

# Reasons why West Africa continues to be a hotbed for hepatocellular carcinoma

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## ABSTRACT

Hepatocellular carcinoma (HCC) exhibits a huge disease burden on West Africa, with a large proportion of all HCC cases worldwide occurring in the sub-region. The high HCC prevalence is due to the endemicity of a number of risk factors, most notably hepatitis B, C and HIV. West African HCC also displays a poor prognosis. Generally speaking, this is owing to more aggressive tumours, late patient presentation and inadequate management. Exposure to chronic viral hepatitis, more carcinogenic West African strains of hepatitis B virus and carcinogens such as aflatoxin B<sub>1</sub> all encourage tumour growth. Lack of patient confidence in the healthcare system contributes to poor health-seeking behaviors and management of the disease can be lacking, due in part to poor health infrastructure, resources available and lack of access to expensive treatment. There is also much we do not know about West African HCC, especially the effect rising obesity and alcohol use may have on this disease in the future. Suggestions for improvement are discussed, including surveillance of high-risk groups. Although there is much to be done before West African HCC is thought to be a curable disease, many steps have been taken to move in the right direction.

**Key words:** Aflatoxin, hepatitis B, hepatitis C, hepatocellular carcinoma, liver cancer

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third-most common cause of cancer mortality and the sixth most common cancer worldwide. It is the most common primary liver cancer, with its incidence rising globally. In addition, recent annual incidence (782000) and mortality (746000) rates of HCC are similar, illustrating the poor prognosis of this cancer.<sup>1</sup>

HCC exhibits a male preponderance; with a peak age of onset 5 years earlier than women. This is thought to be due to higher rates of risk factors in men, including viral hepatitis, high alcohol intake and obesity. Testosterone levels have also been linked to HCC development.<sup>1,2</sup>

Other risk factors for HCC development include any disease leading to cirrhosis, such as non-alcoholic fatty liver disease

(NAFLD), alcoholic liver disease (ALD) and metabolic disorders [Figure 1]. Aflatoxin exposure and smoking are the more general risk factors. In the setting of cirrhosis, hepatitis B and C infection confer the highest risk of HCC development following with alcohol and non-alcoholic fatty liver disease. Of course, rarer conditions such as primary biliary cirrhosis and hemochromatosis can all contribute to cirrhosis development.<sup>3</sup>

Geographically, HCC prevalence displays a distinct pattern. The disease occurs overwhelmingly in developing countries, though rates in developed nations, such as the US have been shown to be rising.<sup>4</sup> China is the most affected country, accounting for over 50% of HCC incidence. Sub-Saharan Africa accounts for the vast majority of the remaining 300,000 cases, with incidence rates over 20 per 100,000 reported for Nigeria and Gambia.<sup>4</sup> In many African countries, the age of HCC development is much younger, with the peak of incidence being in middle age (men: 60-65, women: 65-75) compared to over 75 years in developed countries.<sup>4</sup>

## THE SITUATION IN WEST AFRICA

On reviewing current literature, HCC in Africa appears to be a more aggressive, incurable tumour than in the

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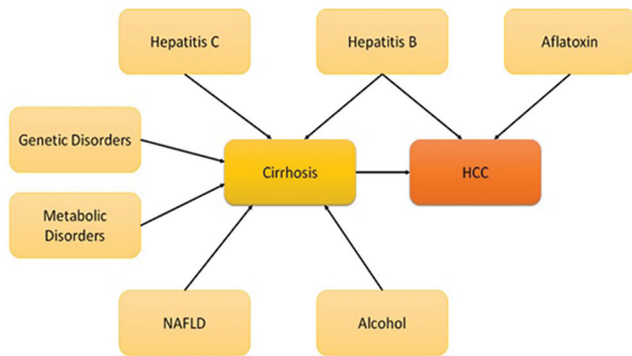


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**Figure 1:** Summary of contributing risk factors to HCC development factors for HCC

developed world, though this claim may be confounded by the tendency of patients to present very late. In any case, these differences are due to the common presence of multiple risk factors in African populations; HBV and HCV infection being the most relevant to the area. Some explanations for the characteristic features of HCC in Africa are discussed below.

