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TOPIC HIGHLIGHT

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Problem of hepatocellular carcinoma in West Africa

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Abstract

The incidence of hepatocellular carcinoma (HCC) is known to be high in West Africa with an approximate yearly mortality rate of 200000. Several factors are responsible for this. Early acquisition of risk factors; with vertical or horizontal transmission of hepatitis B (HBV), environmental food contaminants (aflatoxins), poor management of predisposing risk factors and poorly-managed strategies for health delivery. There has been a low uptake of childhood immunisation for hepatitis B in many West African countries. Owing to late presentations, most sufferers of HCC die within weeks of their diagnosis. Highlighted reasons for the specific disease pattern of HCC in West Africa include: (1) high rate of risk factors; (2) failure to identify at risk populations; (3) lack of effective treatment; and (4) scarce resources for timely diagnosis. This is contrasted to the developed world, which generally has sufficient resources to detect cases early for curative treatment. Provision of palliative care for HCC patients is limited by availability and affordability of potent analgesics. Regional efforts, as well as collaborative networking activities hold promise that could change the epidemiology of HCC in West Africa.

Key words: Liver cancer; West Africa; Aflatoxin; Surveillance; Hepatitis B

Core tip: It is known that outside the region of East Asia, sub-Saharan Africa has the highest incidence of hepatocellular carcinoma (HCC). Within Africa the West African region remains the focus of significant disease activity. We reviewed the main issues responsible for this pattern. Although intervention efforts, such as primary prevention through hepatitis B vaccination, has led to reductions of chronic hepatitis B infection in some countries such as Gambia and Senegal, there remains a huge gap in secondary prevention, which are responsible for continuing high mortality to incidence ratio of HCC in West Africa. Collaborative clinical care and basic science translational research holds promise towards changing the current trend.

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INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes almost 85% of all primary liver cancers, and is known to be the 5th most commonly diagnosed cancer globally[1]. In 2012, about 782000 and 746000 new cases and deaths respectively, had HCC as their primary diagnosis[2]. Sub-Saharan Africa is the most affected region of the world, after Eastern Asia owing to the high prevalence of risk factors for this cancer in these continents. Although a description of the burden of HCC in developing countries, highlighting the sub-Saharan African situation has recently been reported by Kew[3], the countries of West Africa have reported more than average incidence of HCC, a situation deserving in depth understanding. In this article, we systematically reviewed the problem of HCC in West Africa: contributing factors, primary and secondary prevention efforts, as well as the provision of palliative care to patients. This review provides an overview of current efforts and suggests opportunities for strategic intervention.

EPIDEMIOLOGY OF HCC IN WEST AFRICA

There is a high incidence of HCC in West Africa. In countries like Gambia, Guinea-Conakry and Sénégal, the incidence of HCC has been reported to range between 30-50/100000 and 12-20/100000 in men and women, respectively[4]. The West African region comprises 16 countries. It has an area approximating 6.1 million km^2, bordered in the north by the Sahara desert and the east by Mount Cameroon and Lake Chad. Aside from shared economic interests, such as the Economic Community of West African States, there are similarities in the dress, cuisine, music and culture of people living in this geographical enclave. These factors may indeed underlie the way that HCC presents.

The mortality rate of HCC is almost the same as its incidence in this region of the world. Individual national cancer registry data are limited. However, the global cancer registry database has provided estimates of incidence and mortality by gender for primary liver cancer; of which HCC constitutes approximately 85%. Taking into account the incompleteness of cancer registration in this region, these data highlight the high case fatality rate of HCC. The most affected country is The Gambia, followed by Guinea, Liberia and Sierra-Leone in that order (Figure 1).

As most affected persons are middle-aged, HCC contributes to decreased economic development of this region. Whereas the incidence of HCC in most developed countries show that the highest affected is 75 years and older, and similar patterns among high risk Asian populations, the situation is different in West Africa. There is a significant male preponderance of this tumour, being the most commonly encountered malignancy in men in several West African countries (Table 1). The rates of HCC in men in countries like Gambia and Mali tend to peak at 60 to 65 years while females peak between 65 and 75 years[5]. A study has reported peak age of 40 years from this region[6].

