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Pesticide in the Mississippi River floodplain and its possible linkage to colon cancer risk in the US

Hongbing Sun

GEMS Department, Health Studies Institute, Rider University, Lawrenceville, NJ, USA

ABSTRACT
Result of this study shows that elevated colorectal cancer risk in Mississippi River floodplain of the United States is likely linked to historically high pesticide application. Mississippi River basin produces about 80% of major US crops and has about two-thirds of US pesticides used for agriculture. Historically, heavy pesticide application and agricultural irrigation were reported to result in high pesticide residues in surface water, fish and wells of Mississippi embayment. Risk ratio of colorectal cancer incidence in 86 counties of Mississippi River floodplain was about 29% higher than that of other counties in the 48 contiguous states. Risk ratio of colon cancer mortality in 63 counties of Mississippi embayment was 33% higher than that of other counties in the 48 states between 1999 and 2016. Risk ratios of colorectal cancer incidence and colon cancer mortality in Mississippi River floodplain are higher after smoking and diabetes factors were filtered off. Previous studies have linked exposure to pesticide with type-II diabetes and the latter was linked to increasing colon cancer risk by about 27%. Result here suggests that pesticide may be an independent risk factor directly associated with elevated colon cancer risk in Mississippi River floodplain.

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Mississippi River floodplain; pesticide application; irrigation; environmental toxin; colon cancer

1. Introduction

Mississippi River (MSR) floodplain in this paper refers to the flat alluvial regions in the MSR basin (Figure 1(a)), and Mississippi embayment (ME) to the main section of the MSR floodplain north of the Mississippi River delta (Figure 1(b)). It has been known that there is a high colorectal cancer (CC) prevalence in the MSR region (ACS 2018; Lansdorp-Vogellar et al. 2015). About 80% of the US corn and soybeans, and much of the cotton, rice, sorghum and wheat are produced in the MSR basin (area outlined by the MSR basin line in Figure 2(f, e) of later section) because of the suitable climate and soil conditions (Goolsby & Pereira 1995). It

CONTACT Hongbing Sun hsun@rider.edu 2083 Lawrenceville Road, Lawrenceville, New Jersey, 08648, USA

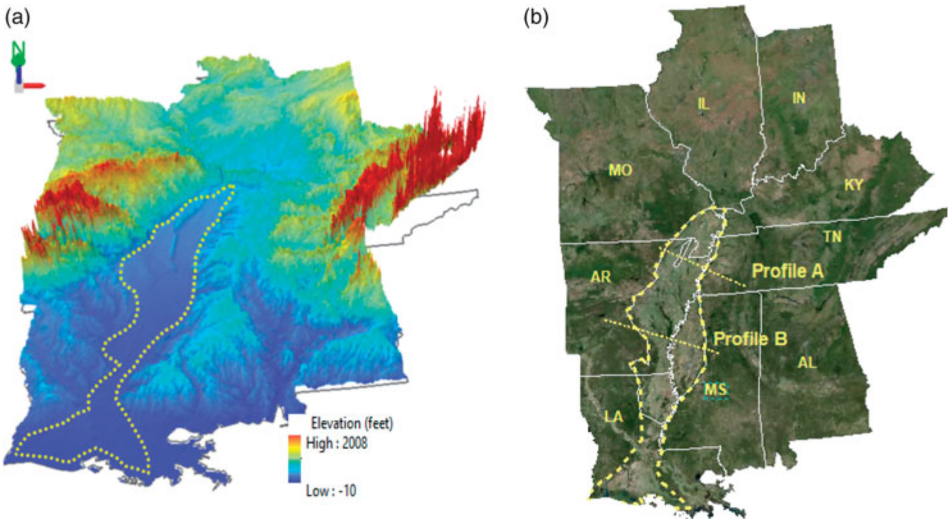

Figure 1. (a) elevation (vertically exaggerated) and (b) satellite maps showing the regional landscape patterns of the Mississippi River (MSR) floodplain (dash line) and Mississippi embayment (ME) alluvial region (north part of the MSR floodplain before the delta, cutting off by white solid lines between LA and MS) and locations of two cross-section profile lines. Note the flat landscape in the MSR floodplain.

was estimated that about two-thirds of all pesticides used for agriculture in the United States were applied to crop and pasture lands in the MSR Basin. The ME region is the most irrigated and change insecticide to pesticide demanding agricultural region in the MSR basin. Historically high agricultural pesticide application in the MSR floodplain created long-lasting soil and water pollution in the region (Garbarino et al. 1995; Gilliom 2007; Goolsby and Pereira 1996). Many studies have examined the possible linkage between cancers and exposure to pesticide in farm workers and their families (Guyton et al. 2015; Lee et al. 2007; Samsel and Seneff 2013). Exposure to pesticide has been linked to increased type II diabetes and the latter has been linked to increased CC risk (Evangelou et al. 2016; Everett and Matheson 2018; Park et al. 2019; Peeters et al. 2015). Though progresses have been made, association of pesticides with elevated CC risk of the MSR region has not been well studied, particularly in the ME region of the MSR flood plain where water irrigation and agricultural insecticide demand have been historically high (Gianessi & Puffer 1991).