## Reasons for HCC prevalence in Africa compared to developed countries

### Chronic HBV infection

HBV infection is suggested to be the most important risk factor in the development of HCC, because of its direct carcinogenic mechanisms, as well as its ability to cause cirrhosis. HBV infection is endemic throughout most of Africa, with up to 80% of individuals acquiring the virus before their 10<sup>th</sup> birthday.<sup>5,6</sup> Vertical transmission from mother to child in the perinatal period or early childhood is the biggest cause of this. It is estimated that 20% of the population of Africa carries HBV. Being infected so young increases the likelihood of a chronic infection, ensuring a longer duration of infection, predisposing to HCC.<sup>5,6</sup>

### Chronic HCV infection

HCV predisposes to HCC development indirectly through the development of cirrhosis. HCV infection is very prevalent within West Africa, with infection rates of up to 9.9%.<sup>5</sup> Prevalence is thought to be so high due to reuse of needles (after perceived sterilisation in hot water) and the use of unscreened blood products, though there has been some attempt to include HCV in screening, but this remains uncommon.<sup>5,7</sup>

### West African HBV strain virulence

HBV genotype E is the most common strain in West Africa,<sup>8</sup> with HBV genotype A (particularly A3) being common in the area. It has been suggested that HBV genotype A (specifically, A1) is more prone to carcinogenesis than others, in a sub-Saharan population, though the mechanism is not fully understood.<sup>9,10</sup> Genotype A also demonstrates more genetic diversity within West Africa than the rest of the world.<sup>11</sup>

### HIV co-infection with HBV/HCV

Since the provision of anti-retroviral therapy (preferably in the form of tenofovir),<sup>12</sup> HIV-positive individuals who are able to obtain treatment in sub-Saharan Africa are living longer. Therefore, relatively more patients are experiencing complications of hepatitis-induced chronic liver disease, not AIDS. It has been demonstrated in developed countries that HIV co-infection leads to decreased HBV clearance and a quicker time to cirrhosis and other liver-related problems.<sup>13</sup> A recent large study in Nigeria demonstrated that HBV co-infection is associated with a significant decrease in survival, compared to HBV-negative HIV-infected individuals, a trend that can be counteracted through the use of tenofovir-containing HAART.<sup>14</sup> The larger sample size involved favours this study over the conflicting evidence found in previous smaller studies in the developing world, with both positive and negative findings acquired.<sup>13</sup> However, more investigation into the link between HIV, viral hepatitis and HCC is required.

Additionally, it is not yet fully understood the long-term effect HIV will have upon those currently immune to HBV of whether it will detrimentally affect the good coverage developed as a result of recent immunisation efforts such as in the Gambia.<sup>5,15</sup>

### Aflatoxin

Aflatoxins are a group of well-described carcinogen that act synergistically with HBV to promote HCC and directly cause DNA damage in hepatocytes. High exposures are recorded throughout West Africa due to poor processing and long-term storage of crops allowing *Aspergillus spp.* growth.<sup>5,16</sup>

### Iron overload syndromes

Iron overload is carcinogenic due to hepatic iron deposition hastening cirrhosis. There are two common aetiologies of this in West Africa, which often combine:

1. Polymorphisms of the ferroportin gene in those of sub-Saharan African descent have been documented, and can predispose individuals to iron overload.<sup>17</sup>
2. Locally fermented alcoholic drinks are often stored in ungalvanised iron barrels, contributing to dietary iron overload.<sup>5,18</sup>

These factors do not cause iron overload by themselves. The ferroportin polymorphisms act synergistically with a dietary excess to cause disease.<sup>19,20</sup>

### Inadequate management of chronic liver disease

Management of liver disease is poor in many West African countries. Numerous factors contribute to this. The healthcare systems are often poorly funded, falling far below the US\$34 per capita recommended by the World Health Organisation.<sup>21</sup> Commonly, they are pay-per-service, as in Nigeria, so that only the well-off can afford expensive antiviral treatments. Poor funding leads to poor performance, with less or outdated equipment available,

lower quality teaching and potentially a “brain-drain” of medical professionals.<sup>5</sup>

Many African healthcare systems fail to refer and tier the care they give successfully. For example in Nigeria, it has been found that just 10% of the primary care system’s patient load is served, as many individuals self-present in hospitals. This is due to lack of patients’ confidence in the tiered healthcare system.<sup>5,22</sup> Lack of confidence leads to poor health-seeking behaviour, contributing to the late disease presentation of HCC and to the use of untested alternative medications that can often be hepatotoxic, further exacerbating liver disease and hastening HCC development. Due to this association, alternative medicines are a huge problem in this field, especially if awareness is not raised.<sup>5,22,23</sup>

In addition, HBV vaccination, despite receiving funding from Global Alliance for Vaccines and Immunisation (GAVI) has not been rolled out throughout the whole of West Africa, despite promising results in South Africa, Senegal and Gambia, where up to 84% coverage was achieved.<sup>24</sup> This suggests there are logistical issues with the fight against HBV and HCC, not simply funding.<sup>5,25-27</sup> HBV vaccination is key to the prevention of viral infection and therefore will play a large role in combatting HCC in the region.

