Mycotoxins and Carcinogenesis

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Intruduction

Hepatocelluar carcinoma(HCC) in recent years has become one of the most frequently occurring tumors worldwide, occupying 5th place(average of men and women) in the classification of all malignancies. The estimated incidence of new cases in about 500,000 per year, and since the prevalence is estimated to be similar, the survival of patients on the whole is 1 year. Areas with a very high incidence(>20 cases/100,000 inhabitants) include sub-Saharan Africa, the Western coast of Africa, which includes Gambia, Guinea, and Mali, and South Africa; in Asia a very high incidence is found in the southeastern countries(Korea, Hongkong, Thailand, and Mongolia) and in large areas of China and Japan. European countries at high risk(11-20 cases/100,000) include Italy and Spain, and those at intermediate risk(5-10 cases/100,000) include France, United Kingdom, and Germany. A low incidence(<5 cases/ 100,000) is found in the United States, Canada, and Scandinavia. The Latin American countries are included in the areas of high incidence. Asia has the highest number of cases(about 76% globally) followed by Africa, Europe, United States, Australia. Incidence adjusted by age and sex has yielded estimated values of 18 cases/100,000 males and 6 cases/100,000 females in developing countries, these estimates being 2.5-fold those reported in developed countries. In the Unites States the incidence of HCC increased from 1.4/100,000 per year from 1976-1980 to 2.4/100,000 per year from 1991-1995. Changes in incidence have also involved age. In fact, from 1981-1985 the peak incidence of HCC occurred in patients aged 80-84 years, where as from 1991-1995 the peak was noted in subjects aged 74-79 years. A shift in incidence towards younger persons was noted in the last two decades.A characteristic of HCC is to grow on cirrhotic liver: in facts, in western countries it develops on cirrhotic livers in more than 90% of cases, whereas in Asia and Africa the percentage of cases of HCC is higher in noncirrhotic than cirrhotic liver.

Risk Factors

The main risk factors of HCC are the hepatitis B(HBV) and hepatitis C(HCV) viruses, which together account for three quaters of all cases worldwide. Other risk factors include aflatoxin B1 intake, alcohol consumption, and some hereditary diseases, among which are hereditary hemochromatosis, hereditary tyrosinemia, and α1 anti-trypsin deficiency. The attributable risk fraction for each risk factor varies according to the country examined. Whereas HCV has the greatest attributable risk in developed countries(60% in the USA, Europe, and Japan), it is responsible for a limites number of cases in most areas of Asia and African where, on the country, HBV is mainly responsible. Aflatoxin B1 probably does not play a role in developed countries, whereas it is definitely responsible, with a risk, however, not quantifiable, for numerous cases in Africa and Asia.

Role of Aflatoxin B1: Many epidemiologic studies including the role of hepatitis virus have been studied and have shown that many patients with HCC(as high as 70%) have anti-HCV antibody in the serum. HCV therefore represents the most important risk factor for HCC in western countries. Instead of hepatitis virus, aflatoxin B1(AFB1) has also long been associated with the development of HCC, because areas with a large consumption of this toxin coincide with areas with a high incidence of HCC. It is produced by a fungus of the genus Aspergillus in large areas of Asia and sub-Saharan Africa where, for climatic reasons(heat and humidity) and because of storage techniques, the fungus represents a common contaminant of foods(grain, corn, peanuts, legumes, etc.), producing large quantities of toxin.

However, it was recently observed that areas that have a high incidence of HCC and high aflatoxin intake correspond to areas in which HBV infection is endemic and that patients at higher risk of developing HCC are those who are exposed to both HBV and AFB1 risk factors. A case control study using biomakers of exposure to AFB1, such as urinary metabolites of AFB1 or the blood concentration of AFB1 adducts, did not confirm the responsibility of AFB1 in the development of HCC; for this reason it has been proposed that in addition to a high intake of AFB1, patients who previously were exposed to HBV should be considered at higher risk of developing HCC. One possible means by which AFB1 can lead to HCC is to provoke a specific mutation of codon 249 of the p53 tumor suppressor gene. However, this mutation has almost always been found in patients who had previous contact with the HBV.

