin have been known to occur, as is shown in Table 1. The disease is thus rare among the white races of Europe and North America, and also among the Caucasoid Indians and Japanese of S.E. Asia. On the other hand, it has an exceptionally high incidence rate among the Chinese, particularly those of the southern coastal provinces of China. High rates, though slightly lower than those of the mainland Chinese, are reported among immigrant Chinese

in various countries as well as among other mongoloid races related to the Chinese in S.E. Asia, e.g. Malays, Phillipinos and Indonesians. NPC was also found to be fairly common among certain African tribes in E. Africa, especially Kenya, and in N. Africa, e.g. Tunisia.

Our data leave little doubt that racial susceptibility plays an important role in the aetiology of NPC in the Sudan. The high-risk tribes are those of predominant 'African' blood, e.g. Fur, Nuba and Nilotics, whereas the low-risk tribes are those of predominant 'Arab' blood, e.g. Shaigia and Gaaliien; intermediate frequencies are seen in the fairly mixed tribes, e.g. Baggara. As noted earlier, the high-risk tribal groups live in contrasting ecological and climatic conditions. Moreover, more than one-quarter of the NPC cases among those ethnic groups in this study have been diagnosed in patients living away from their original tribal homes for many years in places where they have migrated for work, mostly in Khartoum and other large towns in the central and northern regions (which are low-risk areas).

Since historically there have been movements of populations across Arabia and parts of Africa and Asia, it is tempting to speculate on a common ethnic denominator for the high-risk groups in these areas. We are currently studying these historical and geographical aspects in relation to NPC epidemiology in detail and will report our findings in due course.

EBV studies

Within recent years significantly high anti-EBV titres have been reported in NPC patients from various parts of the world. Our findings in the Sudan confirm this and give support to the hypothesis that there is a possible association between NPC and EBV. All the 41 cases in our series in which EBV studies were done were histologically of the anaplastic carcinoma type. It would have been useful to compare the EBV titre levels in the anaplastic and the squamous cell carcinoma groups as the latter type is rare in the younger age groups in the Sudan and as yet we have not seen it in patients under 14 yr of age. It might well be that the anaplastic and squamous cell types of NPC have different aetiological backgrounds, the former being the one related to race and EBV. In Uganda de-The [11], noting that primary EBV infection occurred during the first two years of life and reached its peak by the age of three, suggested that peri-natal infection with the virus was an important risk factor for the development of Burkitt's lymphoma. In the Sudan, with the younger NPC patients (the youngest so far recorded being 3 yr old) a similar hypothesis might be considered. This age pattern makes the possibility of a chemical carcinogen a remote one and strengthens the case for a viral carcinogen. A hypothesis envisaging abnormal virus response in genetically susceptible individuals certainly seems worthy of serious consideration in the aetiology of NPC.

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