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The global geographical overlap of aflatoxin and hepatitis C: Controlling risk factors for liver cancer worldwide

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Abstract

About 85% of hepatocellular carcinoma (HCC, liver cancer) cases occur in low-income countries, where the risk factors of dietary aflatoxin exposure and chronic hepatitis B and C (HBV and HCV) viral infection are common. While studies have shown synergism between aflatoxin and HBV in causing HCC, much less is known about whether aflatoxin and HCV synergize similarly. From an exposure perspective, we examine whether there is a geographical overlap in populations worldwide exposed to high dietary aflatoxin levels and with high HCV prevalence. While HCV is one of the most important risk factors for HCC in high-income nations (where aflatoxin exposure is low), we find that HCV prevalence is much higher in Africa and Asia, where aflatoxin exposure is also high. However, within a given world region, there are some inconsistencies regarding exposure and cancer risk. Therefore, there is a need to control risk factors such as aflatoxin and hepatitis viruses in a cost-effective manner to prevent global HCC, while continuing to evaluate biological mechanisms by which these risk factors interact to increase HCC risk.

Keywords

hepatocellular carcinoma; hepatitis C virus; aflatoxin; hepatitis B virus; liver cancer prevention

Introduction

Hepatocellular carcinoma (HCC, liver cancer) is the third leading cause of cancer deaths worldwide, with an estimated 749,000 new cases annually (IARC 2008). Eighty-five percent of HCC cases occur in low-income nations (Thun et al. 2010). Three key risk factors for HCC in high-risk regions worldwide are chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) and foodborne aflatoxins (Viviani et al. 1997; Hall et al. 2003). Globally, about 52% and 25% of HCC cases are attributable to HBV and HCV, respectively (Montalto et al. 2002). It has also been estimated that aflatoxin exposure may account for 5–28% of total HCC cases worldwide (Liu and Wu 2010), and the population attributable risk for aflatoxin-related liver cancer is about 23% in the high-risk regions of Africa and East Asia (Liu et al. 2012).

Previous research has documented the synergistic interactions of aflatoxin exposure and HBV infection in increasing HCC risk (Qian et al. 1994; Wang et al. 1996; Kirk et al. 2005; Liu et al. 2012). However, much less is known about whether aflatoxin and HCV synergize to increase liver cancer risk in human populations. Moreover, although HBV vaccination is becoming more readily available worldwide, no vaccine for HCV currently exists. With

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increasing prevalence of HCV infection in some populations worldwide, HCV-related disease may become an increasingly important issue in global public health in the near future.

Hepatitis C

Hepatitis C is a disease caused by its eponymous virus (hepatitis C virus) that can lead to severe liver damage if infection becomes chronic. Currently, 75–85% of all acute HCV cases become chronic (CDC 2011a). Chronic HCV has a global prevalence of about 2.35%; however, significant increases in HCV prevalence in the last ten years have been reported in many countries (Lavanchy 2011). HCV is an important etiologic factor for HCC globally, with an estimated 25% population attributable risk (Perz et al. 2006). The current belief is that HCV infection is the main risk factor for HCC in Western countries (Lata 2010). Extrapolation of available data suggests that HCV cases will dramatically increase in the two most populous nations worldwide, China and India; as well as Europe, Japan, and Pakistan (Lavanchy 2011).

Common routes of HCV exposure include sharing needles with infected individuals, receiving infected blood, and accidental exposure to infected blood. HCV transmission through sexual intercourse is not as common as is the case with HBV (Immunization Action Coalition 2007). HCV is the most common blood-borne infection in the United States (Armstrong et al. 2006). Prior to screening for HCV, blood transfusion was one of the most common modes of transmission in developed countries (Prati, 2006). Nosocomial transmission of HCV is problematic worldwide, due to suboptimal sterilization of medical equipment in hospitals and other healthcare institutions (Santos et al. 2010). With increasing prevalence in recent years (Lavanchy, 2011), HCV has become an important public health concern worldwide, which must be addressed to minimize the global burden of chronic liver disease, including liver cancer.

Aflatoxin

Aflatoxins are a group of approximately 20 related fungal metabolites of which aflatoxin B₁, the most toxic of the aflatoxins, is one of the most potent naturally-occurring hepatocarcinogens known. Produced by the fungi *Aspergillus flavus* and *A. parasiticus*, aflatoxin is found primarily in maize, peanuts, and tree nuts; and is a major contaminant of food in low-income nations, particularly in Africa and Asia. Cytochrome P450 enzymes in the liver metabolize aflatoxin into aflatoxin-8,9-exo-epoxide, which can bind to DNA, initiating a series of genetic changes leading to liver cancer (Groopman et al. 2008).

