Review

Fumonisin as a Risk Factor to Esophageal Cancer: a Review

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Abstract

Among several types of cancer, esophageal is the sixth most common type found worldwide, with variable incidence rates that are more prevalent in Western countries and in South Central Asia. In Brazil, this neoplasm represents 2% of all malignant tumors and is the fifth leading cause of death. Brazilian estimated data demonstrated that, in 2008, the incidence of this cancer will be 7,900 cases in men and 2,650, in women, which corresponds to crude mortality rates of 8.35/100,000 and 2.72/100,000, respectively. Literature data has demonstrated several risk factors to esophageal cancer, such as: the consumption of tobacco, alcohol, hot beverages; malnutrition; obesity and gastric esophageal reflux, which causes Barrett´s esophagus. Fumonisins play significant roles in this neoplasm. Fumonisins are substances found in moldy foods, which are potential sources of nitrosamines, and are present in moldy corn. This substance was isolated in regions with high incidence of esophageal cancer in 1988, and currently is considered an important risk factor to esophageal cancer.

Keywords: Esophageal cancer; Fumonisin; Epidemiology

Introduction

Cancer is defined as a chronic, multicausal disease, which is manifested by disordered growth of cells, which have suffered DNA damage and that can be spread throughout the body, compromising the functioning of the cells and normal tissue.1-2

Among the diverse types of existent neoplasms, esophageal cancer is the sixth most common type in the world, with variable incidence rates, more prevalent in Western countries and in South Central Asia.3 In Brazil, this neoplasm represents 2% of all malignant tumors, being the fifth cause of death for cancer.4 Estimates from the Brazilian National Cancer Institute (INCA) indicate that, in 2008, the incidence of this type of cancer will be of 7,900 cases in men and 2,650, in women,5 which corresponds to crude mortality rates of 8.35/100,000 and 2.72/100,000, respectively.

Among the various histologic classifications of esophageal cancer, the predominant types are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma occurs in more than 80% of the cases and affects with more frequency the middle and inferior third of the esophagus, occurring in the upper third in only 10 to 15% of cases.[5] Adenocarcinoma, which appears in the distal part of the esophagus, in the presence of chronic gastric reflux and gastric metaplasia of the

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epithelium (Barrett´s Esophagus), is developed in the interior of columnar dysplastic epithelium, mainly in the gastroesophageal junction (cardia).[3, 6-7]

In accordance with the World Health Organization (WHO),[3] squamous cell carcinoma is most prevalent in Western countries that have the habit of using smoked or chewed tobacco, alcohol, hot beverages and malnutrition. Adenocarcinoma, on the other hand, is found in industrialized countries, with gastric esophageal reflux as a principle determinant, which causes Barrett´s Esophagus, beyond other factors such as obesity, alcoholism and smoking.[6] Fumonisins, substances derived from the grain of moldy corn, have been isolated in places with high incidence of esophageal ; therefore, they are also correlated as risk factors for this neoplasm.[8]

Objective

This article has as objective to make a bibliographical revision on the role of fumonisin as a possible risk factor for esophagus .

Methodology

A systematic search was made through data bases to elucidate the existence of studies that show a possible relation between of the esophagus and the presence of fumonisins in foods, as moldy corn and its derivatives, beyond other cereals, as sorghum and rice .[9]

Result

Fumonisins are toxins produced by *Fusarium genus fungi*, with the species *Fusarium moniliforme* and *Fusarium proliferatum* isolated the most in corn grains ,[9-12] sorghum, rice and other cereals grains in Brazil and worldwide.[9]

Among the most predominant isolated and characterized types of fumonisins discovered are fumonisins B1, B2 and B3 (FB1, FB2 and FB3),[12-14] with fumonisin (FB1) the most toxic among them [10,13] and of greater concentration[9-10,15] in naturally contaminated products.

