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Epidemiology of Liver Cancer in Africa: Current and Future Trends

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Abstract

Hepatocellular carcinoma (HCC) is a disease of global public health significance with mortality on the rise, despite the preventable nature of its risk factors especially in Africa. It is now the sixth most common cancer worldwide, fifth in males, and ninth in females. HCC incidence and mortality are predicted to increase in African countries constrained by limited resources to combat endemic levels of viral infection and synergistic environmental risk factors. The changing nature of HCC etiology is particularly illustrated here with the traditional risk factors like viral hepatitis coexisting alongside high human immunodeficiency virus (HIV) prevalence and rapidly increasing urbanization that have promoted a sharp increase in additional risk factors like coinfection, type 2 diabetes mellitus, and obesity. Although there are some differences in etiology between North Africa and sub-Saharan Africa, risk factors like chronic viral hepatitis B and C, aflatoxin exposure, and iron overload predominate. Aggressive hepatitis B genotypes, combined with hepatitis B virus/hepatitis C virus/HIV coinfections and aflatoxin exposure, promote a more aggressive molecular phenotype. In parallel to a better understanding of the molecular etiology of HCC, policy and planning initiatives to address the burden of HCC must be anchored within the reality of the limited resources available. Establishment and coordination of cancer registries across Africa is needed to improve the quality of data necessary to galvanize action. Preventive measures including hepatitis B vaccination programs, measures to prevent maternal-to-child and child-to-child transmission, delivery of universally accessible antiretroviral and antiviral treatments, and reduction of dietary aflatoxin exposure can contribute markedly to reduce HCC incidence. Finally, the development of biomarkers and new therapeutic interventions will need a better understanding of the unique genetic and epigenetic characteristics of HCC on the continent. We present a narrative review of HCC in Africa, discussing present and future trends.

Keywords
- hepatocellular carcinoma
- epidemiology
- Africa
- HBV/HCV/HIV/ aflatoxin coinfections
- iron overload

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Liver cancer is a disease of global and public health significance. Despite its well-known preventable risk factors, mortality remains very high. The number of new cases has risen from 746,000 in 2012 to 841,080 in 2018, accounting for 5% of all cancers in the world.[1] It is the sixth most common cancer worldwide; fifth in males and ninth in females.[1] Males are more predisposed to HCC with male-to-female ratios as high as 4:1.[2–4] This gender difference has been hypothesized as being due to the higher exposure to carcinogens such as tobacco and alcohol, as well as the natural protective influences of estrogen against liver inflammation.[5–7]

Hepatocellular carcinoma (HCC) is the fourth most common cancer on the African continent, where its prevalence and etiology show some differences between North and sub-Saharan Africa (SSA).[8] Its incidence in a part of North Africa is twofold higher than in SSA, due to the unusually high prevalence in Egypt (4.6% in men) of hepatitis C virus (HCV) infection, which remains the primary risk factor in this country.[9] Compared with 0.2% in Morocco and Algeria and 0.7% in Libya.[8] In the other parts of North Africa excluding Egypt (Maghreb), the incidence of HCC is lower than in SSA,[9] due to lower levels of viral hepatitis, as well as low consumption of alcohol and aflatoxin exposure.[9]

In SSA, HCC is the second leading cancer for men and the third for women.[10] The high rates of HCC in SSA are driven by risk factors such as hepatitis B virus (HBV), HCV, aflatoxin exposure, alcohol, dietary iron overload, and the rising incidence of diabetes mellitus and obesity within the confines of limited and dysfunctional health care system.[11] Twelve African countries: Egypt, The Gambia, Guinea, Ghana, Liberia, Burkina Faso, Senegal, Equatorial Guinea, Mozambique, Cape Verde, and Guinea Bissau are in the top 25 countries with the highest rates of liver cancer in the world.[12]

In the 2018 World Health Organization (WHO) ranking of health care systems, the lowest third was a cluster of SSA countries, which unfortunately also have the highest burden of HCC in the world.[13] It is estimated that 78 (interquartile range [IQR] 68–89) million people are chronically infected with HBV in SSA, emphasizing the consequence of non-implementation of appropriate vaccination and disease management programs, combined with an absence of structured surveillance programs for HCC in the region.[14] Late presentation of HCC associated with limited screening and management resources result in an overall mortality to incidence ratio of 0.95 in SSA.[15]

The changing etiology of HCC in many African countries is in a transition stage, where traditional risk factors like viral hepatitis have combined with emerging factors to contribute to the rising incidence of HCC. Emerging risk factors such as diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), coinfection, and the nutritional transition have the potential of compounding the problem of HCC in Africa because these risk factors (e.g., NAFLD) are more difficult to manage than infectious pathogens.[16] Factors like coinfection (HBV/HCV/human immunodeficiency virus [HIV]) in SSA also result in a more aggressive, earlier onset.[17]

African countries will have to urgently implement pragmatic HCC-related policies if they aim to meet WHO 2030 guidelines. The WHO's ambitious but feasible goal of eliminating viral hepatitis by 2030 has the potential to have a major impact on the burden of HCC especially in SSA where 80% of the cases occurring in people under the age of 45 years are attributed to HBV; and in Egypt where hepatitis C accounts for 84% of cases with a median age of 58 years (IQR 53–63).[18]

This article reviews the traditional and emerging etiologies of HCC in Africa before providing a brief explanation of African HCC cancer pathways, the article then discusses HCC policy planning issues and expected future trends before making concluding comments (►**Fig. 1**).