The risk of HCC in individuals co-exposed to both aflatoxin and chronic HBV infection is up to 30 times greater than in individuals with only one of these risk factors (Groopman et al. 2008). HBV-positive individuals contribute to a substantial portion of total global aflatoxin-induced HCC cases, with these cases occurring primarily in China, Southeast Asia, and sub-Saharan Africa (Liu and Wu 2010).

Due to the known human carcinogenicity of aflatoxin, over 100 nations worldwide have set standards for maximum allowable aflatoxin levels in food. In low-income nations, however, such standards are less frequently enforced due to lack of monitoring, especially among subsistence farmers; and the lack of technologies to detect and reduce aflatoxin levels (Wu 2004).

Co-exposure of HCC risk factors: HBV, aflatoxin and HCV

In recent years, a better understanding of possible mechanisms of synergy between HBV and aflatoxin in inducing HCC has emerged, and is reviewed in Wild and Gong(2010). Aflatoxin is associated with a G-to-T transversion in codon 249 of the *TP53* gene, a mutation that has been shown to cooperate with a HBV X protein (HBx) mutation in altering cell proliferation and chromosome stability of hepatocytes(Jiang et al. 2010). It has been shown that there is a significant overlap of high aflatoxin exposure and high HBV prevalence in certain regions of the world, particularly Asia, Southeast Asia, and sub-Saharan Africa (Liu and Wu 2010).

In a recent animal study, HCV-transgenic (HCV-Tg) and wild-type (WT) mice were administered either aflatoxin B₁ or vehicle for twelve months (Jeannot et al. 2011). Tumors and preneoplastic lesions were observed in 50% of the HCV-Tg mice treated with AFB1 compared to WT suggesting that there may be greater than an additive effect of HCV and aflatoxin in inducing liver cancer, as is the case with HBV and aflatoxin. Although several key differences exist between the mechanisms by which HBV and HCV act on hepatocytes, both viruses are likely to cause oxidative stress associated with inflammatory responses, as well as direct cancer promotion by the oncogenic effects of the viruses (McGivern and Lemon 2011).

To understand whether co-exposures to aflatoxin and HCV are likely to increase the global burden of HCC in populations, we examined geographical overlaps between the prevalence of HCV and aflatoxin exposures in different parts of the world. HCV prevalence data were obtained from Lavanchy (2011), while aflatoxin exposures and HBV prevalence were obtained from Liu and Wu (2010) and other sources. Age-standardized rates of HCC in different nations were obtained from the IARC GLOBOCAN database (IARC 2008).

Prevalence of key risk factors for liver cancer worldwide is listed in Table 1, which includes nations grouped by world region according to the World Health Organization (WHO), average adult aflatoxin exposures (in nanograms per kilogram bodyweight [bw] per day) and prevalence of HBV, HCV, and HCC in multiple nations per region. This table includes those nations for which all categories of prevalence data were available in the public literature. In some cases, data were compiled across multiple countries in a given region if prevalence of exposures across the countries was similar.

Prevalence of liver cancer and its risk factors worldwide

As shown in Table 1, Africa and Asia (including Southeast Asia and the Western Pacific) have some of the highest burdens of liver cancer, with several nations having rates exceeding 10 cases per 100,000 in the population. However, within these regions, there is inconsistency in liver cancer rates from nation to nation. For example, among the African nations for which data were available on the three risk factors, liver cancer rates range from 2.7 per 100,000 in Tanzania to as high as 36.1 in The Gambia. This may be partly due to the large geographic size of regions as well as the number of individual nations per region in Africa and Asia. Likewise, India, Indonesia, and Malaysia have relatively low liver cancer rates (below 10 cases per 100,000) compared with other Asian nations, several of which have rates exceeding 20 per 100,000 (Thailand, China, Mongolia, and Korea). Thailand, however, has a high incidence of intrahepatic cholangiocarcinoma in the northeast that results in an increase in the rate of primary liver cancers (McGlynn and London, 2011): another type of primary liver cancer unrelated to aflatoxin, HBV, and HCV. By comparison, North American, Latin American, Eastern Mediterranean, and European nations have consistently low liver cancer rates: below 10 per 100,000 in the population.

