

## Prevention of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is considered to be a major malignant tumour in the world today. Among the reasons for this belief are two that are especially germane when considering the need to prevent the tumour – its high incidence and its grave prognosis.

HCC is the sixth most common human tumour, with approximately 750 000 new cases occurring each year.<sup>1</sup> Furthermore, its incidence increases year by year. More than 80% of global HCCs occur in economically developing countries in the Asia-Pacific region and sub-Saharan Africa.<sup>1</sup> HCC ranks third in annual cancer mortality rates, and has the shortest survival time of any cancer in both males and females.<sup>1,2</sup> Its prognosis is especially poor in black and Chinese patients.

So prevalent is HCC and so poor the results of treatment and the prognosis in resource-poor parts of the world that prevention of the tumour is an urgent priority in these regions. Because the risk factors for HCC are known in more than 90% of cases and almost all these are potentially preventable, prevention of the tumour should be an attainable goal in these regions.

Chronic hepatitis B and C virus infections, dietary exposure to the fungal toxin aflatoxin, cirrhosis of any cause, iron storage diseases and the metabolic syndrome, either alone or in a variety of combinations, cause almost all HCCs worldwide. Because of the differing causation of the tumour in different regions, strategies for its prevention will need to be tailor-made for each region. For the immediate future the emphasis should be on researching and introducing practical and economical interventions, especially in resource-poor regions with high incidences of HCC.

### Prevention of hepatocarcinogenic hepatitis viral infections

Chronic infection with hepatitis B or C viruses accounts for a substantial majority of global HCCs. Prevention of these infections would therefore go a long way towards eradicating this tumour.

#### Hepatitis B virus infections

Approximately 390 million people worldwide are chronically infected with the hepatitis B virus (HBV). Chronic infection with this virus causes 55% of global HCCs and 80% or more of these tumours in the Asia-Pacific and sub-Saharan African regions.<sup>3</sup> In the latter regions, the infection is almost always acquired in infancy or early childhood, as a result of either perinatal or horizontal transmission of the virus. Infections acquired this early in life have a considerably greater likelihood of progressing to chronicity than those acquired in later years: infants and young children persistently infected with the virus face a lifetime relative risk of developing HCC as high as 100, with one-quarter or more developing the tumour.<sup>4</sup> Drug treatment of chronic HBV infection has generally been unrewarding in preventing the development of HCC, and the urgent need for an effective vaccine administered very early in life is self-evident.

A safe and effective vaccine against HBV became available in the early 1980s. After a slow start, the vaccine is now included in the Expanded Programme of Immunization (EPI) in almost all countries worldwide. More importantly, with the support of funding from the Global Alliance for Vaccines and Immunization (GAVI), the Vaccine Fund, and other governmental and non-governmental agencies, the great majority of economically developing countries in which the virus is endemic and the risk of HBV-induced HCC high, now include HBV vaccine in their EPI. The highest level of protection is achieved when the first dose of the vaccine is given as soon after birth as possible, together with HBV immune globulin-induced passive immunoprophylaxis, and the second and third doses at 1 month and 6 months of age.

The most encouraging results of vaccination against HBV to date have been achieved in Taiwan, which has a high incidence of chronic HBV infection and HBV-induced HCC. Immunisation of newborns was begun in 1984, with universal coverage achieved in 1986, coverage of all preschool children in 1987, and extension to older children and adults in 1990. The incidence of chronic HBV infection in those vaccinated has been reduced from around 10% of the population in the pre-immunisation era to 1%, and the occurrence of HCC in those immunised has decreased by 70% in comparison with matched individuals not receiving the vaccine.<sup>5</sup> These results augur well for the eventual elimination of both HBV infection and HBV-induced HCC.

Regrettably, in many of the regions of sub-Saharan Africa and the Asia-Pacific region where the incidence of HBV-induced HCC is high, financial constraints, competing public health priorities (HIV/AIDS, malaria, tuberculosis, measles and diarrhoeal illnesses), and poor delivery services not able to adequately access rural areas of the countries mean that the full three-dose course of immunisation is not being received by approximately half of the infants. Because of this shortfall, as well as the generally long interval between the acquisition of chronic HBV infection and the development of HCC, it is estimated that it will take between 3 and 5 decades before the hoped-for elimination of HBV-induced HCC will be realised. Nevertheless, there is little doubt that HBV vaccine will prove to be the first anticancer vaccine.

