Epidemiology and aetiology of hepatocellular carcinoma in Sub-Saharan Africa

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How to cite this article: Mak D, Kramvis A. Epidemiology and aetiology of hepatocellular carcinoma in Sub-Saharan Africa. Hepatoma Res 2021;7:39. https://dx.doi.org/10.20517/2394-5079.2021.15

Received: 10 Feb 2021 First Decision: 24 Mar 2021 Revised: 27 Mar 2021 Accepted: 13 Apr 2021 Published: 17 May 2021

Academic Editors: Guang-Wen Cao, Antonio Bertoletti Copy Editor: Yue-Yue Zhang Production Editor: Yue-Yue Zhang

Abstract

With the highest annual fatality ratio (mortality-to-incidence ratio), reported for a human cancer, hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related deaths worldwide and its distribution is not uniform. In Sub-Saharan Africa (SSA), HCC is the second leading cause of cancer-related deaths for men and the fourth for women in 2020, with average age-standardised mortality rates of 8.2 and 4.2 per 100,000 persons/year, respectively. In this region, HCC presents in younger age groups and has a median survival rate of ~3-4 months. The major risk factors for HCC include viral [hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV)] and environmental [dietary aflatoxin and iron overload] factors, with more than 50% being attributable to HBV, which is endemic in SSA. HCC control efforts in SSA are faced with a number of unique challenges, including resource restrictions, a paucity of good data, few cancer registries, inaccessibility of treatment for HBV and HCV, co-infection with human immunodeficiency virus (HIV), exposure to co-carcinogen aflatoxin B1, unique (sub)genotypes of HBV and changing natural history and aetiology of HCC as a result of antiretroviral therapy rollout for HIV and changing lifestyles. The unique features of HCC in SSA, together with the challenges faced in its prevention and appropriate public health intervention, diagnosis and treatment, all suggest that HCC in SSA is deserving of an in depth understanding by further focused research. Considerable motivation of policymakers, work and resources are required to reduce the burden of this cancer on the subcontinent.

Keywords: Liver cancer, hepatitis, Africa, carcinogens, risk factors
GLOBAL DISTRIBUTION OF PRIMARY LIVER CANCER

Primary liver cancer (PLC) as a primary cancer includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma and other rare types, with the exclusion of secondary liver cancer. HCC, which originates from hepatocytes, is the most common histological subtype, constituting 75%-90% of the total PLC cases diagnosed globally. As the most frequently diagnosed subtype, HCC is often used interchangeably with PLC. With an annual fatality ratio (mortality-to-incidence ratio) of 0.92 using Globocan 2020 data, the highest reported for a human cancer worldwide, PLC ranks as the third leading cause of cancer-related deaths worldwide (8.2% of total cancer-related deaths in 2020)[1-3]. Globally, the distribution of PLC is non-uniform and of all the new cases recorded in 2020, the vast majority occurred in regions such as Asia and Africa[3].

The continent of Africa encompasses a wide geographic area of 30.4 million square kilometres and is the world’s second largest continent, making up 6% of the Earth’s total surface, and consisting of many low-middle income countries (LMICs). With 1.34 billion people[3], Africa is also the second most inhabited continent and accounts for 16% of the global population. The majority (83.6%; 1.1 billion) of the African population lives to the south of the Sahara Desert that covers the northern third of the continent. Although both North African and SSA countries share the same continent, they differ in regards to climate and ethnic and cultural backgrounds of their populations. In particular, as a consequence of historical migrations, North African countries are closely tied to the Middle East and parts of Europe[4]. Therefore, almost every distinctive feature of cancer in Africa prevails predominantly in SSA, and none more so than PLC[5].

INCIDENCE AND SURVIVAL RATES OF LIVER CANCER IN SUB-SAHARAN AFRICA

In 2020, SSA had the fourth highest number of diagnosed PLC cases worldwide after South-Eastern Asia, South Central Asia and Northern America, with more than 38,000 new cases of PLC[5]. Of all PLCs in SSA, 77% are HCCs (varying from 67% to 88% by region). Globally, the second leading subtype is intrahepatic cholangiocarcinoma (CCA) that arises from the biliary epithelium and constitutes the remaining 15%-20% of diagnosed PLC cases[6-8]. Other rare forms that account for fewer than 1% of cases include angiosarcoma (inner lining of blood vessels), hepatoblastoma (hepatocyte precursors) and epithelioid haemangioendothelioma (endothelial cells)[5,6,9]. Very few studies have differentiated between these PLCs in SSA[8]. In a systematic review that included three studies performed in SSA, one in Nigeria and two in South Africa, it was concluded that there was no gender disparity and that the major risk factors for CCA, including primary sclerosing cholangitis, Clonorchis sinensis and Opisthorchis viverrini infection, are rare in this setting[10]. In SSA, PLC is the second leading cause of cancer-related death for men and the fourth for women in 2020. The high fatality rate in SSA black Africans suggests that the recorded annual death from the malignancy is virtually the same as the number of cases diagnosed in the population at that time, thus highlighting the inadequacy in the preventive, screening and treatment programs that are currently available on this subcontinent.

Figure 1, compiled using data from the International Agency for Research In Cancer (IARC) registry in 2008[11], 2012[12], 2018[13], illustrates that age-standardised incidence rates (ASIRs) are not uniform in SSA. Western and Central Africa are characterised by decreases in ASIRs in both sexes between 2018 and 2020, whereas an increase occurred in both sexes in Western Africa and in Eastern African women only in the most recent year. The average ASIR of HCC in Sub-Saharan African men and women is 18.9 and 8.0 per 100,000 persons/year, respectively[14].

According to GLOBOCAN 2020[2], variations in the ASIR also occur between different countries in SSA. Of the 11 West African countries, The Gambia and Guinea have high rates (ASIR > 20) and the remaining nine
Figure 1. Liver cancer age-standardised incidence rate (ASIR) per 100,000 persons-year in 2008, 2012 and 2020, compiled using data from [2,11,13] respectively. ASIR for males are shown on the left and females on the right of the histogram.

(Benin, Burkina Faso, Cote d’Ivoire, Guinea Bissau, Ghana, Nigeria, Togo, Niger and Mali) have intermediate incidences (5 < ASIR < 20). In Central Africa, the incidence is intermediate in the Republic of Congo and low in Cameroon and Gabon. Of the 10 East African countries, four (Kenya, Zimbabwe, Uganda and Rwanda) and seven (Malawi, Ethiopia, Tanzania, Mauritius, Zambia, Reunion, Mozambique) have intermediate and low incidences (ASIR < 5), respectively. Of the four Southern African countries, two have intermediate incidences (Botswana and Swaziland) and the remaining (Namibia and the Republic of South Africa) have a low incidence of PLC.

