LIVER CANCER IN AFRICA

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Abstract

After hepatocellular carcinoma is diagnosed, life expectancy is counted in months or weeks in Africa. The main cause of this cancer is infection with hepatitis B, hepatitis C, and food poisoning with aflotoxin. ***N Scheff.*** Liver Cancer in Africa. ***Med J Therapeut Africa. 2007;3:236-43.***

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Introduction

Hepatocellular carcinoma is a rapidly lethal cancer, with life expectancy after diagnosis rarely exceeding 3 years in developed countries, and 3 months elsewhere. In Africa, the predominant risk factors for the development of liver cancer, known for over 2 decades, include chronic infection by hepatitis B, infection by hepatitis C and long-term exposure to foodstuffs contaminated with aflatoxin. Studies of the molecular environment have increased our understanding of these carcinogens and the complex pathways by which they interact with the host genome to cause cancer. There are safe and effective vaccinations for children against infection by hepatitis B. Aflatoxin contamination may be eliminated through safe farming and food storage practices, although these practices have yet to be implemented in most of Africa. Antiviral drug therapies may prevent virus-associated liver cancer by reducing or eliminating viral replication, if treatment starts before the liver is compromised. However, liver cancer continues to be acute in developing African countries where poverty and limited resources make prevention and treatment especially difficult.

Search Methods

OVID, MEDLINE, PubMed and WHO databases were searched for articles published from 01 January 1985 through 02 August 2007 by means of the terms: "hepatocellular carcinoma"; "HCC"; "HCC epidemiology"; HCC Etiology"; "hepatocellular carcinoma in Africa"; "hepatitis B virus"; "hepatitis C virus"; "hepatitis B in Africa"; "hepatitis C in Africa"; "HBV"; "HCV"; "aflatoxin." Additional relevant studies were found in the reference lists of selected articles. The majority of the epidemiological and molecular data for hepatitis B in Africa, as well as many other relevant references, were generously provided by Professor Anna Kramvis, Molecular Hepatology Research Unit, Department of Internal Medicine, the University of the Witwatersrand, Johannesburg, South Africa.

Hepatocellular carcinoma Worldwide

Worldwide, over a half million humans are diagnosed with hepatocellular carcinoma each year, and it is the third most frequent cause of cancer deaths, Table 1. The major risk factors are infection with hepatitis B (HBV); infection with hepatitis C (HCV); alcohol consumption; long term exposure to aflatoxin B1; tobacco smoking; diabetes with obesity and fatty liver; and iron overload (hemochromatosis).(1)

Epidemiologic studies have tracked the worldwide variation in the oncogenic influence of the major risk factors. The predominant risk factor for hepatocellular carcinoma worldwide appears to be chronic infection with HBV. Whether or not the chronic HBV infection results in cancer depends on several cofactors and varies throughout the world. Identified cofactors include age at time of infection, gender, history of exposure to other environmental and behavioral carcinogens, and the specific genotype of the infecting virus. The interactions of these factors must be better understood as they pertain to given populations before appropriate therapies and preventive interventions can be applied.(2,4-5)

Infection by HCV is the second most predominant etiologic factor. WHO estimates that approximately 180 million humans, 3% of the world's population, are currently infected, 130 million of whom are chronic HCV carriers at risk for liver cirrhosis or liver cancer. It is estimated that 3 to 4 million humans are newly infected each year, 70% of whom will develop chronic hepatitis.(6) This data is confounded in cases of HBV/HCV co-infection because HCV can mask the expression of the hepatitis B "s" antigen in the blood (HBsAg) even when the virus is present in the liver.(7)

Studies at the molecular level have broadened our understanding of how risk factors interact with the host genome in the pathogenesis of liver cancer. They have also lead to the introduction of promising therapies for humans with chronic viral infections. We know, for example, that HBV and HCV are different in structure: HBV has a DNA genome and replicates through an RNA intermediate requiring an active viral reverse transcriptase (RT) polymerase enzyme; HCV is an RNA virus with no RT activity and

