More than 80% of global hepatocellular carcinoma (HCC) patients are estimated to occur in sub-Saharan Africa (SSA) and Eastern Asia. The most common risk factor of HCC in SSA is chronic hepatitis B virus (HBV) infection, with the incidence highest in West Africa. HBV is highly endemic in SSA and is perpetuated by incomplete adherence to birth dose immunization, lack of longitudinal follow-up care, and impaired access to antiviral therapy. HBV may directly cause HCC through somatic genetic alterations or indirectly through altered liver function and liver cirrhosis. Other risk factors of HCC in SSA include aflatoxins and, to a lesser extent, African iron overload. HIV plus HBV co-infection increases the risk of developing HCC and is increasingly becoming more common because of the survival of patients with HIV infection. Compared with the rest of the world, patients with HCC in SSA have the lowest survival. This is partly due to the late presentation of HCC with advanced symptomatic disease as a result of underdeveloped surveillance practices. Moreover, access to care and resource limitations further limit outcomes for the patients who receive a diagnosis in SSA. There is a need for multipronged strategies to decrease the incidence of HCC and improve its outcomes in SSA.

For reference, SSA is geographically composed of four regions: Central, West, East, and Southern Africa. The regional age-standardized incidence rates of liver cancer (for all ages, standardized to the world population) are 8.3, 6.5, 4.9, and 4.8 per 100,000 person-years in Western, Central, Southern, and Eastern Africa, respectively. Incidence of HCC in SSA is highest in West Africa, with highest incidence in Gambia and Guinea (Fig 1 and Table 1). The trends in liver cancer incidence over time have been studied only in individual cohort studies and hence may not suggest universal trends in SSA. A study from Uganda and Gambia showed that the incidence of HCC has been increasing over time until mid-to-late 2000s. Mortality closely parallels the incidence rate in SSA because of the high case fatality rate (Fig 1). In South Africa, from 1999 to 2015, the overall mortality attributable to liver cancer significantly decreased in men (−4.9%) and women (−2.7%). The same study also showed a racial disparity in mortality, with White South Africans having significantly lower mortality than their Black counterparts. Mortality closely parallels the incidence rate in SSA because of the high case fatality rate (Fig 1). In South Africa, from 1999 to 2015, the overall mortality attributable to liver cancer significantly decreased in men (−4.9%) and women (−2.7%). The same study also showed a racial disparity in mortality, with White South Africans having significantly lower mortality than their Black counterparts. The incidence and mortality rates are likely underestimated in these efforts as there are multiple hindrances to data collection efforts, such as inadequate trained personnel, inadequate funding and infrastructure, poor access to health care and diagnosis, inadequate population surveys, or unreliable vital statistics.
RISK FACTORS OF HCC IN SSA

The predominant risk factor of HCC in SSA is chronic HBV infection.22 In SSA, HCC affects men more than women; although the risk increases with age, patients in SSA tend to be younger than those in other parts of the world.21 The higher level of androgens in men is linked to an increased risk of HBV-induced HCC.23 HCC is seen at an earlier age group in SSA because of genetic factors, HBV infection during childhood or birth, impact of prevailing HBV genotypes (and their genetic variants), and aflatoxin