Some reasons for the characteristic epidemiological pattern of HCC in West Africa are discussed as follows.

Failure to identify at risk populations

It is not uncommon for some patients in West Africa to be found to have hepatitis B viral infection, for the first time, when they present to hospitals with decompensated liver disease. This late diagnosis is not only as result of lack of health-seeking behaviour, but likely to be due to some additional factors. As the performance of healthcare delivery is often suboptimal in this region, many hepatitis B surface antigen (HBsAg)-positive patients seek herbal and alternative medications as the initial port of call prior to attending orthodox care. Since few individuals receive adequate management for chronic hepatitis B, there is a tendency to progress to cirrhosis. Malignancy, on the background of poor hepatic reserve, with additional consumption of traditional remedies; of unknown toxicities, tip the patients to liver failure on first hospital presentation.

Low hepatitis B virus immunisation adherence

Significant declines in HBsAg prevalence and low rates of childhood HCCs have been realised in countries that introduced Hepatitis B virus (HBV) vaccine[7]. One study in the region has revealed that HBV vaccination is capable of decreasing chronic HBsAg carriage by up to 83%[8]. This observation has been replicated in studies from Senegal and South Africa[9,10]. However, many countries in the region have ensured complete adherence to whole course of HBV vaccination. The Global Alliance for Vaccines and Immunisation funding and the World Health Organisation (WHO), supporting HBV vaccination programmes, have played an important role in the implementation of HBV vaccine programmes in Africa. Despite this effort, HBV vaccine coverage remains low estimated at 70% according to the WHO/UNICEF 2012 data.

Poor treatment of liver diseases

The treatment of liver diseases is generally inadequate in many countries of West Africa. Large number of patients overwhelms the limited number of trained medical personnel, inadequate infrastructure for training curricula, mass emigration of medical professionals and paucity of clinical guidelines adapted to the local setting are important in this regard. It was not until recently that hepatitis C virus (HCV) treatment guidelines for low and middle

Table 1 Summary of some studies indicating male preponderance of hepatocellular carcinoma relative to other cancers in West Africa

Country	Liver cancer relative to cancer elsewhere	Source of study population	Coverage
Niger[55]	Most common in men; M:F ratio of 1.4:1	National cancer registry	National
The Gambia[56]	Most common in men; 2nd in women	National cancer registry	National
Ghana[57]	Most common in men, 3rd in women; M:F ratio of 1.2:1	Southern Ghana	Mortality data from a tertiary centre
Nigeria[58]	Most common in men; M:F ratio of 2.4:1	South East Nigeria	Cancer mortality data
Nigeria[59]	Most common in 50-59 years old	South West Nigeria	Pathology reports
Côte d'Ivoire[60]	Second in men; less common in women	Cancer registry	National
Mali[61]	Most common cancer in men; cervical cancer leads in women	Cancer registry	National
Guinea-Conakry[62]	Most common in men; second in women	Cancer registry	Regional