In other reports, the frequency of PLC was expressed in another way: the tumour accounted for 1.9% of all malignant diseases in Nigeria (2009-2013) [15], 2.2% in Malawi (2008-2010), 4% in Uganda (1991-2010) [16], 5% in Eastern Cape Province, South Africa (1998-2012) [17] and 7.6% in Zimbabwe (2006) [18]. In The Gambia, 60% of all malignant diseases in males and 20% of those in females are PLC [19]. According to the National Cancer Registry of The Gambia, covering the years 1990-2009, The Gambia, one of the poorest countries in the world [20], has the highest recorded incidence of PLC among Sub-Saharan African countries (31.6 and 16.9 per 100,000 persons/year in men and women, respectively) [19], which is higher than that recorded by GLOBOCAN 2020 [2]. This incidence rate is 3.4 and 5 times higher than that in white men and women in the United States, respectively [21].

Even within SSA countries, the frequency of PLC is not equally distributed. This phenomenon is most obvious in South Africa, where the tumour occurs appreciably more often in rural inhabitants and at a younger age than in their urban counterparts [14]. In a more recent study, HCC was significantly associated with a rural birthplace (P < 0.05), being male and living in an urban area for 14 years or less [22]. It is likely
that these variations at the subcontinental and local level reflect the disparities in the geographical distribution of certain environmental, viral and socioeconomic factors that all, to some extent, play a contributory role in the development of PLC.

Despite these findings, published incidences of PLC in the Sub-Saharan African subcontinent are believed to underestimate its true burden as a consequence of the many instances where the malignancy is either inconclusively diagnosed or is not recorded in a cancer registry\textsuperscript{[14]}. It has been suggested that the limited number of reliable cancer registries in SSA and the challenges associated with diagnosing PLC as a result of scarce resources are the major reasons for the under-diagnosis and under-reporting of PLC. SSA continues to have low coverage of high-quality population-based cancer registration with < 5% population coverage, with low or no mortality registration quality\textsuperscript{[22]}. Most missed PLC cases were predicted to occur in resource limited settings, with 11 of the top 15 countries in terms of underestimation being in SSA\textsuperscript{[24]}. Moreover, from the available data, it is evident that the survival rate of people with PLC in SSA is generally poor, wherein these rates are much lower than that reported in East Asia and even more so when compared to developed countries\textsuperscript{[25-27]}. The median survival rate of PLC patients in North Africa is significantly higher than that of SSA: 10.9 (95%CI: 9.6-12.0) months in Egypt compared to 2.5 (95%CI: 2.0-3.1) months in other African countries \((P < 0.0001)\textsuperscript{[28]}\). In South Africa, the mean survival period of rural blacks is only 6 weeks from diagnosis and 11.2 weeks from the onset of symptoms\textsuperscript{[29]} and in The Gambia the median survival of HCC patients was estimated at 91 days (range: 4-789 days)\textsuperscript{[30]}. The 5-year survival rate of patients with PLC in Uganda and The Gambia is 3.2\%\textsuperscript{[31]} and 3\%\textsuperscript{[32]}, respectively, much lower than 9\% in Denmark\textsuperscript{[33]} and 14.8\% (whites: 14.3\% and blacks: 11.3\%) in the USA\textsuperscript{[34]}. In a recent study that looked at PLC mortality trends in South Africa between 1999 and 2015, it was evident that mortality rates are influenced by age, sex and race\textsuperscript{[35]}. The mortality rates increased with age and are higher among black Africans compared to whites in all age groups-with a peak black African-to-white mortality rate ratio of 6 in men and 3 in women at ages 30-39 years. The average mortality-to-incidence ratio for black African men and women was 4 and 3.3, respectively, compared to 2.2 and 1.8 in their white counterparts\textsuperscript{[35]}. Similarly, in the USA, blacks are more likely to have larger tumour size, more advanced tumour stage/with metastatic disease and lower levels of alpha-fetoprotein and are less likely to present with cirrhosis\textsuperscript{[35,36]}. These disparities in results between the USA and SSA are more likely a consequence of differing prevalence rates of major risk factors including [hepatitis B virus (HBV) and/or hepatitis C virus (HCV)], obesity and diabetes\textsuperscript{[27]}, as well as lack of resources, which may limit access to high-quality care\textsuperscript{[39]}. Considering that, in SSA, most cases of PLC are only detected during the advanced stages of the disease, resectability is only 1\%-2\%, and remission or prolongation of survival are seldom achieved\textsuperscript{[20]}.

Another distinctive feature of PLC in SSA that can be inferred from previous case studies is that the disease presents at a much younger age when compared to those found in regions outside Africa. The median age of diagnosis of HCC (interquartile range, IQR; range) is 45 years (35-57; 8-95), being three years younger in males than females. Moreover, the median age of patients with HBV-associated HCC is 42 years compared to 55 years in those with HCV alone and 47 years in HBV/HCV co-infected individuals\textsuperscript{[20,29]}. In the USA, those of African descent are more frequently diagnosed with PLC at a younger age than Caucasians\textsuperscript{[40]}. However, as cautioned by Shimakawa and Lemoine\textsuperscript{[41]}, these studies should be interpreted with care because there are very few longitudinal studies from Africa\textsuperscript{[42]} and the median age of the African population is significantly lower than that of non-African countries. Therefore, more HCC surveillance studies to determine age-specific incidence of PLC would be beneficial.
The unique features of HCC in SSA, together with the challenges faced in its prevention and appropriate public health intervention, diagnosis and treatment, all suggest that PLC in SSA is deserving of an in depth understanding, with focused research.

AETIOLOGY AND RISK FACTORS FOR HCC IN SSA

Similar to most other cancers, HCC is a multistage disease that results from a culmination of pathologically induced damages that evolve over time. However, unlike most other cancers, HCC is unique in that it develops in the context of well-known and readily identifiable risk factors including viral [HBV, HCV and hepatitis D virus (HDV)], host (hereditary haemochromatosis) and environmental (dietary aflatoxin, alcohol exposure, iron overload, obesity and diabetes mellitus) factors. Other risk factors that are still under investigation include cigarette smoking, oral contraceptives and human immunodeficiency virus (HIV) infection. HCC almost invariably occurs in the setting of histologically abnormal liver such as chronic hepatopathy and/or cirrhosis or in association with genetic disorders such as haemochromatosis, Wilson’s disease, alpha 1-antiprotease (antitrypsin) deficiency and cystic fibrosis.

It is well established that neoplastic lesions usually originate on a bed of chronic necroinflammation that sequentially progresses from fibrosis to cirrhosis and finally culminates in HCC. However, cirrhosis is not a condition sine qua non in HCC development. Interestingly, a proportion (10%-57%) of HCC cases may occur in the non-fibrotic or minimal fibrotic liver, which may suggest a possible shift in the underlying aetiology of HCC, particularly in developed regions of the world. In Western countries, this progression towards the malignancy arises in 46% of patients, with a history of anabolic steroid use and metabolic syndrome (obesity and diabetes mellitus) that is associated with non-alcoholic fatty liver disease (NAFLD). In less developed countries, non-cirrhotic HCC occurs in chronic viral hepatitis patients more frequently than in the more developed Western countries: 53% of the cases in South Africa compared to only 9.5% in the USA. However, the reduced frequency of cirrhosis may be a consequence of lack of detection rather than its absence because resource constraints in SSA obviously limit access to examination by biopsy. In SSA, the cirrhosis is macronodular, typically asymptomatic, and it is caused predominantly by chronic HBV infection, whereas, in low-incidence regions such as the USA, the cirrhosis, although usually macronodular, it may be micronodular, is commonly symptomatic and caused by HCV infection, prolonged alcohol abuse, metabolic syndrome and hereditary hemochromatosis.