Dominant Role of Hepatitis B virus and Cofactor Role of Aflatoxin B1 in Hepatocarcinogenesis in Quidong, China: We assessed the separate and combined effects of hepatitis B virus, hepatitis C virus(HCV), and aflatoxin in causing hepatocelluar carcinoma(HCC) in Quidong, China. A consecutive series of 181 pathologic-diagnosed HCC cases were studied for hepatitis

B surface antigen(HBsAg), anti-HBV X gene sequence, anti-HCV, the 249ser-p53 mutation, and chronic hepatitis pathology. Each of the 181 incident HCC cases had markers for HBV infection and hepatitis pathology; only 6 of 119 cases were coinfected with HCV. The 249ser-p53 mutation was found in 54%(97/181) of HCC cases and in all 7 cases with tissue for analysis from the hepatitis cohort but in none of 42 matched cases from Beijing. The estimated cumulative dose of aflatoxin B1 in these 7 cases ranged from 0.13 to 0.49 mg/kg. Follow-up data through 13.25 years on a cohort of 145 men with chronic HBV hepatitis showed that the relative risk from aflatoxin exposure was 3.5(1.5-8.1). A similar relative risk was found using 249ser-p53 mutation as a marker for aflatoxin exposure. In conclusion, HBV hepatitis is ubiquitous in Quidong HCC cases, whereas HCV contributes little to its risk. The 249ser-p53 mutation appears to results from coexposure to aflatoxin and HBV infection. Even modest levels of aflatoxin exposure tripled the risk of HCC in HBV-infected men.

Determinants of formation of aflatoxin-albumin adducts; a seven-township study in Taiwan: Dietary exposure to aflatoxins is one of the major risk factors for hepatocelluar carcinoma. Individual susceptibility to aflatoxin-induced hepatocarcinogenesis may be modulated by both genetic and environmental factors affecting metabolism. A cross-sectional study was performed to evaluate determinants of the formation of aflatoxin covalently bound to albumin(AFB1-albumin adducts). In total 474 sujects who were free of liver cancer and cirrhosis, the detection rate of AFB1-albumin adducts was significantly higher in males(42.5%) than in females(21.6%). The formation of detectable albumin adducts was moderately higher in hepatitis B surface Ag carriers(42.8%) than in non carriers(36.6%). The detection rate of AFB1-albumin adducts tended to increase with the increasing number of null genotypes of glutathione S-transferase M1-1 and glutathione S-transferase T1-1.

In conclusion, this cross sectional study has assessed the relative contributions of environmental exposure and host susceptibility factors in the formation of AFB1-albumin adducts in a well characterised Chinese adult population. This study further emphases the necessity to reduce aflatoxin exposure in people living in an area endemic for chronic hepatitis B virus infection.

Conclusion

Hepatocelluar carcinoma is currently one of the most frequently occurring tumors worldwide and it has highly negative prognosis. THe main risk factors are HCV and HBV. Each one is prevalent in different areas of the world, HCV in western countries, Japan, and Australia, HBV in large areas of Africa and Asia. They are responsible for neoplastic degeneration of the liver, mainly through cirrhosis. Alcohol is also considered a risk factors for HCC, but only indirectly

after progression of liver cirrhosis and only in heavy drinkers. AFB1 has recently been redimensioned as the etiologic factors in HCC, because although its consumption is high those countries, such as Africa and Asia, where the incidence of HCC is high, it seems to be only a cofactor of neoplastic degeneration.

What should health professionals do in the next few years to reduce the incidence of HCC? They should: (1) extend the universal campaigns of vaccination against HBV, which is the most frequent etiologic factors of HCC, above all in developing countries where the virus is endemic; (2) reduce AFB1 intake through the appropriate storage and treatment of foods.; (3) reduce the incidence of HCV infection through diffusion of educational programs on the knowledge of the contaminated materials and above all, targeting groups at high risk, such as drug users, people practicing body piercing, and homosexuals, awaiting the implementation of avaccine to prevent HCV infection

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