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Fungi and Their Mycotoxins: an Underappreciated Role in Cancers

Fungi (moulds) produce a wide variety of toxic chemicals called mycotoxins. Animal and human studies show that these mycotoxins have many adverse health effects, including allergy/asthma/rhinitis, immunotoxicity, hemorrhage, neurotoxicity, damage to many organs such as kidneys and liver, mutagenesis, and cancer [1,2].

Some mycotoxins increase the risk of several human cancers [3,4]. Exposure to mycotoxins can occur through food, water, air, or dust. Most of the data linking mycotoxin exposure and human cancers have dealt with foodstuffs contaminated with common moulds, such as *Fusarium*, *Aspergillus*, and *Penicillium* [3,4]. Significant exposure can also occur in humans and animals exposed to air and dust from mouldy environments, such as swine barns [5].

Aflatoxins are some of the most carcinogenic compounds known to man, causing cancer in every animal model tested [6], making them Category 1 carcinogens [7]. They are commonly produced by several *Aspergillus* species in poorly stored grains and peanuts [4,6]. Aflatoxins are converted by mammalian p450 enzymes into intermediate adducts that promote a number of mutations, including some that impair function of tumour p53 suppressor genes [6]. They also promote mammalian liver cancer by causing mutations in the tumour oncogenes, N-ras and c-K-ras, and by amplifying expression of the oncogene c-myc [8,9]. They can also induce an increase chromosome numbers in liver cells and significantly reduce the number of normal

tetraploid liver cells [10].

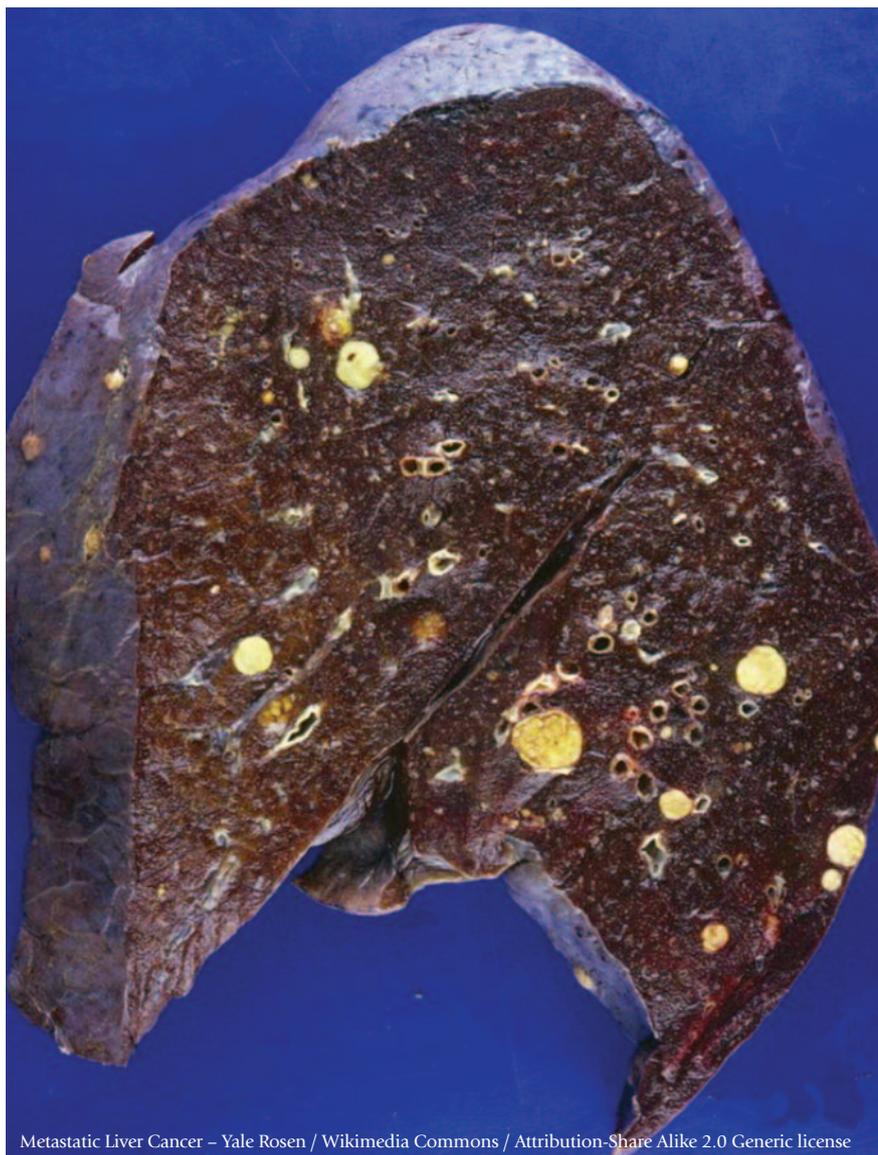
Aflatoxins are a major cause of liver cancer that seem to work synergistically with hepatitis C [6,11]. It has been estimated that foodborne aflatoxin exposure causes between 25,200 and 155,000 new liver cancer cases annually worldwide [11]. Improvements in diet and food storage can significantly reduce both foodborne aflatoxin exposure and liver cancer rates. A program in Qidong, China, reduced foodborne aflatoxin exposure by ~97% by using better food storage methods and a switch from corn to rice as a staple grain (rice is much less likely to be contaminated with aflatoxin than corn). Liver cancer rates in young adults fell by > 50% following implementation of these measures [12].