While various reasons may account for these differences, geographic locations as an indicator of varying aetiopathological risk factors may be one possible explanation. Genetic differences may be another reason. Exome sequencing has led to the identification of gene expression signatures in HCC and an algorithm for molecular classification of HCC has been developed. One particular signature is found to be highly associated with HCC patients of African origin, younger than 63.5 years, with HBV infection, high C>A and p53 mutations. This molecular signature is not associated with cirrhosis, alcohol consumption or smoking. Further subtype classification has been attempted using multiplex molecular profiling of HCC. Broadly, transcriptome analysis delineated a proliferative and a non-proliferative HCC type, which differ in histological, molecular, epigenetic and immunological features, oncogenic pathway activation, phenotype and prognosis. Chronic HCV infection and alcohol consumption are aetiological factors associated with the non-proliferative HCC, which is characterised by low levels of AFP, retention of well-differentiated cancer cells and relatively good prognosis. Proliferative HCC, characterised by high serum AFP levels, leads to more aggressive tumours and poor prognosis and is associated with HBV infection. This unifying molecular classification aims to lead to stratified therapy strategies. However, this classification has been based on studies carried out on HCC patients from Asia, Europe and North America, in which African and indigenous populations have been under-represented. In the largest,
integrative genomic analysis carried out by the Cancer Genome Atlas Research Network, only 7% (14 of 196) of HCC samples were classified as black or African[64]. Thus, more research is required to confirm that this classification holds in HCC from under-represented populations. Indeed, HCC from indigenous American ancestry could not be classified using this unified classification system[69]. It is interesting to note that Peruvians display early-onset HCC with relatively low HBV DNA viral loads[70], comparable to what is observed in Southern African HCC patients infected with Subgenotype A1[71,72].

Hepatitis viruses
Mono-infection from HBV and HCV are well-established independent risk factors for HCC and the relative importance of each virus varies globally[73]. It is reported that, of the 770,000 cases of HCC that occurred worldwide in 2012, more than half (56%; 95%CI: 52%-60%) were attributable to HBV and 20% (95%CI: 18%-22%) to HCV[74,75]. HCV is the leading cause of HCC in Egypt (84%), whereas HBV is the leading cause in other African countries (55%)[84], where hepatitis B surface antigen (HBsAg)-positivity predominates compared to anti-HCV in HCC patients[76]. In SSA, 50% of all liver cancers are attributable to HBV and 17% to HCV[77]. Overall, only ~3% of HCC patients in Africa are co-infected with HBV and HCV[26,77]. It is interesting to note that the risk factors for PLC also differ between southern and western SSA. In southern SSA, 40% of HCC are attributed to alcohol consumption, 29% to HBV, 20% to HCV and 11% to other factors; the respective figures for western SSA are 29%, 45%, 11% and 15%[78]. Limited data from SSA intimate that HDV infection may play a role in hepatocarcinogenesis in this region.

Hepatitis B virus
HBV, a small-enveloped DNA pararetrovirus with an RNA intermediate, is the prototype of the family Hepadnaviridae, genus Orthohepadnavirus. HBV is the second most important human carcinogen following tobacco smoking[79] and was responsible for 887,000 deaths in 2015[80]. Accordingly, HBV is one of the most important aetiological risk factors for hepatocarcinogenesis[81]. The worldwide prevalence rates for HBV infection vary from 0.1% to more than 20%[82]. In particular, HBV causes approximately two out of three cases of PLC in less developed countries, with most cases aggregating in East Asia and SSA[74].

Epidemiology
An estimated 70%-98% of adult black Africans show serological evidence of previous exposure to HBV[84] and an estimated 65-70 million are chronically infected with HBV[85]. This is probably an underestimate as a result of a paucity of good quality data from SSA[45]. Six of the top 10 sources of uncertainty in the global estimate in adults were SSA nations, with the corresponding number in children, aged 5 years, being 8/10. The two SSA countries, Nigeria and the DRC, together with India and Indonesia account for about 57% of HBV infections globally, with SSA having the highest prevalence in children aged 5 years[86].

Different geographical regions have been categorised into four distinct groups based on the viral serological prevalence of the HBsAg: high (≥ 8%), higher-intermediate (5%-7.99%), lower-intermediate (2%-4.99%) and low (< 2%) [Figure 2][85,86]. Except for Algeria, Eritrea and the Seychelles, most countries in Africa are of higher-intermediate endemicity [SA (6.7%), Zambia (6.1%) and Kenya (5.2%)] or highly endemic for HBV [Swaziland (19%), Zimbabwe (14.4%), Cameroon (12.2%) and Mozambique (8.3%)]. This high prevalence of HBsAg corresponds to the high incidence of HCC in SSA. It is known that in this region HBV infection mainly occurs at a young age, with most acquiring HBV before the age of 30 years (81.5% and 71.4% in South Africa and Togo, respectively)[14,86], and thus are at a high risk of developing HCC (relative risk ranging 9-23.3)[86].
Transmission
The transmission of HBV occurs predominantly by percutaneous or mucosal exposure to infected blood and other body fluids of an infected person. Mother-to-child (perinatal/vertical) remains the most common route of viral transmission in areas of high prevalence such as Asia, whereas unprotected sexual contact or intravenous drug use are the main routes of infection in areas of low prevalence, such as Canada\textsuperscript{[90]}. Thus, the latter cases only acquire the infection later on in life, with the majority (95%) experiencing spontaneous resolution of acute infection\textsuperscript{[91]}. In contrast, in SSA, most infections are acquired horizontally within the first five years of life\textsuperscript{[92,93]}, presumably via contact with household members, unsafe injection practices and medical procedures\textsuperscript{[94]}, tribal tattooing, scarification and circumcision practices\textsuperscript{[94]}. In a population-based case-control study in The Gambia, compared to controls, HCC cases had earlier birth order, a proxy for young maternal age and maternal HBV viraemia at birth, suggesting that perinatal transmission may increase the risk of HCC\textsuperscript{[95]}. Unlike East Asia, perinatal transmission of HBV in SSA is less important, partly because of the lower frequency of hepatitis B e antigen (HBeAg)-positivity, which is a major determinant of perinatal transmission\textsuperscript{[92,96,97]}. Studies from the pre- or early HBV immunisation period have reported very high infection rates in infants with HBsAg prevalence exceeding 10% in Sub-Saharan African countries including Nigeria\textsuperscript{[98]}, Senegal\textsuperscript{[99]} and South Africa\textsuperscript{[100,101]}. In these populations, fewer than 10% resolve the acute infection, with the remainder progressing onto various sequelae related to chronic hepatitis B, including cirrhosis, liver decompensation or HCC\textsuperscript{[91]}. Place of residence
Comparison of HBV exposure and carrier rate between rural- and urban-born Africans is important to the epidemiology of the virus, considering that a vast majority of the population resides in rural areas in SSA. More specifically, rural-born and urban-born black Africans show variation in the burden of HBV-related HCC. In a study of 380 black Africans with HCC in South Africa, Kew \textit{et al.}\textsuperscript{[102,103]} observed that those born and residing in a rural environment (45%) had a higher rate of HBsAg alone (anti-HCV negative) than rural-urban (37%) and urban-born (18%) black Africans. Moreover, rural-born and -residing HCC cases are diagnosed at a younger age than those who migrate to urban cities and their urban-born and -residing counterparts (34.75 years vs. 50.9 years vs. 46.7 years, respectively)\textsuperscript{[103]}. For the period 2000-2012, a higher
prevalence of previous exposure to HBV was found in rural-born than in urban-born South African adult HCC cases (65% vs. 35%, $P < 0.001$) who were also born prior to the introduction of routine HBV vaccination in 1995\cite{22}. However, in agreement with an earlier study carried out in the 1980s\cite{104}, there was a lack of statistical significance in HBsAg-positivity between rural-\cite{105} and urban-born cases ($P = 0.3$)\cite{22}. Thus, HCC participants born in urban environments are just as likely to have been infected with HBV during early childhood when compared to those born in rural areas and subsequently moved to an urban area\cite{106}. Thus, the differences in incidence and age of onset of HCC in rural and urban southern African Blacks cannot be attributable to differences in HBV status alone\cite{104}. Exposure to co-carcinogens such as dietary exposure to aflatoxin\cite{107} and iron overload\cite{108} may be more frequent in rural rather than urban environments and when individuals move from a rural to urban environment exposure to the co-
carcinogen is minimised\cite{104}.