FIG 1. Age-standardized incidence and mortality rates of liver cancer in African countries across different regions of sub-Saharan Africa. (A) Eastern Africa, (B) Southern Africa, (C) Central Africa, and (D) Western Africa. ASR, age-standardized rates (incidence and mortality). Reproduced from GLOBOCAN 2018.17
| Sub-Saharan Nations    | Crude Incidence Rate | Age-Standardized Incidence Rate* | Crude Mortality Rate | Age-Standardized Mortality Rate* |
|-----------------------|----------------------|----------------------------------|----------------------|----------------------------------|
| West Africa           | 4.3                  | 8.3                              | 4.3                  | 8.2                              |
| The Republic of the Gambia | 14.7                | 23.9                             | 15.9                 | 26.2                             |
| Guinea                | 12.1                 | 21.8                             | 10.8                 | 19.5                             |
| Ghana                 | 9.3                  | 15.4                             | 9.3                  | 15.4                             |
| Liberia               | 8.5                  | 15.2                             | 8.7                  | 15.4                             |
| Burkina Faso          | 6.6                  | 13.8                             | 6.4                  | 13.5                             |
| Senegal               | 6.6                  | 12.6                             | 6.6                  | 12.6                             |
| Guinea-Bissau         | 6.6                  | 11.9                             | 6.7                  | 12                               |
| Mauritania            | 7                    | 11.3                             | 7.2                  | 11.5                             |
| Cabo Verde            | 8                    | 10.7                             | 8.5                  | 11.2                             |
| Sierra Leone          | 5.3                  | 10                               | 4.8                  | 9.5                              |
| Côte d'Ivoire         | 4.5                  | 8.4                              | 4.5                  | 8.4                              |
| Niger                 | 3.5                  | 7.3                              | 3.4                  | 7.2                              |
| Togo                  | 3.9                  | 6.9                              | 3.9                  | 6.9                              |
| Mali                  | 3.1                  | 6.3                              | 2.9                  | 5.9                              |
| Nigeria               | 2.6                  | 5.1                              | 2.6                  | 5.1                              |
| Benin                 | 2.6                  | 5.1                              | 2.7                  | 5.3                              |
| Central Africa        | 3.6                  | 6.5                              | 3.5                  | 6.5                              |
| Sao Tome and Principe | 3.8                  | 8.3                              | 3.8                  | 8.3                              |
| Democratic Republic of the Congo | 4.3 | 8 | 4.3 | 8.1 |
| Cameroon              | 3.9                  | 6.1                              | 3.6                  | 6.0                              |
| Republic of the Congo | 3.8                  | 5.9                              | 3.4                  | 5.4                              |
| Chad                  | 2.6                  | 5.5                              | 2.4                  | 5.3                              |
| Central African Republic | 3.1               | 5.1                              | 2.8                  | 4.8                              |
| Equatorial Guinea     | 3.3                  | 4.7                              | 3.2                  | 4.9                              |
| Angola                | 1.9                  | 3.6                              | 1.8                  | 3.5                              |
| Gabon                 | 2.7                  | 3.3                              | 2.5                  | 3.3                              |
| Southern Africa       | 4.1                  | 4.9                              | 3.9                  | 4.7                              |
| South Africa          | 4.3                  | 5.0                              | 4.2                  | 4.8                              |
| Lesotho               | 3                    | 4.4                              | 3                    | 4.4                              |
| Botswana              | 2.7                  | 3.9                              | 2.6                  | 3.8                              |
| Eswatini              | 2.7                  | 3.9                              | 2.5                  | 3.9                              |
| Namibia               | 1.9                  | 2.8                              | 1.8                  | 2.9                              |
| East Africa           | 2.7                  | 4.8                              | 2.6                  | 4.7                              |
| Rwanda                | 5.9                  | 10.1                             | 5.6                  | 10.2                             |
| Uganda                | 4.1                  | 7.6                              | 3.5                  | 6.7                              |
| Zimbabwe              | 3.4                  | 6.9                              | 3.4                  | 7.0                              |
| Mozambique            | 3.9                  | 6.6                              | 3.8                  | 6.7                              |
| Burundi               | 3.6                  | 6.3                              | 3.6                  | 6.6                              |
| France, La Réunion    | 9.6                  | 6.0                              | 10.1                 | 6.1                              |
| Madagascar            | 3.4                  | 5.8                              | 3.5                  | 6.5                              |
| Comoros               | 3.5                  | 5.7                              | 3.4                  | 5.8                              |
| Kenya                 | 2.6                  | 5.3                              | 2.6                  | 5.3                              |
| South Sudan           | 3.1                  | 5.1                              | 3.1                  | 5.2                              |

(Continued on following page)
TABLE 1. Incidence and Mortality Rates of Hepatocellular Carcinoma in All the Sub-Saharan Nations (data presented as per 100,000 persons) (Continued)

| Sub-Saharan Nations         | Crude Incidence Rate | Age-Standardized Incidence Rate | Crude Mortality Rate | Age-Standardized Mortality Rate |
|----------------------------|----------------------|---------------------------------|----------------------|---------------------------------|
| United Republic of Tanzania | 2.6                  | 4.9                             | 2.6                  | 5                               |
| Somalia                    | 1.7                  | 3.4                             | 1.6                  | 3.3                             |
| Eritrea                    | 1.8                  | 3.3                             | 1.7                  | 3.2                             |
| Mauritius                  | 5                    | 3.2                             | 4.2                  | 2.7                             |
| Ethiopia                   | 1.5                  | 2.7                             | 1.5                  | 2.7                             |
| Djibouti                   | 2                    | 2.6                             | 1.8                  | 2.4                             |
| Rwanda                     | 5.9                  | 10.1                            | 5.6                  | 10.2                            |
| Uganda                     | 4.1                  | 7.6                             | 3.5                  | 6.7                             |

*Standardized to the world population.

exposure. Rural regions have a higher incidence of HCC than urban areas, presumably because of high levels of HBV infection seen in rural areas. We will review multiple reasons for the high prevalence of chronic HBV infection in Africa in later sections of this review. In addition to viral hepatitis, there are other unique risk factors for HCC in the region. These include frequent exposure to aflatoxin via grain-based diets prevalent in the region and African dietary iron overload. The interplay between these additional risk factors and a high burden of HIV in the background of co-infection with HBV may in part explain the high incidence of HCC in this region.

**HBV**

Chronic HBV is a global health problem, and its global prevalence in the general population was 3.5% (about 257 million persons), as per the WHO 2017 global hepatitis report. Viral hepatitis was responsible for 887,000 deaths in 2015, and mortality from viral hepatitis increased by 22% between 2000 and 2015. Western Pacific has the highest prevalence of chronic hepatitis B infection but has decreased the infection in the upcoming generation of children to < 1% as a result of multiple successfully implemented strategies targeted at birth immunization, mass seroprevalence assays, regional verification of viral control, and inhibiting mother-to-child transmission of chronic hepatitis B infection. Africa is second to the Western Pacific WHO region in terms of the prevalence of chronic HBV infection (6.1%, 60 million vs 6.2%, 115 million). It is hyperendemic (> 8% prevalence of chronic carriers) in some sub-Saharan countries like Nigeria, Gabon, Cameroon, and Burkina Faso; endemic to an intermediate degree (2%-7.99% prevalence) in Kenya, Zambia, Ivory Coast, Liberia, Sierra Leone, and Senegal; and comparatively endemic to low degree (< 2% prevalence) in North African countries, such as Egypt, Tunisia, Algeria, and Morocco (Fig 2). In SSA, HBV transmission occurs predominantly through horizontal route among individuals of the same generation in early childhood. Primary infection occurs mostly through percutaneous infection from saliva, blood, unsterile needles, unsafe blood transfusions, and tribal scarification (practice of scratching, etching, burning or branding or superficially cutting patterns, or images into skin as permanent body modification), among other vehicles. Birth dose and childhood immunization against HBV in Africa were attempted successfully in certain countries. Several studies from Africa showed a decrease in the prevalence of chronic HBV infection after the introduction of hepatitis B immunization in routine childhood immunization schedules. However, only 19% of 47 African countries introduced birth dose vaccination by July 2017 despite WHO recommending universal HBV birth dose vaccination by 2005. There are numerous challenges associated with effective and timely immunization in African countries, such as lack of infrastructure to maintain vaccines in target temperature range from manufacture to recipient (cold chain management), inadequate access to health care in rural areas, high prevalence of home births, inadequacy of national health policies, and cultural practices of inhabitants, among others.