Colorectal cancer (CRC) is the second deadliest cancer worldwide (2017's data) and the third deadliest cancer in the United States in 2016 (CCS 2018; ACS 2018). There was an annual average of 44,089 deaths for CC, and 6562 deaths for rectal cancer (RC) between 1999 and 2016 in the United States alone based upon the database of the US Centers for Disease Control and Prevention (CDC, https://wonder.cdc.gov). Only up

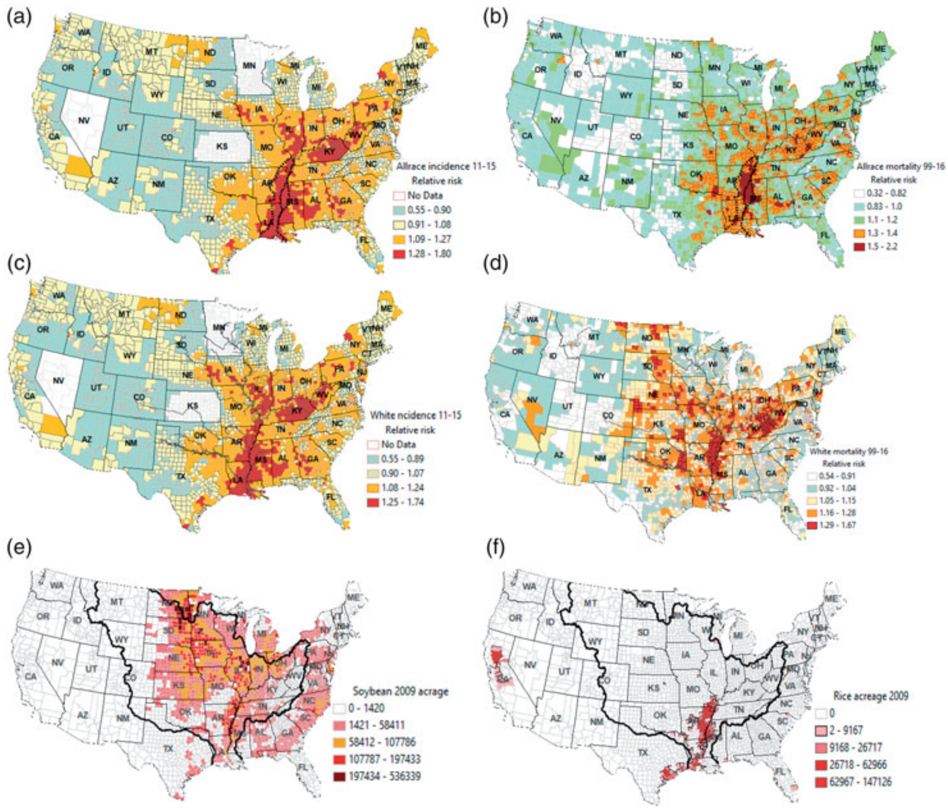

Figure 2. (a)–(d) Spatial patterns of CRC incidence (2011-2015), CC mortality (1999-2016) relative risk, (e) soybean and (f) rice acreage in 2009 in the 48 US states. MSR flood plain is outlined by dash line in a) and Mississippi embayment (ME) region is outlined by solid line in (b). They are the same lines shown in satellite map in Figure 1. Thick zigzag lines in (e) and (f) show the boundary of the MSR basin. Main stream branches of the MSR are shown in (c) and (d).

to 20% of the CRC cases were reported to have a familial basis and the majority of the CRC cases were reported to be linked to broad environmental causes, including risky behaviors and environmental factors (Freeman et al. 2011; Haggar and Boushey 2009; Johnson et al. 2013). Therefore, there is a strong case for linking CC occurrence to potential environmental risk factors in the United States.

According to 2010's US census survey, about 59% of the total population and roughly 50% of the population aged 55 and older resided in the states they were born in the United States (Ping 2011). Percentages of the long-term residence are even higher in the MSR region; 79% of Louisianans, 72% of Mississippians, 61% of Arkansans, 66% of Missourians and 67% of Illinoisans never moved out of the states they were born (Ping 2011). Long-term residence in the MSR region allows a relatively reliable statistical analysis of the possible association between spatial patterns of CC risks of the population and potential environmental risk factors (Das, Kalita, & Pal 2017; Lansdorp-Vogellar et al. 2015).

