

Review Article

Role of Aflatoxin B1 as A Risk for Primary Liver Cancer in India

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Introduction

Hepatocellular Carcinoma (HCC), a primary liver cancer, is currently the sixth most often diagnosed neoplastic disease and the third most common cause of cancer-related death globally [1,2]. In 2018, this cancer caused 830,000 deaths and 906,000 new cases worldwide [1]. HCC imposes a substantial disease burden, particularly in low and middle human development index nations or in risk subpopulations lacking systematic surveillance programs and rapid diagnostics-to-treatment strategies [1]. It is a potentially life-threatening disease curable by several medical procedures if diagnosed at early stages [3-5]. It has been seen that Geographical differences in incidence and prevalence are also shown within populations [1,2,6,7]. The hepatotropic Hepatitis B (HBV) and Hepatitis C (HCV) viruses, alcohol abuse, metabolic fatty liver disease, and exposure to aflatoxin B1-contaminated foods are the primary etiologies of HCC [8].

According to studies on the global epidemiology of HCC these numerous etiologies can primarily serve as separate risk factors in some places, but they typically have a synergic pro-oncogenic effect in relation to HCC [9]. Additionally, each predisposing risk factor contributes in a different proportion depending on the region [2,10]. Since early detection, primary prevention, and workable management plans all depend on the identification of such factors by population and area.

Abstract

The most well-known primary liver cancer in the world is Hepatocellular Carcinoma (HCC). Its prevalence is alarmingly increasing and has drawn public attention on a global scale. With regard to regional variation, racial differences, and socioeconomic level, it occurs more frequently in underdeveloped countries than in industrialised ones. Aflatoxin use is one of the main risk factors for HCC. Aflatoxin B1, a genotoxic hepatocarcinogen, is thought to induce cancer by causing DNA adducts in target liver cells that result in genetic alterations. HCC may result from a mutational impact caused by DNA adducts at the codon 249 hotspot in exon 7 of the P53 tumour suppressor gene, which interacts with the guanine bases of liver cell DNA. Aflatoxin-contaminated food affects about 4.5 billion people worldwide, mostly in developing nations with poor incomes. Treatment of crops that are prone to fungal contamination, proper food handling techniques, and the use of chemopreventive intervention are all part of prevention. Additionally, in order to maintain efficient food regulation systems and reduce the risk of aflatoxins contaminating food, a networked collaboration of several sectors, including public health, agricultural departments, and the media, is needed.

Keywords: Aflatoxin B1; Hepatocellular carcinoma; DNA adducts; Chemopreventive agents; Interventions; Dietary changes

With the exception of ambient aflatoxins, the classical causal agents of HCC cause liver damage and cellular inflammation (necroinflammation), which progresses to multistage fibrosis, cirrhosis, and finally HCC [11]? However, cirrhosis is not necessary for 30% of HCC patients to manifest themselves. Since the typical age of discovery of late-stage HCC is frequently above the age of 50, the underlying mechanisms that govern the natural course of liver disease may manifest themselves within a period of 20 to 30 years.

The variations in the global prevalence of HCC are also influenced by co-factors such as ethnicity, gender, age, or tobacco smoking [11]. However, the occurrence of HCC will not depend only on the prevalence of each etiological factor but also on the measures taken to limit them. Fortunately, most of them are preventable. For example, the early onset of HCC in children and young adults in Alaska Natives was eliminated by introducing newborn and catch-up vaccination schemes that reduced the number of HBV carriers [12]. In contrast, within the high endemic regions for HBV infection in Asia and Africa, the lack of aflatoxin-neutralizing control measures contributes to higher HCC incidence rates than non-exposed populations [13].

Role of Aflatoxin B in Causing HCC in India

According to reports, India has a low incidence of HCC, ranging from 0.2% to 1.9% [14]. Compared to China, Japan, and other Southeast Asian nations like India, the age-adjusted incidence of HCC in Indian populations is low [14]. Chronic viral carriers who are exposed to other known risk factors, such as aflatoxin B1 exposure, have a much higher risk of developing HCC (AFB1)[15,16].

Aflatoxins, a secondary metabolite produced by *Aspergillus flavus* and *Aspergillus parasiticus*, are powerful human carcinogens linked to HCC [17], and they have also been shown to significantly increase the risk of developing the disease in India. Even though the serum levels were undetectable, the impact appears to be a cumulative process as seen by the AFB1 deposits in HCC liver tissue [17]. Aflatoxin is metabolised by specific P450 enzymes in the liver to a reactive oxygen species (aflatoxin-8,9-epoxide), which can subsequently attach to proteins to induce acute toxicity (aflatoxicosis) or to DNA to cause lesions that progress over time, according to numerous epidemiological studies[18].