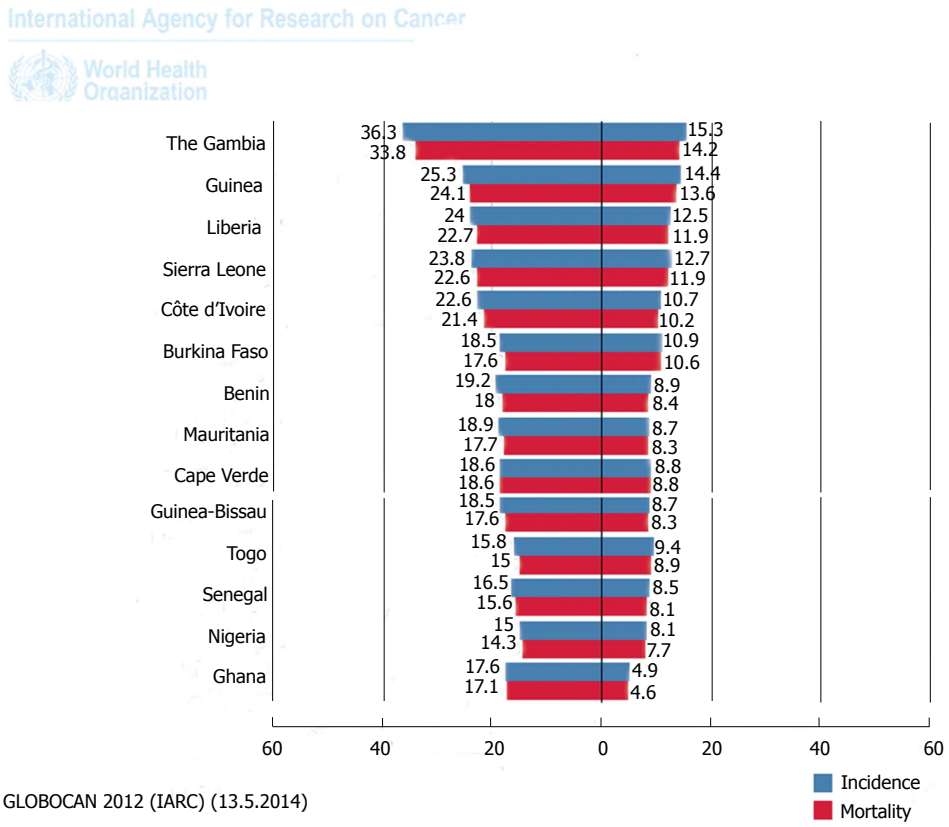

Figure 1 Multiple clustered bar charts labelled by incidence and mortality rates per 100000 population of West African countries (data from Globocan 2012 from International Agency for Research on Cancer[54].

income countries were commissioned by the WHO[11]. Inadequate funding prevents the optimal treatment of those affected, as the cost of these medications is prohibitive for most sufferers in these countries[12]. Patients tend to present to hospitals when they have noticed symptoms or when a close relative gets diagnosed with an associated complication of viral hepatitis.

Inadequate public health intervention

The burden of disease imposed by viral hepatitis has been completely ignored by the international health agenda these last decades as the focus has been put on human immunodeficiency syndrome (HIV), tuberculosis, and malaria, three major infectious diseases issues which have been the main recipient of health care resources and funding[13]. Yet, if the mortality and morbidity from cirrhosis and liver cancer were grouped, the burden of viral hepatitis would have to be seriously considered by the international health authorities[14]. The lack of public health campaigns is complicated by a plethora of traditional healers.

There is also a scarcity of coordinated health programmes that could inform governments in the region regarding the problem of liver diseases. With significantly high prevalence of HBsAg and anti-HCV in Nigeria, it was only in 2009 that a guideline for the treatment of HBV was produced. Similarly, the WHO and World Hepatitis Alliance estimate that only 17 countries in the whole of Africa that have designed national guidelines on viral hepatitis, of which only 3 sub-Saharan African countries (Cameroon, Rwanda and Mauritania) have implemented guidelines on HBV mother-to-child transmission. With