This study will examine the crop patterns (as proxy of various pesticide application), hydrological setting, concentrations of pesticides and chemicals of past measurements in water and fish tissues and their spatial relations to CC and CRC risk patterns in the MSR floodplain and other parts of the 48 contiguous US states. This is the first study in which geography of CC risk and hydro-agricultural pesticide use and other environmental toxins are analyzed together. The result of this study will help identify the possible environmental risk factors related to the development of CC and the possible remedial measures that can be taken to reduce CC risk in the MSR floodplain. Because the MSR floodplain is also the region with high total cancer mortality rates based upon the US CDC data (http://wonder.cdc.gov), preliminary results of this study may have implications for future studies of other cancers in the MSR floodplain as well.

2. Materials and methods

2.1. Data

Pesticide data of urine and serum samples of the US population were obtained from the National Health and Nutrition Examination Survey (NHANES)'s pesticide database. 2,4- Dichlorophenol (2,4-DCP, metabolite of 2,4-dichlorophenoxyacetic acid and other chlorophenols) residues in urinary samples of 13,161 people between 2003 and 2012 were selected as representative of common pesticides because of its relatively long data record. p,p′-DDE (metabolite of DDT- dichlorodiphenyltrichloroethane) in serum of 3684 people between 2003 and 2014 were obtained to analyze the persistence of some insecticides in people.

Crop acreages of corn, soybean, rice and upland cotton (as proxies of various pesticide applications) of individual counties in the 48 contiguous US states between 2007 and 2017 were obtained from the US Department of Agriculture Farm Service Agency (USDA FSA) that collected data from farm producers who participated in the program (USDA FSA 2018). Geographical patterns of historical crop acreage between 1850 and 2016 were obtained from Yu and Lu (2018) that were based on historical inventories and high-resolution satellite images of multiple sources. Pesticide residues in untreated and treated water were obtained from the Pesticide Data Program of USDA (USDA-PDP 2018). Trend data of pesticide use in the US crops between 1960 and 2008 were obtained from a report of the US Geological Survey (USGS) by Fernandez-Cornejo et al. (2014). A 100-meter resolution digital elevation model (DEM) of the 48 contiguous US states was obtained from the USGS map data website (USGS National map 2018). Pesticide measurement data in water and fish tissues and arsenic (As) concentrations in well waters of the ME alluvial regions were obtained from two USGS reports by Kingsbury et al. (2014) and Kleiss et al. (2000). Concentrations of arsenic in the top 5 cm of soil from 4844 sites in the 48 US states were obtained from a USGS report by Smith et al. (2014). US irrigation maps in 2002, 2007 and 2012 were obtained from the USGS irrigation map data site (USGS irrigation 2018).

Age adjusted incidence rates of CRC at county level between 2011 and 2015 were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute (SEER 2018). Age adjusted mortality rates of CC as the underlying causes of death between 1999 and 2016 were obtained from the CDC's database (CDC Wonder 2019). Mortality rates in the CDC's database were from death certificates of the US residents and each death certificate identifies a single underlying cause of death and demographic data. Long-term trend data of CC incidence and CRC mortality rates between 1960 and 2015 were also obtained from SEER. Whether statistics of colon cancer (CC) and rectal cancer (RC) were discussed separately or together as colorectal cancer (CRC) depends on how the source data were given in the CDC or SEER's database. All rates from the CDC database were adjusted to the US standard population of 2000. Given that incidence rate of RC is only about 0.44 times of CC rates (ACS, 2018) and mortality rates of RC is only about 0.15 times of CC rates in the 48 US states between 1999 and 2016, environmental causes identified in this study may reflect more of CC cause than RC cause when they were reported as CRC. Age adjusted percentages of adults reported 'smoke everyday' in the United States between 1996 and 2013 surveyed by the Behavioral Risk Factor Surveillance System (BRFSS) of all races were obtained from the CDC database as well. A person reported 'smoke everyday' was defined as the person who, at the time they participated in the survey, reported smoking every day. Diagnosed Diabetes Prevalence between 2004 and 2013 were obtained from CDC's Diabetes County Level Indicator for all counties in the 48 states. A person has diagnosed diabetes when he or she reported ever being told by a health professional that he or she had diabetes (types 1 and 2 diabetes were reported as one measure) in NHANES survey.

2.2. Statistical methods

2.2.1. Spatial analyses of crop-pesticide, CRC and CC risk, soil-water arsenic, smoking and diabetes distributions in the MSR floodplain

A 100-meter resolution DEM map of 8 states surrounding the MSR floodplain was plotted using ArcGIS (version 10.4, ESRI software. It was used for all spatial plots in this paper). DEM map illustrates elevation of the area surrounding the MSR floodplain and easiness of soil water drainage in the MSR floodplain. Soils in low elevation area have poor water drainage and a likely reducing (anoxic) condition that favors a relatively slower decomposition and longer retention of pesticide than soils in high elevation area (Tiryaki & Temur 2010). Relative concentrations of pesticides in water and fish tissues and arsenic level of well waters in the ME region modified from Kleiss et al. (2000) were presented for spatial comparison. Two elevation profiles across the MSR floodplain were plotted to illustrate correlations between the elevation change and CC risk in the floodplain. Flat low elevation area of the MSR floodplain tends to have higher CC risks that will be discussed later.