Ochratoxins, nephrotoxic mycotoxins produced by some *Aspergillus* and *Penicillium* species, can damage DNA and have been linked to renal cancer in experimental animals [3,7]. Fumonisin, mycotoxins produced by *Fusarium* fungi, have been linked to human oesophageal and liver cancer, as well as causing neural tube defects [3,4]. Zearalenone (ZEN) is mycotoxin that binds to oestrogenic receptors and may be related to hormone sensitive cancers such as breast and endometrial cancer [3]. Other common mycotoxins known to damage DNA and cause cancer in experimental animals include sterigmatocystin, citrinin, patulin, penicillinic acid and leteoskyrin [7].

At least 33 mycotoxins are known mutagens and thus have a high possibility of being carcinogenic. Common mutagenic mycotoxins include altertoxin



Aspergillus ear rot symptoms on corn ear (left) and growth of *Aspergillus flavus* in artificial culture (right). Reproduced with kind permission of Iowa State Agricultural Extension.



Metastatic Liver Cancer – Yale Rosen / Wikimedia Commons / Attribution-Share Alike 2.0 Generic license

(from *Alternaria* species), kojic acid (produced by many *Aspergillus* species and found in malted rice and sake), and versicollin (produced by the common indoor mould *Aspergillus versicolor* [1]).

Cancer patients, especially those on chemotherapeutic drugs or with bone marrow transplants, have a significantly higher risk for many life-threatening fungal infections, especially *Candida* and *Aspergillus* [13]. Among leukemia patients, 10-20% develop life threatening *Candida* infections and >5% will develop life-threatening *Aspergillus* infections [13]. While much evidence suggests that cancer and chemotherapy can predispose patients to severe fungal infections, there is now evidence that fungal infections may promote the development and progression of cancer.

Candida species are yeasts (fungi) that commonly grow in the digestive, urinary, genital and skin areas of humans. There is a known link between *Candida* overgrowth in the mouth and a significantly increased incidence of oral squamous cell carcinoma [14]. Cell culture and animal studies show that *Candida albicans* can produce sufficient quantities of acetaldehyde and N-nitrosobenzylmethylamine (NBMA) to be mutagenic and carcinogenic [14,15]. *C. albicans* can increase the risk of carcinogenesis by many mechanisms, e.g. production of carcinogenic byproducts, triggering inflammation, increasing adhesion of metastatic tumour cells, induction of the Th17 response, and molecular mimicry [16]. *Candida* overgrowth may be linked to higher rates of cancer in tissues other than the mouth.

Infection or colonisation of other fungi such as *Aspergillus* can also promote cancer; experimental infection of mice approximately doubled the rate of growth of mammary tumours [17].

Many fungal infections can mimic many types of cancer, including cancer of solid organs, skin cancer, and leukemia/lymphoma. Other fungal infections, including paracoccidioidomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis, mucormycosis, and blastomycosis, can mimic both the clinical and radiological findings of lung cancer [18]. A case series was presented of 27 patients initially diagnosed clinically and radiologically with primary or secondary lung cancer, which later proved to be fungal infections, and all patients responded well to antifungal therapy [19].

A number of antifungal drugs have significant anti-cancer effects. The anti-fungal drug, Itraconazole, has anti-angiogenic properties; it significantly reduces recurrence and progression of ovarian clear cell carcinoma and advanced prostate cancer in humans [20,21]. From work on cell cultures and laboratory animals, the anti-fungal drug, thiabendazole, is useful in preventing progression and metastases of melanoma and fibrosarcoma [22].

Some anti-cancer drugs also have anti-fungal properties. Many common cancer chemotherapy drugs (including taxanes, tamoxifen, busulfan, bleomycin, methotrexate and cisplatin) inhibit both growth of the common human fungus *Candida albicans* and prevent *C. albicans* from changing from the yeast to hyphal form [23,24]). The latter form is more virulent and produces more severe human infections [24].

Probiotic intestinal bacteria, like *Lactobacillus* and *Bifidobacterium*, have both anti-fungal and anti-cancer effects. Oral supplementary probiotic bacteria are associated with significantly lower risk of many infections, including vulvovaginal candidiasis and antibiotic-related diarrhea [25,26]. Several human studies show that supplementation with oral *Lactobacillus casei* strain *Shiroda* is associated with significantly lower rates of recurrence of bladder and colorectal cancer [27]. Probiotic bacteria may help prevent both cancer and fungal infections by several

mechanisms, including stimulating the body's immune system, producing nutrients (vitamins and short-chain fatty acids), and suppressing growth of fungi in the body.

Many viruses – the Epstein-Barr virus, papilloma viruses, and hepatitis B and C viruses – promote human cancers by integrating their DNA into human cells [14]. It is therefore possible that integrated fungal DNA can also be found in human cancer cells. In 1996, White [28] proposed that many human cancers may be a result of hybridisation between fungal and mammalian cells, but this has not yet been confirmed, although some recent research has confirmed that several types of cancers can be caused and spread by fusion of different types of human cells. In 1911, the German Scientist, Aichel proposed that cancer could be spread by



Figure 2. *Aspergillus flavus* spores on damaged corn kernels. Reproduced with kind permission of Iowa State Agricultural Extension.

fusion of motile leukocytes and cancer cells [29]. In 2013, American scientists reported that a metastatic melanoma found in the brain tumour of a 68 year-old man contained all the alleles of both

melanoma cells and leukocytes and were almost certainly a result of lymphocyte-melanoma cell fusion [30]. Fusions of cancerous human cells with non-cancerous cells of a different type have been seen; Wang [31] reported that prostate cancer cells can fuse with stromal cells to form tumours of increased malignancy and survivability. Future genetic studies should examine whether fungal chromosomes and/or genes are present in human cancer cells.

Fungi and their mycotoxins probably have been considerably underestimated and underappreciated in ways they might affect the development and spread of many types of cancers, which indicates that much more research and clinical attention should be paid to preventing and treating cancers caused by fungi and mycotoxins. ●

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