

2010

HIV and Hepatocellular and Esophageal Carcinomas Related to Consumption of Mycotoxin-prone Foods in Sub-Saharan Africa

Jonathan H. Williams

Jessica A. Grubbs

Jerry W. Davis

Jia-Sheng Wang

Pauline E. Jolly

See next page for additional authors

Follow this and additional works at: <http://digitalcommons.georgiasouthern.edu/environ-health-facpubs>

 Part of the [Environmental Health Commons](#), [Environmental Health and Protection Commons](#), and the [Environmental Public Health Commons](#)

Recommended Citation

Williams, Jonathan H., Jessica A. Grubbs, Jerry W. Davis, Jia-Sheng Wang, Pauline E. Jolly, Nii-Ayi Ankrah, William O. Ellis, Evans Afriyie-Gyawu, Natalie M. Johnson, Abraham G. Robinson, Timothy D. Phillips. 2010. "HIV and Hepatocellular and Esophageal Carcinomas Related to Consumption of Mycotoxin-prone Foods in Sub-Saharan Africa." *The American Journal of Clinical Nutrition*, 92 (1): 154-160.
<http://digitalcommons.georgiasouthern.edu/environ-health-facpubs/10>

This article is brought to you for free and open access by the Department of Environmental Health Sciences at Digital Commons@Georgia Southern. It has been accepted for inclusion in Environmental Health Sciences Faculty Publications by an authorized administrator of Digital Commons@Georgia Southern. For more information, please contact digitalcommons@georgiasouthern.edu.

Authors

Jonathan H. Williams, Jessica A. Grubbs, Jerry W. Davis, Jia-Sheng Wang, Pauline E. Jolly, Nii-Ayi Ankrah, William O. Ellis, Evans Afriye-Gyawu, Natalie M. Johnson, Abraham G. Robinson, and Timothy D. Phillips

HIV and hepatocellular and esophageal carcinomas related to consumption of mycotoxin-prone foods in sub-Saharan Africa¹⁻⁴

Jonathan H Williams, Jessica A Grubb, Jerry W Davis, Jia-Sheng Wang, Pauline E Jolly, Nii-Ayi Ankrah, William O Ellis, Evans Afriyie-Gyawu, Natalie M Johnson, Abraham G Robinson, and Timothy D Phillips

ABSTRACT

Background: Promotion of the HIV epidemic by aflatoxin is postulated but not yet established. Sub-Saharan populations commonly consume food contaminated by mycotoxins, particularly aflatoxins (predominantly found in peanut, maize, rice, and cassava) and fumonisins, which occur primarily in maize. Aflatoxin promotes hepatocellular cancer, and fumonisin may promote esophageal cancer.

Objectives: This analysis was undertaken to test the hypotheses that consumption of mycotoxin-prone staple foods is 1) related to the incidence of HIV infection in Africa and 2) related to “signature” cancer rates confirming exposure to aflatoxins and fumonisins.

Design: World Health Organization data for causes of death and the Food and Agriculture Organization per capita consumption data for commodities in sub-Saharan Africa were used. Per capita Gross Domestic Product and the percentage of Muslims (%Muslim) were the socioeconomic data sets exploited. Relations between causes of mortality, consumption of mycotoxin-prone foods, and socioeconomic variables were evaluated. Models for HIV transmission as a function of maize consumption and %Muslim were estimated.

Results: HIV and esophageal cancer deaths were significantly related to maize but were inversely related to %Muslim and rice consumption. HIV infections were minimized (74 compared with 435/100,000 people; odds ratio: 2.41; 95% CI: 1.73, 3.24; $P \leq 0.0001$) by the combination of low maize consumption and above-median %Muslim. Hepatocellular cancer deaths were positively related to rice but negatively related to maize consumption.

Conclusions: HIV transmission frequency is positively associated with maize consumption in Africa. The relation between cancer and food suggests that fumonisin contamination rather than aflatoxin is the most likely factor in maize promoting HIV. Changes to the quality of maize may avoid up to 1,000,000 transmissions of HIV annually. *Am J Clin Nutr* 2010;92:154–60.

INTRODUCTION

Large variations in HIV transmission rates are observed between African social groups and nations, and these differences have been the focus of significant research to understand the epidemiology of the disease and to develop interventions against the spread of the disease. Early research established links between social behavior and transmission rates. Many of these factors, such as male circumcision (1), other sexually transmitted diseases (2), faith (3), and partner concurrency (4) have been further studied and proven important (5) through detailed study, models, or clinical trials.

Food and nutritional factors have not received that same attention from a transmission perspective, but micronutrients in particular have been studied for their role in the progression of HIV (6). Mycotoxin contaminants in foods may also be important in the HIV epidemic, for instance, chronic aflatoxicosis is associated with immune suppression (7) and a reduction in essential nutrients and may result in deficiencies known to promote HIV progression (8). HIV infection combined with high concentrations of the aflatoxin-albumin adduct biomarker have been associated with a decreased potential for antibody responses, decreased immune cytotoxic activity, and decreased numbers of regulatory T cells, which may result in hyperactivation of the immune system (9). Thus, dietary sources of aflatoxin are a potential factor in the HIV epidemic.