Relative risks of age-adjusted CRC incidence between 2011 and 2015 and age-adjusted CC mortality rates between 1999 and 2016 of 3110 counties or county equivalents in the 48 contiguous US states were calculated using the R software based web program 'SpatialEPiApp' by Moraga (2017). 'SpatialEPiApp' uses the Bayesian disease mapping model that incorporates the integrated Nested Laplace Approximation (INLA) approach as a computationally efficient alternative of Markov Chain Monte Carlo methods in the calculation of relative risk (Besag, York, & Mollié 1991; Moraga 2017). Improvement of a risk map over the traditional choropleth map is that weights of neighboring counties' values are considered. This risk map method has been used in production of disease atlas in other regions (Hansell et al. 2014).

Choropleth maps of county level smoking, diabetes, acreages of the US main crops including corn, soybean, upland cotton and rice and water irrigation level between 2002 and 2016 as indicators of pesticide application and water interaction were analyzed. Spatial patterns of historical crop acreage at county level between 1850 and 2016 from Yu and Lu (2018) were examined for historical changes.

2.2.2. Risk ratio (RR)

Risk ratios (RRs) of CRC incidence and CC mortality rate and their 95% confidence intervals (95%CI) were calculated between the 86 counties in the MSR floodplain (area outlined by the dash line on the satellite map of Figures 1 and 2(a)) and other counties in the 48 contiguous US states. RRs of CRC incidence and CC mortality risks were calculated between 63 counties in the Mississippi embayment (ME) of the MSR floodplain and other counties in 48 contiguous US states. In addition, RRs for CC mortality rates between 36 counties in the Holocene alluvium region (southeastern part of the ME, depicted in Figure 4 of a later section) and the rest of the 48 states were calculated as well. SEER*STAT software (http://seer.cancer.gov/seerstat/) from SEER of US National Cancer Institute, was used to calculate the RRs. Calculation of RR in SEER*STAT used the Fay-Tiwari's method which assumes Poisson independent rates and has been used in many previous studies (Fay 1999; Zhu, Pickle, and Pearson 2016). Regression trends of smoking (averaged between 1999 and 2012) and diabetes prevalence (averaged between 2004 and 2013) and risk levels of CRC incidence and CC mortality rates (averaged between 1999 and 2016) were used to filter off smoking and diabetes factors in the RR calculation of CRC incidence and CC mortality between ME region, MSR floodplain and rest of the 48 contiguous states.

3. Results

3.1. Higher CRC incidence and CC mortality risks in the MSR floodplain

RR of CRC incidences of 86 counties in the MSR floodplain to that of other counties in 48 contiguous states (area depicted in Figures 1, 2(a)) is 1.29

Table 1. Risk ratios (RR) of CRC Incidence and CC mortality of counties in the Mississippi River region to that of other counties in the 48 contiguous US states.

	Risk Ratios (RR)	low 95% RR	Upper 95% RR
CRC Incidence-Mississippi River floodplain			
All races, sexes	1.29	1.26	1.33
white, all sexes	1.22	1.17	1.29
all races, male	1.29	1.23	1.34
all races, female	1.22	1.17	1.27
CRC Incidence-Mississippi embayment area			
All races, sexes	1.26	1.22	1.31
white, all sexes	1.22	1.2	1.24
all races, male	1.23	1.18	1.31
all races, female	1.17	1.1	1.23
CC Mortality-Mississippi embayment area			
All races, sexes	1.33	1.3	1.37
white, all sexes	1.21	1.16	1.25
all races, male	1.38	1.33	1.43
all races, female	1.28	1.23	1.33
CC Mortality-Holocene alluvial area			
All races, sexes	1.43	1.39	1.47
white, all sexes	1.16	1.11	1.21
all races, male	1.50	1.44	1.56
all races, female	1.43	1.37	1.49
Smoking filtered CRC incidence and CC mortality, **Mississippi embayment (ME) and Mississippi River floodplain (MSR)**			
All races, sexes-CRC-MSR	1.38	1.36	1.40
All races, sexes-CRC-ME	1.31	1.29	1.34
All races, sexes-CC-MSR	1.46	1.42	1.56
All races, sexes-CC-ME	1.61	1.56	1.66
Diabetes filtered CRC incidence and CC mortality, **Mississippi embayment (ME) and Mississippi River floodplain (MSR)**			
All races, sexes-CRC-MSR	1.32	1.30	1.34
All races, sexes-CRC-ME	1.26	1.24	1.28
All races, sexes-CC-MSR	1.36	1.34	1.38
All races, sexes-CC-ME	1.45	1.42	1.47

For the risk ratio calculation, counties in the Mississippi River floodplain or Mississippi embayment area or Holocene alluvial area were considered as "exposed area" while counties outside these areas were considered "non-exposed areas" (see Figures 1, 2 and 4 for geographical location).

