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Hepatitis B-Aflatoxin Synergistic Interaction and the Risk of Liver Cancer

William Opoku-Nkoom*

Department of Import and Export Control, Food and Drugs Authority, Ghana

***Corresponding Author:** William Opoku-Nkoom, Department of Import and Export Control, Food and Drugs Authority, P.O. Box CT 2783, Cantonment-Accra, Ghana.

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Abstract

Among all cancers, the second highest number of years of productive life lost due to premature death or disability is attributable to liver cancer. Hepatitis B and aflatoxins are the two major risk factors of primary liver cancer, and both have similar geographic distributions, notably in sub-Saharan Africa and South-East Asia. The climatic conditions in these geographic regions favour the proliferation of the mould and production of the fungal toxins (aflatoxins). The co-existence of hepatitis B and aflatoxins produces a significant multiplicative effect in the pathogenesis of primary liver cancer, through mechanisms including over expression of cytochrome P450 enzymes involved in the metabolism of aflatoxins, interference with nucleotide excision repair, and free radical overload. Efforts to limit aflatoxin contamination in food commodities through strengthened agricultural extension systems; and dietary exposure, involving dietary diversification, may go a long way in reducing the risk of liver cancer. Also, strengthened systems of food monitoring at national and international levels in ensuring aflatoxin food safety and government commitment to fighting hepatitis B viral infection in at-risk populations cannot be over-emphasised, as far as food safety and health are concerned.

Keywords: *Aflatoxins; hepatitis B; food safety; liver cancer*

Abbreviations: AFB1-N7-Gua: aflatoxin B1-DNA adduct; FAO: Food and Agricultural Organisation; HBsAg: hepatitis B surface antigen; HDI: human development index; IARC: International Agency for Research on Cancer; IFPRI: International Food Policy Research Institute; NER: nucleotide excision repair; WFP: World Food Programme; WHO: World Health Organisation

Introduction

According to recent reports, liver cancer is the sixth most common cancer [1], the second leading cause of cancer deaths [2] and the cancer with the second highest disability adjusted life years [1]. It is noteworthy that developing countries, i.e. countries with low and medium human development index (HDI), particularly sub-Saharan African and South-East Asia bear the greatest burden of liver cancer, with estimated 83 per cent incidence and mortality rates [3].

The high endemicity of hepatitis B with the concomitant heavy dietary exposure to aflatoxins in tropical and sub-tropical low and medium HDI economies may be the reason for the striking geographical discrepancy in the burden of liver cancer. This review is on the two major causes of liver cancer, their synergistic interaction and plausible measures to control their impacts and the burden of liver cancer, in at-risk populations, notably sub-Saharan Africa and South-East Asia.

Hepatitis B

Hepatitis B is a viral infection of the liver. According to the World Health Organisation (WHO), highly endemic regions are sub-Saharan Africa and South-East Asia, where 5-10 per cent of the adult population are chronically infected [4].

The WHO further estimates that about 20-30 per cent of chronic hepatitis B patients die from hepatitis B-related liver cancer or cirrhosis [4]. Overall, hepatitis B viral infection accounts for about 45 percent of liver cancer cases and 30 percent cirrhosis, with much higher proportions in low and medium HDI countries [5].

Aflatoxins

Aflatoxins are a family of fungal toxins produced by *Aspergillus flavus* and *Aspergillus parasiticus*, which are in abundance in hot humid climates. They are present in both human food and animal feed, and are of great importance in food safety and public health, due to their potency as immunosuppressants, mutagens, carcinogens and teratogens. Some food commodities that may contain aflatoxins include maize, groundnut, rice, wheat, sorghum, millet, cocoa beans, and other cereals, legumes, nuts and seeds. Animal products like milk, eggs and meats may also have aflatoxins because of the animal consumption of aflatoxin-contaminated feed. A report by the International Food Policy Research Institute (IFPRI) on mycotoxin food safety risk highlights the presence of aflatoxins in human breast milk and umbilical cord blood samples from Ghana, Nigeria, Sierra Leone and other tropical developing countries [6]. This thus points to chronic dietary aflatoxin exposure in these geographic regions.

Available information depicts that aflatoxin contamination often occurs in the field prior to harvest [7]. Post-harvest contamination may also occur if crop drying is delayed and if moisture is allowed to exceed critical limits for the growth of the mould during storage [7]. Insect infestation and rodent invasion are also known to facilitate the growth of the mould in stored commodities [7].

According to some researchers, temperature and moisture are the two major factors that regulate the production of aflatoxins in food commodities [8]. This puts tropical countries at elevated risk for aflatoxin exposure because the climate characterised by high temperatures and humidity, favour the proliferation of the mould. Optimal temperature for the growth of the mould is between 25-32°C, humidity levels above 62 percent, and moisture content of 18 percent (for starchy cereals) and 9-10 percent (for oil-rich nuts and seeds) are established for maximum production of aflatoxins and their metabolites [8].

According to the World Bank, European Union regulation of aflatoxins cost African countries US $ 670 million in annual export losses [6]. By implication, the best quality foods would always get exported and the poor quality ones would be left for the local consumers especially the poor who could only afford limited food variations and may easily compromise on food safety.

Direct correlation between consumption of aflatoxin-contaminated food and the incidence of primary liver cancer has been found in many studies in several geographic regions, with the strongest association reported in sub-Saharan Africa [9]. It is documented that between 5-28 per cent of liver cancer cases globally are attributable to dietary aflatoxin exposure [9]. The classification of aflatoxins, notably aflatoxin B1 (the commonest and the most potent) by the IARC as group I human carcinogen, dates back in 1988 and reaffirmed in 2002 [10].