A literature review indicated that fumonisin exposure is associated with an increased risk of esophageal cancers (10). Fumonisin is predominantly a contaminant of maize (11) resulting from fungal growth (*Fusarium verticillioides*) after damage by pests such as the cornstalk borer (*Busseola fusca*). Fumonisin is involved in sphingolipid metabolism, ceramide synthesis (12), cell signaling (13), membrane characteristics (14), and membrane porosity (15). Unlike aflatoxin, fumonisin has been proposed as a positive factor in HIV pathology (14), and, in isolation, it has not been reported to be strongly immunotoxic in animals or humans (10). Interactions and synergies between aflatoxin and fu-

¹ From the College of Agriculture and Environmental Sciences, University of Georgia, Griffin, GA (JHW, JAG, and JWD); the College of Public Health Sciences, University of Georgia, Athens, GA (J-SW); the College of Public Health, University of Alabama Birmingham, Birmingham, AL (PEJ); the Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana (N-AA); the Department of Biochemistry, University of Science and Technology, Kumasi, Ghana (WOE); the Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA (EA-G); and the College of Veterinary Medicine, Texas A&M University, College Station, TX (NMJ, AGR, and TDP).

² The US Agency for International Development is not responsible for the content of this article.

³ Supported by US Agency for International Development agreement ECG-A-00-0700001-00 to the Peanut Collaborative Research Support Program located at the University of Georgia.

⁴ Address correspondence to JH Williams, College of Agriculture and Environmental Sciences, 1109 Experiment Street, Griffin, GA 30223. E-mail: jhtimwil@uga.edu.

Received September 30, 2009. Accepted for publication April 9, 2010.

First published online May 19, 2010; doi: 10.3945/ajcn.2009.28761.

monisin are documented in regard to the risk of liver cancer (16). It is also possible that immune suppression may be enhanced by coexposure to aflatoxin and fumonisin (17).

The staple foods most prone to aflatoxin contamination are considered to be peanuts, maize, cassava, and rice (18). Consumption of peanuts is recognized as a contributing factor to aflatoxicosis and an increased incidence of hepatocellular cancer in African countries (19). Maize, in particular, may also be an important source of exposure to aflatoxin, because whereas maize is usually less contaminated than peanuts, people in Africa consume much larger quantities of maize than peanuts. Maize is also commonly contaminated with fumonisin. Dried cassava may be contaminated by aflatoxin, but a significant fraction of cassava is eaten fresh, which reduces the risk of exposure via this commodity. Imported polished rice is usually not contaminated, but locally grown rice may be contaminated if the drying and storage conditions before milling and polishing are favorable for the growth of *Aspergillus flavus*.

The mean survival time with HIV in Africa is 11 y, with 95% CIs of 2 y for South African and 3 y for East African populations (20). Thus, HIV deaths in 2004 are mostly the result of infections that occurred in 1993, or a weighted average for those between 1990 and 1996. Unless otherwise specified, "HIV" is used herein to denote the HIV transmission rate for 1993.

This research was undertaken to explore potential involvement of mycotoxin-prone foods in the HIV epidemic and to determine whether further studies are justified.

METHODS

Data sources

Data for most socioeconomic drivers of the HIV epidemic are not available at the national level for countries in sub-Saharan African (SSA), being mostly documented at the local or regional levels within each nation. For example, tribes are seldom confined to national boundaries and may differ with regard to the practice of male circumcision (1), which is now considered a key intervention to protect against HIV; however, the prevalence of male circumcision is not documented as part of the national census data. However, statistics on faith exist for all nations, and, at the national scale, the Muslim faith provides an integrating social demographic related to HIV infections (3) and establishes a baseline (the lowest percentage) for male circumcision. Other major African religions do not directly influence circumcision. Per capita Gross Domestic Product (GDP) is another standard data set across SSA.

Data for both 1993 and 2003 pertaining to continental SSA nations was obtained from the World Fact Book (21) for the percentage of Muslims (%Muslim) and per capita GDP. Food and Agriculture Organization (FAO) data for the per capita consumption of staple foods for 38 nations were available and accessed for both 1993 and 2003 (22). The 2004 mortality rates from all causes in the countries for which food data were available were collected from the World Health Organization (WHO) (23). For hepatocellular and esophageal cancer relations to foods, both the 1993 and 2003 data were used; however, because the resulting regression parameters were not statistically different between the years, only the results for 1993 are presented. Descriptive statistics for these data are provided in **Table 1**.