(95% CI: 1.26–1.33, Table 1). RR of CC mortality rates of the 63 counties in the ME alluvial region of the MSR floodplain (area depicted in Figures 1, 2(b), 3(b)) to that of other counties in the 48 contiguous states is 1.33 (95% CI: 1.30–1.37, Table 1). RR of CC mortality rates of the 36 counties in the Holocene alluvial area of the ME region (area depicted in Figure 4) to that of other counties in the 48 states is 1.43 (95% CI: 1.39–1.47). RR value larger than 1 indicates a significant risk. RRs of both incidence and mortality are generally higher for male than for female and lower for white. Counties with higher CRC incidence risks are largely confined to the MSR floodplain except for states with high smoking rates (Kentucky-KY and West Virginia-WV) and high diabetes prevalence (Mississippi-MS and Alabama-AL) (Figures 2 and 3). High RRs of CC mortality rates are clustered around the ME alluvial region, particularly in the Holocene alluvial region between Arkansas (AR) and Mississippi (MS) states. High CC risk of the ME region coincides with the region of high water irrigation-rice acreage and the region of high upland cotton acreage that demands high insecticide application (Figures 2, 3 and 5). CC risks in the ME region are still significantly higher than the US national average when only white population was considered (Figures 2 (c,d) and Table 1).

County-level Pearson correlations between smoking rates and CRC incidence, CC mortality risks are $r = 0.55$ and 0.57 with both significance levels $p = .00$; correlations between diabetes prevalence and CRC incidence, CC mortality risks are $r = 0.57$ and 0.54, respectively, with both

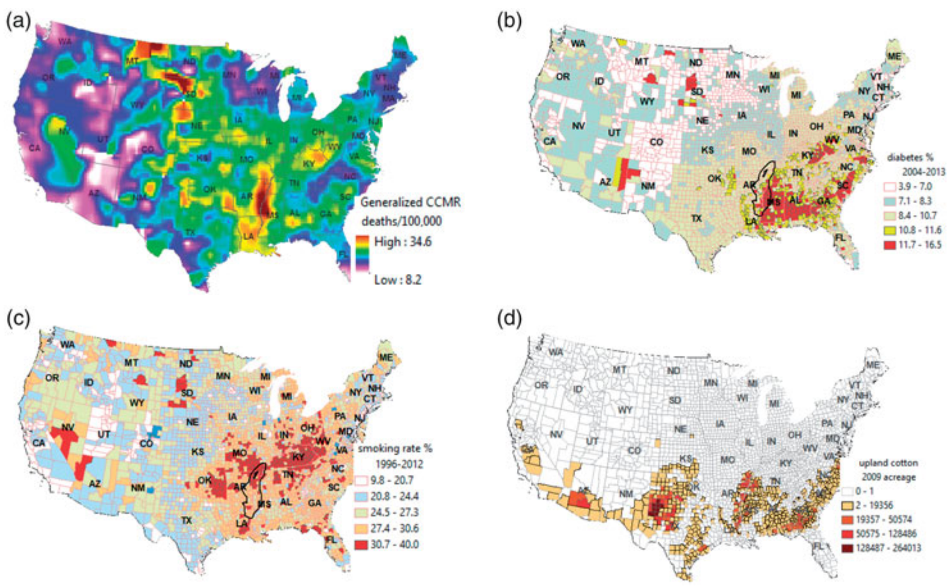

Figure 3. (a) isopleth map of generalized colon cancer mortality rates (CCMR, 3 cell average), and choropleth maps of (b) diabetes prevalences, (c) smoking prevalences and (d) upland cotton acreage in the 48 contiguous US states.