Vertical transmission of HBV (from mother-to-child) is a less common means of transmission in SSA compared with the Asia-Pacific region, where it is the predominant transmission route. A recent systematic review and meta-analysis confirmed that antiviral treatment of pregnant women combined with birth dose immunization and immunoglobulin administration at the time of birth reduces risk of mother-to-child transmission. However, this has not been recommended in SSA by the WHO or African Health ministries because of the low perinatal transmission rate and lack of clinical trials in the continent. Currently, birth dose immunization alone is the standard recommended by WHO for African countries for decreasing mother-to-child transmission, but this occurs only in < 3% of infants born in Gambia despite Gambia being one of the first countries in SSA to have implemented national HBV immunization. WHO estimated that only 10.5% of all patients worldwide with HBV infection knew of their diagnosis as of 2016 and only 5% of those eligible for treatment had received antiviral treatment. Effective treatment of chronic HBV infection requires surveillance and screening practices, longitudinal care, periodic blood investigations, access to health care, and affordability of
medications. In resource-limited SSA, this is a major hurdle. In SSA, <1% of HBV-infected individuals were aware of their diagnosis despite the availability of reliable testing modalities and up to 15% entered care with liver cirrhosis. Tenofovir, WHO-preferred treatment for chronic hepatitis B, is available for purchase from the private sector hospitals and pharmacies, but most patients cannot afford its lifelong supply as they have to pay out of pocket in private sector. Public sector hospitals serve most of the African population who cannot afford care in the private sector. Although tenofovir is available as part of antiretroviral therapy and is accessible to all through the public sector hospitals, it is not accessible to monoinfected hepatitis B patients. Nationally funded actional plans in the public sector have been adopted by some African nations, but published experiences of such executions are limited to the PROLIFICA study in Gambia and another pilot program in Ethiopia. These are examples of large screen-and-treat operations at a national level that demonstrate virologic control can be achieved with mass screening and prompt linkage to care and easy access to medications.

The combined ineffectiveness of providing universal immunization to newborns in Africa and the major hurdles involved in the treatment of patients with chronic hepatitis B infection are the main reasons behind the majority of them...
being at risk for development of the HCC, a late sequela of the infection.34

Chronic HBV infection leads to liver cirrhosis over time, and its risk is higher in those with positive HBeAg, an elevated HBV DNA level, and HBV genotype C.44 HCC occurs in HBV-related cirrhosis at an annual rate of 2.3%. Accumulation of mutations in numerous driver genes, p53-RB pathway, β-catenin or WNT pathway, phosphatidylinositol 3-kinase-mammalian target of rapamycin pathway, and NRF2-KEAP1 pathway of hepatocytes is seen in HCC developing from cirrhosis.46 Chronic HBV infection can also directly lead to HCC.46 A high number of HBV-DNA integrations are randomly noted in the chromosomes of HBV-infected livers.47 HBV genome integrates into the TERT gene in high clonal proportion.48 HBx gene of the HBV genome likely interferes with telomerase activity during hepatocyte proliferation.47 HBV also affects epigenetic mechanisms, and the viral genome-encoded proteins have been associated with malignant potential.46 The protein encoded by the Hbx gene, HBx protein, is a transactivating factor. It transactivates binding sites for AP-1 and NF-κB, activates p53-RB and β-catenin pathways, and is also involved in transcriptional modulation.46 Occult chronic HBV infection (persistent viremia in the context of negative HBsAg and positive HBcAg) also leads to HCC carcinogenesis.59 This could mean that we are underestimating the proportion of HCCs attributable to HBV, as most studies do not include checking HBV DNA levels to ascertain etiology.47

In SSA, HBV genotype E predominates and is seen through the region (especially West and Central Africa).50 This is followed by genotype A, which is the predominant genotype in Uganda and Cameroon. Both these genotypes have a high oncogenic potential compared with the others.27 Perinatal vertical transmission of HBV is more likely to occur if the mother is HBeAg-positive and has a high viral load.51 Although HBeAg clears at an early age in Africans, younger African mothers have a higher risk of vertical transmitting HBV infection.52 HCC patients are more commonly seen with first birth order in the family, a marker of younger maternal age,52 and could be a result of the interaction between the phenomena that older age is protective of vertical transmission and the fact that vertically acquired HBV infection has a higher likelihood of progression to HCC.53