Major risk factors	Incidence data	Mortality data
• Hepatitis B (HBV) >50%, globally • Hepatitis C (HCV) >25% globally[a] • Alcohol consumption • Aflatoxin • Tobacco smoking • Obesity/diabetes/fatty liver • Iron overload (hemochromatosis)[b]	• 551,000 new cases a year • 5th most common cancer • 83% of all new cases of cancer in developing countries • 54% of all new cases of cancer in China	• 529 000 deaths • 8.8% of all cancer deaths • 3rd most frequent cause of cancer death
[a]In the United States, HCV accounts for about 25% of liver cancer whereas chronic HBV, having 1/3 to ¼ of the prevalence of HCV, produces fewer cases of HCC. Globally, the situation is reversed, with HBV being the more common cause. (2) [b]Hereditary hemochromatosis is due to mutations at the C282Y or H63D loci. It is a hereditary disease affecting 1 in 400 Americans. Early diagnosis and treatment can prevent sequellae, which include diabetes, heart failure, cirrhosis, and liver cancer. Treatment consists of therapeutic phlebotomy to keep iron saturation of the transferrin protein at less than 50%.(3)		

Table 1. Major Risk Factors and Worldwide Statistics for Hepatocellular Carcinoma. (Adapted from Ref 1).

replicates by RNA replication. Both viruses, however, use viral proteins to interfere with cell proliferation and growth in the host genome.(8) In addition, researchers have identified molecular biomarkers in the host genome that make hepatocytes more susceptible to hepatocarcinogenesis. This may also lead to new therapies and preventive interventions.(9)

Diagnosis of hepatocellular carcinoma is usually made after the cancer has spread or invaded the portal vasculature, making early intervention difficult. Typically, a lesion is undetectable until it is about 2 cm, usually after 4 to 12 months of growth. While surgical removal of small, single tumors can produce a cure, usually the disease is advanced at the time of discovery and treatments prolong life by only a few months or, rarely, up to 2 years. Transplantation may be effective in a small number of instances.(10) However, these are all expensive therapies, requiring highly specialized clinical resources and are all but unavailable in developing countries.

In resource-limited countries, the most promising lines of defense against hepatocellular carcinoma are: vaccinations against HBV, which have been available for over 2 decades; interventions to prevent exposure to risk factors; and therapies for viral infections that may limit liver damage. Donations from private organizations, predominantly the Global Alliance for Vaccinations and Immunizations (GAVI), are helping developing countries incorporate HB vaccinations into their immunization efforts. Unfortunately, many less developed countries lag in this effort.(11) Currently, there is no vaccine for hepatitis C. Like HIV/AIDS, HCV infection is characterized by the continuous emergence of virus variants, which prevents detection by the host's immune system and development of effective vaccines. There are antiretroviral therapies for chronic HBV and combination therapy with interferon alpha 2 and ribavirin for HCV that may suppress viral replication and decrease the hepatocarcinogenic effects of the virus.(12-15) These therapies are also expensive and for the most part unavailable to infected humans in developing countries.

There are also means for limiting exposure to environmental carcinogens such as aflatoxin B1. Using safe farming and food storage practices industrialized countries have virtually eliminated aflatoxin contamination of food supplies.(16) This effort is difficult to implement in countries which lack the money, resources and cultural opportunities to modernize farming and food storage practices.(17,18)

Hepatocellular carcinoma in Africa

Hepatocellular carcinoma is endemic in China, Taiwan, Korea and Africa, where the incidence is between 20 and 100 cases per 100,000 humans.(2) From 1993 to 1997 in Africa, the highest age-standardized incidence rates of hepatocellular carcinoma were found in sub-Saharan Africa in The Gambia with a rate of 48.9 per 100,000 humans. By comparison, during the same period, Algeria had the lowest incidence rate of liver cancer at 0.9 per 100,000 humans.(19)

The combination of chronic HBV and exposure to aflatoxin B1 appears to be the dominant risk for hepatocellular carcinomain sub-Saharan Africa, although HCV infection may be a confounding factor.(5) Recent studies have examined variation in the natural history of hepatocellular carcinoma in predominantly HBV-endemic regions, such as Asia and Africa. In these areas, males are 8 times more likely to develop hepatocellular carcinoma than females, whereas the male to female ratio is 2:1 in North America and Europe.(20) Variation in the natural history of chronic HBV infection appears to correspond with this variation in incidence of hepatocellular carcinoma. In most HBV-endemic areas outside Africa, HBV infection is characterized by high rates of viral replication after infection which is usually indicated by hepatitis B e antigen [HBeAg] seropositivity. Following is a slow waning in viral titer over time. In Asian populations active replication often persists into late adulthood.