According to Soriano and Dragacci,[13]the contamination by these fungal toxins can occur in the pre-harvest period of corn,[13,16]due to the conditions of temperature (the more elevated, the greater the production), latitude (the lower, the greater the production), water activity (when maximized, greater production), damages in the grains (enhance the penetration of insects or microorganisms present on the surface of the grains, favoring the growth of fungi) and synergic effects of various mycotoxins present in the same grain. In a study done by the State of Parana, Brazil, the finding was verified that contamination can also occur before storage, as the grains are taken to cooperatives where they are submitted to the drying processes, enabling the proliferation of fungi.[15]

In accordance with Bullerman and Draughon 10 and also Cançado and Freitas,[17] production of fumonisins by *F. moniliforme* can occur in various storage conditions. According to the studies conducted, the following was observed: the optimum growth temperature of this species can be seen to oscillate between 22.5° and 27.5°C; [18] the optimum osmotic potential is -10 bars[19] the ideal relative humidity is between 18.4 and 23%, with growth inhibited from 28% of humidity [20-21] and in relation to the amount of O2 and CO2 in the environment, this fungus can grow in levels of 0% of O2 and 60% of CO2 at 26°C, but in similar CO2 levels found in atmospheric air, the growth diminishes, only occurring at 12°C, suggesting the anaerobic character of species.[21]

Another form of contamination of the grain occurs during its processing, depending on the type of alkaline solution used (toxicity related to end items), the utilization of water during the processing of the food (which can lead to the accumulation of fumonisins, for its hydrosolubility) and the temperature between 22.5° and 27.5°C (when very close to the considered optimum temperature for the growth of *Fusarium*, greater the amount of fumonisins found in the grain).[13]

FB1 is analogous to sphinganine[8-9,22] and thus, leads to an inactivation of the ceramide synthase enzyme,[8] which provides a block in the biosynthesis of sphingolipids, inhibiting the formation of ceramide and sphingomyelin .[8,12] This mycotoxin, when ingested together with the diet, causes an increase of the free sphinganine, mainly in the kidneys, liver,[8-9] lung and heart,[9] beyond the increase of free sphingosine (inhibition of the reacylation of the sphingosine derived from sphingolipid turnover or of the growth medium),[8,22] This alteration is possible to be monitored, since a small concentration of sphinganine that accumulates in the interior of the cells can appear in peripheral blood.[9,22]

At the cellular level, with consequences of the interruption in the metabolism of the sphingolipids, there is damage in the activity of protein kinase in the growth

and differentiation, favoring carcinogenicity and lipid peroxidation,[8] since the lipids are important components in the structure of the cellular membrane.[9] Moreover, fumonisins inhibit the protein synthesis of the DNA, inducing oxidative stress, promoting the fragmentation of the DNA and blocking of the cellular cycle.[10]

According to Lino et al.,[10] since the discovery and characterization of these fungal toxins, the techniques of its detection and quantification have been perfected, effected principally by chromatographic analysis. According to these authors, the method most currently used to this end is high performance liquid chromatography, also called HPLC or LC,[10,15] due to its high sensitivity and capacity to demonstrate more precise determinations and to separate non-volatile species.[10]

Aiming to prevent the consumption of contaminated food of these fungal toxins, security limits in some countries have been adopted. In Switzerland and Canada, the value of fumonisins in corn and its derived products cannot exceed 1.0 to 2.0 ppm, respectively.[14] In South Africa, corn destined for human consumption have suggested tolerance levels of fumonisins of 300-400 ppb, whereas these same levels of tolerance, corn destined for animal consumption must be inferior to 5 ppb for equines, 10 ppb for swines and 50 ppb for poultry and cattle 13. Legislation was not found in the National Health Surveillance Agency (ANVISA – Ministry of Health) or in the Ministry of Agriculture, Livestock and Food Supply, which establishes acceptable levels of fumonisin in foods for human or animal consumption.