Traditional Etiologies

Hepatitis B

The 2017 WHO Global Hepatitis Report estimates the overall HBsAg prevalence in the WHO Africa region at 6.1% (95% uncertainty interval 4.6–8.5).[19] In support of this high level of hepatitis B prevalence, Stanaway et al showed an increase in the yearly estimate of viral hepatitis deaths from 0.89 million in 1990 to 1.45 million in 2013, higher than the estimates for deaths from malaria, HIV, or tuberculosis.[20] Also recorded in the same period was the observation that viral hepatitis increased from the 10th to the 7th leading cause of death globally.[21] HBV has been identified as the second most dangerous carcinogen after tobacco,[22] but is almost entirely vaccine preventable. HBV is a major risk factor for the development of HCC in most regions of Africa, especially SSA, where HBV-related liver cancer is the most common malignancy of men in 12 countries[23] and the most common cause of premature death.[2] In SSA overall, HCC is the second leading cancer in men and the third for women.[24] SSA has been described by the WHO as a hyperendemic region for HBV infection. While HBV is responsible for 50% of HCC globally, it accounts for 55% of HCC in SSA.[4,25] The prevalence of HBsAg positivity varies across the regions of Africa, with HCC occurrence mirroring that of HBsAg. The prevalence of chronic HBV infection is due in part to the lack of screening of pregnant women for HBV infection and consequent poor protection of babies of infected mothers. In a study done in Namibia, 5.3% of pregnant women were found to be infected with HBV.[26] There is also poor uptake of the hepatitis B birth dose vaccine. Despite a longstanding recommendation from WHO for use of the birth dose vaccine for prevention of chronic HBV infection, which was reiterated in 2017, as of 2019, only 10 of the 47 countries in Africa had incorporated the WHO recommendation of routine birth dose vaccine into the Expanded Program on Immunization (EPI) and HBV vaccine coverage as part of this program is only 77%.[27]

Being born in Africa has been shown in a study to be associated with early development of HCC.[28] In Africa, viral hepatitis, especially hepatitis B infection, is acquired at an early age, often exacerbated by HIV coinfection and exposure to carcinogens such as dietary aflatoxins and iron overload. HBV-induced HCC tends to occur in the late 30s and early 40s,[4] at least a decade earlier than in Western countries,

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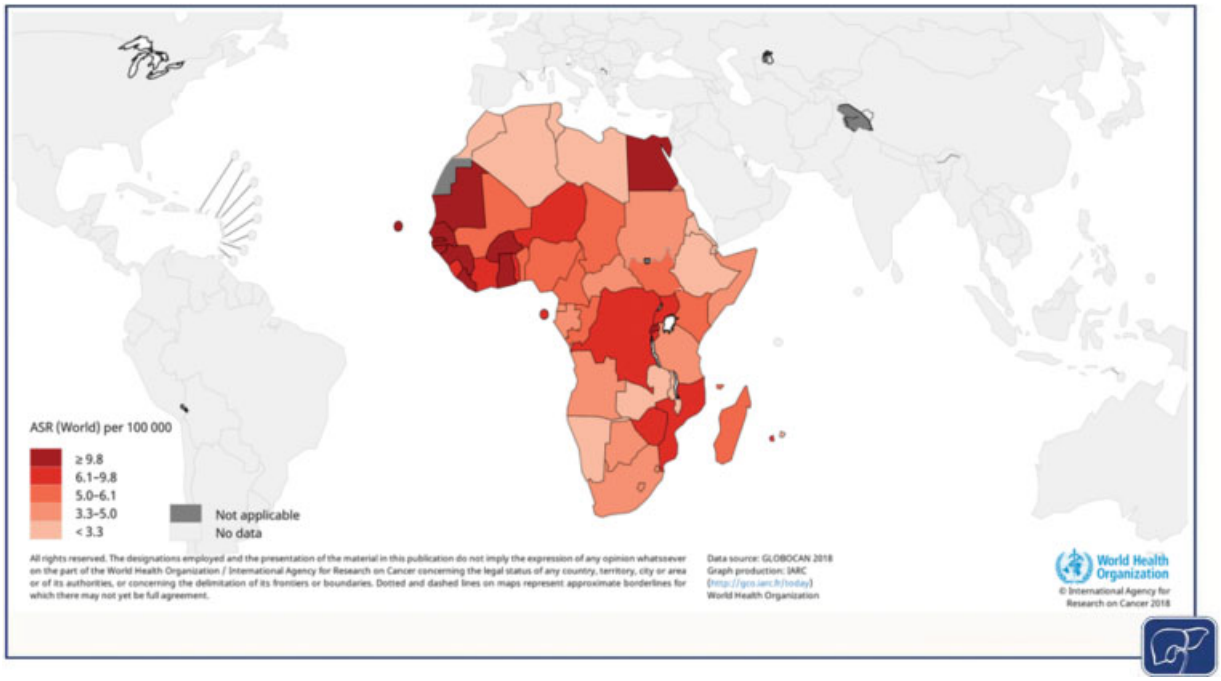

Fig. 1 Estimated age standardized mortality rates from liver cancer across Africa 2018. Source: IARC-GLOBOCAN 2018.

where HBV and HCV infection are typically acquired in adolescence or later and HCC rarely develops before 45 years of age.[29,30]

A multicountry observational study from the Africa Liver Cancer Consortium showed a substantial difference in age of onset of HCC in Egypt in North Africa compared with 11 other African countries, with a mean age of 58 years in Egypt versus 46 years in the other African countries. HCV accounted for 84% of HCC in Egypt, whereas HBV was the leading cause in the other African countries, responsible for 55% of 1,082 HCCs.[4] Notably, median survival after HCC diagnosis was substantially longer in Egypt at 10.9 months (9.6–12.0) compared with 2.5 months (95% confidence interval [CI] 2.0–3.1; $p < 0.0001$) in the other African countries.[4] This was likely due in part to the significantly higher rate of HCC diagnosis while under surveillance, as 93% of HCC patients in Egypt were diagnosed with Barcelona Clinic Liver Cancer (BCLC) stages A, B, or C disease, while only 28% of patients from other African countries were diagnosed at BCLC stages A, B, or C.[4] In addition, treatment options for HCC were limited in the other African countries, while 76% of HCC patients in Egypt received HCC-specific treatment, only 3% of patients in the other African countries received specific treatment for HCC (►**Fig. 2**).[4]

While the exact causes for the early onset of HCC in SSA are not completely elucidated, we can infer from the available data that a multifactorial combination of country of birth, early age of acquisition of HBV, and specific HBV genotype or subgenotype are important factors.[32–34] Recent studies have shown that in Southern Africa, HBV genotype A, particularly subgenotype A1, causes more aggressive liver disease, progressing faster to HCC.[35] While studies from outside the continent have shown that genotype C and certain mutants HBV strains are important in early progression to HCC.[36] HBV genotype C is not widely distributed in Africa[36,37] however, a multicenter study in North Africa identified genotype D as an independent risk factor for HCC.[9] In Western Africa, HBV genotype E is most prevalent.[38] Genotype E appears to have a relatively lower replicative rate, but is nonetheless highly oncogenic. Consequently, it is associated with HCC in patients with relatively lower viral loads compared with the viral loads seen in genotype C-infected HCC patients in Asia. This has raised the question whether patients with HBV genotype E should be treated at lower viral load cut-offs than the currently recommended cut-offs which are primarily based on data from Asian centers (►**Fig. 3**).