HIV and HCC

Africa is the epicenter of the AIDS epidemic and accounts for up to 71% of AIDS patients worldwide.54 Antiretroviral therapy has changed a once highly fatal disease entity into a chronic illness with markedly improved survival. This has let other comorbidities such as liver disease to become a major concern, which once did not have a chance to manifest in HIV-infected individuals.27 Co-infection with HIV and HBV is common because of shared means of transmission, and there are close to around 2-4 million patients.55 The mean proportion of HIV patients with HIV-HBV co-infection in SSA is 7.8% and varies from 0% to 28.4% in different regions of SSA.52 The co-infection rates among HIV-positive children and pregnant women were 3.8% and 7.4%. These rates are based on too few population-based surveillance programs and mostly arise from observational cohort studies. West African countries seem to have the highest co-infection rates, followed by Southern African countries. The least co-infection rate is seen in East Africa. Studies in patients with HIV of South Africa and West Africa reported occult infections (as evidenced by positive HBV DNA and negative HBsAg) to be around 10%-33%. Multiple studies in the United States and Europe have shown that HIV co-infection with HBV enhances the hepatocarcinogenic potential.56 The immune T-cell response against HBV is impaired in HIV-HBV-co-infected patients leading to higher levels of HBV replication, decreased rates of resolution of HBV infection, and increased rates of HBV reactivation.57 HIV infection by itself also increases reactive oxygen, activates hepatic stellate cells, and promotes immune-mediated injury by Kupffer cells in the liver. HIV infection also causes an increased translocation of gut bacteria, leading to increased lipopolysaccharide-induced toll-like receptor activation. HIV medications also have a hepatotoxic effect leading to increased risk of HCC.53 Certain mutations of HBV genome, such as PreS deletion, are associated with increased risk of HCC in HBV monoinfected individuals and are also found more commonly in the HBV-HIV-co-infected individuals.58 However, cohort studies of co-infected individuals with HBV genome mutations are required to study the risk of HCC they confer. A study from Africa revealed that HIV-HBV-co-infected individuals did not have an increased incidence of HCC, but this was done at a time when the survival for patients with HIV was quite poor.59 However, systematic cohort studies evaluating the natural history of HBV-HIV–co-infected individuals in Africa are still lacking.

Aflatoxins

Aflatoxins derived from Aspergillus flavus and Aspergillus parasiticus are carcinogens and are synergistic with HBV infection in causing HCC.60 They are also partly responsible for young age of onset of HBV-associated HCC in SSA.61 Metabolites of aflatoxins intercalate into the host genome, leading to specific gene mutations, particularly of the p53 tumor suppressor gene.62 The population attributable risk of aflatoxins is 21% in chronic HBV carriers and 8.8% in HBsAg negative populations.63 The warm and humid climate coupled with the staple diet (consisting of maize and rice) that is sensitive to aflatoxin production and improper postharvest storage practices is the reason behind the high prevalence of aflatoxin contamination of foods in SSA.64 High aflatoxin concentrations were found in foods such as nuts in Nigeria, rice grains in Ghana, peanuts in Zambia, locally brewed alcoholic drinks in Kenya and Ethiopia, and
cow milk in Cameroon.27 Aflatoxin exposure will only become worse with global warming, and there is a general lack of awareness about this issue among the general public of Africa.64 There is a lack of effective interventions that have decreased this exposure systematically.

**African Dietary Iron Overload**

Rural dwellers in Africa (mainly in Nigeria) consume large quantities of home-brewed beer, which are made by fermenting locally produced crops in large iron or steel containers.27 The resultant beer contains a high concentration of bioavailable iron leached from iron and steel ware.65 This leads to an accumulation of iron in livers of certain African individuals with functional differences in ferroportin, a protein for iron transport found in hepatocytes.66 The iron accumulation in the liver is a risk factor for the development of HCC irrespective of liver disease.67 It is termed African dietary iron overload.

**NAFLD**

According to the WHO, obesity is an emerging problem of the developing world, with its associated comorbidities on the rise in Africa.68 The main risk factors are morbid obesity and type 2 diabetes, which are magnified by rapid urbanization, physical inactivity, nutrition transitions, socioeconomic changes, and aging.69,70 In Africa, the combination of obesity, type 2 diabetes, and NAFLD is associated with the late presentation of larger tumors not amenable to curative therapy.71 Several studies have demonstrated that once NAFLD sets in, Africans are at similar risk of progression to cirrhosis and HCC as Whites.72,73

**MANAGEMENT OF HCC AND ACCESS TO CARE IN SSA**

Patients generally first present in a district hospital setting where they would be attended to in general medical or internal medicine facilities, before referral to the tertiary centers. Unfortunately, by the time a definitive diagnosis has been made, most patients would be of poor performance status and may have unfavorable prognostic markers.