Clinically, it has also been suggested that a lack of adaptable guidelines for African populations leads to inadequate care of those that do receive it.<sup>5</sup> A lack of guidance may contribute to the lack of surveillance in at-risk groups, again causing late presentation. The World Gastroenterology Organisation produced resource-based levels of care guidelines in HCC to help this,<sup>28</sup> though it is unknown how widely adopted they are in practice.

Inadequately managed hepatitis relates to HBV viral load. Viral load is often directly correlated to time to cirrhosis and HCC in West Africa, meaning poor management of chronic liver disease is associated with more HCC.<sup>5,29-33</sup>

Furthermore, increasing reports of lamivudine-resistant cases of HBV in West Africa are a concern, even in cases of lamivudine-based triple therapy. Therefore, it is highly recommended that tenofovir-based regimens are used preferentially to prevent HBV disease progressions.<sup>34-37</sup>

In summary, West African HCC accounts for a huge proportion of HCC mortality every year. This is due to the high prevalence of multiple strong risk factors in the West African population. The tumour is known to be aggressive, presenting in a young population in these countries, with poor survival rates. Numerous factors contribute to this, including medical, social and economic issues.

## GAPS IN CURRENT KNOWLEDGE

It is well-established in West Africa that HBV is endemic and highly hepatocarcinogenic. HCV infection is known to be a

major risk factor worldwide, though HBV is more prevalent in West Africa. However, a Gambian study suggested that HCV is implicated in 19-20% of HCC cases compared to 2.4% in West Africa as a whole.<sup>38,39</sup> Sub-Saharan Africa, in general, has a high prevalence of HCV, but research in the area remains scarce, with some data suggesting HCV screening of blood-products has only increased marginally in very few African countries since 2004.<sup>7,40</sup>

HIV/HBV co-infection remains an area requiring further work, in the long-term particularly as anti-retrovirals are becoming more readily available. There are limited data suggesting co-infection with HBV is associated with adverse outcomes of ART and liver disease, an area that requires further work in this region.<sup>41,42</sup>

Viral negative causes are also important. Aflatoxins have been considered carcinogens in HCC since the late 70s and 80s,<sup>43,44</sup> consequently much work has been done observing how aflatoxin mutations affect their carcinogenicity, but the exact mechanism by which it interacts with HBV or causes HCC independently remains unclear.

Lastly, in recent years the amount of obesity and alcohol use in West Africa has increased.<sup>44</sup> It has been documented that many countries in West Africa are on the “nutrition transition” as under-nutrition becomes less prevalent and rates of obesity and hypertension are rising, for example a recent study found obesity rates in Ghana to be 20-62%. Although data on diabetes and obesity in the region are suboptimal, if this rise is not controlled then the importance of tackling NAFLD in these countries will be ever increasing in the coming decades, especially as diabetes prevalence is rising with obesity.<sup>45-47</sup>

Alcohol-related liver disease (ALD) has been previously found to account for a tiny proportion of chronic liver disease in West African populations.<sup>48</sup> However, the small number of heavy binge drinkers has been rising for some time,<sup>49</sup> so it is unknown how prevalent ALD is at this time.

## SUGGESTIONS TO IMPROVE OUTCOMES IN THE FUTURE

We know the extreme prevalence of the risk factors mentioned above and inadequate management of the disease are the cause of the poor mortality seen in West African HCC.

Reducing the prevalence of risk factors, such as hepatitis B and C, in countries where the diseases are so endemic is difficult. However, continuing education and awareness of transmission is important, as is widening access to anti-viral drugs, which may be available through the Global Fund for hepatitis B in the future. Currently, while antivirals are only subsidised for hepatitis B patients co-infected with HIV, it may also prove cost-effective to provide this for all

chronic hepatitis B patients. Attention to effective universal coverage for birth dose hepatitis B vaccine is all important for future generations. Exposure to aflatoxin can be much reduced through better storage of crops, and good changes are being seen in many areas.

Management could be improved effectively through surveillance of high-risk groups to diagnose cancer at a curative stage. Although CT/MRI availability is scarce throughout West Africa, using alpha-fetoprotein and ultrasonography have been shown to be significantly effective at reducing mortality,<sup>23</sup> though ultrasound may only be available in tertiary centres in urbanised areas.

For the future, links with organisations, such as WHO, the EU and GAVI should be taken advantage of fully, to effect HCC treatment strategies in the sub-region, particularly in widening access to vaccination and antiviral drugs. Smaller-scale ventures aiding training and management of liver disease are also worthwhile, such as the links set up between the UK's Royal College of Physicians and the Tropical Health and Education Trust. Although there is much to be done until HCC in West Africa is thought to be a curable disease, steps are being taken every day to move forward in the right direction and decrease this terrible disease's burden.

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