Hepatitis C

The prevalence of chronic HCV infection varies globally with the highest viremic prevalence of 6.3% (4.5–6.7) in Egypt, equivalent to 5.6 (4.0–6.0) million HCV-infected individuals.[47] The overall HCV seroprevalence in SSA is 3.0% with an estimated viremic (HCV ribonucleic acid [RNA]) prevalence of 1.0% (0.7–1.6) or 11.0 (7.0–16.0) million HCV-infected individuals. The remarkably high prevalence of HCV infection in Egypt is due to extensive iatrogenic transmission during national campaigns against schistosomiasis between the 1920s and the early 1980s. The prevalence of HCV in HCC patients is also high in central and western Africa, with HCV prevalence of 1.7% in South Africa, 1.6% in Zimbabwe and Namibia, 2.7% in Ethiopia, 3.9% in Angola, and 6.1% in Burkina Faso.[48] HCV, HBV, and diabetes mellitus have been shown to be the main etiologic factors for HCC in North Africa. A multicenter case–controlled study in Tunisia, Morocco, and Algeria showed 60% anti-HCV and 18% HBsAg positivity and an 18% prevalence of diabetes mellitus among HCC patients.[9]

In a study done in Italy, the risk of developing HCC was increased 17-fold in HCV-infected persons compared with

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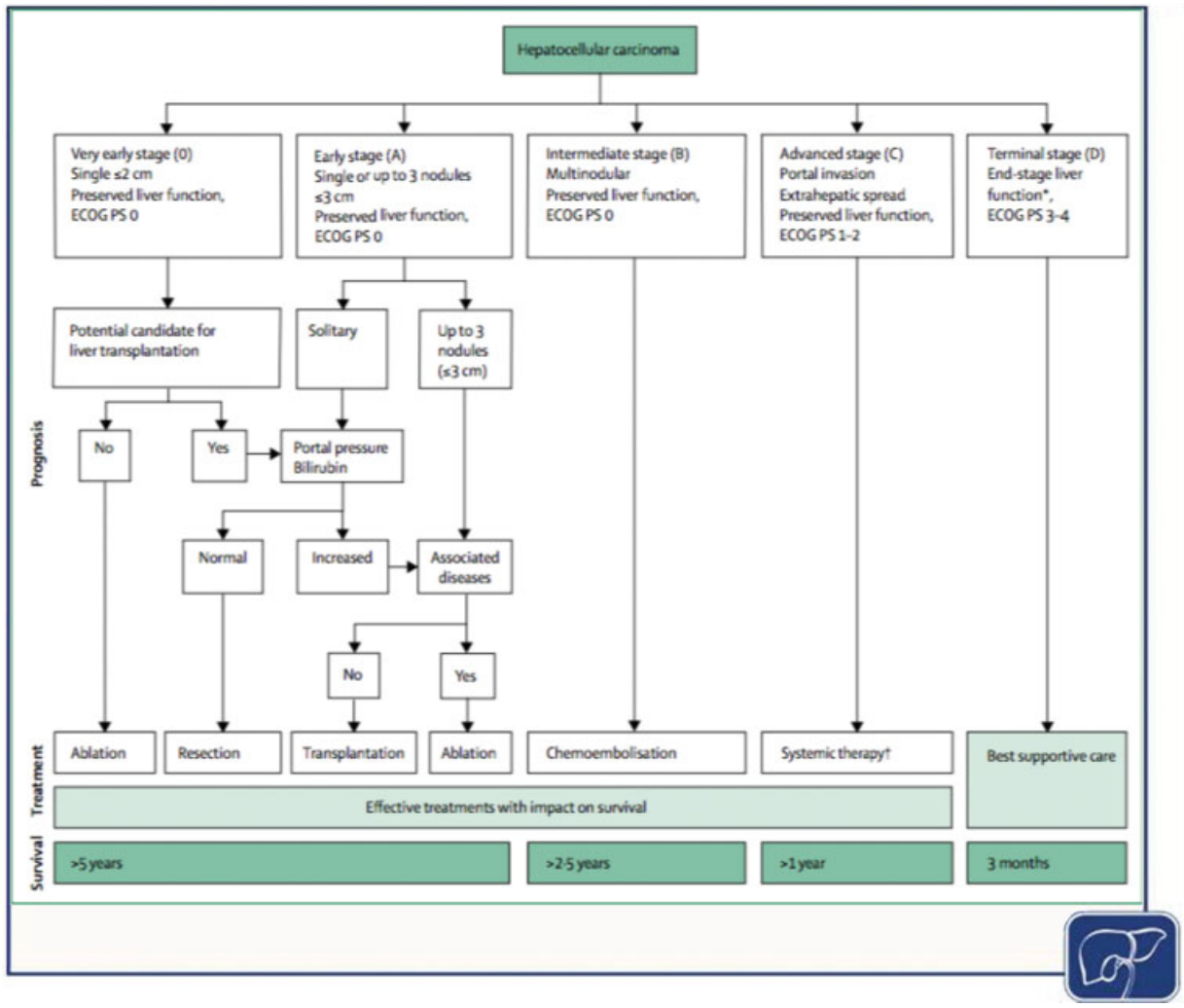

Fig. 2 Barcelona Clinic Liver Cancer (BCLC) staging[31]: The BCLC staging of hepatocellular carcinoma and treatment allocation . Adapted from Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *The Lancet*. 2018.