HCC in SSA has significantly poorer median survival compared with Egypt and all other countries (Fig 3). Most patients in SSA tend to present with symptoms to a district hospital where they would be attended by internal medicine services and eventually referred to tertiary centers. In one of the most comprehensive international multicenter retrospective studies comparing HCC outcomes in Egypt and SSA, patients in SSA were diagnosed with more severe liver dysfunction (Child-Pugh scores B and C 64% v 93%), worse Eastern Cooperative Oncology Group performance status (Eastern Cooperative Oncology Group 2-4 15% v 67%), and advanced Barcelona-Clinic Liver Cancer (BCLC) stage (BCLC stage D 7% v 72%).22 This is likely a reflection of the lack of HCC surveillance programs, the absence of trust in health systems, and poor health-seeking behavior in SSA.74,75 Only 3% of the patients with HCC received any disease-specific treatment in tertiary care centers of SSA (Table 2).22 None of them underwent liver transplantation, and sorafenib was used only in 1% of them despite 23% presenting in BCLC stage C.22 Tertiary referral centers can provide care to select few in SSA who can afford it financially, and hence, overall treatment rate for patients with HCC is probably much lower.22 Anecdotally, the care providers in SSA are of varying cadres, ranging from clinical officers (United States equivalent of advanced practice provider), medical officers who have trained in a medical school and internship but are nonspecialized, to consultants with specialization in surgery, internal medicine, and other specialties.

There are 102 establishments in all of Africa that provide treatment for patients with cancer, 38 of which are in South Africa.76 Close to 22 African nations do not have palliative care facilities. An estimated 88% of all patients who report moderate to severe pain eventually die without receiving any pain treatment.77 Lack of provider training and unreasonable fears of patients toward opiates contribute to this trend.77 Liver transplantation in SSA is reported to be performed at two centers in South Africa, and it is practiced in a limited number of private health care facilities.78 There are less than two surgeons per 100,000 inhabitants in SSA (excluding South Africa), in comparison with 35 surgeons in England per 100,000 inhabitants,76 and oncologic surgery is mainly performed by general surgeons in SSA.79,80 East, West, and Central Africa had the highest unmet need for surgical care.81

In a cross-sectional study of a cancer center in Tanzania, only 50% of cancer-directed systemic therapies were available and more than 70% of patients did not receive adequate therapy.82 Evidence-based systemic therapy is generally available at a great cost and is affordable to a minority of patients in SSA. Cancer drugs in SSA cost close to 4 months of average income, and as most patients are not insured, only a few can afford them.74 Less than 1% of HCC clinical trials take place in Africa.83 A survey of radiology training programs in SSA does not mention training in interventional radiology, and there are too few general radiologists in comparison with the patient population.84 Despite the advent of experimental use of radiation therapy for HCC, 3D conformal radiotherapy is scarcely available in SSA and usually dedicated to potentially curable cancers as an essential component, such as cervical and breast cancers.

**FUTURE DIRECTIONS**

Measures for primary prevention of HBV infection, such as HBV birth vaccination and follow-up programs, measures to prevent maternal-to-child transmission of HBV, and screening of pregnant women for HBsAg have been started in many regions of SSA.85 These should be pursued with vigor to achieve 100% coverage. Delivery of universally accessible antiviral treatments, screening programs for
TABLE 2. Treatment Approaches Used in Egypt and Sub-Saharan Countries in the Africa Liver Cancer Consortium Study

| Treatment Used                          | Egypt (n = 1,251), No. (%) | Sub-Saharan Africa Countries (n = 1,315), No. (%) |
|----------------------------------------|----------------------------|-----------------------------------------------|
| Any treatment                          | 956 (76)                   | 43 (3)                                        |
| Liver transplantation                   | 10 (< 1)                   | 0                                             |
| Resection                              | 26 (2)                     | 8 (< 1)                                       |
| Radiofrequency ablation                | 406 (32)                   | 0                                             |
| Transarterial chemoembolization        | 451 (36)                   | 5 (< 1)                                       |
| Sorafenib                              | 63 (5)                     | 12 (1)                                        |

HCC, and reduction of dietary aflatoxin exposure can markedly reduce HCC incidence and improve mortality. The African Cancer Registry Network (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. The AIDS Malignancy Consortium is a National Cancer Institute (NCI)—supported clinical trials group with a strong presence in Africa, helping investigating new treatment and prevention of interventions and studying the pathobiology of malignancies in people living with HIV both in the United States and internationally, has a strong interest in helping patients with HCC and HIV. Novel guidelines for the management and treatment of HCC in SSA, which would be dependent on the resources available, are badly needed. Such effort led by most authors plus other colleagues in SSA is already underway. Finally, the development of biomarkers and new therapeutic interventions will need a better understanding of the unique genetic and epigenetic characteristics of HCC in SSA. Clinical and genetic research collaborations centered on African populations are required for achieving this.

In conclusion, HCC is very common in SSA because of the endemcity of chronic HBV infection. Other risk factors that are unique to SSA are rural background, aflatoxin exposure, and dietary African iron overload. There are multiple methods to decrease the incidence and transmission of HBV, which have been inadequately used in SSA. In SSA, HBV infection is the most common etiologic cause HCC, and this risk is increased with HIV co-infection. Compared with higher-income countries, patients with HCC living in SSA have among the poorest reported survival. This is due to the late presentation of these tumors in the symptomatic phase and inadequate surveillance practices. Most of the patients do not undergo standard treatment for HCC in SSA. This is due to inadequate infrastructure, personnel, and lack of access to health care within many rural communities. Comprehensive multipronged strategies are required to decrease the incidence and improve detection and the treatment of HCC in SSA.

