Hepatocellular carcinoma and African iron overload

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Abstract
Both hepatocellular carcinoma (HCC) and iron overload are important health problems in Africa. Chronic hepatitis B virus (HBV) infection is recognised as a major risk factor for HCC, but iron overload in Africans has not been considered in pathogenesis. Up to half the patients with HCC in Africa do not have any recognised risk factors such as preceding chronic HBV infection, and other risk factors remain unidentified. HCC is an important complication of HLA-linked haemochromatosis, an iron loading disorder found in Europeans. It is proposed that African iron overload might also be a risk factor for HCC.

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Although the annual incidence of hepatocellular carcinoma (HCC) is low in North America and western Europe, it is probably the most common malignancy occurring in men worldwide.1 The highest incidence of 100 cases per 100 000 of population annually has been reported in the southern African country of Mozambique.2 The association of HBV infection and HCC in Africa is widely recognised,3 while exposure to aflatoxins4 5 and alcohol6 are also possible aetiological factors. Longtime investigators in the field are convinced that other as yet unidentified associations must exist.7 Cirrhosis of various causes is recognised to be important in the aetiology of HCC.1 Cirrhosis secondary to HBV is regarded as the most important risk factor in Africa, China, and South East Asia,3 8 while alcoholic cirrhosis seems to be more important in North America and western Europe.9 Cirrhosis secondary to primary biliary cirrhosis, autoimmune chronic active hepatitis, chronic hepatitis C infection, and HLA-linked haemochromatosis are also associated with the development of HCC.1 While it has been well reported that iron overload in Africans is an important cause of cirrhosis,10 11 this condition has not been regarded as part of the aetiology of HCC in Africa.12 We review evidence that suggests that iron overload may contribute to the high incidence of HCC in Africa.

More than just hepatitis B
Studies in epidemiology, comparative pathology, and molecular biology have consistently shown a strong association between persistent HBV infection and subsequent development of HCC.1 3 13 In sub-Saharan Africa 80% of persons acquire HBV infection by the age of 10 years, and of those infected about 20% become chronic carriers.14 15 Similar HBV prevalence rates apply to Asia.8 Despite these very high rates of endemicity, and the strong relation between HBV infection and the development of HCC, the reasons why only a small number of people with persistent HBV infection develop HCC are not known.

In South East Asia chronic HBV infection accounts for most of the cases of HCC. By contrast, in Africa, a considerable proportion of HCC is not explicable on this basis. Two particularly well performed studies illustrate this point. In 1975, a prospective study in Taiwan looked at 22 707 male Chinese to evaluate the incidence of HCC and its association with HBV infection.8 Of these subjects, 3454 (15%) were found to be carriers. Follow up to December 1986 showed excess deaths from HCC in the HBsAg positive subjects. Of the 152 who died of HCC, 143 were carriers. Only nine of the original 19 253 who were HBsAg negative developed HCC. The evidence from Africa is different. In a case controlled study of 140 adults and their 603 family contacts in the Gambia, only 53% of all cases of hepatoma could be attributed to persistent HBV infection.15 Similar findings have been reported in southern Africa, where only 18 to 44% of patients with HCC have evidence of persistent HBsAg in non-malignant hepatic tissue12 16 and only 29 to 58% have such evidence in serum assays.7 12 Furthermore, the risk estimates between persistent HBV infection and development of HCC show wide variation within Africa.17 These findings would suggest the existence of different susceptibility levels for the development of HCC in the face of chronic HBV infection or different exposure rates to other carcinogens, particularly in the African population.15 17 18

HLA-linked haemochromatosis and HCC
Although iron is essential for life, iron overload is toxic and potentially fatal. The liver is an important site of iron storage and is particularly susceptible to injury in iron overload. This liver damage is particularly evident in homozygous HLA-linked haemochromatosis, one of the most common inherited disorders in European populations with a prevalence of up to 0·45%.19 The disease is characterised by increased intestinal iron absorption and progressive parenchymal iron overload. The affected subjects typically show clinical symptoms of parenchymal organ damage including...
Iron has been shown to be mutagenic and might directly initiate carcinogenesis in the liver. In vitro, iron enhances and the withholding of iron inhibits the growth of human hepatoma cell lines. Support for a direct carcinogenic effect of iron is provided by the finding that patients with HLA-linked haemochromatosis who are most likely to develop HCC have the highest mobilisable iron concentrations. Alternatively, excessive hepatic iron may play an indirect part in the multi-step process of malignant transformation by inducing hepatocellular damage and cirrhosis.

Until recently, all reported cases of HCC complicating HLA-linked haemochromatosis had arisen in cirrhotic livers, and patients without cirrhosis were not considered at increased risk. Early diagnosis and repeated venesection of patients with HLA-haemochromatosis were believed to prevent malignant transformation by preventing tissue iron accumulation, which causes hepatic damage and ultimately, cirrhosis. Several investigations have now reported the development of HCC in patients with HLA-linked haemochromatosis who do not have cirrhosis. Fellows and colleagues described two patients with primary haemochromatosis but not cirrhosis in whom HCC supervened despite removal of excess iron by venesection therapy. In another report a 67 year old man with a 32 year history of HLA-linked haemochromatosis complicated by cirrhosis had reversal of cirrhosis by phlebotomy therapy yet developed HCC. The occurrence of HCC in non-cirrhotic patients with HLA-linked haemochromatosis is compatible with a possible direct carcinogenic effect of iron.