Analysis

Initially simple correlations between socioeconomic variables, consumption levels of food staples, and all causes of mortality were evaluated (**Table 2**). No significant positive relation between cassava consumption and HIV, hepatocellular cancer, or esophageal cancer was detected, so this staple was dropped from further investigation. We then focused on regression analyses of causes of death (HIV infection and esophageal and hepatocellular cancers) as functions of the environmental variables; these cancers were considered "indicators" of fumonisin and aflatoxin exposure, respectively (**Table 3**). In the case of hepatocellular cancers, we also evaluated hepatitis B virus (HBV) as a cofactor.

The possible roles of both %Muslim and GDP as factors in the HIV epidemic were evaluated by using a multifactor regression model of HIV deaths as a function of %Muslim, GDP, and the interaction of GDP with %Muslim. This model established that %Muslim integrated any effects of GDP on HIV because only the %Muslim coefficient was statistically significant ($P < 0.05$) in the multifactor model (data not presented). GDP was not included in further analyses.

To determine the relative importance of factors that affect the overall international variance for HIV, we used single or multifactor regression and linear regression using restricted data sets that excluded, or considered separately, data such as statistical outliers (**Table 4**).

For an effect analysis of the %Muslim and maize consumption factors on the risk of HIV, 4 treatments were established by classifying nations according to whether the HIV data were above or below the median for both %Muslim and maize consumption; the mean HIV infection frequency for each group was analyzed to

TABLE 1

Descriptive statistics for mortality data (23) from 2004 and for environmental variables (21, 22) from 1993

	Mean	SE	Median	Range	Minimum	Maximum
HIV/AIDS ¹	281.45	50.85	166.69	1451.85	11.51	1463.36
Esophageal cancer ¹	3.47	0.59	1.91	13.07	0.17	13.24
Hepatocellular cancer ¹	10.10	1.19	8.41	30.34	1.25	31.59
Muslim (%)	27.13	4.85	17.80	93.99	0.01	94.00
Gross Domestic Product (US\$/y)	687.59	136.03	400.00	4085.00	115.00	4200.00
Cassava (kg per capita/y)	19.55	3.69	12.50	95.50	0.00	95.50
Peanut (kg per capita/y)	2.46	0.54	1.00	13.00	0.00	13.00
Maize (kg per capita/y)	41.57	6.63	26.00	141.00	0.00	141.00
Rice (kg per capita/y)	22.16	4.68	10.00	105.00	0.00	105.00

¹ Deaths per 100,000 persons.

TABLE 2

Correlation coefficients (*R*) between selected causes of death (2004), environmental factors, and per capita consumption of commonly recognized sources of mycotoxin exposure in sub-Saharan Africa (1993) (*n* = 37)¹

Data year and variable	HIV	EC	HCC	%Muslim	GDP
HIV/AIDS	1				
Esophageal cancer	0.428 ²	1			
Hepatocellular cancer	-0.325 ²	-0.531 ²	1		
%Muslim	-0.451 ²	-0.258	0.513 ²	1	
GDP	0.222	0.026	-0.294 ³	-0.274	1
Cassava	-0.237	-0.316 ²	0.121	-0.279	-0.106
Peanut	-0.252 ³	-0.387 ²	0.248	0.224	0.103
Maize	0.685 ²	0.554 ²	-0.339 ²	-0.339 ²	-0.033
Rice	-0.437 ²	-0.388 ²	0.283 ³	0.667 ²	-0.077

¹ %Muslim, percentage of Muslims; GDP, Gross Domestic Product; EC, esophageal cancer; HCC, hepatocellular cancer.

² $P \leq 0.01$.

³ $P \leq 0.05$.

determine the effects and relative risks associated with these environmental factors (Table 5). Analyses used both Excel (Microsoft Office 2007; Microsoft, Redmond, WA) and SAS version 9.2 (SAS Institute Inc, Cary, NC). The figures were prepared with Excel and Grapher version 7 (Golden Software, Golden, CO).

Assumptions

We tested and confirmed the assumptions that conservative patterns exist between causes of death and food-consumption patterns in SSA. The consequence of the year for which the consumption data were derived was evaluated by generating 2 correlation matrices using the 2004 mortality data against either the 1993 or 2003 food data. The resulting correlation coefficients were then taken as variables for a regression using the 1993/2004 *R* values as predictors of the 2003/2004 *R* values. The 1993 coefficients were excellent predictors of the 2003/2004 coefficients ($R^2 = 0.95$), justifying the presentation of only the 1993-based results.

We also assumed the following:

- 1) HIV-related mortality rates in 2004 were not differentially influenced by national differences in the use of antiretroviral therapies (ARVs). The US President's Emergency

Plan for AIDS Relief (PEPFAR) was launched in 2003 to deploy ARVs and was still being established in 2004—the year in which the WHO data were collected.

- 2) Tribal differences in the practice of male circumcision in the non-Muslim fractions of the national populations are not a source of bias.
- 3) Different food-processing techniques across the region have little effect on the fraction of contaminants that are removed from the foods before consumption. This assumption is least certain for fumonisin, because milling technologies may vary the fraction of fumonisin retained in the meal (24).