AFFILIATIONS

1Memorial Sloan Kettering Cancer Center, New York, NY
2University of Massachusetts Medical School—Baystate Health, Springfield, MA
3Department of Global Health, Faculty of Medicine and Health Sciences, African Cancer Institute, Stellenbosch University, Cape Town, South Africa
4University of Zimbabwe College of Health Sciences, Harare, Zimbabwe
5The University of North Carolina at Chapel Hill, Chapel Hill, NC
6Cairo University, Cairo, Egypt
7MD Anderson Cancer Center, Houston, TX
8Weill Medical College at Cornell University, New York, NY

CORRESPONDING AUTHOR

Ghassan K. Abou-Alfa, MD, MBA, Memorial Sloan Kettering Cancer Center, 300 East 66th St, New York, NY 10065; e-mail: abou-alf@mskcc.org.

SUPPORT

Supported by the AIDS Malignancy Consortium of the National Cancer Institute, United States.

AUTHOR CONTRIBUTIONS

Conception and design: V. V. Pavan Kedar Mukthinuthalapati, Vikash Sewram, Ghassan K. Abou-Alfa

Administrative support: Elizabeth Yu Chiao, Ghassan K. Abou-Alfa

Provision of study materials or patients: Ntokozo Ndlovu

Collection and assembly of data: V. V. Pavan Kedar Mukthinuthalapati, Vikash Sewram, Ntokozo Ndlovu, Asfahal Omar Abdelaziz, Ghassan K. Abou-Alfa

Data analysis and interpretation: V. V. Pavan Kedar Mukthinuthalapati, Vikash Sewram, Stephen Kimani, Elizabeth Yu Chiao, Ghassan K. Abou-Alfa

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).
REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018

2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, et al: Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol 5:1749-1768, 2019

3. Calle EE, Rodriguez C, Walker-Thurmond K, et al: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348:1625-1638, 2003

4. Baeccker A, Liu X, La Vecchia C, et al: Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. Eur J Cancer Prev 27:205-212, 2018

5. Villanueva A: Hepatocellular carcinoma. N Engl J Med 380:1450-1462, 2019

6. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008

7. Kudo M, Finn RS, Qin S, et al: Lenalidomibe versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018

8. Bruix J, Qin S, Merle P, et al: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389:56-66, 2017

9. Abou-Alfa GK, Meyer T, Cheng AL, et al: Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 379:54-63, 2018

10. Zhu AX, Kang Y-K, Yen C-J, et al: Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040: A phase 2 randomised, open-label, non-comparative, non-inferiority trial. Lancet 392:2902-2907, 2018

11. Zhu AX, Finn RS, Edeline J, et al: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet 19:940-952, 2019

12. Cheng AL, Qin S, Ikeda M, et al: Ibritinib+PV: Efficacy and safety results from a phase III study evaluating atezolizumab (atezo) + bevazicizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with advanced hepatocellular carcinoma (HCC). Ann Oncol 30:ix186-ix17, 2019

13. Yau T, Kang Y-K, Kim T-Y, et al: Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. J Clin Oncol 37, 2019 (suppl; abstr 4012)

14. Yang JD, Hainaut P, Gores GJ, et al: A global view of hepatocellular carcinoma: Trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 16:589-604, 2019

15. Global Cancer Observatory, WHO. 2018. https://gco.iarc.fr/todayonline-analysis-table?v=2018&mode=population&mode_region=region&population=900&populations=900&key=asr&sex=0&cancer=11&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=4&ages_group%5B%5D=17&group_cancer=1&include_nmsc=1&include_nmsc_other=1

16. Estimated Age-Standardized Incidence and Mortality Rates (World) in 2018, Africa, Both Sexes and All Ages, Global Cancer Observatory. WHO. 2020. IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France. https://gco.iarc.fr/, Last accessed May 8, 2020

17. Cancer in Sub-Saharan Africa. Lyon, France: International Agency for Research on Cancer; 2018. Contract No.: 167

18. Dasgupta P, Henshaw C, Youden DR, et al: Global trends in cancer incidence rates of primary adult liver cancers: A systematic review and meta-analysis. Front Oncol 10:171, 2020

19. Mak D, Sengayi M, Chen WC, et al: Liver cancer mortality trends in South Africa: 1999–2015. BMC Cancer 18:798, 2018

20. Kew MC: Epidemiology of hepatocellular carcinoma in sub-Saharan Africa. Ann Hepatol 12:173-182, 2013

21. Yang JD, Mohamed EA, Aziz AOA, et al: Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: A multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol Hepatol 2:103-111, 2017

22. Yu MW, Cheng SW, Lin MW, et al: Androgen-receptor gene CAG repeats, plasma testosterone levels, and risk of hepatitis B-related hepatocellular carcinoma. J Natl Cancer Inst 92:2023-2028, 2000

23. Rajorjya N, Combet C, Zoulim F, et al: How viral genetic variants and genotypes influence disease and treatment outcome of chronic hepatitis B. Time for an individualised approach? J Hepatol 67:1281-1297, 2017

24. Yang JD, Altekruse SF, Nguyen MH, et al: Impact of country of birth on age at the time of diagnosis of hepatocellular carcinoma in the United States. Cancer 123:81-89, 2017

25. Kew MC, Fujita Y, Takahashi H, et al: Comparison between polyclonal and first and second generation monoclonal radioimmunoassays in the detection of hepatitis B surface antigen in patients with hepatocellular carcinoma. Hepatology 6:636-639, 1986