Dietary aflatoxin exposure in African and Asian nations vary substantially from nation to nation. On average, however, these aflatoxin exposures are much higher than those of populations in North America and Europe. Prevalence of HBV and HCV is higher as well. Mongolia (15.6%), Cameroon (13.8%), Burundi (11.3%), Gabon (9.2%), and Uganda (6.6%) have some of the highest HCV rates in the world (Lavanchy 2011).

In general, higher prevalence of these three risk factors – HBV, HCV, and aflatoxin – translates to higher HCC rates in populations worldwide. However, within a geographical region, there appear to be inconsistencies. For example, Burundi and Cameroon have higher estimated aflatoxin exposure, HBV prevalence, and HCV prevalence than the Democratic Republic of Congo; and comparable levels to The Gambia. Yet the Democratic Republic of Congo and The Gambia have higher HCC rates than Burundi and Cameroon (IARC 2008). Likewise, although the Republic of Korea does not have particularly high levels of aflatoxin exposure, HBV, or HCV in comparison with other Asian nations, it has an extremely high HCC rate (23.5 per 100,000). These and other such examples may be because of additional HCC risk factors that are not accounted for by considering aflatoxin, HBV, and HCV alone; the lag time between exposure to risk factors that may have been higher in the past and HCC diagnosis; or differences in accuracy of reporting exposures or cancer cases among these countries.

Egypt has the highest recorded prevalence of HCV in the world; the national prevalence of HCV is estimated at 14–20% (Lavanchy 2011; Frank et al. 2000). This extremely high level of HCV amongst Egyptians occurred before the mid-1980s, where parenteral antischistosomal therapy (PAT) mass-treatment campaigns resulted in widespread transmission of HCV through inadequately sterilized syringes (Frank et al. 2000; Abdel-Wahab et al. 2007). Dietary aflatoxin exposures in Egypt are relatively high, at 7–57 ng/kg bw/day (Liu and Wu 2010). According to IARC, HCC is the third most common cancer in Egypt (ASR=9.3/100,000). Co-occurrence of aflatoxin and HCV in the Egyptian population has been shown in various epidemiological studies to be common (Abdel-Wahab et al. 2007; Abdel-Wahab et al. 2008; El-Kafrawy et al. 2005). The unique epidemiology of HCV and aflatoxin in Egypt may be useful in future studies for understanding the dynamics between the two risk factors in causing HCC.

Industrial nations have comparatively lower exposures to aflatoxin and lower HBV and HCV rates. Some of the highest HCV rates in industrial nations are seen in Japan (2.3%), Korea (1.68%), Eastern European nations (2.83%), and the United States (1.8%); relatively much lower than in the low-income nations listed above. Yet HCC rates in many industrial nations and regions (Australia, Canada, United States and all European regions) exceed 3 per 100,000; some have extremely high HCC rates (Japan and Korea). Such trends may reveal the involvement of other risk factors of HCC such as alcohol consumption and Type 2 diabetes. They may also reflect a lag time between the introduction of interventions to reduce HCC risk factors, such as the HBV vaccine, and reduction in HCC risk.

With a few exceptions, such as Egypt and Mongolia, most nations have lower HCV than HBV prevalence. Thus, although there appears to be a geographical overlap between aflatoxin exposure and HCV worldwide, the total number of persons affected by both risk factors is smaller overall than the number of persons affected by both aflatoxin and HBV. However, with the HBV vaccine becoming ever more widespread in low-income nations (Ni et al. 2010; Chang et al. 2009; Viviani et al. 2008) and no corresponding vaccine available for HCV, the relative importance of these two viruses in global cancer risk may change in the future.

Prevention of HCC by controlling its risk factors

Vaccination against HBV

In the last two decades, there have been significant reductions in HBV in certain parts of the world, and its corresponding chronic liver diseases, including cancer. Researchers claim that the HBV vaccine has already reduced HBV and its related diseases in Taiwan (Ni et al. 2010; Chang et al. 2009). In West Africa, the Gambia Hepatitis Intervention Study was established in 1986 to implement nationwide HBV vaccination and examine its impact on chronic liver diseases (Viviani et al. 2008), which thus far shows a positive outcome. Despite these successes, there are still about 350 million HBV carriers worldwide (Franceschi and Raza 2009); hence, there is a need to improve HBV vaccine coverage in all countries as a long-term strategy to reduce risk of HBV-related liver cancer.

Minimizing new HCV infections and improving the health status of already HCV-positive individuals

With HCV prevalence rising most rapidly in the world's two largest national populations, China and India, along with other Asian and Middle Eastern nations, it is becoming an increasingly important global public health concern (Lavanchy 2011). Although HCV has a larger attributable fraction in contributing to liver cancer in high-income nations, HCV prevalence is actually higher and increasing rapidly with population growth in low-income nations (Franceschi and Raza 2009).