By comparison, viral replication declines steeply

after adolescence in sub-Saharan Africa, with almost no persistent replication detected in individuals over 25 years of age. This is according to data presented over time by the Gambia Hepatitis Intervention Study (GHIS), which in 1986 was the first program in Africa designed to assess the efficacy of HB vaccination in the prevention of chronic liver disease and hepatocellular carcinoma. Reports discussing these data give conclusions that the data produced during the Gambia study is applicable in various degrees throughout sub-Saharan Africa.(5,21-23)

In 2006, Kirk, Bah and Montesano suggested that this variation may be attributable to the variation in routes of HBV transmission. In Asia, chronic HBV-infected mothers deliver infants who may be infected around the time of birth. These children have a high likelihood for chronic, active infection. Among Gambians, HBV transmission occurs more frequently in early childhood, not perinatally, and this may accelerate HBV replication decay.(24) However, it is also possible that HBV persists undetected in the liver, because HBV-infected Gambians also have a relatively high prevalence of HVC.(5)

HBV in Africa

According to Professor Kramwis, Africa has 12% of the world's population, and approximately 18% of the its HBV infections. Sixty-five million HBV chronically infected humans live in Africa.(25) Of the 1.3 million deaths attributed to HBV-related diseases recorded annually worldwide, approximately 250,000 occur in Africa, almost 1 in every 5. Most Africans become infected with HBV during childhood, and 8% to 10% of humans in the general population become chronically infected.(26) The Baka pygmies of eastern Cameroon have the highest exposure to HBV.(27)

Young children are the most likely to develop chronic infection. Ninety percent of children are infected during the first year of life and 30% to 50% of children between 1 and 4. The risk of death from HBV-related cirrhosis or liver cancer in Africa has been estimated at approximately 25% for humans who become chronically infected during childhood.(28) Thus 1 in 4 children infected with HBV die of it in Africa's developing countries.

Chronic carriage of HBV is indicated by the persistence of HBsAg (the hepatitis B "s" antigen) 6 months after exposure. (In non-chronic infections, HBsAg appears before the onset of symptoms, persists during overt disease, and disappears 3 to 6 months after clinical recovery.) After decades of chronic infection, HBsAg carriers go on to develop hepatocellular carcinoma. It has been hypothesized that, since the hepatocarcinogenic process involves a complex interplay between the virus and host hepatocytes, both genomes contribute to the final pathogenic outcomes, either individually or synergistically.(29)

HBV is transmitted by several routes. In Africa, most primary HBV infections are transmitted either perinatally (around the time of childbirth), or horizontally before the age of 10 years by HBV-infected humans living in the same household. Perinatal transmission occurs at a low rate, however, and is high only when mothers are HBeAg positive HBV carriers.(30-34) Medical procedures, including tonsillectomy, indiscriminate injections and the reuse or use of nonsterilized syringes have been shown to increase the risk of HBV infection, as has sexual activity.(35-39)

HBV may be grouped into 8 genotypes based on genetic variation in HbsAg. Globally, there is significant geographic variation in the prevalence of HBV genotypes.(40-44) There is also growing evidence that different HBV genotypes may result in different clinical outcomes, including variation in persistent infection, viral replication and hepatocellular carcinoma risk. For example, the relative risk of developing hepatocellular carcinoma is 4.5 (95% CI, 1.86 to 10.90) times higher in black Africans living south of the Sahara who are infected with genotype A (subgenotype B1) compared with those infected with non-A genotypes.(45)