RESULTS

Correlation coefficients between environmental variables and selected causes of mortality were often highly significant, particularly so for maize (Table 2).

Dietary patterns and socioeconomic parameters

The consumption rates of maize, cassava, rice, and peanuts varied significantly across nations (Figure 1), providing varied levels of potential risk to aflatoxins and fumonisins. %Muslim was positively correlated with rice consumption, but inversely so

TABLE 3

Regression models for deaths (per 100,000 population) due to hepatocellular cancer and esophageal cancer as functions of 1993 consumption of mycotoxin-prone staple foods and socioeconomic factors in sub-Saharan Africa¹

Cause of death and independent variable	Regression equation	R^2	<i>P</i>
Hepatocellular cancer vs peanut	$y = 8.77 + 0.5437x$	0.062	NS
Hepatocellular cancer vs rice	$y = 8.51 + 0.072x$	0.196	0.089
Hepatocellular cancer vs maize	$y = 1.43 - 0.49x$	0.318	<0.001
Hepatocellular cancer vs %Muslim	$y = 6.69 + 0.126x$	0.263	0.001
Esophageal cancer vs peanut	$y = 4.49 - 0.417x$	0.150	0.018
Esophageal cancer vs rice	$y = 4.54 - 0.048x$	0.151	0.018
Esophageal cancer vs maize	$y = 1.43 + 0.049x$	0.308	<0.001
Esophageal cancer vs %Muslim	$y = 4.31 - 0.031x$	0.067	0.122
Confounding food vs social factor relations			
Peanut vs %Muslim	$y = 1.78 + 0.025x$	0.050	NS
Rice vs %Muslim	$y = 4.68 + 0.644x$	0.445	<0.001
Maize vs %Muslim	$y = 54.15 - 0.464x$	0.115	0.040

¹ %Muslim, percentage of Muslims.

TABLE 4

Parameters of the regression models for HIV-related mortality (per 100,000 population) in 2004 as a function of the prevalence (1993) in Muslims and per capita maize consumption in sub-Saharan Africa¹

	Coefficient	SE (\pm)	P value	R ²
Regression model 1: HIV on %Muslim				
Intercept	409.83	62.91	<0.001	—
%Muslim	-4.733	1.581	0.005	—
Regression model 2: HIV on maize consumption				
Intercept	63.02	54.38	0.254	—
Maize consumption	5.255	0.946	<0.001	—
Regression model 3: HIV on %Muslim, maize consumption, and their interaction				
Intercept	127.31	72.27	0.087	—
%Muslim	-0.907	1.598	0.574	—
Maize consumption	5.882	1.183	<0.001	—
%Muslim \times maize consumption	-0.089	0.051	0.087	—
Regression model 4: HIV on %Muslim, maize consumption, and their interaction				
Intercept	0	—	—	—
%Muslim	1.025	1.198	0.398	—
Maize consumption	7.370	0.853	<0.001	—
%Muslim \times maize consumption	-0.113	0.050	0.0324	—

¹ %Muslim, percentage of Muslims.

with maize consumption (Table 2). %Muslim was also inversely correlated with HIV ($R = -0.45$, $P < 0.01$) and positively correlated with deaths from both hepatocellular cancers ($R = 0.513$, $P = 0.001$) and HBV ($R = 0.44$, $P = 0.003$; further data not shown). The HBV/%Muslim result introduces the possibility that ritual circumcision, which may promote the transmission of HBV, is a confounding factor for the relation of hepatocellular cancer with diet.

Environmental factors associated with HIV

Significant correlations and regression relations exist in SSA between maize consumption and HIV and inversely so between % Muslim and HIV (Tables 2 and 3). Maize consumption, as a single variable, accounted for 47% of the SSA variance in HIV

(Figure 2 and Table 3). The data for Botswana, Swaziland, and Zimbabwe are outliers well above the general regression line, and exclusion of these countries resulted in a relation in which 67% of HIV variations in the remaining data set were attributable to maize consumption. The regression model for these 3 nations differed statistically from the overall model, only in the intercept term.

The HIV/%Muslim model showed that 20% of variations in HIV were accounted for by this social factor (Table 4). Some of the modeled effect of %Muslim on HIV was attributable to the confounding effect of nations with high %Muslim also consuming less maize. Regressions using multiple parameters (%Muslim and maize) to estimate HIV showed a significant interaction between maize diets and %Muslim. The best model (as measured by the R^2 value) depended on forcing the line

TABLE 5

HIV transmission frequency analysis for countries above or below the median maize consumption (26 kg/y) and above or below the median Muslim prevalence [percentage of Muslims (%Muslim): 17.8]