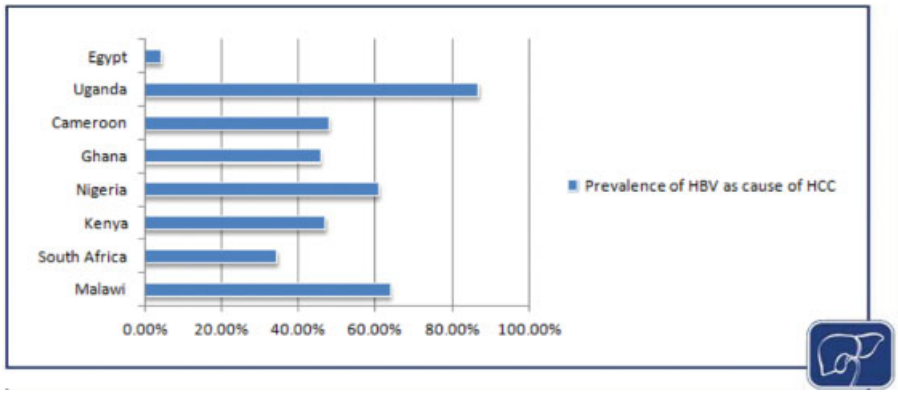

Fig. 3 The prevalence of hepatitis B as a risk factor for hepatocellular carcinoma (HCC) in 9 African countries: Egypt,[39] Uganda,[40] Cameroon,[41] Ghana,[42] Nigeria,[43] Kenya,[44] South Africa,[45] and Malawi.[46]

HCV-negative controls (95% CI, 14–22).[49] The annual rate of development of HCC in persons with HCV-related cirrhosis ranges from 1 to 5%.[50] HCV coinfection with HBV or HIV, the presence of diabetes mellitus, obesity, and other factors including male sex, older age, age at infection, and heavy alcohol ingestion are important cofactors that contribute to the risk for progression to HCC.[50,51] Viral factors such as the specific HCV genotypes and subgenotypes are also important.[52]

There has been a growing concern and controversy about an apparent unexpected increase in the number of HCC cases

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developing following direct acting antiviral (DAA) therapy for HCV, as well as higher than expected rates of recurrence following surgical resection in patients receiving DAA treatment. A multicenter study in Spain showed a surprisingly high 27% recurrence rate of HCC in patients who received DAA.[53] Similarly, an Egyptian prospective study also demonstrated an apparent increase in risk of recurrence, with an incidence rate ratio of 3.83 (95% CI: 2.02–7.25).[54] However, a subsequent meta-regression study, adjusting for follow-up and age, showed no association of DAA therapy with higher HCC incidence (relative risk [RR] 0.68; 95% CI: 0.18–2.55; $p = 0.55$) or recurrence (RR 0.62, 95% CI: 0.11–3.45, $p = 0.56$).[55] Subsequently, DAA therapy has been confirmed to improve liver-related mortality due to decompensation and HCC.[56] Although the incidence of HCC is reduced by DAA, the rate of recurrence of HCC remains a problem in cirrhotic patients treated with DAAs especially in those with unclassified nodules prior to therapy.[57] Even though the risk of decompensation and mortality is reduced by achieving sustained virologic response (SVR), there still exist the risk of HCC.[58] Two recent studies have also demonstrated a reduction in all-cause mortality in patients who achieved SVR compared with those who did not.[56,59]

Aflatoxin Exposure

Dietary fungal aflatoxins, of which the most important is aflatoxin B1 derived from *Aspergillus flavus* and *Aspergillus parasiticus*, are classified as class 1 carcinogens by the International Agency for Research on Cancer.[60] Aflatoxin metabolites intercalate into the host genomic deoxyribonucleic acid (DNA) and lead to a specific pattern of gene mutations, including most classically a mutation in TP53, the gene encoding the p53 tumor suppressor, that results in a substitution of arginine for serum at position 249 of the p53 protein.[61] Epidemiologic studies have shown a synergistic interaction between aflatoxin exposure and chronic HBV infection in the causation of HCC.[62] Studies in woodchucks chronically infected with woodchuck hepatitis virus, which is a hepadnavirus closely related to HBV, also show a synergistic hepatocarcinogenic effect of aflatoxin B1 with hepadnaviral infection.[63]

The tropical climate of SSA provides an ideal environment for *Aspergillus* proliferation on agricultural legume and grain crops in the late stages of maturity prior to harvest and also after harvest if there is a high moisture content during storage. It is not unusual to find staple foods and condiments in open markets across Africa with very high levels of aflatoxin contamination. Studies from across Africa have demonstrated aflatoxin concentrations of 49 parts per billion (ppb) in nuts and seeds in Egypt, 1,862 ppb in nuts and nuts products in Nigeria, 66 ppb in rice grains in Ghana, 35 ppb in sorghum in Kenya, 39 ppb in peanuts in Zambia, 87 µg/kg in peanut butter in West Sudan, and contamination of 42% of cow's milk samples in Cameroon.[64–69] Several studies have also shown that locally brewed alcoholic drinks also frequently have aflatoxin levels far above the recommended limits for human consumption.[70–72]

It is also postulated that in Egypt and some parts of North Africa, aflatoxin contamination of food products may also be playing a role in the rising incidence of HCC. A study in Egypt showed that both local and imported samples of peanut butter were positive for aflatoxin B1 (17.5 and 20%, respectively), with concentrations that ranged from 3 to 25 µg/kg.[73]

Hepatitis B virus and dietary exposure to aflatoxin coexist in most parts of Africa, areas with the heaviest burden of and the youngest patients with HCC.[2]