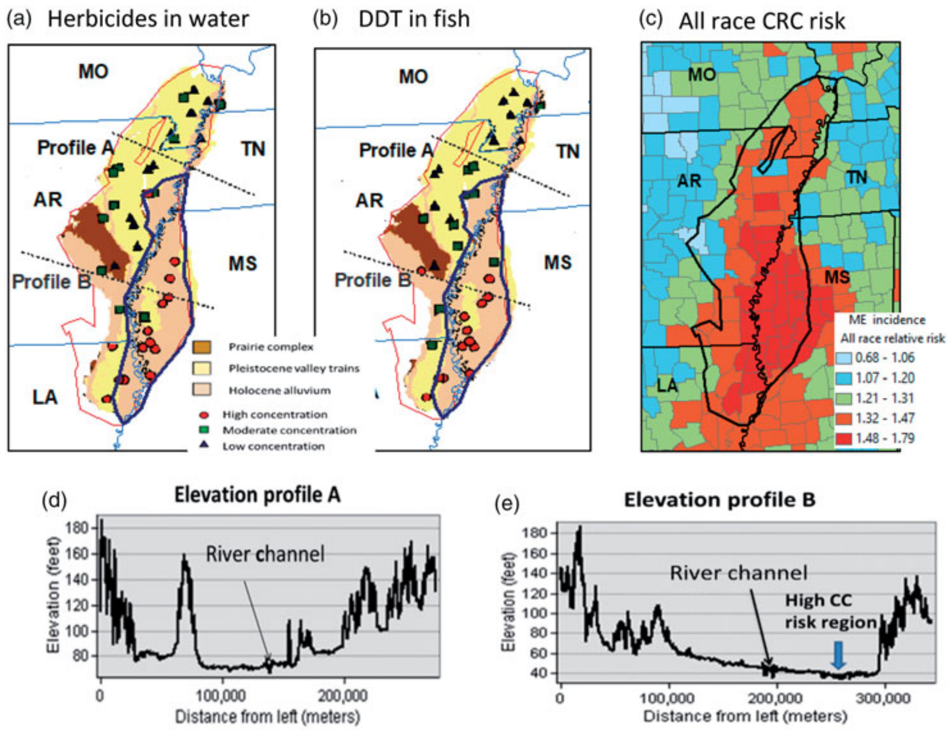

Figure 4. (a) Herbicide detections in water; (b) DDT in fish tissue in the Mississippi embayment (ME) between 1997–1998 (Modified from Kleiss et al. 2000); (c) zoomed in high CC incidence risk around the ME between AR and MS; (d) and (e) elevation profiles crossing the MSR flood plain. Holocene alluvium region is indicated by color legend in (a) and (b).

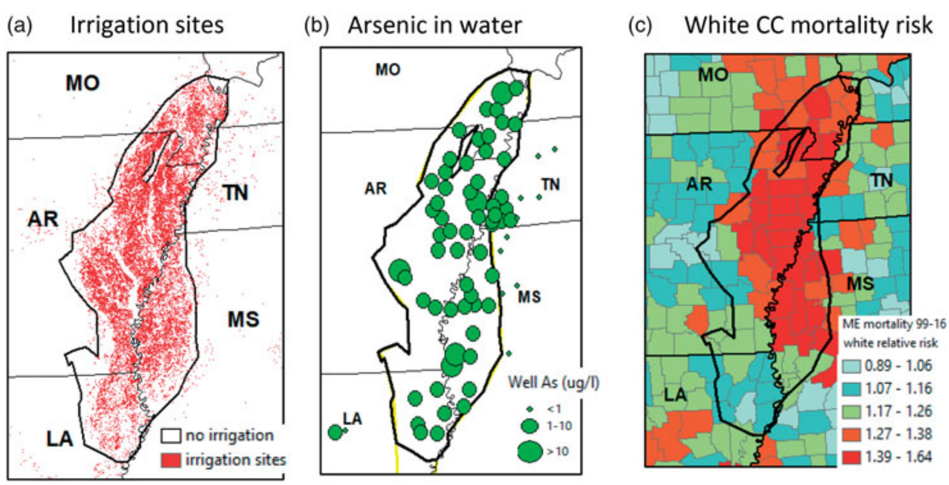

Figure 5. (a) agricultural irrigation sites in the Mississippi River Basin (2012, data from USGS Irrigation, 2018); (b) higher arsenic concentrations measured in well water in the ME region (Data from Kingsbury et al. 2014); (c) zoomed in mortality risk map of white population in ME region.

$p = .00$. They imply that roughly 30% ($R^2 \approx 0.3$) of spatial variations of CRC and CC risks in the 48 states may be explained by either smoking or diabetes prevalence.

RRs of county level CRC incidence in the ME region and MSR floodplain are 1.31 (95% CI: 1.29–1.34) and 1.38 (95% CI 1.36–1.40) for smoking filtered data and 1.26 (95% CI: 1.24–1.28) and 1.32 (95% CI: 1.30–1.34) for the diabetes filtered data respectively. RRs of county level CC mortality rates in the ME region and the MSR floodplain are 1.61 (95% CI: 1.55–1.66) and 1.46 (95% CI: 1.42–1.50) for smoking filtered data and 1.45 (95% CI: 1.42–1.47) and 1.36 (95% CI: 1.34–1.38) for diabetes-filtered data, respectively. RRs of CC mortality risk are higher than RRs of CRC incidence risk in the ME region.

3.2. High crop acreages, higher pesticide residues in water and fish tissues and higher arsenic in soil and well water in the MSR floodplain

About 24% of upland cotton and 10% of soybeans were concentrated in the ME region of the MSR floodplain, and about 70% of rice crop was concentrated in the strip of the MSR floodplain (58% in ME region) between 2010 and 2014 based on estimation of the USDA National Agriculture Statistical Service (USDA-OCE 2018). Annual individual crop distribution between 2007 and 2017 varied slightly from these estimations (USDA-FSA 2018). Spatial patterns of the overall historical crop acreages between 1850 and 2016 from Yu and Lu (2018) were similar to that of recent years with high crop acreages in the MSR floodplain. However, crop types cannot be deciphered for these historical data.