	Low %Muslim	High %Muslim	Total	Value	95% CI
Low maize					
Deaths or transmissions ¹	268 \pm 74.3 [9]	74 \pm 23.3 [10]	342		
Per capita maize consumption (kg/y) ²	16.2	10.9			
%Muslim	8.3	72.1			
High maize					
Deaths or transmissions ¹	435 \pm 105.3 [14]	291 \pm 135.4 [4]	726		
Per capita maize consumption (kg/y) ²	72.6	66.7			
%Muslim	9.5	38.7			
Total HIV deaths or transmissions	703	365			
Case control (high maize/low %Muslim vs low maize/high %Muslim)				2.41 ^{3,4}	1.79, 3.24
Relative risk for maize				1.31	1.20, 1.42
Relative risk for Muslim				0.52	0.44, 0.68

¹ Mean (\pm SD) estimates of deaths in 2004 or transmissions per 100,000 persons in 1993; n in brackets.

² Values are means.

³ Odds ratio.

⁴ $P < 0.001$.

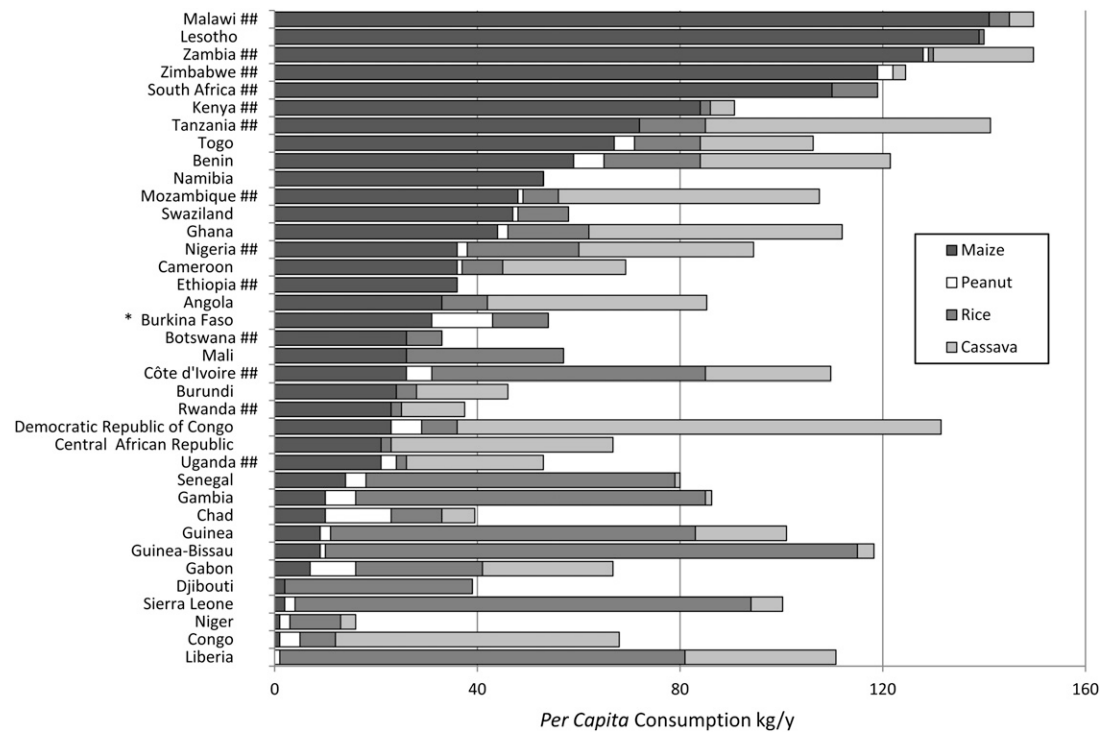


FIGURE 1. Per capita consumption of 4 mycotoxin-prone foods in sub-Saharan African countries in 1993. *Denotes median country for maize consumption. ##Denotes 2004 President's Emergency Plan for AIDS Relief country.

through zero ($R^2 = 0.74$), whereas the epidemiologically more sensible model (Table 4, model 3) with an intercept and the interaction term accounted for a major part ($R^2 = 0.56$) of the variations in HIV data across nations.

The analysis of the effects of maize consumption and %Muslim on HIV (Table 5) found that the combination of below-median %Muslim and above-median maize consumption resulted in an odds ratio of HIV of 2.41 (95% CI: 1.79, 3.24) greater than the opposite combination.

Cancers associated with environmental factors

As shown in Table 2, esophageal cancer deaths were related to maize consumption ($R = 0.55$, $P < 0.001$) but inversely related to consumption of peanut, cassava, and rice and to hepatocellular cancer ($R = -0.53$, $P < 0.01$). Rice consumption was associated with hepatocellular cancer, whereas maize consumption was negatively related to this disease. The latter relation was maintained in regression analyses involving combinations of maize with all other environmental variables (data not presented). HIV rates were negatively correlated ($R = -0.33$, $P < 0.05$) with hepatocellular cancer and positively so with esophageal cancer.