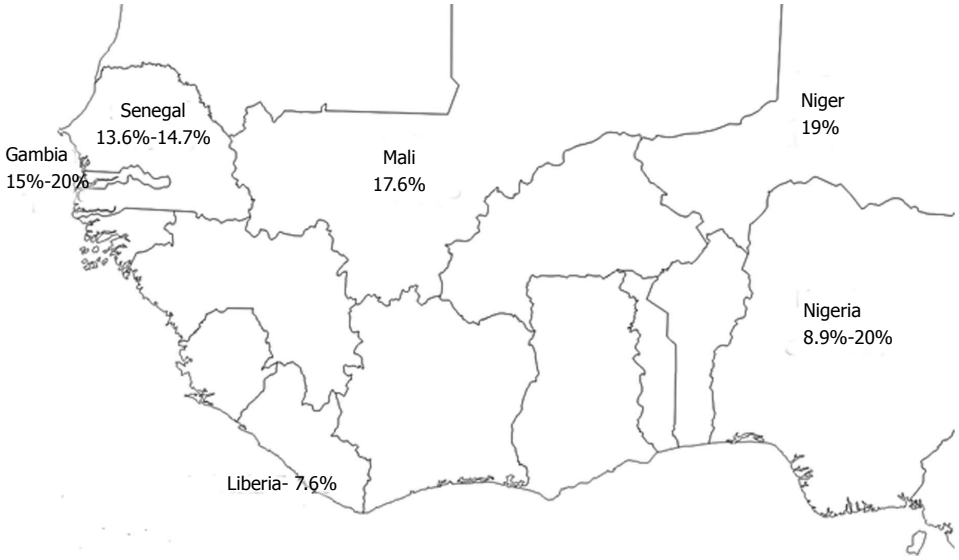

Figure 2 Prevalence of hepatitis B surface antigen carriage in some West African countries.

the prohibitive cost of antivirals and a fee-for-service system of healthcare, only those who can afford medication get treated. This ultimately results in a large pool of those who could have been treated for viral hepatitis going on to develop HCC.

HIGH RATE OF RISK FACTORS

Hepatitis

HBV, described as a potent carcinogen, is endemic in West Africa demonstrating varied prevalence. The infection rates of HBV vary between 8%-20% in this region[15].

West Africans have longer durations of HBV infections relative to individuals in the developed world who tend to get the infection much later in life. By age of 10 years, 80% of infected people in Africa have acquired HBV[16] and a high carriage rate of up to 20% (Figure 2). Inadequate data in the literature from this region may actually be modulating the true problem of HBV and its sequelae in the West African region.

HCV infection affects more than 8.4 million people in West Africa[11]. Although the transmission route of HCV in this region is not well established, and most cases are thought to be due to use of unsterile sharps, and receipt of unscreened blood products, sexual transmission may have a modest effect[17]. Owing to incorrect assumptions, anti-HCV serology was not part of routine screening for blood products until early 2000s. However, it is now known that the prevalence of HCV in West Africa varies from 2.5%-9.9%[17]. Although less prominent than HBV, HCV contributes to HCC in West Africa, particularly for those above 60 years[5].

The distribution of HBV genotype differs from one region of the world to another, and which could be a determinant factor in the clinical outcome of HBV infection. For example, in central and West Africa genotype E has been documented to predominate[18,19]. Studies from Asia have demonstrated an increase in the development of HCC among patients with HBV genotype C, compared to genotype B[20-23]. A study in South Africa has shown that HBV genotype A had a greater hepatocarcinogenic potential than other non-A genotypes[24].

Aflatoxin

This mycotoxin, produced by the fungus *Aspergillus spp*., grows on mainly legumes and cereals in humid conditions in parts of West Africa. These foods are mostly consumed unprocessed as staples in West Africa. Subsistence farming, poor farm produce storage and suboptimal processing systems facilitate widespread exposure tothis toxin (Figure 3). Aflatoxin and HBV infection can synergistically increase the risk of HCC. A possible molecular mechanism has been suggested by studies in HBV transgenic mice[25]. That study suggested that chronic inflammatory damage of the liver alters the expression of carcinogen metabolizing proteins and may thus moderate the binding of aflatoxin to DNA. Further research in the region has confirmed a significant increase in the risk of cirrhosis in patients exposed to aflatoxin[26]. Additional research in this area could be far-reaching; and may enhance policy decisions regarding drying, storage, processing and consumption of foods such as cereals that are consumed in large amounts in the countries within this region.

Alcohol

Although not as affluent as developed countries, alcohol consumption goes on, albeit to an undocumented level in West Africa. Locally-brewed fermented drinks in Africa have been reported to significantly contribute to HCC. These studies postulated that the brewing containers (Figure 4) release iron in consumers of these drinks, which leads to an iron overload syndrome. Almost a tenth of some populations in sub-Saharan Africa have been noted to have iron overload[27,28]. Iron levels have

Figure 3 Fungus-infested malt, a product of cereal used in the fermentation of local alcohol beverage "burukutu". Cereals are widely consumed in West Africa and are a source of aflatoxin, which has been shown to potentiate the hepatocarcinogenicity of hepatitis B virus (Picture by Pantong Mark at Jos, Nigeria).