As a parameter of reference for detention of fumonisins in corn grain, the values from 0 to 10,500 ng/g are used, in which the corn is classified as "good" for consumption, while the values of 600 to 63,200 ng/g indicate that the grain encountered is "obviously moldy"[23] and, therefore, should not be consumed.

Discussion

The relation between diet and is complex. In the economically developed countries, this relation is based on the metabolic and hormonal influences in the process of carcinogenesis. In contrast, in the countries less developed, the diet as an etiologic factor of occurs through chemical carcinogenesis, that is, involves components of the diet and contaminants (nitrosamines and mycotoxins), beyond the deficiency of specific nutrients and biological agents such as papillomavirus, the hepatitis virus and Helicobacter pylori.[6]

Fumonisins are as toxic for humans as they are for animals. In humans, they possess a strong correlation with esophageal .[12] In animals, they can be present when the ingestion of rations contain corn or residue of corn contaminated with these mycotoxins.[22]

Studies point to the ingestion of these low-quality rations can lead to the emergence of pathologies such as equine leukoencephalomalacia, pulmonary edema and hydrothorax in swines, and hepatotoxicity and hepatocarcinogenicity in rats.[8-13] These ingestions can also lead to renal toxicity in sheep,[10] atherosclerosis in monkeys, cerebral hemorrhage in rabbits, and immunosuppression in domestic birds.[8]

These mycotoxins were described the first time in 1988, from samples of moldy corn, originating from the region of Transkei, South Africa, an area of high incidence of esophageal [9-11,13,24] and, therefore, fumonisins were correlated to this neoplasm, verifying later that other areas of equally high incidence, such as China, Iran, northern Italy and the southeast of the United States [8,24] also presented considerable levels of these mycotoxins in corn and corn-based products.[9]

An epidemiologic study conducted by Segal et al. [25] in Soweto, South Africa, demonstrated an increased risk for esophageal associated with the consumption of a traditional beer, umqombothi, produced and consumed by the population. This traditional beer is made with a low alcohol concentration (3%), corn (27.8%), sorghum (37.6%) and sorghum malt (34.6%). The result of this study showed that when this beer is produced with 57% of corn, which has a reduced amount of thiamine, niacin and riboflavin, it becomes a risk factor for the development of esophageal in the region of Soweto.

In another study, Franceschi et al. [26] studied the relation between the consumption of corn and the risk of of the upper digestive tract in 107 patients with oral , 107 with of the pharynx and 68 with esophageal , in the province of Pordenone, Italy. The population has a high incidence of this neoplasm and has the habit to drink and smoke, along with the high consumption of corn. The results had shown a highly significant association with the frequent ingestion of corn for oral, pharynx and esophageal with an adds Ratio of 3.3, 3.2 and 2.8 respectively.

In an inquiry lead in Veneto, Italy, Rossi et al. [27] had reported an increased risk 4.5 times greater for esophageal among the individuals who ate two or more slices of polenta (cornmeal) per day.

Two mechanisms exist that can explain why corn presents the most important factor of risk in societies where the consumption of this cereal is part of the basic diet. First, corn is a poor source of B-complex vitamins,

particularly riboflavin and niacin.[28] Deficiencies of such vitamins result in the inflammation of the mucosa, which can prejudice the epithelial tissue and formation of the tumor. Another explanation is the presence of fungal contaminants, which can be present in grains stored in humid conditions with elevated temperatures.

We can conclude that in animals and humans, clear evidence exist that fumonisins can lead to the development of hepatic and esophageal .[14,17,29] The International Agency for Research on (IARC) categorized fumonisins as carcinogens of group 2B (possible carcinogens for humans) based on sufficient evidence of esophageal and hepatic .[14,29]

Conclusion

More studies in Brazil are necessary to establish clear and concise relations regarding esophageal and its determinants originating from grains that can be contaminated by fumonisin, which is predominant in the basic Brazilian diet, aiming to generally clarify to the population the forms of prevention and, in this way, to explore the reduction of mortality rates of esophageal that are still similar to those of its incidence.

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