Aflatoxin is a relatively neglected risk factor for HCC in SSA, and this inattention may prove costly, as aflatoxin exposure may contribute to a multiplicative increase in risk for HCC and also be partly responsible for the young age of onset of HBV-associated HCC in SSA.[74] The relative paucity of research on the role of aflatoxin in development of HCC in SSA and effective prevention of aflatoxin-induced liver carcinogenesis is reflected in fact that the entire Abstract books of the first Conference on Liver Diseases in Africa (2018) and the annual meetings of the European Association for the Study of the Liver in both 2018 and 2019 had no mention of aflatoxin in any research abstract. To reduce the contribution of aflatoxin to risk of HCC, it is imperative that agricultural extension services be deployed to train farmers, particularly in rural communities, in optimal methods for harvesting and storage of crops that are prone to aflatoxin contamination. Where possible, regulations should be enacted and enforced to limit the entry of aflatoxin-contaminated crops into the food supply. Finally, in the long term it might be possible to either encourage the use of alternate staple foods that are less prone to aflatoxin contamination, such as with the switch from corn to rice in parts of China that led to a substantial decrease in aflatoxin exposure, as well as to develop aflatoxin-resistant variants of crops such as corn and other grains that are less prone to fungal infection or toxin production (►**Fig. 4**).

Iron Overload

Iron overload is a proven risk factor for HCC, independent of any underlying liver disease[75,76] In the setting of iron overload where the total body iron exceeds 5 g, the storage protein becomes denatured when the safe level of sequestration is exceeded, releasing large amounts of the metal into the



Fig. 4 Mold contaminated grains used for preparing local alcoholic brew. Photo credit: Pantong Mark, Jos, Nigeria, 2014.

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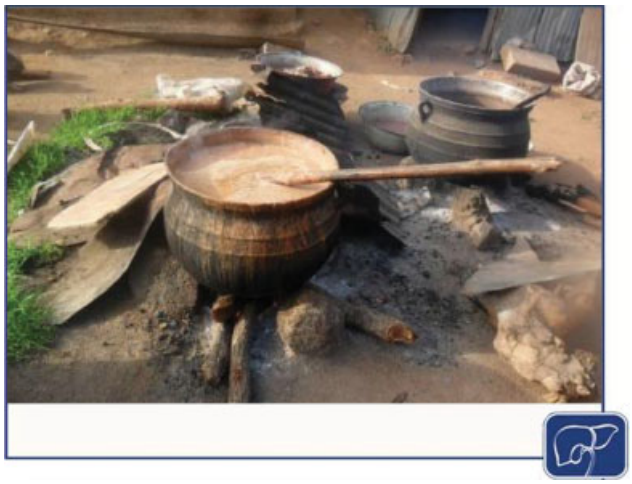

Fig. 5 Iron pots used for preparing local alcoholic brew. Photo credit: Pantong Mark, Jos, Nigeria, 2014.

cytoplasm of the hepatocytes. Thus, the liver is the organ most affected by iron overload.[76] Excess iron in the liver was first well-documented in two human diseases: hereditary hemochromatosis (HH) and African dietary iron overload (previously named Bantu visceral siderosis) (►**Fig. 5**).[76]

Geographical Distribution

African dietary iron overload (formerly called Bantu siderosis) was first identified in the southern and central parts of SSA among rural dwellers who consumed large quantities of home-brewed beer with high iron content (46–82 mg/L), several orders of magnitude higher than the commercially brewed counterpart (< 0.5 mg/L).[76] This results in hepatic iron concentrations similar to those in HH and may be complicated by portal fibrosis or, less often, by cirrhosis.

The method of brewing this beer entails fermenting locally produced crops such as sorghum, millet, corn, and barley in steel/iron barrels that are mostly used chemical containers, especially in Nigeria.[23] The resulting drink is contaminated by a high concentration of ionized, highly bioavailable iron leached from the iron and steel ware. Recently, studies have shown that genetics may also play a role in this dietary iron overload, as not all persons who drink the home-brewed beer are affected; a combination of excess iron and functional differences in ferroportin appears to be the probable cause of the iron overload.[77]

Emerging Etiologies

Nonalcoholic Fatty Liver Disease

According to the WHO, obesity is an emerging problem of the developing world, with its associated comorbidities on the rise in Africa.[78] The prevalence of obesity is higher in the urban compared with the rural areas of Africa.[79] This may be a reflection of changing lifestyles, especially with regards to caloric intake and sedentary lifestyles in the rapidly urbanizing cities across Africa.[80] A study done in Cameroon demonstrated a change toward an increase in the waist circumference over a 10-year period in an urban population.[81] This reflects a changing culture toward westernization of the urban areas with dramatic changes in lifestyle and diet.[82] With the rising prevalence of obesity and type 2 diabetes mellitus (T2DM), NAFLD, which is the hepatic manifestation of the metabolic syndrome and a leading cause of chronic liver disease globally, is expected to rise.[83]

In North African countries and SSA, T2DM is the most common form of diabetes (90–95%). The main risk factors for T2DM include obesity, rapid urbanization, physical inactivity, aging, nutrition transitions, and socioeconomic changes.[84,85] NAFLD and T2DM are both considered to be components of the metabolic syndrome. A study done over a 34-year period has shown T2DM to be on the rise across the African continent, with the age-standardized prevalence of diabetes increasing from 3.4 (1.5–6.3) to 8.5% (6.5–10.8), and from 4.1 (2.0–7.5) to 8.9% (6.9–11.2) for men and women, respectively.[86]

This unrecognized burden of obesity and T2DM with the associated risk of NAFLD which can progress to HCC without cirrhosis, poses a major challenge to the early detection and effective management of HCC. Even in developed countries, the early detection of HCC is problematic. In Africa, the combination of obesity, T2DM, and NAFLD is associated with the late presentation of larger tumors not amenable to curative therapy.[87] It was previously thought that Africans do not have as much hepatic fat as they do subcutaneous abdominal fat which was thought to confer some protection against steatosis compared with visceral fat. However, several studies have demonstrated that once NAFLD sets in, Africans are at similar risk of progression to cirrhosis and HCC as Caucasians.[88,89]