Most African genotype A isolates appear to belong to subgenotype B1 as a consequence of trade and travel along the eastern coast of Africa by Asians. This subgenotype is mainly found in the southern and eastern regions of Africa, including South Africa, Malawi, Tanzania, Uganda, the Congo and Somalia. Subgenotype A2 or the 'European' subgenotype of A has been isolated from South African carriers of the virus. It has been suggested that this subgenotype originated in southern Africa and was introduced to Europe by European (Portuguese) sailors who traveled to South Africa in the 15th century.(46)

HCV in Africa

Although HBV is the predominant risk factor for hepatocellular carcinoma in Africa, HCV has an estimated attributable fraction of 23% in The Gambia (reduction in numbers of humans who would have a disease if a risk factor were eliminated). These attributable risk estimates of the burden of hepatocellular carcinoma resulting from hepatitis viruses are comparable with IARC estimates of 60% and 20% of hepatocellular carcinoma cases attributable to HBV and HCV respectively throughout sub-Saharan Africa, suggesting that The Gambia shares common HCC risk factors with the rest of Africa.(5,47) In contrast to HBV, most humans infected with HCV become chronic carriers. However, confounding this issue is the difficulty of differentiating liver cancer originating from HBV and HCV infection. The cyclical process of hepatocyte destruction, regeneration and development of fibrosis and eventually cancer requires decades of chronic infection and in many ways is the same with either virus. Data from the Gambia Liver Cancer Study

(GLCS) demonstrate an OR with combined HBV/HCV infection of 35, roughly equivalent to the sum of the individual ORs (17 + 17 - 1 = 33).(21,48-51)

Other studies have estimated the HCV prevalence in sub-Saharan Africa at 3%, although HCV prevalence data in Africa are not as reliable as the data on HBV infections.(52) Kirk, Bah and Montesano suggest that this is due to the variability and selectivity of the populations studied, inconsistent HCV testing methods, and a lack of data regarding mode of transmission.(5)

The highest HCV prevalence and incidence rates in Africa are found in Egypt. From 1992 to 2005, 1,012 cases of hepatocellular carcinoma were diagnosed at Egypt's Gastroenterology Center, Mansoura University. The number of humans with hepatocellular carcinoma increased yearly from 9 in 1992 to 80 in the first 5 months of 2005. Previous treatment for chronic HCV infection in these patients was 76.6%; schistosomiasis was present in 37.6% of the hepatocellular carcinoma observed; HBV accounted for 3.3%; and HBV/HCV accounted for 3.6%.(53,54)

In developed countries, most incidence of HCV infection can be attributed to intravenous drug use.(55) In sub-Saharan Africa, most cases of HCV are not attributable to intravenous drug use. There is strong epidemiologic evidence that the HCV prevalence observed in Egypt is explained by widespread parenteral transmission during an antischistosomiasis campaign conducted in the 1960s.(56) The exact mechanisms by which HCV is transmitted in Africa are unknown. WHO estimates that up to 40% of medically related injections given in sub-Saharan Africa may be unsterile and that HCV transmission through re-use of contaminated syringes and medical equipment appears plausible.(57,58)

Aflatoxin (AFB1) in Africa

Many agricultural products are vulnerable to attack by a group of fungi that produce toxic metabolites called mycotoxins, which includes aflatoxin. The aflatoxin problem was first recognized in 1960, when a severe outbreak of "Turkey 'X' Disease" in the UK killed over 100,000 animals.(59) Peanut meal in the animals' feed had become infected with the fungus Aspergillus flavus, and so its toxic metabolites were named aflatoxins. Today, it is estimated that ~4.5 billion humans living in developing countries are chronically exposed to uncontrolled amounts of the toxin.(60) In Africa, food products contaminated with aflatoxin B1 include cereal (maize, groundnuts [peanuts], sorghum, pearl millet, rice, wheat), oilseeds (groundnut, soybean, sunflower, cotton), spices (chilies, black pepper, coriander, turmeric, zinger), tree nuts (almonds, pistachio, walnuts, coconut) and milk.