Figure 4 Iron pots used in brewing local beer in a typical West African setting (Picture by Pantong Mark, Jos, Nigeria).

been reported to be significantly higher among Africans with liver cancer than controls[29]. A genetic polymorphism in the ferroportin-1 has been demonstrated in a southern African study population, and thought to be associated with decreased iron excretion[30]. The interaction between alcohol, HBV and iron overload could be far-reaching to predispose West Africans to HCC. Studies have found that the incidence of HCC is 200 fold in haemochromatosis if the patients are above 55 years of age, have HBsAg seropositivity and who additionally drink alcohol[31,32].

HIV and hepatitis co-infection

The impact of HIV infection on chronic viral hepatitis B and C, as well as on the response to hepatitis B immunisation antibody generation are subjects deserving further studies in this region. Data from developed countries have established definite links between HIV/HBV and HIV/HCV co-infections, as well as HCC[33,34]. Prior to the provision of highly active antiretroviral treatment to Africa, most HIV patients died earlier due to opportunistic infections before they developed complications of HBV or HCV. Recent experience emerging from well monitored HIV centres in West Africa[35] confirms that most co-infected patients are expected to survive longer and the impact on the overall burden of HCC will eventually emerge. Furthermore, the impact of HIV infection on the long-term efficacy of the HBV vaccine in West Africa remains to be determined and might pose serious consequences for the gains already made in places that have attained a wide HBV vaccination coverage[36].

CLINICAL PRESENTATIONS OF HCC IN WEST AFRICA

The natural history of untreated HCC and the associated clinical features have been well characterised from developed countries[37]. Early HCC is often asymptomatic and is devoid of pathognomonic features. Certain features that distinguish HCC presenting in developed countries relative to West African countries are summarised in Table 2. Whereas 5%-10% of HCC patients in the West and almost 30% in Japan are diagnosed with early disease[38], almost all persons diagnosed with HCC in West Africa are diagnosed very late[5,39]. The presence of a painful right upper abdominal mass and swelling, weight loss and early satiety signify advanced disease[40].

Weight loss is the commonest symptom of HCC, often attributed to "witchcraft" in West African populations. Right upper abdominal pain, abdominal swelling and jaundice are not uncommon. Other symptoms include anorexia and confusion. To ease diagnosis, most clinicians in sub-Saharan Africa recognise a prospective HCC patient either as: one with abdominal pain and a hard nodular hepatomegaly, or "a triad of abdominal pain, swelling and jaundice". A few studies from the region[5,41] have corroborated the stated features (Figure 5).

DIAGNOSTIC CHALLENGES OF HCC IN WEST AFRICA

Challenges of diagnosis of HCC in developing countries have been recently highlighted[3]. According to the international guidelines the diagnosis of HCC relies on specific radiological aspects using computed tomography (CT) or magnetic resonance imaging (MRI) scans and/or histopathological analysis. However, in sub-Saharan Africa, these diagnostic tools are rarely used in clinical practice because: (1) CT or MRI scans with contrast are not available in many countries or are expensive and not free of charge; and (2) liver biopsy is an invasive and costly procedure requiring well trained hepatologists, histopathologists and laboratory technicians, who are not always at post. Moreover most percutaneous liver biopsies are not image-guided and hence there is a high chance of mis-diagnosis. Owing to low sensitivity, serum alpha-fetoprotein (AFP) is no longer recommended by most international guidelines (indeed in some guidelines it is used in combination with radiological features) to be used for this purpose[42], although almost all centres in West Africa still rely on it. As one third of HCC do not secrete AFP,

Table 2 Relative differences in risk factors, clinical features, surveillance and management of hepatocellular carcinoma between West Africa and developed countries