Their synergy - hepatitis B and aflatoxins

Hepatitis B and aflatoxins are independent causative agents of primary liver cancer, and both have similar geographic distributions. Co-existence of hepatitis B and aflatoxins produces a great multiplicative interaction that increases liver cancer risk by 12-fold than in someone infected with hepatitis B alone which already causes 5-fold increase in the risk of liver cancer, according to WHO expert group on aflatoxins and health [7]. Some authors have also demonstrated a considerable variation in the risk of liver cancer mortality to the tune of 3.5 folds across the communities from which their study populations were drawn. These researchers showed that the variation in the risk of mortality from liver cancer across the communities was strongly correlated positively with local levels of aflatoxin B1 exposure [11]. It is noteworthy in their study that 91 percent of the liver cancer deaths were seropositive for the hepatitis B surface antigen (HBsAg).

These observations are consistent with the analysis of Kew reporting a striking multiplicative effect between exposure to aflatoxin B1 alone (RR = 0.3-1.1) and exposure to aflatoxin B1 in the presence of chronic hepatitis B infection (RR = 59.4-70.0) [9]. Furthermore, it was showed that hepatitis B-infected patients with liver tumour were 10 years younger in those with urinary aflatoxin B1-DNA adduct (AFB1-N7-Gua) than those who were adduct negative. This thus confirms the cohort report of some other investigators documenting elevated risk of liver cancer in subjects who were HBsAg seropositive and had high concentrations of aflatoxin metabolites in their urine, compared to subjects with high aflatoxin exposure only, or HBsAg-seropositivity only [12]. AFB1-N7-Gua is a marker for biologically effective dose of aflatoxin exposure. Formation of AFB1-N7-Gua leads to mutations in the host genome and the development of primary liver cancer [13]. A dose-response relationship was shown between urinary AFB1-N7-Gua and the risk of liver cancer in chronic hepatitis B carriers, with the relationship even stronger in the presence of both aflatoxin B1 and its metabolite, M1 [9].

To explain the multiplicative effects on liver cancer between hepatitis B virus and aflatoxins, it is suggested that the hepatitis B virus over expresses cytochrome P450 enzymes that produce the genotoxic metabolites of aflatoxins [2,13], and consequently the extent to which these metabolites bind to DNA [14]. Cytochrome P450 enzymes are a superfamily of hemoproteins important in redox metabolism of endogenous compounds and are involved in carcinogenesis [13]. This is demonstrated in the higher concentrations of AFB1-N7-Gua in HBsAg seropositives compared to their seronegative counterparts [8]. Other interactions including interference with nucleotide excision repair (NER) and altered methylation of genes have also been suggested as plausible mechanistic pathways [2]. AFB1-N7-Gua is mainly repaired by NER pathway but the viral antigen decreases NER efficiency, leading to the persistence of AFB1-N7-Gua and thus induction of mutation [2, 13, 14]. Moreover, necrosis/apoptosis of liver cells, from viral replication and chronic inflammation induces free radical overload resulting in increased hepatocyte mutation [2,13]. It is also suggested that aflatoxin exposure may affect susceptibility to chronic viral infection and replication [14].

Strategies for curbing the menace

These strategies may be considered at various levels, from the individual, through community, national and global. On hepatitis B, it is advised to know one's status and get vaccinated. According to the WHO, hepatitis B vaccine has been available since 1982 and there is 95 per cent efficacy [4]. Let's remove stigma and demystify hepatitis B because the hepatitis B patient could live a full productive life with early diagnosis and close monitoring.

On aflatoxins, practical measures within reach at individual and household levels to reduce exposure involve dietary diversity. Dietary diversity is the number of individual food items or food groups consumed over a given period of time [15]. It has been validated to reflect access to variety of foods and nutrient adequacy. This tool is recommended by the FAO, IFPRI and WFP for measuring food consumption and food security [15].

Strengthening agricultural extension systems that promote management and post-harvest practices to reduce aflatoxin levels in the field and during storage may go a long way in reducing fungal colonisation and toxin production in food commodities. These may include agricultural practices like crop rotation, weed control, cultivation of mould-resistant or drought tolerant varieties, and timed harvesting [8]. Irrigation to reduce drought stress has also been found to reduce fungal infection and aflatoxin production, notably in peanut where inverse relationship between the amount of water supplied and fungal invasion with aflatoxin production, has been documented [16].

Post-harvest contamination could be controlled through effective drying methods; sorting for insect damage, discoloured and shrivelled seeds [7]; the use of adequate packaging material and the building of adequate structures to regulate moisture and to keep away insects and rodents. Insects and rodents are well noted for their roles in the spread of fungal spores [7]. Strengthened systems for food monitoring at all levels for aflatoxins is also emphasised, and to this end, engagement of policy-makers for high political will may be crucial as far as food safety is concerned.

Conclusion

HBsAg seropositivity and dietary exposure to aflatoxins, notably aflatoxin B1, are independent causative agents of primary liver cancer with significant multiplicative synergistic interaction which put sub-Saharan Africa and South-East Asia at heightened risk of liver cancer. Notwithstanding, with strict measures at the level of the individual, households, community, country and global, coupled with strong political will to reduce dietary aflatoxin exposure and to fight hepatitis B, can drastically reduce the burden of liver cancer in worst affected regions.

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