Viral loads

From studies in Asia, higher viral loads of HBV have been shown to be a risk factor for the development of HCC\cite{109,100,106}. Such studies are limited in Sub-Saharan African populations. Among 124 HBsAg-positive HCC cases and 125 asymptomatic carriers (ASCs) of HBV identified in a cohort of black Southern Africans, the reported geometric mean viral loads were 553,618 copies/mL (approximately 118,000 IU/mL) and 16,084 copies/mL (approximately 3400 IU/mL), respectively\cite{111}. In a Sudanese study, HCC patients were found to have higher median viral load compared to patients with chronic or acute hepatitis, cirrhosis and ASCs\cite{112}. In a Kenyan study, consisting of a small number of HCC patients, viral loads did not differ significantly when compared to those in ASCs, cirrhotics and chronic hepatitis patients\cite{113}. Low to moderate HBV DNA levels were associated with the risk of HCC in a Senegalese cohort of men with HCC\cite{110}. In a Gambian case-control study, comparing HCC cases with HBsAg-positive ASCs, HBV DNA levels were found to be strongly associated with HCC independent of HBeAg status. The risk increased notably above 10,000 copies/mL (~2000 IU/mL)\cite{114}. Similarly, in a South African case-control study comparing HCC cases to unrelated cancer controls, the risk of HCC increased with increasing HBV DNA levels above the threshold of 2000 IU/mL, in a dose-response manner\cite{22}. However, whereas the latter study showed a negligible risk at levels lower than 2000 IU/mL, the former study showed some risk. This discrepancy in risk at low HBV-DNA levels may be attributed to marked differences in population characteristics, controls used and HBV genotypes, all of which may influence the amount of viral load. Genotype E prevails in The Gambia, whereas Subgenotype A1 is the dominant HBV strain in South Africa. Genotype E-infected individuals are characterised by a higher frequency of HBeAg-positivity compared to individuals infected with Subgenotype A1\cite{115}. Moreover, environmental risk factors in West Africa such as aflatoxin B1 (AFB$_1$)\cite{40}, which is classified as a human carcinogen by IARC, may play an important role, especially at low viral loads. In fact, in vitro experiments have shown that exposure to AFB$_1$ can lead to reduced viral replication\cite{116}. In the 1980s, aflatoxin contamination in South African commercial foodstuffs was shown to be low (0.66 μg/kg) in comparison to Mozambique (ranging 0.7-6.43 μg/kg)\cite{117}. This was also confirmed in another study in 2004 which reported low rates of mycotoxin contamination in staple foods such as maize in South Africa\cite{118}. In any case, suppression of HBV, even if only for a finite period, may significantly reduce risk for developing HCC\cite{119}. Long-term follow-up studies are needed to further determine the role of low HBV DNA levels as a risk factor for HCC in SSA.

Occult HBV infection

Functional cure is defined as the loss of HBsAg and is used as an endpoint for current anti-HBV therapies. However, the risk of HCC is not eliminated with the loss of HBsAg.

Occult HBV infection (OBI) is defined as the presence of replication-competent HBV DNA [i.e., episomal HBV covalently closed circular DNA (cccDNA)] in the liver and/or HBV DNA in the blood of people who
test negative for HBsAg by currently available assays.\textsuperscript{[120,121]} OBI retains several of the oncogenic mechanisms of overt HBV, including production of pro-oncogenic proteins and the propensity of the viral DNA to integrate into the host’s genome.\textsuperscript{[122,123]} A 12\% prevalence of OBI was previously reported in South African HCC cases,\textsuperscript{[124]} which was significantly lower than that reported in an earlier South African study (48.4\%).\textsuperscript{[125]} When adjusted for sex, age group, country and province of birth, number of years lived in urban area, place of birth, alcohol consumption, HIV status and anti-HCV, the associated odds ratio (OR) for HCC in black South Africans was found to be 2.60 (95\%CI: 0.90-7.53) for seronegative OBI, increasing to 5.10 (95\%CI: 2.06-12.62) for anti-Hbc-positive OBI.\textsuperscript{[126]} This risk is consistent with a previous meta-analysis of retrospective studies (OR = 6.08; 95\%CI: 3.45-10.72).\textsuperscript{[127]}

**Genotypes, subgenotypes and mutants**

In areas with a high prevalence of HBV, such as Southeast Asia and SSA, there is a corresponding high incidence of HCC, with an attributable fraction (AF)\textsuperscript{[128]} (estimated by combining HBV prevalence with the risk for HCC) of 69\% and 50\%, respectively, in these regions.\textsuperscript{[129]} The different genotypes prevailing in these two geographical regions may be responsible for this observed difference in AF.\textsuperscript{[128]} HBV is classified into at least nine genotypes, A-I, with a 10th putative genotype. Genotypes A, D and E circulate in SSA, with Subgenotype A1 being the prevalent subgenotype of Genotype A,\textsuperscript{[130]} which has been shown to have a higher hepatocarcinogenic potential than other (sub)genotypes.\textsuperscript{[131]} Various mutations occurring in this and other (sub)genotypes have been shown to occur more frequently in HBV isolated from HCC patients.\textsuperscript{[112,113]} For example, basic core promoter (BCP) mutations (1753V and 1762T/1764A), preS2 deletion, preS2 initiation codon and ps2F22L mutations were more frequent in strains isolated from HCC patients than in those from non-HCC controls.\textsuperscript{[112,113,130,131]} The combination of BCP and preS2 mutations may suggest the emergence of naturally occurring immune escape variants with a persistent HBV infection that leads to HCC development. A higher prevalence of cancer-related HBV mutations 1762T/1764A and PreS deletions were isolated from HBV/HIV co-infected compared to HBV-mono-infected Chinese adults.\textsuperscript{[132]} As suggested previously,\textsuperscript{[133]} these mutations may be potential biomarkers that can be used for screening high-risk individuals for developing HCC. Such a screening strategy is cost-effective, which is important in resource-limited regions such as SSA.