In Africa, early epidemiologic studies showed a clear association between exposure to aflatoxin B1 contaminated foods and risk of HCC.(61) Evidence of continuing dangerous levels of exposure includes a recent epidemic of acute aflatoxin poisoning resulting in the death of hundreds of Kenyans.(62)

The identification of aflatoxin B1 biomarkers in molecular epidemiological studies has permitted a better understanding of aflatoxin in hepatocellular carcinoma pathogenesis.(63-70) The p53 gene, TP53, is known as the "tumor-suppressing gene and "the guardian of the genome," because it delivers a message to cancerous cells to program their own self-destruction. A molecular-centered review of ~1,000 hepatocellular carcinoma tumors data taken from the IARC p53 mutation database demonstrate a clear association between a particular kind of mutation (249ser mutation), exposure to AFB1, and incidence of hepatocellular carcinoma.(71) The data suggest that the 249ser mutation may represent past exposure to AFB1 and prove useful in epidemiologic studies to predict hepatocellular carcinoma risk, target preventive interventions, or serve as an intermediate endpoint in chemoprevention trials.(5)

Therapeutics and Prevention

Attempted cures for hepatocellular carcinoma include liver transplants and tumor ablation by sound waves, gene therapy and pumpkin seeds.(72)

New surgical methods and other therapies are described as emerging with greater potential response and lower risk and cost.(73) Currently medical treatments including surgery, chemotherapy, chemoembolization, ablation, and proton beam therapy are expensive and effective only for patients with small tumors and excellent liver function.(74)

Most interventions in developing countries are aimed at preventing exposure to carcinogens or treating viral infections. In the United States 5 drugs have been approved for treating chronic viral infections: conventional interferon (IFN)-alpha, lamivudine, adefovir dipivoxil, pegylated IFN-alpha-2a and entecavir. Treatment of HCV with antiretrovirals has resulted in sustained viral response (SVR), or non-detectable virus 6 months after end of treatment (EOT) about 19 to 29% of the time. When there is no virus at EOT, the virus will relapse after treatment has stopped, with 90% of relapses occurring in the first 12 weeks. If the virus remains undetectable for 24 weeks after EOT, the relapse rate is 1 or 2 % in patients that have been followed up to 7 years. The case is different with HBV which can and does "hide," while still being present in a non-replicative state, although antiviral therapy in the treatment of HBV has also been proven effective. Although these drugs appear to reduce the incidence of hepatocellular carcinoma, they are expensive and unavailable in most developing countries. Even in developed countries where resources are available, less than 10% of humans with chronic HBV and HCV have received antiviral therapy and the incidence of liver cancer is doubling.(75-84)

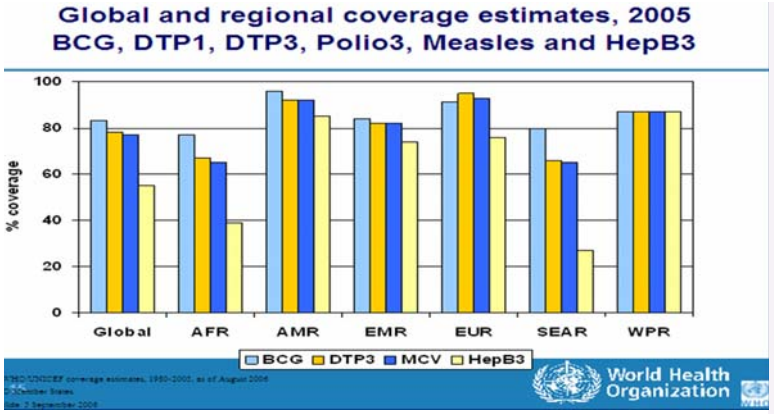

Figure 1. Global and regional coverage estimates, 2005. BCG, DTP1, DTP3, Polio3, measles and HepB3,(WHO/UNICEF).