Parameter	Developed countries	West African countries
Predominant risk factor	Hepatitis C virus[2,63]	Hepatitis B virus[5]
Predominant co-factor	Alcohol	Aflatoxin B1[64]
Peak incidence	8th decade[65]	5th decade[57]
Stage at presentation	High chance of early stage at diagnosis[38]	Often advanced stage at presentation[3]
Surveillance	Routine; although compliance is about 12% in a study in the United States[66]	Not known and not routine
Median survival	Overall survival of > 16 mo in a study from United States[67]	Most die at initial presentation
Diagnosis	Radiological (multi-phasic dynamic CT or MRI) ± liver biopsy[68]	Tumour markers (occasionally, grey-scale ultrasound scan ± liver biopsy)[12,48]
Treatment	Curative therapies and palliative care; according to guidelines	Mainly palliative; often suboptimal

CT: Computed tomography; MRI: Magnetic resonance imaging.

and most of the tertiary centres use only grey scale ultrasound scan systems, a lot of those patients with hepatic lesions are missed and/or confused with other common inflammatory conditions such as amoebiasis, peritoneal and hepatic tuberculosis, lymphoma, cholangiocarcinoma and secondary hepatic tumours. The import of the foregoing is the fact that the rates of HCC being reported are unlikely to reflect the true picture of the burden of the disease in West Africa.

TREATMENT OF HCC IN WEST AFRICA

Owing to very late presentations and poor health infrastructures, the outcome of HCC in West Africa is generally dismal and curative management is impossible, treatment only relying on palliative care for the most part. Yet, very few centres have proper palliative care, as opiates are often unavailable and healthcare workers are not trained to use them. The vast majority (80%-90%) of cancer patients in sub-Saharan Africa only seek medical attention when cancers have reached an advanced stage, where end-of-life strategies are the only option. In 2009, only 12% of cancer patients in sub-Saharan Africa with moderate to severe pain were estimated to have been treated with opioid analgesics, an essential component of palliative care[43].

The management of pain for palliative patients has been also hampered by lack of knowledge and training and apprehension that opioid analgesics would cause severe digestive side effects and addiction. The so-called "opiophobia", among healthcare professionals is frequently observed in Africa[44] and is known to lead to under-prescription of pain relief medication. In The Gambia, it was found that only 12 HCC patients (48%) of HCC patients receive analgesics without any oral morphine prescription (personal communication).

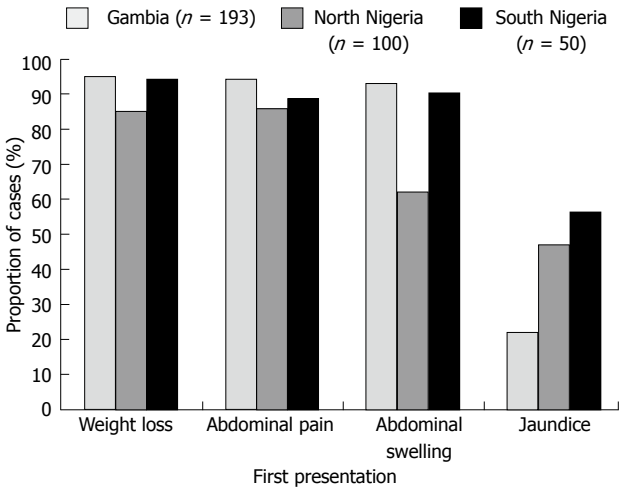

Figure 5 Summary of most common clinical presentations of hepatocellular carcinoma in three West African communities: Gambia, Northern and Southern Nigeria. Note the similarity of clinical presentation in three study sites in two countries in the region. Number of hepatocellular carcinoma patients in parentheses.

REASONS FOR LOW SURVIVAL OF HCC IN WEST AFRICA

Data on HCC survival in Sub-Saharan Africa are almost non-existent. A recent unpublished study conducted in Nigeria reported a median survival of 4 mo in 100 clinically diagnosed HCC patients[45] and preliminary data from the Prevention of Liver Fibrosis and Cancer in Africa programme in The Gambia found a median survival of 61 d (unpublished data). Worldwide data on cancer survival have shown that the 5-year relative survival was lowest in Uganda and Gambia, relative to other countries such as China[46].