#### Hepatitis C virus infections

Chronic hepatitis C virus (HCV) infection is the predominant cause of HCC in most economically developed countries. Some 170 million people worldwide are currently estimated to be persistently infected with this virus,<sup>6</sup> and the incidence is increasing in a number of countries. The infection is almost invariably acquired in adulthood, mainly as a result of the illicit use of injectable drugs and unwise sexual practices. Despite recent improvements in the results of treating chronic HCV infection with antiviral drugs, the overall impact of this therapy is relatively small because the majority of chronically infected individuals are unaware that they are infected. Nevertheless, effective antiviral treatment of patients

known to be infected with HCV will lessen the risk of malignant transformation.<sup>7</sup>

Extensive research over many years has failed to produce a vaccine against HCV, and there appears to be little likelihood of such a vaccine becoming available in the near future. Other methods for preventing the spread of this virus must therefore be introduced and rigorously enforced.<sup>8</sup> The ways in which chronic HCV infection are acquired are generally more amenable to intervention than those responsible for the great majority of chronic HBV infections. Efforts to prevent infection should focus on identifying persons at increased risk of HCV infection and providing them with appropriate counselling. In addition, the following practices should be introduced on as wide a scale as possible:

- With regard to illicit intravenous drug users, programmes for the exchange of needles, syringes and other drug paraphernalia should be introduced as soon as possible, and on as wide a scale as possible, to minimise spread of the virus.
- All donated blood should be screened for hepatitis viruses. Regrettably, this is not currently the case in many resource-poor countries, especially in sub-Saharan Africa, where as many as 45% of blood transfusions are estimated to be unscreened.<sup>9</sup>
- All medical, paramedical and dental practitioners should be educated to avoid the use of unnecessary injections and to improve the safety of their injection and infusion techniques.
- In addition, patients known to be chronically infected with hepatitis viruses should be treated with antiviral drugs.

### Exposure to aflatoxins

Aflatoxins are difuranocoumarin derivatives produced by *Aspergillus flavus* and *A. parasiticus*. These fungi contaminate a variety of crops, particularly in tropical and sub-tropical countries with warm, humid climates. Maize, groundnuts and fermented soy beans are particularly prone to contamination, especially in subsistence farming communities. Contamination takes place both during growth of the crops and as a result of their improper storage. Aflatoxin B1 is most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen. The hepatocarcinogenic effects of aflatoxin B1 and HBV are multiplicatively synergistic.<sup>10</sup>

Relatively simple pre-harvest intervention involves ensuring adequate irrigation of the crops and spraying with fungicides. In the long term, contamination might be prevented by genetically engineering foodstuffs that are resistant to infection with *Aspergillus* species. The likelihood of contamination during storage is increased by excessive moisture and damage to the crops. Methods to combat this include sun drying of the crops and removal of visibly mouldy plants by hand-sorting before storage, the use of well-ventilated rainproof storage facilities, storage in jute rather than plastic sacks and on shelves rather than on the ground, and use of fungicides to prevent spread of the fungus. A study confirming the effectiveness of post-harvest intervention has been performed in a rural region of Guinea.<sup>11</sup>

If dietary exposure cannot be prevented, secondary prevention, defined as preventing the carcinogen from reaching its target or interacting with tissue nucleophiles, could be considered. Two drugs have been tried. Chlorophyllin, a derivative of natural

chlorophylls, acts as an 'interceptor molecule', complexing with and inactivating aflatoxins. A single trial in China reduced aflatoxin-DNA adducts and urinary secretion of aflatoxin by 55%.<sup>12</sup> Supplementing the diet with foods rich in chlorophylls, such as spinach and other leafy green vegetables, could be considered as an alternative. Oltipraz is a potent inducer of the expression of glutathione -S-transferase, thereby enhancing phase II inactivation of aflatoxins.<sup>13</sup> It may also have an inhibitory effect on phase I enzymes.<sup>14</sup>

### Iron storage diseases

Although essential for the growth of cells, iron is toxic in excessive amounts. The liver is particularly subject to the toxic effect because it is the major site of iron storage. Both forms of iron storage disease – hereditary haemochromatosis (HH)<sup>15</sup> and dietary iron overload in black Africans<sup>16</sup> – are complicated by the development of HCC.

Prevention of HCC in HH involves the early screening for potential sufferers and de-ironing by regular blood-letting (usually in the form of donations for blood transfusion).

Dietary iron overload occurs in many countries in sub-Saharan Africa, where as many as 15% of black men may be affected<sup>16</sup> due to consumption of large volumes of traditional beers with a high iron content as a result of being brewed in iron pots. A hereditary predisposition is likely but not proven. Dietary iron overload and aflatoxin exposure have a multiplicative effect on mutagenesis.<sup>17</sup>

Prevention will require education about the health hazards of alcohol brewed in this way, together with the provision of alternative containers to be used for brewing the beer. Such a programme has yet to be attempted on a large scale.

### Cirrhosis, whatever the cause

All aetiological forms of cirrhosis may be complicated by HCC formation. The scope for preventing malignant transformation once cirrhosis is established is limited. Attention should therefore be focused on preventing the development of cirrhosis.

### Metabolic syndrome

The metabolic syndrome, a constellation of obesity, hypertension, hyperlipidaemia and insulin resistance, which can lead to non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and cirrhosis, may be complicated by the development of HCC.<sup>18</sup> It is likely that NAFLD mediates the malignant transformation.<sup>18</sup> Prevention predominantly consists of the avoidance of obesity.

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