Pesticides in stream water were generally higher in the MSR basin than in streams of other parts of the country (Goolsby & Pereiraa 1996; Gilliom 2007). Concentrations of herbicides in water and DDT concentration in fish tissues were particularly higher in the Holocene alluvial deposit than in the Pleistocene valley train regions (Kleiss et al. 2000) (Figure 4). A more recent study by USGS also reported that shallow groundwater in alluvial region of the MSR floodplain is more vulnerable to surficial water contamination (Kingsbury et al. 2014). They reported that total concentration of pesticides was the highest in groundwater less than 20 years old underlying the Memphis area (lower left corner of Tennessee).

Previous USGS survey data between 1998 and 2004 indicated that arsenic concentrations in groundwater greater than EPA's maximum contamination level (MCL) are primarily in the ME alluvial regions (Figure 5) (Kingsbury et al. 2014; Tollett et al. 2003). Approximately 60% of the wells have arsenic levels above the 1/10 of the EPA recommended arsenic level (10 ug/l) (Kingsbury et al. 2014). Arsenic level in the top 5 cm of soil of this area is also relatively higher than other areas in the MSR floodplain (Data from Smith et al. 2014). The ME alluvial region is the region with intensive agricultural irrigation and where most of the rice crop was concentrated (Figures 2(f) and 5(a)). Long grain rice in the United States (most are produced in the ME region) was reported to have high mean arsenic level at 0.26 μg As g^{-1} (comparing to average arsenic level of Bangladeshi rice at 0.13 μg As g^{-1}) by Williams et al. (2005).

3.3. Prevalence of pesticides in urine and serum samples, and trends of pesticide application and CC incidence in the United States

Because geographically related pesticide data on people are not available, the US national representative data were analyzed. 2,4-DCP (2,4-D metabolite) residues were detected in 87% of the total urinary samples among 13,161 people based upon NHANES data between 2003 and 2014. The levels were generally higher in women than in men. Lipid adjusted p,p′-DDE (DDT metabolite) was found in 89.5% of the 3,684 serum samples (1781 men and 1903 women) examined in NHANES studies between 2003 and 2014. There were apparent age dependent increases in concentrations of p,p'-DDE and the concentrations were higher in aged women than in men (Figure 6(a)).

There is roughly a 15-year gap between peaks of US insecticide applications (peaked around 1970) and CC incidence (peaked around 1985) (Figure 6(b)). Decline of herbicide application in the US started in 1980, but this trend might have been reversed in more recent years.

4. Discussion

4.1. High CRC- CC risk and pesticide residues in the MSR floodplain

Area of high CRC incidence risk in the MSR region roughly follows the waterways in the MSR floodplain except for the two states (KY and WV) with high smoking rates and the two states (MS and AL) with high diabetes prevalence (Figures 1 and 2). This is also apparent in the white population only plots. There is a progressive increase of CC risks with decreasing distance to the MSR floodplain, ME region and the Holocene alluvial part of the MSR floodplain in the 48 states (Figures 2, 3 and 4). RR values of 1.29 (95% CI, 1.26–1.33) for CRC incidence and 1.33 (95% CI, 1.3-1.31) for CC mortality in the MSR region to the rest of the 48 states indicate the significant CRC and CC risks in the MSR floodplain, particularly the Holocene alluvial area of the floodplain (Figures 4 and 5, Table 1). Though diabetes filtered RRs of CRC incidence and CC

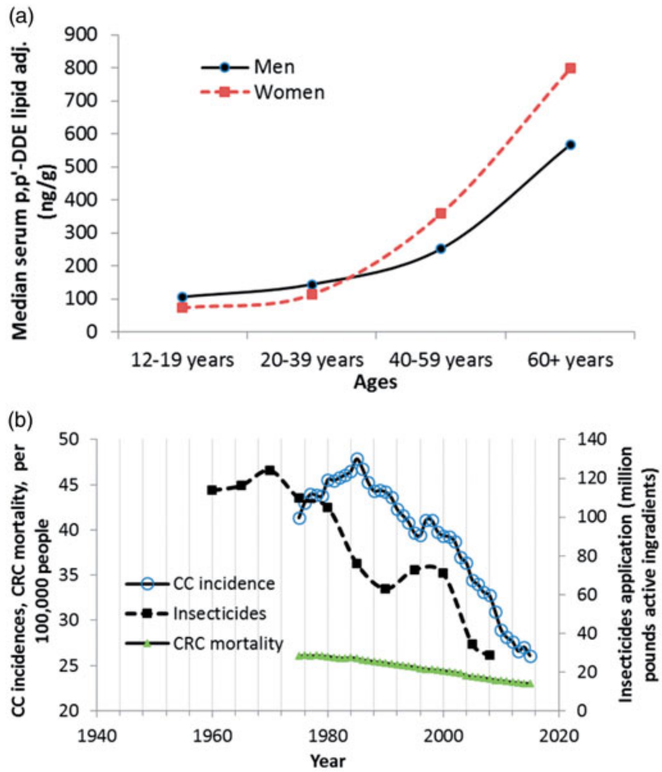

Figure 6. (a) concentrations of p,p′-DDE, a metabolite of DDT between 2003 and 2014 in serum samples of 1781 men and 1903 women vs. age; (b) trend of insecticide application vs. trends of CC incidence and CRC mortality rates in United States.

mortality are only slightly higher than their pre-filtered levels, smoking filtered RRs of CRC incidence and CC mortality rates are significantly higher than their corresponding pre-filtered RRs in the ME region and the overall MSR floodplain (Table 1).