26. Okeke E, Davwar PM, Roberts L, et al: Epidemiology of liver cancer in Africa: Current and future trends. Semin Liver Dis 40:111-123, 2020

27. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf. Last accessed May 8, 2020

28. Bruix J, Pastore R, Brink A, et al: Progress toward hepatitis B control and elimination of mother-to-child transmission of hepatitis B virus—Western Pacific region, 2005-2017. MMWR Morb Mortal Wkly Rep 68:195-200, 2019

29. Schweitzer A, Horn J, Nikolajczyk RT, et al: Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 386:1546-1555, 2015

30. Garve R, Garve M, Türp JC, et al: Labrets in Africa and Amazonia: Medical implications and cultural determinants. Trop Med Int Health 22:232-240, 2017

31. Garve R, Garve M, Türp JC, et al: Labrets in Africa and Amazonia: Medical implications and cultural determinants. Trop Med Int Health 22:232-240, 2017

Kedar Mukthinuthalapati et al

Research Funding: Bayer, Exelixis, CASI Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Incyte, Agios, Polaris, Puma Biotechnology, QED Therapeutics

Travel, Accommodations, Expenses: Polaris

No other potential conflicts of interest were reported.
32. Garve R, Garve M, Türp JC, et al: Scarification in sub-Saharan Africa: Social skin, remedy and medical import. Trop Med Int Health 22:708-715, 2017
33. Kiire CF: The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: A view from tropical and subtropical Africa. Gut 38:S5-S12, 1996 (suppl 2)
34. Breakwell L, Tewi-Benissan C, Chids L, et al: The status of hepatitis B control in the African region. Pan Afr Med J 27:17, 2017 (suppl 3)
35. Menendez C, Sanchez-Tapia JM, Kahigwa E, et al: Prevalence and mother-to-infant transmission of hepatitis viruses B, C, and E in Southern Tanzania. J Med Virol 58:215-220, 1999
36. Brown RS Jr, McMahon BJ, Lok AS, et al: Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. Hepatology 63:319-333, 2016
37. Lemoine M, Thursz MR: Battlefront against hepatitis B infection and HCC in Africa. J Hepatol 66:645-654, 2017
38. Razavi-Shearer D, Gankrelidze I, Nguyen MH, et al: Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: A modelling study. Lancet Gastroenterol Hepatol 3:383-403, 2018
39. Coffie PA, Egger M, Vinikoor MJ, et al: Trends in hepatitis B virus testing practices and management in HIV clinics across sub-Saharan Africa. BMC Infect Dis 17:706, 2017 (Suppl 1)
40. Beguelin C, Fall F, Seydi M, et al: The current situation and challenges of screening for and treating hepatitis B in sub-Saharan Africa. Expert Rev Gastroenterol Hepatol 12:537-546, 2018
41. Desaegel H, Aberra H, Berhe N, et al: Treatment of chronic hepatitis B in sub-Saharan Africa: 1-year results of a pilot program in Ethiopia. BMC Med 16:234, 2018
42. Spearman CW, Athenee M, Ally R, et al: Hepatitis B in sub-Saharan Africa: Strategies to achieve the 2030 elimination targets. Lancet Gastroenterol Hepatol 2:900-909, 2017
43. Lemoine M, Shimakawa Y, Njie R, et al: Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in the Gambia: The Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. Lancet Glob Health 4:e559-67, 2016
44. McMahon BJ: The natural history of chronic hepatitis B virus infection. Hepatology 49:545-555, 2009
45. Totoki Y, Tatsuno K, Cvoington KR, et al: Trans-ancestry mutational landscape of hepatic cellular carcinoma genomes. Nat Genet 46:1267-1273, 2014
46. Kanda T, Goto T, Hirotsu Y, et al: Molecular mechanisms driving progression of liver cirrhosis towards hepatitis B-related liver cancer in chronic hepatitis B and C infections: A review. Int J Mol Sci 20:1358, 2019
47. Mason WS, Gill US, Litwin S, et al: HBV DNA integration and clonal hepatocyte expansion in chronic hepatitis B patients considered immune tolerant. J Hepatol 151:986-998.e4, 2016
48. Meyerson M, Counter CM, Eaton EN, et al: hEST2, the putative human telomerase catalytic subunit gene, is up-regulated in tumor cells and during immortalization. Cell 90:785-797, 1997
49. Kew MC: Hepatocellular carcinoma in African Blacks: Recent progress in etiology and pathogenesis. World J Hepatol 2:65-73, 2010
50. Shimakawa Y, Bottomley C, Njie R, et al: The association between maternal hepatitis B e antigenaemia and the risk of perinatal transmission of hepatitis B e antigenaemia in Gambian children. BMC public health 14:532, 2014
51. Gentile I, Borgia G: Vertical transmission of hepatitis B virus: Challenges and solutions. Int J Womens Health 6:605-611, 2014
52. Shimakawa Y, Bottomley C, Njie R, et al: The association between maternal hepatitis B e antigen status, as a proxy for perinatal transmission, and the risk of hepatitis B e antigenaemia in Gambian children. BMC public health 14:532, 2014