HIV/HCV/HBV Coinfection in HCC

Sub-Saharan Africa is also the epicenter of the global HIV pandemic[90] and coinfection with HIV and HBV is common.[91,92] The advent of antiretroviral therapy has modified the outcome for HIV-infected patients; a once highly fatal disease entity is now fast becoming a chronic illness. This has led to improved survival, but has also created room for morbidities that were hitherto not seen due to their rapid mortality. One such morbidity is varying manifestations of liver disease, which are increasingly becoming a major source of mortality in HIV patients.[93]

Leading the liver diseases that affect HIV patients are HBV and HCV, which share routes of transmission with HIV.[94] The quality of the T cell response is significantly impaired in HIV-1–HBV coinfected patients, with the HBV-specific T cells rarely producing more than one cytokine, and therefore responding to fewer HBV proteins than in monoinfected patients.[95] Also involved in the pathogenesis of HIV–viral hepatitis coinfection are several other mechanisms, including oxidative stress induced by HIV, which produces reactive oxygen species (ROS) and activates hepatic stellate cells,[96] immune-mediated liver injury via the activities of Kupffer cells and hepatic stellate cells,[97] and bacterial translocation via increased lipopolysaccharides.[98]

As life expectancy increases, patients with HIV live long enough to develop hepatic fibrosis, cirrhosis, and ultimately

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HCC.[99] HIV acts as a catalyst for progression to cirrhosis and HCC in the setting of HIV/HBV or HIV/HCV coinfections.[99] Studies have demonstrated accelerated disease progression in the setting of HIV coinfections.[94,100,101] HCC surveillance is virtually absent in the algorithm of care for viral hepatitis in HIV patients in most care centers in Africa. Investigators from Uganda have demonstrated high rates of significant fibrosis (FibroScan score > 9.3 kpa) among HIV coinfected patients.[102] Other studies have demonstrated accelerated progression from fibrosis to HCC.[94,96,103] We have also demonstrated that the probability of survival at 3 months was 22 versus 48% in HIV-infected and uninfected patients, respectively ($p = 0.02$). Further, median time to death was significantly shorter in HIV-infected versus uninfected patients all with advanced liver disease (23 [IQR 12–88] days vs. 80 [IQR 26–177] days; $p = 0.04$).[104] A recent study has also demonstrated an increased risk of HCC in HIV patients with detectable viremia and low CD4 counts even in the absence of cirrhosis.[105]

Pathogenesis of Hepatocellular Carcinoma

The common conditions that influence the progression of HCC tumorigenesis across the different etiologic agents include a multistep process involving a combination of inflammation, oxidative stress, epigenetic changes, fibrosis, and liver cirrhosis.[106,107] Although the precise mechanism of hepatocellular tumorigenesis is still unknown, there is considerable understanding of the processes involved.[108] A host of genetic aberrations are involved in the whole process of hepatocarcinogenesis and the etiology influences the genetic aberrations that occur.[85]

In patients with HBV a critical role is played by HBx, a protein that causes many cellular alterations directly by interfering with apoptosis, DNA repair mechanisms, and indirectly via large increases in intracellular ROS, causing more than 20 types of oxidative DNA damage which is mutagenic.[109,110] The HCV core protein has a role in the development of HCC by activation of signal transducer and activator of transcription 3 and interleukin (IL)-6, enhancing telomerase activity. This can lead to transformation in the hepatocytes that have potential oncogenic implications. Infected HCV cells have also demonstrated increased mutations in the genes such as the BCL-6, TP53, and β-catenin (CTNNB1).[111] In both HBV and HCV, telomerase activity is implicated. The promoter region of the telomerase reverse transcriptase (TERT) is the site of frequent somatic mutations.[89] It is found to be the first mutation in preneoplastic lesions of liver cirrhosis and also the last step of transformation of an adenoma into HCC.[112] In fact, TERT mutation is the most common mutation in HCC with up to 60% of HCC having this mutation.[113]

The relationship between aflatoxin exposure and HCC occurrence has been highlighted by molecular biological studies on the *p53* tumor suppressor gene, the gene most commonly mutated in many human cancers. Many studies of *p53* mutations in HCC occurring in populations exposed to high levels of dietary aflatoxin have found high frequencies of G:C → T:A transversions, with clustering at codon 249. Apart from this genotoxic mechanism, there is recent evidence that has demonstrated that aflatoxins can also cause epigenetic modifications that may lead to differing HCC molecular phenotypes.[114] DNA methylation, histone modification, and noncoding RNAs have all been demonstrated.[114] There is also evidence for interplay of this fungus and its metabolites aflatoxin B1 with other risk factors of HCC in the early progression to HCC. Some studies have demonstrated a synergistic interaction between hepatitis B and aflatoxins. This was initially described in animal models but has also been shown in humans.[74,115] Patients exposed to both carcinogens show a 59.4-fold increase in the risk of developing HCC as HBV is thought to potentiate the genotoxic effect of aflatoxins.[116]

In nonalcoholic steatohepatitis (NASH)-related HCC, the transition that occurs from a dysplastic hepatic cell to a malignant cell involves multiple steps that affect signaling pathways. Here, activation of oncogenic mechanisms is via genetic, metabolic, immunologic, and endocrine pathways.[117] The development of hepatic inflammation and fibrosis is affected by deregulated activation of nuclear factor-kappa B (NF-κB). While chronic activation of NF-κB increases the production of tumor necrosis factor (TNF) and HCC development,[118] there is also overexpression of miR-21 in mouse models of NASH which promotes HCC growth and migration of HCC cell lines.[119]

Policy and Planning

The publication of the WHO guidelines for management of hepatitis B and C are signs that these forgotten diseases (compared with HIV and malaria) are increasingly capturing the attention of global health institutions. The global health sector strategy of the WHO on viral hepatitis, started in 2016, aims to achieve a 90% reduction in new cases of chronic hepatitis B and C and to reduce mortality due to hepatitis B and C by 65% by 2030. The global political landscape is in favor of the elimination of viral hepatitis which accounts for over 80% of all liver cancers in Africa.[120]