African iron overload and HCC
Severe iron overload is common in sub-Saharan Africa, achieving a prevalence of more than 10% in some populations. The condition has been most frequently reported and best recorded in southern Africa where the prevalence of HCC is also higher than in the rest of the continent. Iron overload, however, has been reported in all regions of sub-Saharan Africa including Tanzania and Uganda in east Africa, and Ghana and Nigeria in west Africa. Iron overload in Africa is related to the consumption of a traditional fermented beverage with high iron content. The consumption of this type of beer occurs in east and west Africa (Hakim J, Okwanga N, personal communications), but has been best described in southern Africa. While African iron overload has been perceived as having a purely environmental aetiology (excessive dietary iron present in traditional beer), recent evidence points to an interaction between the amount of dietary iron and a possible non-HLA-linked iron loading gene as being potentially important in pathogenesis. This form of iron overload is characterised pathologically by massive deposition of iron in both macrophages and hepatocytes, and subsequently by fibrosis and cirrhosis.

While hepatic concentrations of iron in African iron overload commonly rival those found in HLA-linked haemochromatosis, an association between HCC and this common African form of iron overload is not widely recognised. One reason for this lack of recognition is that certain publications from the 1950s and 1960s influenced medical practitioners and investigators to disregard African iron overload as a factor in the aetiology of HCC. These papers, referring to work performed in South Africa, put forth the assertion that there is no convincing evidence for an association between siderosis and HCC. If you consider the studies upon which this opinion was based, you are struck by the paucity of data actually tackling the issue and left with the conclusion that the question of an aetiological relationship between African iron overload and HCC was not adequately investigated at that time.

A further reason that African iron overload has been regarded as fairly benign, when compared with HLA-linked haemochromatosis, is that a large proportion of the excess iron is in macrophages of the reticuloendothelial system where it is thought to be comparatively harmless. This fact has led to the misconception among some health professionals that all excess iron is in the reticuloendothelial system. Several considerations support the concept that the pathogenesis of iron-loading and the details of the histological distribution of iron in HLA-linked haemochromatosis and African iron overload differ. Iron loading in HLA-linked haemochromatosis occurs because a genetic defect leads to excessive iron absorption from a diet with normal iron content, whereas in the African condition iron overload generally develops in subjects who consume a diet with high amounts of bioavailable dietary iron and possibly have a different genetic defect. Furthermore, iron loading in HLA-linked haemochromatosis is predominantly parenchymal, whereas iron accumulation in African iron overload is prominent in macrophages as well as in hepatic parenchymal cells. The point to be emphasised here is that iron loading of hepatocytes is a feature that is common to both African iron overload and HLA-linked haemochromatosis. Early descriptions of the histology of African iron overload clearly showed that hepatocytes may be as severely affected by iron loading as macrophages. Furthermore, a substantial proportion of patients with the African condition have iron loading that extends to other organs in a manner similar to HLA-linked haemochromatosis.

A third reason that African iron overload has been regarded as comparatively non-toxic is the concept that serum iron and transferrin saturations concentrations are generally normal in this condition, becoming increased only after the condition is advanced and cirrhosis...
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Hepatocellular carcinoma, iron overload, and transferrin: An analysis of the presence of iron overload conditions marked by a high transferrin saturation rate and the expected occurrence in patients with the African condition. Italian investigators have suggested that iron overload conditions, as in HLA-linked haemochromatosis, lead to the development of HCC. The cytopathogenic mechanisms of hepatocellular damage in iron overload conditions remain unclear. Possible pathways include the presence of parenchymal cells in iron overload, as in HLA-linked haemochromatosis, to cirrhosis or the development of HCC. Italian investigators have suggested that excess iron facilitates persistent HBV and hepatitis C virus (HCV) infection and can act as a cofactor in the pathogenesis of HCC in patients with viral hepatitis. Evidence showing that iron overload directly facilitates iron chelator desferrioxamine that inhibits HBV virion replication in vitro is in keeping with the possibility that iron may directly activate HBV multiplication.

The hypothesis that iron overload in Africans is a risk factor for HCC has never been formally tested, but several reports have appeared that provide potentially supportive data. In Strachan's original necropsy series describing iron overload in Africans in 1929, 10 of 114 (8.8%) subjects with considerably increased hepatic iron concentrations died from hepato-metaplasia, compared with one of 159 (0.6%) subjects with normal hepatic iron. In a study of HCC tumor morphology conducted in 90 subjects of rural and urban origins in Johannesburg, South Africa, in the early 1980s, iron content was graded in non-malignant liver tissue. The prevalence of severe hepatic iron overload (defined as grade 3–4/4 hepatocellular iron) was 33.2%, compared with 10.6% of normal hepatic iron. This is in line with the findings of the same study in Africa, as evidenced by the finding in several series that iron overload was found to be common in subjects with HCC than in the general population. If African iron overload is an aetiological factor for HCC, it is eminently preventable through changes in the practices of preparation and consumption of traditional beer, and it is treatable by phlebotomy therapy to remove iron from the body. We propose that prospective studies should be undertaken to examine the possible role of African iron overload in the pathogenesis of HCC.

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