**Hepatitis D virus**

HDV, the only member of the genus Deltavirus, is a satellite virus of HBV, sharing the HBV entry receptor and utilising the HBV envelope proteins for infection, morphogenesis and propagation.\textsuperscript{[134,135]} Thus, HDV can only be transmitted in the presence of a concomitant HBV infection, by coinfection or superinfection. With a RNA genome of ~1700 base pairs, it is the smallest agent infecting humans.\textsuperscript{[136]} In the latest estimates, 12.0 (95\%CI: 8.7-18.7) million people globally were projected to be anti-HDV positive, representing 0.16\% (95\%CI: 0.11%-0.25\%) of the general population, 4.5\% (95\%CI: 3.6%-5.7\%) among HBsAg-positive people and 16.4\% (95\%CI: 14.6%-18.6\%) among those attending hepatology clinics.\textsuperscript{[137]} This estimate is considerably lower than those obtained in another study, which found 0.98\% (95\%CI: 0.61%-1.42\%) in the general population and 14.57\% (95\%CI: 12.93%-16.27\%) in HBsAg-positive individuals.\textsuperscript{[138]} However, there were concerns about the populations selected, the markers and the HBsAg prevalence estimates used in the latter study that may have introduced biases.\textsuperscript{[139]}

HDV is classified into eight genotypes. A high diversity of genotypes prevails in SSA including Genotypes 1 and 5-8, with Genotypes 5-8 previously reported only in SSA, Genotype 5 in West Africa and Genotypes 6-8 in Central Africa. However, strains belonging to these genotypes are being reported in Europe\textsuperscript{[140]} as a result of migrations from SSA.\textsuperscript{[140]}
Relatively few HDV studies, with small sample sizes, mainly using antibody assays and a minority using nucleic acid detection, have been performed in SSA. In fact, there have been performance issues and difficulties with the detection of African HDV Genotypes 5-8\(^\text{[144]}\). SSA is characterised with localised clusters of HDV endemicity, with pooled seroprevalence of HDV in the general population of 7.33% (95%CI: 3.55%-12.20%) in West Africa and 25.64% (95%CI: 12.09%-42.00%) in Central Africa, with the corresponding values in liver disease patients being 9.57% (95%CI: 2.31%-20.43%) and 37.77% (95%CI: 12.13%-67.54%), respectively. In south-eastern Africa, with a paucity of data and none for liver disease patients, the percentage in the general population was considerably lower at 0.05% (0.00%-1.78%)\(^\text{[42]}\).

Co-infection of HBsAg-positive individuals with HDV can accelerate progression to cirrhosis and HCC\(^\text{[124]}\). Globally, the population AF of HDV among HBsAg-positive individuals was found to be 20% for cirrhotics and 18% for HCC patients\(^\text{[437]}\). However, in SSA, there is a significant knowledge gap on the role of HDV in serious liver disease and HCC, with most studies being performed more than 10 years ago. When 300 HBsAg-positive Mauritanian liver disease patients were tested for anti-HDV and HDV RNA, 30% were seropositive, with 62.2% of these being RNA positive. Co-infected patients were > 8 years older than HBV-mono-infected patients, with anti-HDV antibody, in addition to male sex and higher HBV viral loads being associated with advanced liver fibrosis\(^\text{[484]}\). In Senegal, 24% of HBsAg-positive liver disease patients were anti-HDV positive compared to only 7% in controls with no liver disease\(^\text{[146]}\). A study of 53 liver disease patients in Ghana found 11.3% were anti-HDV-positive, including 5.3% of 19 HCC patients\(^\text{[145]}\). In a case control study comparing HCC with patients without liver disease, the prevalence of HBsAg, anti-HCV and anti-HDV were significantly higher in HCC patients (65.90%, 20.26% and 26%, respectively) than in control patients (9.23%, 4.62% and 1%, respectively) \((P < 2.5 \times 10^{-7})\). There was a 16-, 10- and 29-fold odds ratio increased HCC risk in HBV, HCV and HDV infections, respectively. The authors concluded that the highest hepatocarcinogenic viral factor in Cameroon is HDV\(^\text{[146]}\). However, more studies are required to confirm this in SSA, especially considering the high estimated prevalence of anti-HDV among general HBsAg-positive populations of 8.39% (95%CI: 4.73%-12.85%)\(^\text{[145]}\). These studies should increase the number of patients tested, with standardised and sensitive methods, including nucleic acid testing specific for Genotypes 5-8. Furthermore, because SSA is the epicentre of the HIV epidemic and antivirals for HIV are active against HBV and hence HDV, treated and treatment-naïve patients should be differentiated when testing for HDV. To facilitate large general population-based HDV studies in SSA, the use of dried blood spots, for both antibody and RNA assays, has been suggested\(^\text{[147]}\).

**Hepatitis C virus**

HCV is a hepatotropic RNA virus of the family Flaviviridae and the genus Hepacivirus. High prevalence rates of more than 3.5% are reported in Central Africa; moderate prevalence of 1.5%-3.5% are reported in East and North Africa; and low prevalence of less than 1.5% are reported in Southern Africa\(^\text{[146]}\). HCV strains have been classified into 8 genotypes and 105 subgenotypes\(^\text{[149-151]}\). HCV genotypes differ at 30%-35% of nucleotide sites, whereas subgenotypes of the same genotype differ by < 15%\(^\text{[152]}\). Subgenotypes 1a, 1b, 2a and 3a have a global distribution\(^\text{[152-154]}\). Genotypes 1, 2, 4 and 5 have endemic origins in Africa, with Genotypes 1 and 2 occurring throughout Africa, Genotype 4 in Egypt and parts of Central Africa and Genotype 5 in southern Africa and less commonly in some parts of Central Africa\(^\text{[155]}\). Two full-length coding sequences of Genotype 7 have been characterised. Both sequences were identified in the Democratic Republic of Congo\(^\text{[156,157]}\). The high diversity of HCV in SSA suggests that the virus was endemic in this region before its global dispersal 100-200 years ago. Very few African studies have looked at the effect of HCV genotype on the risk of HCC. In Cameroon, patients infected with HCV Genotype 4, in particular Subgenotype 4f or with core gene variants, are at a higher risk of developing HCC\(^\text{[158]}\). The initial spread of Subgenotype 5a, which prevails in South Africa, was estimated in the 1950s, later than the initial spread in Japan, Europe and...
the USA, and thus it is proposed that the progression of HCV-associated HCC will occur later as well.\textsuperscript{[159]}