Acute HCV incidence has decreased substantially in the United States since 1992, which translates into fewer chronic HCV cases (CDC 2011b). Preventive measures against HCV, such as testing and treatment services among at-risk populations, establishing robust surveillance systems, distribution of clean needles, and early diagnosis via screening tests, have all helped to reduce HCV risk in the US (CDC 2011c), and should be implemented more broadly in high-risk populations worldwide (Lavanchy 2011). Educational efforts to inform the public about the risk of HCV transmission through shared needles are critical. Proper sterilization techniques should be adopted for medical equipment so that nosocomial transmission of HCV is minimized (Table 2).

While prevention should be the main focus of HCV control, improvement of the lives of currently infected individuals must be included in the action plan. Research efforts to develop efficient antiviral drugs and/or a vaccine (Barnes et al. 2012) are critical. New candidate drugs such as telaprevir and boceprevir are currently at the frontline of novel therapeutics (Eisentein 2011) to control HCV.

Management of aflatoxin contamination of foodstuffs

Aflatoxin can be managed at various points along the food production chain from field to plate. The preharvest, postharvest, and dietary interventions shown in Table 2, and their costs and efficacy in reducing aflatoxin exposure have been reviewed (Khangwiset and Wu 2010). In brief, methods to control aflatoxin include those that reduce the stress of the host crop plant in field conditions (such as the use of good agricultural practices), reduce the risk of aflatoxin accumulation in storage conditions (proper drying and appropriate temperature and moisture in storage), and reduce aflatoxin bioavailability and its harmful effects in the diet.

Discussion

Our analysis indicates the need for further research to study mechanisms by which aflatoxin and HCV may interact in inducing liver cancer. Although the prevalence of HCV is lower than that of HBV in most countries of the world (Egypt being a notable exception), there is a significant geographical overlap between high aflatoxin exposure and high HCV rates worldwide, particularly in Asia and Africa, where liver cancer rates are highest. Although there are some inconsistencies from nation to nation within these two geographic regions, where some nations with higher exposures to some of the risk factors do not always have higher liver cancer prevalence, in general it is the case that higher liver cancer risk is associated with higher levels of all three of the risk factors of aflatoxin exposure, HBV, and HCV.

The inconsistencies in country-level data of the association between HCC and its most prominent risk factors may be caused by several things. First, there may be inconsistencies in reporting HCC prevalence and risk factors across countries; for example, many cases of HBV, HCV, or HCC may go unreported. Second, in some nations where one or more of the risk factors may be decreasing (e.g., aflatoxin exposure or chronic HBV infection), there may be a lag time between changes in population exposure and HCC diagnoses. Third, there may be additional risk factors playing a role in the etiology of HCC that are not accounted for by assessing prevalence of aflatoxin exposure, HBV, and HCV alone.

With HBV prevalence decreasing worldwide due to widespread vaccination campaigns, HCV prevalence increasing in many parts of the world, and aflatoxin exposures still relatively high in low-income nations, there is likely to be proportionally increasing burdens of aflatoxin-induced HCC, HCV-induced HCC, and possibly HCC caused by both aflatoxin and HCV interacting synergistically or otherwise. Over the last two decades, there has been a significant body of literature examining the synergistic nature of the interaction between aflatoxin exposure and chronic infection with HBV in increasing liver cancer risk in human populations. Such epidemiological studies are needed to examine whether such a synergy exists between the risk factors of aflatoxin and chronic HCV infection. At least one animal study indicates that a synergy may exist between these two risk factors in inducing liver tumors.

As it is primarily low-income nations that are burdened by the two risk factors for liver cancer – high dietary aflatoxin exposure and high HCV prevalence – prevention programs should be developed with a focus on affordability and accessibility. Primary prevention is critical for controlling the spread of HCV in populations. Unlike the case for HBV, no HCV vaccine is currently available for public health purposes, although promising efforts are underway in the development of such a vaccine. Until then, it is critical to focus on public education regarding the risks of HCV transmission through needle sharing, and for health care systems to ensure clean needles for medical and other purposes. Several different cost-effective methods for aflatoxin control in foods are available as well. Taken together, these prevention efforts can reduce HCC risk in the areas of the world where it is most needed.

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Table 1

Aflatoxin exposure, HBV and HCV prevalence, and HCC age-standardized rate (ASR) for select nations worldwide grouped according to WHO regions.