Intervention response modeling

Regression model 3 (Table 4) was used to evaluate sensitivity to the maize factor. After controlling for the mean SSA Muslim population, the model predicts 245 HIV transmissions per 100,000 people for the mean maize consumption, whereas, if the maize factor were totally mitigated (maize = 0.1 kg per capita),

only 103 HIV transmissions per 100,000 are predicted—a 58% reduction in HIV at the SSA scale.

DISCUSSION

The primary purpose of this investigation was to identify and evaluate relations between mycotoxin-prone foods and HIV. The investigation of relations between foods and hepatocellular and esophageal cancers was to confirm exposure to the toxins as a function of the dietary patterns. Evidence that mycotoxin exposure is an epidemiologic significant feature of SSA diets is critical to the interpretation of relations between food consumption and HIV. The role of the socioeconomic variables used is to evaluate (as well as possible) the role of other known drivers of the HIV epidemic that may moderate or confound potential mycotoxin-related effects.

Food-consumption patterns and socioeconomic parameters

As evident in Figure 1, there was significant variation across nations in the potential dietary risk from the foods most prone to mycotoxin contamination. The correlation of dietary variables with the best available socioeconomic variable (%Muslim) indicated that at least some of the known social drivers of HIV are confounded with the dietary environment. The cropping environments where Muslims predominate are less suitable to maize and often more appropriate for rice.

Environmental factors associated with cancer mortality rates

The strong esophageal cancer-maize relation was consistent with expectations based on published correlations between



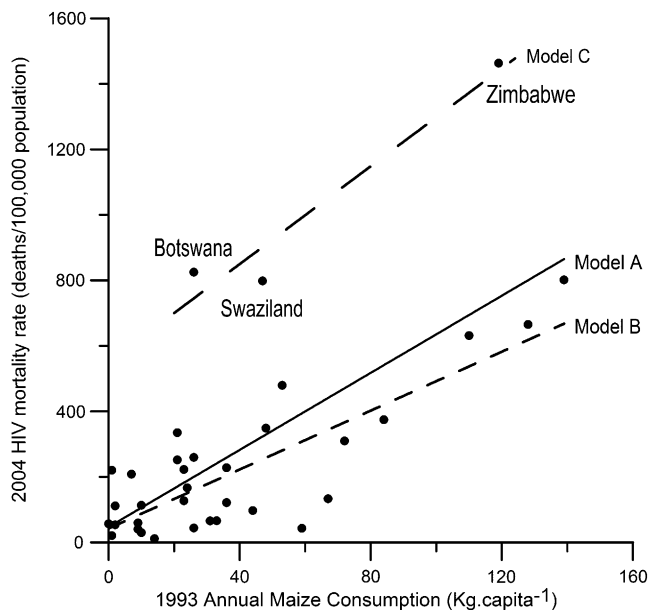


FIGURE 2. Relations between 1993 per capita consumption of maize and 1993 HIV transmission/2004 AIDS death rates in sub-Saharan African countries. Model A (all countries; mean \pm SE): $y = x \times 5.26 \pm 0.94 + 63.0 \pm 54.4$ ($n = 37$; $R^2 = 0.47$). Model B (excluding outliers): $y = x \times 4.98 \pm 0.51 + 42.4 \pm 28.4$ ($n = 34$; $R^2 = 0.67$). Model C (southern African outliers): $y = x \times 7.47 \pm 1.93 + 550.5 \pm 147.2$ ($n = 3$; $R^2 = 0.94$).

fumonisin exposure and this cancer (reviewed in reference 10) and the reported widespread contamination of locally grown maize (11). This result supports the proposition that consumption of maize is a proxy for exposure to fumonisin.

The relations between foods and hepatocellular cancer provided the weakest case for foods to be a proxy for exposure to aflatoxin. Maize, as the predominant source of dietary aflatoxin, was (contrary to expectation) inversely related to aflatoxin's signature cancer, probably because HIV results in death earlier than does hepatocellular cancer. The second most likely source of aflatoxin (peanut) only showed a trend for hepatocellular cancer mortality to increase with peanut consumption, whereas the significant association between rice and hepatocellular cancer is potentially confounded by the parallel relations between rice, %Muslim, and HBV—relations that may derive from the practice of circumcision in unsterile situations. What is not known is how much of the anticipated aflatoxin effect from maize and other foods was masked by the relations between HIV, esophageal cancer, and maize consumption.

Factors associated with HIV

Clearly, maize consumption and HIV transmission (1993)/death rates (2004) are statistically connected (Table 2). The importance of this relation reported here is reflected in both the fact that most of the countries prioritized to receive PEPFAR funds lie above the median for maize consumption (Figure 1) and that the model for HIV infections, based on these variables, projects that a large number of infections may be avoided by addressing whatever is responsible for the correlation between maize intake and HIV.

The HIV rate for Zimbabwe, Botswana, and Swaziland (the statistical outliers) is not explained by the variables considered in this analysis; however, this effect could be a result of migrant labor associated with South African mining because the relation to maize consumption was maintained but differed in the intercept term of the regression model (Figure 2).