With no studies in some African countries or limited studies with small sample sizes in other countries, accurate HCV prevalence data are difficult to obtain.\textsuperscript{[160]} The overall HCV seroprevalence in SSA is 3.0% with an estimated viraemic (HCV RNA) prevalence of 1.0% (0.7%-1.6%) or 11.0 (7.0-16.0) million HCV-infected individuals.\textsuperscript{[161]} The prevalence of HCV varies in the different regions of SSA: West Africa has relatively high prevalence ranging from 1% in Senegal to 6.1% in Burkina Faso with good evidentiary support. The highest prevalence is in Central Africa ranging from 2.1% in the DRC to ~5% in Cameroon and Gabon, with extensive studies having been undertaken in this region. Eastern Africa has a prevalence range from 1.3% in Mozambique to 2.8% in Kenya where there is limited to extensive evidentiary support. Southern Africa, with its limited studies, has the lowest prevalence ranging from 1.1% in South Africa to 1.6% in Namibia and Zimbabwe.\textsuperscript{[160]}

In a meta-analysis of 21 case-control studies, it was shown that patients who tested positive for anti-HCV had a 17-fold increased risk of developing HCC compared to HCV-negative controls (95% CI: 14-22).\textsuperscript{[162]} HCV is associated with HCC development mainly through indirect pathways such as chronic inflammation, cell apoptosis and proliferation. Up to 16% of HCV-infected persons develop cirrhosis 20 years after the infection.\textsuperscript{[163]} The annual incidence of HCC in HCV-induced cirrhosis is on average 2%-3%.\textsuperscript{[164]} The natural history of HCV is highly variable with host and environmental factors playing a role in progression to cirrhosis in patients chronically infected with this virus. Factors such as older age,\textsuperscript{[165]} male sex,\textsuperscript{[166]} heavy alcohol intake,\textsuperscript{[167]} aflatoxin exposure,\textsuperscript{[167]} smoking,\textsuperscript{[168]} diabetes,\textsuperscript{[168]} obesity\textsuperscript{[169]} and co-infection with HIV\textsuperscript{[170]} or HBV\textsuperscript{[171,172]} have all been implicated in enhancing the development of cirrhosis in patients with chronic HCV infection and ultimately leading to HCC.

Early on it was recognised that HCV has a smaller, albeit significant role in the development of HCC in Southern African blacks.\textsuperscript{[102,173]} Relative to individuals serologically negative for HBV and/or HCV, those positive for HBsAg alone have a significant increased risk of 23.3 for HCC, whereas those positive for anti-HCV alone have a statistically significant risk of 6.6. A synergistic effect on risk was evident when markers for both viruses were present (relative risk, 82.5).\textsuperscript{[174]} Higher proportions of women and urban dwellers, and with a higher average age, present with HCV-associated HCC, compared to those with HBV-associated HCC\textsuperscript{[102,173]} 37.5 years vs. 57.3 years, respectively.\textsuperscript{[174]} In a study carried out in the USA, it was concluded that there are differences in the risk of HCC development, which are dependent on the race of the HCV-infected individuals: African Americans are at a considerably lower risk of developing cirrhosis and HCC than are Hispanics and non-Hispanic whites.\textsuperscript{[175]}

**AFLB.**

AFLB, is a powerful hepatocarcinogen that contributes to high morbidity and mortality. Produced by the fungus Aspergillus species (A. flavus and A. parasiticus), AFLB is commonly detected in several food products including peanuts, grain, cereals, legumes and corn.\textsuperscript{[176]} In particular, AFLB is widespread in regions where food products are poorly stored in conditions that are unsanitary and high in temperature and humidity-mostly in tropical regions of SSA and Southeast Asia, including China. It is estimated that 4.5 billion people are at risk of chronic exposure to AFLB-contaminated food.\textsuperscript{[177]} Of the 550,000-600,000 new HCC cases worldwide each year, about 25,200-155,000 (4.6%-28.2%) may be attributable to aflatoxin exposure.\textsuperscript{[167]}

When ingested, the process of metabolising AFLB produces an active substrate known as AFLB,-exo-8,9-epoxide by CYP450 enzyme (CYP1A2 isoform) that plays an important role in the development of HCC.
The substrate binds the guanine bases on the third base of codon 249 of the p53 gene to form aflatoxin-N7-guanine (AFB1-N7-Gua)\(^{178,179}\), which can be detected in 36%-50% of HCC tumour samples collected from individuals in AFB1-endemic areas, most of whom have HBV infections\(^{180-182}\). Assays have been developed to detect and measure AFB1 metabolites in urine\(^{183}\), serum\(^{184}\) and tissues\(^{185}\).

It has been reported that HBV infection is prevalent in regions with high AFB1 contamination, including SSA, Southeast Asia and China\(^{186,187}\). Although AFB1 might have direct hepatocarcinogenic effects, its role in the pathogenesis of HCC is primarily as a co-carcinogen to that of chronic HBV infection\(^{187}\). For example, a previous study using transgenic mice demonstrated that HBV infection, specifically the HBV X protein, modulates the DNA GC → TC transversion at position 249 of the p53 gene mutation by as much as twofold when exposed to AFB1\(^{186}\). In a prospective study in China, individuals exposed to AFB1 had a fourfold increased risk of developing HCC, and this risk increased to 60-fold in individuals who were also carriers of HBV\(^{186}\). In a recent Gambian study, AFB1 exposure was significantly associated with HCC risk (crude OR = 5.0; 95%CI: 1.5-17.2) with a multiplicative effect of AFB1, exposure and HBV preS2 deletions on HCC risk\(^{111}\). More longitudinal and in depth studies are required in SSA to determine the exact roles of the different co-carcinogens in HCC development, together with public health awareness and education campaigns to minimise AFB1 contamination in staple foods.

**Hereditary haemochromatosis and iron overload**

Hereditary haemochromatosis (HH) is an autosomal recessive disorder common among people of Northern European origin that leads to the accumulation of iron in various organs of the body, including the liver\(^{187}\). This pathophysiologic predisposition of iron overload may lead to the development of cirrhosis and ultimately HCC. The mutated human haemochromatosis gene, HFE, located on the short arm of chromosome 6\(^{188,189}\), leads to increased iron absorption and progressive iron storage that results in liver damage and fibrosis, which may eventually lead to HCC\(^{190}\). Risks estimates of HH for HCC of 200 in earlier studies\(^{191,192}\) and 20 in more recent ones\(^{193}\) have been reported. HH is uncommon in Africans\(^{187}\) but has been reported in Cameroonians\(^{194}\), South Africans\(^{195}\) and African Americans\(^{196}\).

Studies in African populations have found that patients with iron overload are not associated with the HH mutation as reported in Northern Europeans\(^{187}\), but it is instead a consequence of drinking traditional beer containing dissolved iron that occurs from using iron drums and cans in which the beer is brewed\(^{190}\). With the replacement of traditional brewing drums with plastic containers, this source of iron overload may be decreasing, but there are no recent studies to substantiate this. Mandishona et al.\(^{195}\) reported a relative risk of HCC of 10.6 (95%CI: 1.5-76.8) when compared to individuals with normal iron status and a population attributable risk of 29 in rural South African Blacks, after adjusting for the confounding effects of HBV/HCV infection and exposure to AFB1. Although the possible causal role of cirrhosis could not be determined in this study because the histological material was obtained by percutaneous biopsy, previous studies have suspected that the deposited iron in hepatocytes and macrophages may play a role in liver organ damage, thus leading to the development of cirrhosis\(^{188}\). Even though the hepatocarcinogenicity of hepatic iron overload has been confirmed in an animal model\(^{200,201}\), many confounding factors, including the consumption of alcohol, makes it difficult to determine whether iron has a direct or indirect role in hepatocarcinogenesis\(^{202}\).

