**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 2534**

**Columns: FIELD OF VISION**

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

**Felizardo RJF *et al*.** Ochratoxin A in hepatocellular carcinoma

Raphael JF Felizardo, Niels OS Câmara

**Raphael JF Felizardo,** Division of Nephrology, Department of Medicine, Federal University of Sao Paulo, CEP 05508-900 Sao Paulo, Brazil

**Niels OS Câmara,** Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, CEP 05508-900 Sao Paulo, Brazil

**Author contributions**: Felizardo RJF collected the materials and wrote the manuscript; Câmara NOS discussed the topic and supervised the publication of this commentary.

**Correspondence to:** **Niels OS Câmara, MD, PhD,** **Professor,** Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, Av. Prof. Lineu Prestes 1730, CEP 05508-900 São Paulo, Brazil.

[niels@icb.usp.br](mailto:niels@icb.usp.br)

**Telephone:** +55-11-30917388 **Fax:** +55-11-30917224

**Received:** February 26, 2013  **Revised:** April 18, 2013

**Accepted:** May 8, 2013

**Published online:**

**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.

© 2013 Baishideng. All rights reserved.

**Key words:** Ochratoxin A; Mycotoxin; Food contamination; Hepatocellular carcinoma; Liver cancer; Egypt

**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.

Felizardo RJF, Câmara NOS. Hepatocellular carcinoma and food contamination: Ochratoxin A as a great prompter.

*World J Gastroenterol* 2013;

**Available from:** URL: http://www.wjgnet.com/esps/

**DOI:** http://dx.doi.org/10.3748/wjg.v19.i0.0000

**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. Aflatoxins 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.

**REFERENCES**

1 **El-Serag HB**, Lau M, Eschbach K, Davila J, Goodwin J. Epidemiology of hepatocellular carcinoma in Hispanics in the United States. *Arch Intern Med* 2007; **167**: 1983-1989 [PMID: 17923599 DOI: 10.1001/archinte.167.18.1983]

2 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]

3 **Wolfson IN**. Letter: Blind defibrillation. *Am J Cardiol* 1975; **36**: 412 [PMID: 1166849 DOI: 10.1002/ijc.1440]

4 **Yu MC**, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S72-S78 [PMID: 15508106 DOI: 10.1016/j.gastro.2004.09.018]

5 **Venook AP**, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; **15** Suppl 4: 5-13 [PMID: 21115576 DOI: 10.1634/theoncologist.2010-S4-05]

6 **Zidan A**, Scheuerlein H, Schüle S, Settmacher U, Rauchfuss F. Epidemiological pattern of hepatitis B and hepatitis C as etiological agents for hepatocellular carcinoma in iran and worldwide. *Hepat Mon* 2012; **12**: e6894 [PMID: 23233864 DOI: 10.5812/hepatmon.6894]

7 **Farazi PA**, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nat Rev Cancer* 2006; **6**: 674-687 [PMID: 16929323 DOI: 10.1038/nrc1934]

8 **Groopman JD**, Cain LG, Kensler TW. Aflatoxin exposure in human populations: measurements and relationship to cancer. *Crit Rev Toxicol* 1988; **19**: 113-145 [PMID: 3069332 DOI: 10.3109/10408448809014902]

9 **Wild CP**, Turner PC. The toxicology of aflatoxins as a basis for public health decisions. *Mutagenesis* 2002; **17**: 471-481 [PMID: 12435844 DOI: 10.1093/mutage/17.6.471]

10 **Wild CP**, Hudson GJ, Sabbioni G, Chapot B, Hall AJ, Wogan GN, Whittle H, Montesano R, Groopman JD. Dietary intake of aflatoxins and the level of albumin-bound aflatoxin in peripheral blood in The Gambia, West Africa. *Cancer Epidemiol Biomarkers Prev* 1992; **1**: 229-234 [PMID: 1339083 DOI: 10.1289/ehp.9302]

11 **Gan LS**, Skipper PL, Peng XC, Groopman JD, Chen JS, Wogan GN, Tannenbaum SR. Serum albumin adducts in the molecular epidemiology of aflatoxin carcinogenesis: correlation with aflatoxin B1 intake and urinary excretion of aflatoxin M1. *Carcinogenesis* 1988; **9**: 1323-1325 [PMID: 3133131 DOI: 10.1093/carcin/9.7.1323]

12 **Ibrahim AS**, Zaglol MH, Badria FA. Case Report Evidence of Relationships Between Hepatocellular Carcinoma and Ochratoxicosis. Unpublished raw data

13 **Harris JP**, Mantle PG. Biosynthesis of ochratoxins by Aspergillus ochraceus. *Phytochemistry* 2001; **58**: 709-716 [PMID: 11672735 DOI: 10.1016/S0031-9422(01)00316-8]

14 **Pfohl-Leszkowicz A**, Manderville RA. Ochratoxin A: An overview on toxicity and carcinogenicity in animals and humans. *Mol Nutr Food Res* 2007; **51**: 61-99 [PMID: 17195275 DOI: 10.1002/mnfr.200600137]

15 **Reddy L**, Bhoola K. Ochratoxins-food contaminants: impact on human health. *Toxins (Basel)* 2010; **2**: 771-779 [PMID: 22069609 DOI: 10.3390/toxins2040771]

16 **Boorman GA**, McDonald MR, Imoto S, Persing R. Renal lesions induced by ochratoxin A exposure in the F344 rat. *Toxicol Pathol* 1992; **20**: 236-245 [PMID: 1475584 DOI: 10.1177/019262339202000210]

17 **Kamp HG**, Eisenbrand G, Janzowski C, Kiossev J, Latendresse JR, Schlatter J, Turesky RJ. Ochratoxin A induces oxidative DNA damage in liver and kidney after oral dosing to rats. *Mol Nutr Food Res* 2005; **49**: 1160-1167 [PMID: 16302199 DOI: 10.1002/mnfr.200500124]

18 **Gagliano N**, Donne ID, Torri C, Migliori M, Grizzi F, Milzani A, Filippi C, Annoni G, Colombo P, Costa F, Ceva-Grimaldi G, Bertelli AA, Giovannini L, Gioia M. Early cytotoxic effects of ochratoxin A in rat liver: a morphological, biochemical and molecular study. *Toxicology* 2006; **225**: 214-224 [PMID: 16857307 DOI: 10.1016/j.tox.2006.06.004]

19 **Tozlovanu M**, Canadas D, Pfohl-Leszkowicz A, Frenette C, Paugh RJ, Manderville RA. Glutathione conjugates of ochratoxin A as biomarkers of exposure. *Arh Hig Rada Toksikol* 2012; **63**: 417-427 [PMID: 23334036 DOI: 10.2478/10004-1254-63-2012-2202]

20 **Li ZW**, Bijl WA, van Nispen JW, Brendel K, Davis TP. Neuropeptide processing in regional brain slices: effect of conformation and sequence. *J Pharmacol Exp Ther* 1990; **253**: 851-857 [PMID: 2140132 DOI: 10.3109/10408444.2010.529103]

21 **Wu Q**, Dohnal V, Huang L, Kuča K, Wang X, Chen G, Yuan Z. Metabolic pathways of ochratoxin A. *Curr Drug Metab* 2011; **12**: 1-10 [PMID: 21222585 DOI: 10.2174/138920011794520026]

**P-Reviewer** Jin B **S-Editor** Gou SX  **L-Editor E-Editor**