Vaccination against HBV in infancy appears to be the most effective approach to prevent hepatocellular carcinoma in developing countries.(85) A safe, effective HBV vaccine has been available since the early 1980s.(86,87) After a decade of follow-up in The Gambia, the GHIS reported HB vaccine efficacy in children at 9 and 4 years of age.(89,90) Chronic HBV carriage prevalence was 10% among unvaccinated children compared with <1% among vaccinated children. Protection against HBV infection was over 80% and protection against chronic carriage over 90%. During similar time periods, HB vaccination programs were initiated in Southeast Asia and China. The HB vaccination has consistently proven highly efficacious in reducing the prevalence of HBV infection and of chronic carriers among the vaccinated populations.(83) Since then, the HB vaccine has been given to millions of humans worldwide and has been found to be one of the safest and most efficacious vaccines in use.(91) While questions remain about the need to ensure protection using booster doses, efficacy against chronic HBV infection remains high for up to 15 years.(92-95) Yet, despite WHO recommendations that all countries incorporate HB vaccine into their routine EPI program by 1997, and despite significant cost reductions (<USD0.50 per dose), WHO/UNICEF reported that by 2005, 45% of children in Africa had received safe and effective HB vaccinations, Figure 1.(96,97)

Heavy lifetime exposures to aflatoxin B1 continue in West Africa, according to GHIS data. In high exposure environments, community interventions aimed at modifying post-harvest practices may have the greatest impact on lowering aflatoxin contamination levels in groundnuts and other subsistence crops. However, because groundnuts are the primary income source for many Gambians, the practice of selling the least visibly contaminated groundnuts and keeping contaminated groundnuts for personal consumption continues.(5) Chemoprevention trials have provided 'proof of principle' that agents which modulate the effective level of aflatoxin B1 exposure by increasing metabolic detoxification (as with oltipraz) or by reducing the bioavailability (as with chlorophyllin) may reduce levels of aflatoxin exposure.(98)

Behavioral interventions, such as modification of food storage practices, require minimal direct expenditures; however, the difficulty in changing cultural practices also must be recognized.(99) A community intervention study in rural Guinea, West Africa, of post-harvest interventions demonstrated a reduction in aflatoxin B1 contamination of food stores. At the other end of the technology spectrum, genetic engineering could produce aflatoxin-resistant crops, however, there are significant scientific, ethical and environmental barriers to this approach.(100)

Conclusions

In Africa, the causes of hepatocellular carcinoma have been documented. Studies have substantiated the high incidence of hepatocellular carcinoma resulting from childhood HBV infection and long-term exposure to aflatoxin B1 in sub-Saharan Africa, as well as the high percentage of the incidence of hepatocellular carcinoma caused by chronic HCV infection in some areas of Africa, such as Egypt.

Although hepatocellular carcinoma is rarely curable through early surgical extirpation, studies worldwide have shown that interventions aimed at preventing or limiting exposure to HBV, HCV, and aflatoxin B1 are effective at lowering the incidence of new cases of liver cancer. In addition, antiviral therapies hold promise for interrupting the effects of infection by HBV and HCV, although these are expensive and unavailable to most in resource-limited countries.

The multiplicative interaction between HBV infection and long-term aflatoxin B1 exposure suggests that reduction in either or both may reduce the incidence of hepatocellular carcinoma in Africa. The combined effect of incorporating continent-wide HB vaccinations and interventions to reduce aflatoxin B1 contamination in Africa's subsistence foodstuffs may be associated with decreases in HBV-related hepatocellular carcinoma.

No vaccination currently exists for HCV and working toward the prevention of HCV transmission through proper sterilization techniques and education appears to be the best course of action. However, a vaccination for HBV has been available for 2 decades, and data from The Gambia Hepatitis Intervention Study (GH IS), as well as studies worldwide, suggest that this vaccination is highly effective in preventing HBV infection.

WHO recommended that all countries incorporate HB vaccine into their routine immunization program by 1997. Of the 132 million children born in 2000 worldwide, 25 to 30% had access to the vaccine.(97) More recently, through the efforts of international partners coordinated by the Global Alliance

on Vaccines and Immunizations (GAVI), HBV-endemic countries with limited resources have started introducing the HB vaccine into their routine EPI.

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