To achieve elimination several coordinated steps have to be in place. The first is the establishment of national viral hepatitis plans to guide implementation strategies. As of December 2017, there were seven countries in SSA who had developed a hepatitis plan: Ghana, Nigeria, Ethiopia, Côte d'Ivoire, Senegal, South Africa, and Mauritania.[121]

Second is the prevention of HBV mother-to-child transmission by using large-scale screening of pregnant women and implementation of the HBV birth dose vaccine. The impact of the HBV vaccine in Africa against the spread of hepatitis has been demonstrated in a small community-based HBV prevalence study in Malawi with no documented HBV infections in children under the age of 5 in a community-based study of the prevalence of hepatitis B and also in Gamba.[46,122] The PROLIFICA project had shown that a large-scale test-and-treat approach is feasible and cost-effective in SSA if a high coverage of community-based screening and good linkage into care is present.[2] Use of nucleoside analogues has been shown to reduce fibrosis and progression to HCC. Whether "a treat all

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infected" approach as in the case of HIV will be feasible and necessary is a subject for further research. Since chronic HBV infection is asymptomatic and progression to active disease silent, this may prove a viable concept in preventing HCC.

There is a shortage of reliable prevalence data on which policy and planning can be based. Therefore, seroprevalence studies should be included in national control programs to aid control of HBV and HCV. The availability of highly effective DAA drugs with ability of achieving 99% SVR for HCV infection has been the big game changer in the hepatitis landscape. The initial issue of cost of DAAs has been overcome with the availability of cheaper generics ($45 in Egypt) which are as effective as the innovator products, through the access programs. Real-world data using generic DAAs has shown SVR of 98.1% compared with originator drugs of 98.2%, $p = 1$.[123] However, a recent study has shown far fewer SVRs among Rwandans with genotype 4r (SVR = 56%).[124] Some Africans with nonsubtypable genotypes G1 and G4 have also shown unacceptably low SVRs of 73% and total failure, respectively. If confirmed, these observations may have important implications for the choice of DAA regimens to achieve elimination of hepatitis C in Africa.[124]

An interesting area beckoning research in Africa is the area of the gut–liver axis and its interaction with aflatoxicosis. Studies have demonstrated the role of gut dysbiosis in hepatic carcinogenesis with some research focusing on the interplay between the microbiome and aflatoxin. These studies have revealed that the gut epithelium is altered by aflatoxicosis, with the gut microbiome aiding removal of the mycotoxins from the gut thereby decreasing absorption. With dysbiosis, binding and absorption of mycotoxin is enhanced.[125,126] This observation is bolstered by the finding that probiotic supplementation significantly reduces the biologically available effective toxic dose of aflatoxin. With their ability of normalizing gut microbiota, probiotics potentially offer an effective dietary approach to reduction of risk for liver cancer.[127]

WHO Global Strategy and the WHO Regional Strategy (for Africa) to Reduce the Harmful Use of Alcohol, has been available since 2010 and accepted already by some countries but with variable implementation.[128] Alcohol is associated with 40% of cases of HCC in Southern SSA and 29% in Western SSA.[129] Definitive measures deliberately addressing specific features of alcohol policy in the continent are needed, these include focusing on alcohol availability, unrecorded and illicit production, outlet licensing, the expansion of formal production, marketing initiatives, and taxation policies.[130]

Several interventions are required to tackle the problem of aflatoxin contamination of food produce on the continent. Aflasafe is a safe natural solution to the problem of aflatoxin: a biocontrol product produced by International Institute of Tropical Agriculture and partners that drastically reduces aflatoxin in crops. It is homegrown in Africa and contains nontoxic strains of Aspergillus native to each community that eventually eliminates the toxin-producing species.[131,132] Local versions are available in 6 countries and in development in 11 other countries. If correctly applied, an 80 to 90% reduction in aflatoxin contamination of crops can be attained. Only one application per cropping season is needed.[131] Aflasafe works from the farmland to the plate to stop contamination of grains from reaching dangerous levels and makes foods like maize and groundnuts safe to eat. This may be the key intervention that will modify the landscape of aflatoxin-induced HCC.

The Partnership for Aflatoxin Control in Africa is an innovative group that aims at coordinating aflatoxin mitigation and management using 5 thematic areas over a 10-year period. These areas include: research and technology for prevention and control of aflatoxins; policies, legislation, and standards for the management of aflatoxins; growing commerce and trade and protecting human health from aflatoxins; enhancing capacity for effective aflatoxin prevention and control; and public awareness, advocacy, and communication.[133]

Though most African countries may not achieve the target of viral hepatitis elimination by 2030, immunization to reduce new HBV infections, screening and treatment of those already infected, and access to cheaper DAA drugs for HCV will all impact the incidence and mortality from HCC in the medium and long term. Safe and effective treatments for HBV exist, but treatment access is severely limited in SSA. The recent WHO Global Policy Report on the Prevention and Control of Viral Hepatitis reported that only 16.7% of WHO-AFRO countries have publicly funded HBV treatment available, despite highly effective nucleoside analogues, such as tenofovir, being available in most countries in SSA at generic prices for the treatment of HIV. This lack of accessibility to affordable, effective HBV treatments needs to be addressed urgently if any gains are to be made in controlling the costly disease burden of HBV-related liver disease and HCC.[4,121]

Future Trends

Though the majority of the risk factors for HCC are preventable or treatable, GLOBOCAN estimates a continued rise in HCC incidence over the next 20 years. Since the etiology of HCC in Africa is virally driven,[120,134–136] elimination of viral hepatitis in SSA will surely influence these epidemiologic trends. It is envisaged that the WHO strategies for elimination of viral hepatitis by 2030, as well as measures to reduce aflatoxin, obesity, T2DM, and NASH/NAFLD, may significantly reduce the incidence of HCC in Africa. Using metrics that include implementation of harm reduction, removal of restrictions on treatment, increasing the number of diagnosed patients, and a sufficient treatment rate to achieve the 2030 target for elimination, the Centre for Disease Analysis has updated the list of countries on target to achieve this goal. Unfortunately, Egypt is the only African country that made the list,[137] however, Rwanda has made great strides in their HCV elimination program.

