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Hepatocellular carcinoma and food contamination: Ochratoxin A as a great prompter

Raphael JF Felizardo, Niels OS Câmara

Raphael JF Felizardo, Division of Nephrology, Department of Medicine, Federal University of Sao Paulo, Sao Paulo CEP 05508-900, Brazil
Niels OS Câmara, Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Sao Paulo CEP 05508-900, Brazil
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Correspondence to: Niels OS Câmara, MD, PhD, Professor, Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Av. Prof. Lineu Prestes 1730, São Paulo CEP 05508-900, Brazil. niels@icb.usp.br
Telephone: +55-11-30917388 Fax: +55-11-30917224
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Core tip: This manuscript is a short commentary to the paper which considered ochratoxin A, a mycotoxin produced by fungi, as an important carcinogen and etiological agent able to induce hepatocellular carcinoma. Based on a recent study, we try to link food contamination with a possible increased incidence on hepatocellular carcinoma cases at eastern populations.

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Abstract

Ochratoxin A (OTA) is a secondary metabolite of Aspergillus and Penicillium, microorganisms that can be hazardous to health when present as food contaminants. OTA is a potent member of a group of mycotoxins. Prolonged exposure to mycotoxins in the diet is related to cancer, among other diseases. Hepatocellular carcinoma (HCC) accounts for 70%-90% of primary liver cancers and is the third leading cause of cancer-related deaths worldwide. In a recent study, Ibrahim *et al* proposed a correlation between the incidence of HCC and contamination with OTA. Analysis of OTA in serum samples showed that HCC patients had the highest incidence of OTA of the subjects examined (5-fold higher than that of the control group). OTA levels were significantly increased in HCC patients. This study demonstrates that chronic exposure to high levels of OTA may be associated with a high risk of liver cancer development. Future epidemiologic studies of HCC should focus on good practices in food preparation, food storage and the consumption of OTA-containing foods.

COMMENTARY ON HOT TOPICS

Food contamination is a public health problem that is monitored worldwide by the Food and Agriculture Organization of the United Nations and by the World Health Organization. Care in food preparation and storage are extremely important to avoid ingestion of various microorganisms and their toxins. High temperatures and humidity during harvest, storage and processing of grains, nuts and other crops, are appropriate conditions for fungal and mold development, especially when food is stocked in an inappropriate manner. Species of *Aspergillus* and *Penicillium* are the major producers of aflatoxins and ochratoxins, mycotoxins that have been classified as potent carcinogens by the International Agency for Research on Cancer and that are well known for liver toxicity.

Hepatocellular carcinoma (HCC) is a major health problem with a rising incidence in western countries[1], though most HCC cases (> 80%) occur in sub-Saharan Africa or eastern Asia. China alone accounts for more than 50% of the world's cases[2]. HCC accounts for 70%-90% of primary liver cancers, making it the third leading cause

of cancer-related deaths worldwide[3-5]. Hepatitis B virus, hepatitis C virus infections and alcohol intake are widely recognized as the main causes of HCC[6,7].

Aflatoxins (AFT) are secondary metabolites produced by some *Aspergillus* species that contaminate food during storage, production and processing. Due to their high toxicity and mutagenic, teratogenic and carcinogenic effects[8], they have long been suggested as possible an etiologic agent of HCC. Mycotoxin poisoning occurring in the presence of hepatitis B virus infection is related to an increased risk of HCC development. AFT are metabolized by hepatic enzymes, generating reactive epoxide species that are able to form a covalent bond with guanine[9]. The resulting adducts can promote cellular and macromolecule damage and have already been described as biomarkers for aflatoxin contamination[10,11].

Though food contamination by certain AFTs is correlated with HCC occurrence, it is unknown if ochratoxin A (OTA) has a role in HCC pathogenesis, as proposed recently by Ibrahim *et al*[12]. Though a possible relationship between OTA and HCC has been statistically analyzed in several regions, there is as yet no consensus.

OTA is an isocoumarin-derived mycotoxin that is most commonly produced by *Aspergillus ochraceus*[13] growing on stored barley, corn or wheat. OTA can be found in a wide range of human foods such as cereals, beer, wine, cocoa, coffee, dried vine fruit and spices, as well as in some meat products and milk. It is a potent, thermostable, immunosuppressive and carcinogenic toxin[14], and its effects are attributable to its ability to interfere with protein synthesis. After being absorbed, OTA is metabolized by the liver and excreted as both bile and in the renal proximal tubules[15]. In experimental animals, OTA induces tumors in the kidney as well as in the liver[15,16]. Although several lines of evidence derived from animal experiments implicate OTA in hepatic carcinogenesis[17,18], no epidemiological data are available to evaluate such relationship. Biomarkers such as reduced glutathione-conjugates, *N*-acetylcysteine-conjugates and DNA-OTA adducts have been detected as products of OTA metabolism by the liver[19,20], but no association between HCC and OTA has been reported.

According to Ibrahim *et al*[12], Egyptians diagnosed with HCC (and defined by high serum levels of alpha-fetoprotein and altered liver enzyme levels) have significantly higher levels of OTA in their sera than control subjects; the increase is approximately 5-fold. The authors also investigated the strength of the association between OTA and HCC and found that HCC was 9.8 times as frequent in an OTA-exposed group of subjects. This evaluation essentially aimed to determine the contribution of OTA exposure to HCC pathogenesis and suggested that OTA is a plausible etiologic factor for HCC.

Ibrahim *et al*[12] encourage the search for new possibilities linking OTA to HCC or other diseases in regions around the world. For instance, OTA is frequently related to Balkan nephropathy, which is characterized by a discrete form of tubulointerstitial nephropathy with insidious presentation and slow progression and high levels of OTA in the urine[15]. Not only humans but also some ruminant and non-ruminant animals can be contaminated by OTA. Metabolic studies show that OTA can persist in the body of pigs; the hazard thus arises due to contamination of animal feed and constitutes an additional source of OTA contamination in human food[21].

This study demonstrated that chronic exposure to high levels of OTA could increase the risk of liver cancer. Future epidemiologic studies of HCC should focus on good practices in food preparation, food storage and the consumption of OTA-containing foods such as cereals and milk by liver-diseased patients. Ibrahim *et al*[12] opened the discussion of this new possible cause of HCC, which should not be ignored.

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