The almost universal association between cirrhosis and the subsequent onset of HCC strongly suggests that chronic necroinflammatory hepatic disease as a result of excess hepatic iron indirectly causes malignant transformation of hepatocytes, as it does with most other causes of HCC. However, studies investigating dietary iron overload in Southern African black populations demonstrated increased risk of HCC.
development even after adjusting for the confounding effect of cirrhosis\textsuperscript{[203,204]}. The mechanisms responsible for a direct hepatocarcinogenic effect of iron have yet to be fully defined, although oxidative stress has been proposed as a mechanism\textsuperscript{[200]}. A multiplicative synergy has been demonstrated between AFB, and iron overload\textsuperscript{[205]}.

In addition to the four major aetiiological factors of HCC in SSA discussed, several risk factors are emerging\textsuperscript{[161]} and becoming progressively more important as Western lifestyles are being adopted. Data on other potential factors associated with lifestyle behaviours (alcohol, smoking and non-alcoholic liver disease) influencing HCC rate are limited in SSA, with our recent study showing minimal effects in South African HCC patients\textsuperscript{[22]}.

**Alcohol and smoking**

As the primary site of alcohol metabolism, the liver is a primary target for alcohol-related injury. Substantial epidemiological data consistently show that excessive consumption of alcohol is associated with increased risk of HCC development, particularly in European and American populations, where chronic HBV infection is less prevalent. For example, studies from the USA, Italy and Taiwan reported 32\%, 45\% and 21\% of HCC cases are attributable to alcohol consumption, respectively\textsuperscript{[206,207]}. In a cross-sectional study that investigated the burden of alcohol consumption in South Africa, researchers observed relative risk of developing PLC in both men and women ranging from 1.5 to 3.6\textsuperscript{[208]}. Furthermore, another South African study demonstrated a fourfold increased risk of HCC after correcting for HBV infection\textsuperscript{[209]}. It has been suggested that alcohol may be associated with HCC only as a consequence of the development of cirrhosis\textsuperscript{[210]}. In addition, it has been suggested that daily ingestion of more than 80 g of alcohol for more than 10 years is generally required before there is significant risk of developing cirrhosis\textsuperscript{[211]}, and it has been shown to have an equivalent increase risk of developing HCC\textsuperscript{[210]}. It should be noted that alcohol-induced HCC can develop in the absence of cirrhosis, and even if one abstains from alcohol consumption after cirrhosis has developed\textsuperscript{[212]}. In South Africa, excessive alcohol consumption has been implicated as a major risk factor for HCC in older white (mean age 60 years)\textsuperscript{[213]} and urban black African men (older than 40 years)\textsuperscript{[209]}. Alcohol has also been suggested to be a risk factor for HCC in patients with no markers for hepatitis viruses in a large African study\textsuperscript{[209]}. Following the global trend, total alcohol per capita consumption among drinkers (≥ 15 years) in litres of pure alcohol have increased in SSA over the period 2000-2016\textsuperscript{[214]}. As with other risk factors, alcohol consumption may act as a co-carcinogen together with HBV infection in the development of HCC\textsuperscript{[206]}.

In South Africa, even though anti-smoking legislation and increased prices of cigarettes have contributed to a decreased consumption by 33\% from 1993 to 2003\textsuperscript{[215]}, several studies conducted prior to this legislation found little or no support for causal relation between cigarette smoking and HCC development in SSA\textsuperscript{[209,214]}, and this has been supported more recently in South Africa\textsuperscript{[22]} and The Gambia\textsuperscript{[25]}.

However, it is important to note that earlier epidemiological studies that investigated the association between smoking and HCC have been inconsistent, and these inconsistencies vary between different population groups and in the presence of potential confounders\textsuperscript{[217]}. With regards to earlier cohort studies conducted in the USA\textsuperscript{[216]}, Japan\textsuperscript{[214]} and Greece\textsuperscript{[209]}, the reports all show evidence of increased risks of PLC among smokers with some also reporting an increase in a dose-response relationship\textsuperscript{[209,221]}. This is inconsistent with other studies that found no risk\textsuperscript{[222]} or reported inconclusive evidence\textsuperscript{[223]}. In a meta-analysis of 38 cohort studies and 58 case-control studies from Europe (Norway and Sweden), North America (the USA) and East Asia (China, Japan, Taiwan, Korea and Philippines), the authors reported that, relative to never smokers, the adjusted relative risk was 1.51 (95\%CI: 1.37-1.67) for current smokers and 1.12
HBV-HIV coinfection occurs in 10% of HIV-infected individuals. Of the almost 38 million HIV-positive individuals globally, two-thirds reside in Sub-Saharan Africa (SSA) could help in elucidating the role of oral contraceptives in hepatocarcinogenesis. Furthermore, N-nitrosodimethylamine, a component in cigarette smoke, has been shown to be hepatocarcinogenic in animals, and various mechanisms have been proposed for the hepatocarcinogenic effect of smoking. The IARC has included PLC on the list of carcinomas associated with smoking. Thus, while awaiting further studies on smoking and HCC in SSA, smoking should be considered as a risk factor for HCC.

Non-alcoholic liver disease and diabetes

In a study that selected a total sample size of more than 8.5 million cases from 22 countries, it was reported that the global prevalence rate of NAFLD was estimated to be 25.2% (95% CI: 22.1%-28.6%). The authors also showed that the highest prevalence occurred in the Middle East, followed by South America, Asia, the USA and Europe, and the lowest in Africa. These findings were reported despite the apparent paucity of studies investigating NAFLD, as shown in Figure 3. While NAFLD and its inflammatory component non-alcoholic steatohepatitis (NASH) are responsible for the third leading cause of death in developed regions of the world, HCC remains the primary cause of death in this group.

In NAFLD/NASH related HCC, several risk factors have been identified including metabolic syndrome and insulin resistance, which lead to changes in the inflammatory cytokines and/or adipokines, persistent inflammation and altered gut microflora and bile composition. In a meta-analysis of cohort studies from mainly developed countries (Europe, the USA, Japan and Korea), the summary relative risk of PLC was 1.89 (95% CI: 1.51-2.36) for those who were obese compared with persons of normal weight. It is likely that NAFLD/NASH plays a role in the increased risk of Sub-Saharan Africans developing HCC, especially considering that changing eating habits, sedentary lifestyles and the wide roll out of antiretroviral therapy (ART) against HIV might be contributing factors to the increasing adiposity and diabetes seen in SSA between 2000 and 2014.