53. Schillie S, Walker T, Veselsky S, et al: Outcomes of infants born to women infected with hepatitis B. Pediatrics 135:e1141-e1147, 2015
54. UNAIDS: UNAIDS Gap Report. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf
55. Kourtis AP, Butlers M, Hu DJ, et al: HIV–HBV coinfection—A global challenge. N Engl J Med 366:1749-1752, 2012
56. Kew MC: Hepatocellular carcinoma in African Blacks: Recent progress in etiology and pathogenesis. World J Hepatol 2:65-73, 2010
57. Dika IE, Harding JJ, Abou-Alfa GK: Hepatocellular carcinoma in patients with HIV. Curr Opin HIV AIDS 12:20-25, 2017
58. Singh KP, Crane M, Audsley J, et al: HIV-hepatitis B virus coinfection: Epidemiology, pathogenesis, and treatment. AIDS 31:2035-2052, 2017
59. Mak D, Babb de Villiers C, Chasela C, et al: Analysis of risk factors associated with hepatocellular carcinoma in black South Africans: 2000–2012. PLoS One 13:e0196057, 2018
60. De Ruyc K, De Boeve M, Huybrechts I, et al: Dietary mycotoxins, co-exposure, and carcinogenesis in humans: Short review. Mutat Res Rev Mutat Res 829:1-13, 2018
61. Kew MC: Synergistic interaction between aflatoxin B1 and hepatitis B virus in hepatocarcinogenesis. Liver Int 23:405-409, 2003
62. Hamid AS, Tesfamariam IG, Zhang Y, et al: Aflatoxin B1-induced hepatocellular carcinoma in developing countries: Geographical distribution, mechanism of action and prevention. Oncol Lett 5:1087-1092, 2013
63. Liu Y, Chang CC, Marsh GM, et al: Population attributable risk of aflatoxin-related liver cancer: Systematic review and meta-analysis. Eur J Cancer 48:2125-2136, 2012
64. Stepman F: Scaling-up the impact of aflatoxin research in Africa. The role of social sciences. Toxins (Basel) 10:136, 2018
65. Kew MC: Hepatic iron overload and hepatocellular carcinoma. Liver Cancer 3:31-40, 2014
66. Moyo VM, Mandishona E, Hasstedt SJ, et al: Evidence of genetic transmission in African iron overload. Blood 91:1076-1082, 1998
67. Molina-Sanchez P, Lujambio A: Iron overload and liver cancer. J Exp Med 216:723-724, 2019
68. WHO: Controlling the Global Obesity Epidemic. https://www.who.int/nutrition/topics/obesity/en/
69. Hali V, Thomsen RW, Henrikson O, et al: Diabetes in sub-Saharan Africa 1999-2011: Epidemiology and public health implications. A systematic review. BMC public health 11:564, 2011
70. Tsevi VC, Mayoh GK, Ha CE: Type 2 diabetes mellitus and obesity in sub-Saharan Africa. Diabetes Metab Res Rev 26:433-445, 2010
71. Wong CR, Nguyen MH, Lim JK: Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. World J Gastroenterol 22:8294-8303, 2016
72. Ascho MS, Hanounen IA, Lopez R, et al: The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 51:1972-1978, 2010
73. Said A, Ghafur A: Epidemic of non-alcoholic fatty liver disease and hepatocellular carcinoma. World J Clin Oncol 8:429-436, 2017
74. Tognarelli J, Ladepe NG, Crossej MME, et al: Reasons why West Africa continues to be a hotbed for hepatocellular carcinoma. Niger Med J 56:231-235, 2015
75. Oliver J, Tsimco C, Gemignani R, et al: Understanding the roles of faith-based health-care providers in Africa: Review of the evidence with a focus on magnitude, reach, cost, and satisfaction. Lancet 386:1765-1775, 2015
76. Stefan DC: Cancer care in Africa: An overview of resources. J Glob Oncol 1:30-36, 2015
77. Ogboli-Nwasor E, Makama J, Yusufu L: Evaluation of knowledge of cancer pain management among medical practitioners in a low-resource setting. J Pain Res 6:71-77, 2013
78. Netcare Hospitals: Transplant Facilities and Services. https://www.netcarehospitals.co.za/Specialised-services/Transplant-facilities-and-services
79. Lavy C, Sauven K, Mkandawire N, et al: State of surgery in tropical Africa: A review. World J Surg 35:262-271, 2011
80. Gyorki DE, Muyco A, Kushner AL, et al: Cancer surgery in low-income countries: An unmet need. Arch Surg 147:1135-1140, 2012
81. Meara JG, Leather AJM, Hagander L, et al: Global surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. The Lancet 386:569-624, 2015
82. Yohana E, Kamuhabawa A, Mujinja P: Availability and affordability of anticancer medicines at the Ocean Road Cancer Institute in Dar es Salaam, Tanzania. East Afr J Public Health 8:52-57, 2011
83. Lamarca A, Mendiola M, Barriuso J: Hepatocellular carcinoma: Exploring the impact of ethnicity on molecular biology. Crit Rev Oncol Hematol 105:65-72, 2016
84. Rabinowitz DA, Pretorius ES: Postgraduate radiology training in sub-Saharan Africa: A review of current educational resources. Acad Radiol 12:224-231, 2005
85. Chotun N, Preiser W, van Rensburg CJ, et al: Point-of-care screening for hepatitis B virus infection in pregnant women at an antenatal clinic: A South African experience. PLoS One 12:e0181267, 2017
86. AFCRN: African Cancer Registry Network (AFCRN). https://afcrn.org/. Last accessed May 8, 2020