Use of the coefficients of determination to partition the sources of transnational variance in HIV cases indicated that much of the overall variance can be accounted for by %Muslim (20%) and maize consumption (67%: 47% all countries and 20% outlier country-specific effects by subtraction). This suggests an important role of food factors in the epidemic, which is clearly deserving of more and vigorous investigation. The relative risk of HIV associated with a high %Muslim country (0.52) compared with the contrasting population is consistent with the reduced risk observed for circumcision in clinical trials within country locations (5).

Probable causality

The basis for the relation between maize and HIV needs careful consideration. Is there an external factor that influences both environmental suitability for maize and also increases transmission? From the known social drivers of the epidemic, we cannot identify any unanalyzed candidate factors correlated to both HIV and maize consumption that could result in this relation. We were able to analyze the %Muslim-based index for circumcision, which works to increase HIV when more maize is consumed.

There is no evidence in the literature of some property of normal maize that could influence the susceptibility of humans to HIV infection. Therefore, contaminants are the most likely basis for the association between maize and HIV. The most common contaminants of maize are aflatoxins and fumonisins, both of which could be determinants of the maize-HIV association.

Features of aflatoxicosis that could promote HIV infection include immune suppression, reduced mucosal IgA, and associated enhanced epidemics in animals as a result of chronic aflatoxicosis (7, 8). Immune modulation has been associated with natural levels of dietary aflatoxins in humans in Ghana (7) and with specifically altered immune function in HIV-infected persons (9). However, these changes are more likely to influence progression rather than transmission, and the consumption data do not support the hypothesis that aflatoxin alone modulates HIV transmission. In our analysis, the AF-prone commodities (rice and peanut) that were associated with hepatocellular cancer were negatively associated (or tended to be so) with HIV infections. Rice was associated with reduced HIV, but this could also have been the result of higher consumption of rice in predominantly Muslim countries in which male circumcision is more prevalent.

The parallel relation between maize and esophageal cancer rates (Table 2) suggests that the HIV-maize relation may depend on either fumonisin or on both fumonisin and aflatoxin. Two actions of fumonisin may be responsible for the observed relation. The most likely mechanism is that fumonisin might increase membrane permeability (25), which could promote HIV transmission. Alternatively, fumonisin may promote HIV infections by interfering with the biosynthesis of ceramide and complex sphingolipids (26), which are implicated in the membrane

properties and in the attachment of HIV to human cells (14). However, the available evidence indicates that fumonisins result in less infective virions (14).

Significance

The parameters of the models indicate that any reduction in exposure to the maize “factor” will have a significant effect on the HIV epidemic. This implies that there is little tolerance for this factor in the diet and also that the potential effect of addressing the cause of the maize-HIV relation will be very significant. Because some 1.7 million new infections are estimated to occur annually in SSA (27), the model predicts that addressing the cause of the HIV-maize relation may prevent up to one million new infections annually. The interaction of these model projections with existing programs promoting behavioral change, circumcision, and condom use is not known; however, this analysis suggests that whereas maize is a major component of the diet, a significant reduction of the risk of transmission is available.

Clearly, these are preliminary findings that need further research. If, as is hypothesized, fumonisin is proven to be an HIV-transmission factor, simple and immediately deployable, practical interventions exist to change the HIV epidemic. Fumonisin is a preharvest contaminant of maize that usually results from insect damage and associated fungal invasion. The use of maize varieties resistant to relevant pests (28) and *Fusarium* (29) and good agronomic management all result in less contamination (30). Fumonisin exposure may also be significantly reduced by steeping (31), because it is water soluble, and by milling technologies (24). With these approaches, it may be possible to reduce the transmission frequency of HIV in SSA to levels comparable with those in developed countries.

We thank Katherine Waters, Bethany Piersol, and Katherine Johnston for their constructive comments and suggestions during the preparation of this manuscript.

The authors' responsibilities were as follows—JHW: was the lead on this manuscript; JAG and JWD: were responsible for data assembly and assisted with the statistical analysis; and J-SW, PEJ, N-AA, WOE, EA-G, NMJ, AGR, and TDP: participated in the manuscript development and revisions to bring a wide range of geographic and disciplinary understanding needed for this research. The authors had no conflicts of interest related to the publication of these results.