Absent surveillance for HCC

In order to detect cases amenable to curative therapy, well-coordinated surveillance for HCC has to be in place. However, as this is not the case in most West African health centres, most HCC cases are detected at advanced stages[1]. Zhang *et al*[47] have recently reported the advantage of surveillance for HCC in at-risk populations in China, in which they noted a reduced mortality rate by 37% relative to a non-surveyed cohort[47]. For sub-Saharan Africa, serum AFP has been recommended for this purpose by the World Gastroenterology Organisation[48]. However, data on the adherence to this recommendation by physicians and compliance by patients are lacking. Data are available to support the fact that surveillance for HCC could improve therapeutic options for HCC[49].

Lack of treatment facilities for HCC

The advantage that surveillance provides would be confounded if treatment for HCC cannot be offered. Less complicated treatment modalities such as percutaneous ethanol injection of tumours could be offered only if the patients present at a relatively early stage. Liver transplant

services are scarce in West African countries. As fee-for-service continues to be the predominant health system in West Africa, specialists would not embark on skills that are rarely utilised.

Alternative treatment for "hepatitis"

There is a flourishing presence of self-acclaimed healers in West Africa (evangelical churches, as well as traditional religious practices) and claims of miraculous healing are an important contributor for the late presentation, as conventional western medical treatment is often a last resort for many of the afflicted.

CONCLUSION

Outlook and recommendations

HCC is a major cause of death in sub-Saharan Africa, estimated to be responsible for annual deaths of 200000 persons[50]. We have highlighted the direct and remote causes that may be contributing to the pattern of disease presentation in West African patients in this article. International and local efforts are underway to help regarding improving the current bleak outlook of this cancer. Deliberate attempts to reduce exposure to aflatoxin post-harvest had yielded encouraging results, which clinical significance could mean reduction of HCC development in at-risk persons[51]. Improvement of healthcare systems that could attract and retain specialists to tackle the risk factors and improvement in health budgetary implementation towards infrastructural facilities could provide a robust platform to changing the current trend.

In view of the multifactorial aetiological factors in the causation of HCC and the fact that little is in place regarding coordinated control of some of the these risk factors, some authors have predicted that the problem of HCC in West Africa is postulated to increase in the next 40-50 years[52]. However, this appears rather pessimistic and suggests that control efforts would not be in place. Already, some groups, such as the Prevention of Liver Fibrosis and Carcinoma in Africa (www.prolifica.eu) consortium have been investigating the impact of treatment of chronic HBV in reducing the incidence of HCC in this region. Already, this collaborative effort, comprising specialists from European and West African institutions, has led to identification of a validated panel of urinary metabolites[53] that could prove to be useful screening tool for HCC in West African populations in the future. Also, the activities of national professional bodies, such as the Society of Gastroenterology and Hepatology in Nigeria in publishing hepatitis treatment guidelines may only be effective if the West African community of states approach hepatitis in a logistical, programmed fashion, as has been done with HIV. More concerted attention is required to tackle HCC in West Africa in a comprehensive manner, involving public health personnel, hepatologists, oncologists, surgeons and palliative care practitioners.

We have thus presented a synopsis of how important HCC is in the West African region of the world; highlighting the high incidence, mortality and case fatality. Primary prevention methods such as HBV vaccination has led to reduction in chronic HBV infection, but its impact on reducing the incidence of HCC is yet to be documented in this sub region. Additionally, the contribution of aflatoxin deserves further study, as well as avoidance of its exposure aimed at maximising the prevention of liver cancer in this population should be a priority. There is hope in the horizon as there have been coordinated collaborative efforts to: (1) determine the impact of primary prevention in epidemiological terms; (2) provide primary prevention with programmes such as HBV vaccination (Gambia Hepatitis Intervention Study of the MRC); (3) secondary prevention and treatment of chronic HBV with the PROLIFICA programme; as well as (4) enhancing early detection of incident cases (PROLIFICA) in the region. Local efforts such as: provision of guidelines adaptable to the economic resources of the countries in the region as well as hepatitis awareness campaigns hold promise with assisting in the effort to curb this tumour. Parallel control efforts such as proper storage of cereals prior to consumption hold promise to reducing the synergistic contribution of aflatoxin to those already chronically infected by HBV. Results from these endeavours could potentially provide the platform to persuade governments in this region to facilitate larger scale universal policies.

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