According to Lin et al. 1977, there is a strong correlation between the occurrence of HCC and the level of aflatoxin contamination in food [19]. Aflatoxin's ability to cause cancer is thought to be due to the covalent adducts that metabolically activated reactive intermediates can form with hepatocyte DNA, which can result in host genome alterations [20]. In primary liver cancer, the p53 gene on chromosome 17 has frequently been shown to be mutated [21-23]. AFB1 is known for having this hotspot mutation, which was first identified in HCC from areas with high dietary aflatoxins levels. Numerous rodent models have been used to study the molecular and cellular mechanisms behind the carcinogenic effects of aflatoxin.

The liver cancer brought on by the Hepatitis C Virus (HCV) seems to be enhanced by aflatoxin [24-26]. In addition to aflatoxin exposure and HBV or HCV infection, other significant risk factors for the development of HCC include alcohol intake, age, and sex of the infected individual [24]. Aflatoxin may be the cause of anywhere between 4.6 and 28.2% of all HCC cases worldwide [27].

According to Henry et al. [28] and IPCS/WHO 1998 [29], India has a chronic HBV prevalence of 2.4–4.7% based on HBsAg seroprevalence. In 1998, IPCS/WHO conducted an aflatoxin-HCC risk assessment to determine the effect that lowering the overall aflatoxin standard from 20 ng/g to 10 ng/g might have on the incidence of cancer in the general population. If the stricter aflatoxin standard were followed in countries with an HBV prevalence of 25%, the incidence of HCC would decrease by about 300 cases per year per billion people, assuming that all food containing higher levels of aflatoxin than the standard was discarded and that there were enough maize and nuts left over to preserve consumption patterns [30]. When chronic HBV infection and aflatoxin exposure are combined, the risk of liver cancer is up to 30 times higher than when aflatoxin exposure alone is involved [19]. According to Wild and Gong [31], chronic aflatoxin exposure in people with chronic Hepatitis B Virus (HBV) infection leads to HCC. Aflatoxin and HBV are common in underdeveloped countries all over the world. In these countries, aflatoxin exposure and HBV prevalence frequently varies significantly between urban and rural areas, with both of these risk factors typically having a greater impact on rural people.

Aflatoxin is a toxin that occurs in tropical and subtropical areas of the world where grains like rice are stored in warm climates [32]. According to reports, stored grains in Southeast Asia have significant levels of aflatoxin in the months following the monsoon. Aflatoxin, a powerful cause of hepatocarcinogenesis, increases the likelihood of HCC formation in grains stored in such a way [20,33]. Aflatoxin exposure and Hepatitis B Virus (HBV) infection have been demonstrated to dramatically increase the risk of dying from liver cancer. Ingestion of aflatoxin is strongly statistically correlated with the prevalence of HCC in different parts of the world, according to Ross et al [34].

Aflatoxin was found in 58% of liver biopsies of HCC cases, according to research by Murugavel et al. [16] from South India, while no cases of cirrhosis were found to be positive for the substance. Therefore, it was possible that the patients had eaten items contaminated with AFB1, which may have contributed to their development of HCC either directly or indirectly. All cirrhosis cases tested negative for aflatoxin, however 58.1% of HCC cases showed the substance in liver biopsies. Furthermore, liver biopsy results showing aflatoxin positivity in 68.8% of HBsAg-negative HCC cases and 46.1% of HBsAg positive patients demonstrated that aflatoxins have a strong connection with HCC in India.

The biomarker-based, prospective Shanghai Cohort study [35] has shown a significant correlation between baseline levels of urine AFB metabolites, particularly the main AFB-DNA adduct, and HCC risk in study participants. In addition to being labelled as a group 1 human carcinogen [36], a number of ecological studies have demonstrated a strong link between dietary aflatoxin exposure and hepatocarcinogenesis [37,38].

Conclusion

Prevention of fungal contamination of grains and ground crops to prevent Aflatoxin exposure are important measures to prevent liver diseases and HCC among those at risk, particularly HBV infected persons in endemic regions of the country. In conclusion, updated healthcare policies focusing on the needs of preventive care should be tailored based on environmental risk factors that influence the effect of the etiological agents related to the incidence and prevalence rate of HCC.

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