WHO region	Countries	Aflatoxin exposure ⁶ [ng/kg bw/day]	HBV prevalence ⁶ [% population]	HCV prevalence ¹² [% population]	HCC ASR per 100,000 ¹
<i>Africa</i>	Burundi	10–180	9–20	11.3	5.6
	Cameroon	10–180	9–20	13.8	9.3
	Dem. Rep. of Congo	0.07–27	6–10	6.4	18.8
	Ethiopia	1.4–36	6–7	1.9	5.2
	Gabon	10–180	9–20	9.2	8.6
	The Gambia	4–115	15–20	2.4	36.1
	Kenya	3.5 – 133	11–15	0.9	6.6
	Mozambique	39–180	4.5–10.6	3.2	4.6
	Nigeria	139–227	13.2	2.1	9.9
	South Africa	0–17	3.3–10.4	1.7	9.5
	Tanzania	0.02–50	5–9	3.2	2.7
	Uganda	10–180	9–20	6.6	8.6
	Zimbabwe	17.5–42.5	10–15	2.0	6.9
<i>Southeast Asia</i>	India	4–100	2.4–4.7	1.5	2.2
	Indonesia	9–122	2.5–5	3.9	6.7
	Thailand	53–73	4.6–8	2.2	29.7
<i>Western Pacific Region</i>	Australia	0.15–0.18	<1	1.1	3.5
	China	17–37	8–10	2.2	25.7
	Japan ³⁹	0.003–0.004	<1	2.3	11.2
	Korea	1.2–6	4–5	1.68	23.5
	Malaysia	15–140	5	1.5	5.7
	Mongolia ⁴⁰	~0	11.8	15.6	54.1
	Philippines	44–54	5–16	2.2	10.6
<i>Eastern Mediterranean</i>	Egypt	7–57	2.2–10.1	14–20	9.3
	Iran	5–8.5	0.41–0.56	0.9	2.1
	Pakistan	7–50	3.3	5.9	2.5
	Sudan	19–186	6–26	2.8	3.9

WHO region	Countries	Aflatoxin exposure ⁶ [ng/kg bw/day]	HBV prevalence ⁶ [% population]	HCV prevalence ¹² [% population]	HCC ASR per 100,000 ¹
<i>North America</i>	Canada	0.2–0.4	1–2	0.1	3.3
	United States	0.26	0.3–2	1.8	4.5
<i>Latin America</i>	Argentina	0–4	0.8–1.1	1.9	3.4
	Brazil	0.23–50	2.1–3.4	1.4	4.9
<i>Europe</i>	Mexico	14–85	<0.3	1	6.3
	Eastern ^a	3.5–4	2–7	2.83	3.0
	Southern ^b	0–4	2–7	1.53	6.6
	Western ^c	0.3–1.3	0.5–1	0.96	4.4

^aThe average for HCV prevalence for Eastern Europe was calculated by averaging across the following countries: Armenia, Azerbaijan, Belarus, Bulgaria, Croatia, the Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, the Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia and Ukraine.

^bThe average for HCV prevalence for Southern Europe was calculated by averaging across the following countries: Bosnia and Herzegovina, Greece, Cyprus, Italy, Malta, Portugal and Spain.

^cThe average for HCV prevalence for Western Europe was calculated by averaging across the following countries: Austria, Belgium, Denmark, France, Germany, Ireland, Luxembourg, Switzerland and the UK.

Table 2

Recommended interventions for liver cancer risk reduction by reducing aflatoxin exposure and HCV risk in human populations.

Interventions to reduce aflatoxin exposure ³⁸		Interventions to reduce HCV risk	
<i>Preharvest</i>	<ul style="list-style-type: none"> • Breeding crop resistance to fungal infection • Good agricultural practices (GAP) • Biocontrol 	<i>Primary</i>	<ul style="list-style-type: none"> • Education and awareness on intravenous drug abuse and safe sex practices • Distribution of clean needles to hospitals
<i>Postharvest</i>	<ul style="list-style-type: none"> • Sorting • Drying • Cool, dry storage • Nixtamalization 	<i>Secondary</i>	<ul style="list-style-type: none"> • Making screening for HCV more available (especially blood donors)
<i>Dietary</i>	<ul style="list-style-type: none"> • Enterosorbents (e.g., clays) • Chlorophyllin • Isothiocyanates (e.g., in cruciferous vegetables) 	<i>Tertiary</i>	<ul style="list-style-type: none"> • Making interferon and ribavirin anti-retroviral therapy more available and affordable