Hormonal contraception

Studies that investigated PLC risk with oral contraceptives use in high-risk Asian and African women uniformly yielded inconclusive or null results. In these regions, it is difficult to determine whether these findings can be explained because of the non-synergistic effect of viral (HBV) and hormonal factors, given that detecting the risk associated with oral contraceptive use (2-3-fold) against the very high background relative risk (20-fold) in HBV carriers may be particularly difficult. Nevertheless, some biological and experimental evidence suggests a possible role of oral contraceptives in hepatocarcinogenesis. In in vitro experiments, oestrogen was reported to stimulate the cellular proliferation of HepG2 cells and the rate of spontaneous mutation. In patients, increased risk of liver disease associated with oral contraceptive use was observed in pills containing more than 50 μg of oestrogen, and regression in disease was noted after cessation of contraceptive use. These findings all suggest that contraceptive use may have potential hepatocarcinogenic effects, which may be dependent on various factors that include the period of exposure, dosage levels and the influence arising from confounding factors. Further long-term prospective studies in SSA could help in elucidating the role of oral contraceptives in hepatocarcinogenesis.

HIV

Of the almost 38 million HIV-positive individuals globally, approximately two-thirds reside in SSA. HBV-HIV coinfection occurs in 10% of HIV-infected individuals, and this increases to 25% when taking OBI into account. HCV-HIV co-infection ranges from 0.7% to 16% in SSA. Clearly, the HIV
Figure 3. Non-alcoholic Liver Disease and Diabetes (NAFLD) prevalence stratified by region, data obtained from[231] and compiled with https://mapchart.net.

epidemic has had a major demographic and health impact. The clinical consequences of HBV-HIV coinfection include higher mortality and morbidity compared to individuals who are mono-infected with either virus[250]. The progression of chronic hepatitis B to cirrhosis and HCC is more rapid in HIV-positive individuals than in those with HBV alone. HIV immunosuppression can cause the loss of anti-HBs and lead to HBV reactivation. HBV can also negatively impact HIV outcomes[251], with ART changing the disease profile and increasing mortality attributed to HBV-associated end-stage liver disease[252].

Studies carried out prior to the ART era in South Africa and Uganda failed to show increases in HCC risk among HIV-infected persons, possibly due to the competing risks of AIDS-related deaths[253,254]. However, an increase in HCC cases has been noted in the ART era in developed countries[255]. Moreover, with the scale up of ART treatment in South Africa, from 4.9% adults accessing ART in 2004[256] to 61% in 2009[257], an upswing in PLC mortality rates in black Africans occurred[35]. In Uganda, a study reported that, with each 10% increase in ART coverage, PLC incidence increased by 12%[258]. The spectrum of liver disease may be shifting from opportunistic infections to sequelae of chronic HBV/HCV infections, medication toxicities, alcoholism and fatty liver[259], possibly as a result of increased longevity following ART. These associations need to be further investigated in case-control and cohort studies in SSA to determine the underlying aetiological risk factors in this group. Moreover, there is a need for focused PLC control efforts and further investigations in ART-treated HIV-infected cohorts who are now surviving longer.

CONCLUSIONS AND FUTURE PROSPECTS
HCC control efforts in SSA are faced with a number of challenges, which are unique to this sub-continent:

· Most countries in this region are LMICs, with resource constraints in terms of both human capacity and infrastructure.
HBV continues to be hyperendemic, with West Africa having HBsAg-prevalence of more than 8%.

Less than 1% of HBV-positive individuals and even fewer HCV-positive individuals are aware of being infected. In SSA, 1.1 million (<1%) of about 60-80 million chronic carriers are diagnosed and only 33,000 (<1%) of those are receiving treatment.[86]

HDV is a neglected infection in this region.

Antenatal HBV screening is hardly performed in SSA (0%-20%).[260]

Only ~10% of newborns receive the birth dose of HBV vaccine.

Direct antiviral agents against HCV are inaccessible to most patients because of high prices.

Contamination of staple foodstuffs with the co-carcinogen AFB1 is not controlled.

The epicentre of the HIV pandemic is in SSA.

There is a paucity of good quality data on HCC in this region.

Very few genomic studies, necessary for the molecular classification of HCC, have been done in patients from SSA.

The number of cancer registries is limited.

Extensive ART implementation is changing the natural history of HCC.

Emerging lifestyle changes may also be influencing the aetiology of HCC.

The HBV genotypes/subgenotypes prevailing in SSA are diverse, with distinct geographical distribution within Africa and differing from those circulating outside the subcontinent. Considering that viral genotypes and subgenotypes have a role to play in the clinical manifestation of the infection, the results from studies investigating HBV-related HCC from other regions cannot necessarily be extrapolated directly to SSA.

Progress in surveillance, prevention and diagnosis of HBV, HDV and HCV infections can play a great role in the successful management of HCC in SSA and the reduction of its serious consequences. There is an urgent need for targeted screening of HCC, especially in high-risk groups. This will provide much needed data, which will inform public health officials and determine the various factors that are at work. Prevention is pivotal in controlling the clinical consequences of HBV infection. Although nationwide HBV vaccination programs have been successfully implemented in SSA, positively contributing to the decline in HBV seroprevalence in children, vaccination is suboptimal because only ~10% of neonates have access to the birth dose. Furthermore, there remains a group of unvaccinated adults who were born prior to the introduction of the HBV vaccine, who are ageing, with increased risk for HCC. Access to treatment should be improved. Although HBV/HIV co-infected individuals receive ART treatment that can also manage HBV infection, HBV mono-infected individuals find it very difficult to access treatment in SSA. HBV
infection has been eclipsed by the blockbusters AIDS, tuberculosis, and malaria (“because of the availability of an HBV vaccine”), with concomitant political inertia in combatting HBV. HCC research has been chronically and grossly underfunded on the subcontinent, with research being performed mainly by research groups in high-income settings. Without a doubt, the COVID-19 pandemic will further aggravate the situation, leading to HCC in SSA being side-lined and neglected, contributing to high morbidity and mortality, especially in the younger age groups.

Changes in the population demographics and prevalence of HCC-related risk factors will dictate the temporal trends in epidemiology of this malignancy in the coming decades. The decline of HBV as a risk factor for HCC may be offset by the emergence of NAFLD and ageing as risk factors for HCC development. Indeed, future prospective cohort studies are required to confirm this. The wider adoption of imaging diagnostic modalities and population-based cancer registries are required to provide reliable data to determine the true incidence of HCC, which is currently underestimated. This will permit clinicians and public policy makers to anticipate and adapt accordingly in terms of public health perspectives, resource allocation and formulation of management guidelines specific for Sub-Saharan African patients with HCC. There is still much work to be done to reduce the burden of this cancer on the subcontinent.

DECLARATIONS

Authors' contributions
Writing and preparation of original draft as part of his PhD thesis, preparation of figures: Mak D
Conceptualisation, resources, review and editing of original draft, synthesis and discussion to yield the finalized version, supervision and financial support of student: Kramvis A

Availability of data and materials
Not applicable.

Financial support and sponsorship
Cancer Association of South Africa (Cansa), and German Research Foundation (Deutsche Forschungsgemeinschaft).

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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