REFERENCES

- Moses S, Bradley J, Nagelkerke NJD, Ronald AR, Ndinya-Achola JO, Plummer FA. Geographical patterns of male circumcision practices in Africa: association with HIV seroprevalence. *Int J Epidemiol* 1990;19:693–7.
- Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;75:3–17.
- Gray PB. HIV and Islam: is HIV prevalence lower among Muslims? *Soc Sci Med* 2004;58:1751–6.
- Morris M, Kretzschmar M. Concurrent partnerships and the spread of HIV. *AIDS* 1997;11:641–8.
- Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007;369:643–56.
- Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004;351:23–32.
- Jiang Y, Jolly PE, Ellis WO, Wang J-S, Phillips TD, Williams JH. Aflatoxin B1 albumin adduct levels and cellular immune status in Ghanaians. *Int Immunol* 2005;17:807–14.
- Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences and interventions. *Am J Clin Nutr* 2004;80:1106–22.
- Jiang Y, Jolly PE, Preko P, et al. Aflatoxin-related immune dysfunction in health and in human immunodeficiency virus disease. *Clin Dev Immunol* 2008;2008:790309.
- Marasas WFO. Discovery and occurrence of the fumonisins: a historical perspective. *Environ Health Perspect* 2001;109(suppl):239–43.
- Kpodo KA, Bankole SA. Mycotoxin contamination in foods in West and Central Africa. In: Leslie JF, Bandyopadhyay R, Visconti A, eds. *Mycotoxins: detection methods, management, public health and agricultural trade*. Wallingford, United Kingdom: CAB International, 2008:103–16.
- Enongene EN, Sharma RP, Bhandari N, et al. Persistence and reversibility of the elevation in free sphingoid bases induced by fumonisin inhibition of ceramide synthase. *Toxicol Sci* 2002;67:173–81.
- Perry DK, Hannun YA. The role of ceramide in cell signaling. *Biochim Biophys Acta* 1998;1436:233–43.
- Brügger B, Glass BR, Haberkant P, Leibrecht I, Wieland FT, Kräusslich H-G. The HIV lipidome: a raft with an unusual composition. *Proc Natl Acad Sci USA* 2006;103:2641–6.
- Oswald IP, Desautels C, Laffitte J, et al. Mycotoxin fumonisin B1 increases intestinal colonization by pathogenic *Escherichia coli* in pigs. *Appl Environ Microbiol* 2003;69:5870–4.
- Gelderblom WC, Marasas WF, Lebepe-Mazur S, Swanevelder S, Vessey CJ, Hall PL. Interaction of fumonisin B(1) and aflatoxin B(1) in a short-term carcinogenesis model in rat liver. *Toxicology* 2002;171:161–73.
- Speijers GJA, Speijers MHM. Combined toxic effects of mycotoxins. *Toxicol Lett* 2004;153:91–8.
- Bandyopadhyay R, Kumar M, Leslie JF. Relative severity of aflatoxin contamination of cereal crops in West Africa. *Food Add Contam: Part A* 2007;24:1109–14.
- Henry SH, Bosch F, Bowers J. Aflatoxin, hepatitis and worldwide liver cancer risks. *Adv Exp Med Biol* 2002;504:229–33.
- Todd J, Glynn JR, Marston M, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. *AIDS* 2007;21:S55–63.
- CIA. The world factbook. 2008. Available from: [https://www.cia.gov/library/publications/the-world-factbook/\(cited 12 February 2009\)](https://www.cia.gov/library/publications/the-world-factbook/(cited 12 February 2009)).
- Food and Agriculture Organization. FAOSTAT. 2008. Rome, Italy: United Nations Food and Agriculture Organization, 2008. Available from: <http://faostat.fao.org/site/609/default.aspx#ancor/> (cited 9 July 2009).
- World Health Organization Statistical Information System. Causes of death (2008). Geneva, Switzerland: World Health Organization, 2009.
- Castells M, Marín S, Sanchis V, Ramos AJ. Distribution of fumonisins and aflatoxins in corn fractions during industrial cornflake processing. *Int J Food Microbiol* 2008;123:81–7.
- Bouhet S, Hourcade E, Loiseau N, et al. The mycotoxin fumonisin B1 alters the proliferation and the barrier function of porcine intestinal epithelial cells. *Toxicol Sci* 2004;77:165–71.
- Merrill AH Jr, Sullards MC, Wang E, Voss KA, Riley RT. Sphingolipid metabolism: roles in signal transduction and disruption by fumonisins. *Environ Health Perspect* 2001;109:283–9.
- WHO/UNAIDS. Global HIV prevalence has levelled off; AIDS is among the leading causes of death globally and remains the primary cause of death in Africa. Geneva, Switzerland: UNAIDS, 2007.
- Munkvold GP, Hellmich RL, Rice LG. Comparison of fumonisin concentrations in kernels of transgenic Bt maize hybrids and nontransgenic hybrids. *Plant Dis* 1999;83:130–8.
- Duvick J. Prospects for reducing fumonisin contamination of maize through genetic modification. *Environ Health Perspect* 2001;109(suppl 2):337–42.
- Blandino M, Reyneri A, Colombari G, Pietri A. Comparison of integrated field programmes for the reduction of fumonisin contamination in maize kernels. *Field Crops Res* 2009;111:284–9.
- Bullerman LB, Ryu D, Jackson LS. Stability of fumonisins in food processing. *Adv Exp Med Biol* 2002;504:195–204.