Based on another Centre for Disease Analysis model, it is unlikely that other African countries will be able to meet the WHO 2030 targets for elimination. Even if the proposed 40 million people are diagnosed and 9 million treated annually by 2025, mortality can only be reduced by 61% in the available time frame, thus not achieving the WHO 2030 target for a 65% reduction.[138]

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The mortality from HCC is also expected to rise globally. The GLOBOCAN projection for Africa as a whole is 108% from 63,562,[1] and an estimated 108% from the 2018 figures for West Africa. Using a modeling method with data on 17 African countries, including Nigeria, Ethiopia, and Gabon, the Center for Disease Analysis projected an increase in mortality from HCC by up to 7% from 40 million cases of viral hepatitis.[138] These figures will definitely rise when the underestimation due to dysfunctional/absent cancer registries, and incomplete data capturing, are taken into consideration.

This problem may however be surmounted with progress in the activities of groups such as the African Cancer Registry Network (AFCRN) whose objective is to improve the effectiveness of cancer surveillance in SSA. AFCRN provides expert evaluation of current challenges and technical support to address the identified barriers. The long-term goal of AFCRN is to strengthen health systems and create research platforms for problem identification prioritizing targets for intervention.

There is a global search for biomarkers of HCC that will predict future occurrence of HCC or lead to early detection of tumors when they are still amenable to curative therapy. These future prospective markers, which are still largely a work in progress, have the potential of altering the abysmal outcome of late diagnosis of HCC especially in Africa. Different strategies and approaches have been considered. Urinary biomarkers have been reported using metabolomics that can discriminate between chronic hepatitis, cirrhosis, and HCC.[139] The PROLIFICA project enrolled 944 patients from The Gambia and Nigeria (189 HCC, 109 cirrhosis, 528 chronic hepatitis B carriers, and 168 healthy controls). Untargeted metabolic profiling was performed and our results showed and validated that there is a reliable signature of metabolic disturbances in HCC compared with pre-HCC liver diseases. These biomarker findings have also been replicated among U.K. patients with smaller tumors and early disease.[140] In Egypt, using soluble cytokines among HCV HCC patients with normal ALT levels, researchers were able to exclude the presence of HCC among patients with 90% sensitivity and 70.6% specificity with soluble TNF-II is 389 pg/mL or IL-8 is $<$ 290 pg/mL, thus making this a possible biomarker.[141]

Another recent study had also demonstrated epigenetic signatures in micro-RNA that have the ability of predicting which patient with cirrhosis will progress to HCC.[142] The use of liquid biopsy to detect early HCC using technology centered around cell-free DNA has also produced results that show a lot of promise for detecting early tumors in HBV-infected patients. A recent pilot study of the HCC screen assay showed a 100% sensitivity and a 94% specificity in the cohort.[143] Discovery of a panel of biomarkers that can be used as a point-of-care screening test could have a major impact on the prevailing late diagnosis and its attendant poor outcome.

The last 10 years have seen the development and availability of more systemic chemoactive products against HCC than in the past 50 years put together. Since the approval of sorafenib, a multikinase inhibitor that improves the overall survival by approximately 3 months, regorafenib, cabozantinib, nivolumab, and pembrolizumab have been approved for second line therapy, with ramucirumab also approved for the subgroup of patients with alpha fetoprotein levels greater than 400 ng/mL. Lenvatinib has also been shown to be noninferior to sorafenib in first line treatment of HCC. Sorafenib consistently improved median time to progression (hazard ratio [HR], 0.40–0.64), except in HBV-positive patients (HR, 1.03).[144] The impact of this drug is yet to be felt on the African continent with only a few studies available. A study reporting real-life experience using sorafenib in a cohort of 130 Egyptian patients, showed a median survival of 5 months (CI: 4.2–5.8) and progression-free survival of 4 months (CI: 3.5–4.5). The disease control rate was 45.4% with 2 patients experiencing complete remission (1.2%).[145]

Immune checkpoint inhibitors have the potential to substantially alter first line treatment for HCC.[146] Unfortunately, it was recently reported that a study of pembrolizumab versus sorafenib in first line treatment of HCC did not meet the target endpoint and was negative. While the details of the study results are awaited, the results of another study comparing nivolumab versus sorafenib in first line are also awaited.[147] The main challenges with the targeted therapy and immune checkpoint inhibitor drugs will be centered around cost and availability, especially in SSA. Clinical trials need to be undertaken in Africa

Conclusion

Hepatitis B and C, especially B, are the most important risk factors for HCC in Africa. The global health community has now acknowledged the public health importance of these viruses with the WHO spearheading a strategy for elimination of viral hepatitis by 2030 through immunization at birth and finding and treating those already infected. Only 10 of 47 African countries have implemented the WHO recommendation for birth dose vaccination of all infants against HBV, while all the WHO Africa countries have added the hexavalent vaccine into their EPI with poor to average coverage. The number of patients on treatment for chronic hepatitis B and chronic hepatitis C are increasing continent-wide.

Aflatoxin has been shown to be important either as a standalone risk factor or in synergism with HBV and HCV infection in the initiation of HCC. The introduction of Aflasafe to check the toxin producing *A. flavus* will hopefully lead to a substantive decrease in aflatoxin-induced HCC.

The aforementioned measures have the potential to dramatically reduce the prevalence of HBV, HCV, and aflatoxin-induced HCC in the coming years if the available preventative strategies are effectively implemented.

However, given the increasing adoption of a western lifestyle in Africa with an associated increase in obesity and T2DM, the contribution of NAFLD/NASH as a risk factor for HCC is expected to rise.

Therefore, efforts to reduce the incidence of HCC should be holistic, targeting infections, toxin exposure, and metabolic risk factors.

There are promising signs for an easier and earlier diagnosis through serum markers, and newer drugs on the horizon may also impact the outcomes of HCC in the near future.

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Conflicts of Interest

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