With about two-thirds of the US agricultural pesticides applied in the MSR basin, Mississippi River is probably the most pesticide polluted river in the United States (Garbarino et al. 1995; Gianessi and Puffer 1991; Goolsby and Pereira 1996; Tiryaki and Temur 2010). High clay contents in the Holocene alluvium area of the ME region can adsorb more pesticides and extend the duration of pesticides in this area (Kingsbury et al. 2014) (Figure 4). Heavy irrigation and long history of pesticide application result in extensive pesticide pollution in both surface and ground water in the low lying MSR floodplain (Figure 5, Bouman, Castaneda, and Bhuiyan 2002; Castaneda et al. 1996). The particularly high spatial coincidence between high CC risk and high water irrigation of the rice-upland cotton strip (~56% of US rice, ~27% of US upland cotton) in the ME region (Figures 2, 3 and 5) implies a possible association of water pollution-pesticide application with high CC risk.

Previous studies of direct link between pesticide application and colon cancer risk have been inconsistent with some pesticide types showing correlation while others not, largely because of the relatively smaller sample sizes and short duration of the studies (Guyton et al. 2015; Jablonowski, Schäffer, and Burauel 2011; Lee et al. 2007; Samsel and Seneff 2013). However, several epidemiological and experimental studies have reported a strong linkage between type II diabetes and exposure to some pesticides such as organochlorine and organophosphate pesticides (Juntarawijit & Juntarawijit 2018; Lee et al. 2007; Park et al. 2019). Organochlorine and organophosphates have been suspected to affect glucose metabolism by blocking cholinesterase activity, oxidative stress, nitrosative stress, physiological stress, adrenal stimulation, and inhibition of paraoxonase (Evangelou et al. 2016; Juntarawijit and Juntarawijit 2018). Connection between CRC risk and diabetes has also been established. CRC risk was reported to be 27% higher in patients with type II diabetes than in non-diabetic controls (González et al. 2017). The idea is that abnormally high levels of insulin (hyperinsulinemia) and glucose create an environment in the colon that can damage the mucosa, or lining of the colon and promotes the development and growth of CC. The significant correlation ($r = 0.54$, $p = .00$) and striking geographical coincidences between geographical distributions of high CC mortality and diabetes (particularly AL, GA, SC, NC and VA in Figure 3) and regions of upland cotton where there were intensive insecticide applications corroborate this association of pesticide, diabetes and CC risk (Figure 3). However, higher RRs for smoking filtered CC data (RR, 1.61, 95% CI: 1.55–1.66) and diabetes filtered CC data (RR, 1.45, 95% CI: 1.42–1.47) than their corresponding pre-smoking and diabetes filtered RRs also indicate exposure to pesticide being a possible independent CC risk factor.

4.2. Pathways of pesticide to people

Various pesticide metabolites found in high percentage (>80%) of NHANES studies including those from farming states, indicates the rampant exposure of general population to pesticide and persistence of some pesticides in nature and their ability to accumulate in human body (Barr et al. 2005; Jablonowski, Schäffer, and Burauel 2011; Jaga and Dharmani 2003). Even though DDT was discontinued in 1972 in the US, DDT and its metabolite still found ways to accumulate in fish (Figure 4) and in fat tissues of people in NHANES surveyed population (Figure 6).

It is generally agreed that people from agricultural region have higher exposure to pesticides than people from non-agricultural region (Huen et al. 2012; Morgan et al. 2008). There are multiple sources and pathways for people to be exposed to pesticide, including pesticide dust, residues in water and food (Morgan et al. 2008).

Given that both surface and ground water in the MSR flood plain are probably the most pesticide polluted water historically, it is likely that long-term low-dose exposure to pesticide residues in drinking water is one of the most important pathways of pesticide to people. Results from previous studies and analyses of the USDA PDP drinking water project data in this study have shown that many public water treatment facilities are not very effective at removing pesticide residues (Donald et al. 2007; Stackelberg et al. 2007; USDA PDP-DWP 2018). It is reported that individual herbicide removal rates in finished drinking water varied from 16% to 84% (with 6.4 herbicides measured on average) in northern Great Plains (Donald et al. 2007). Though switching from the surface water to groundwater can alleviate levels of pesticide residues in the water supplies, trace amount of pesticide still exists in many water wells (USDA PDP-DWP 2018).

Results of previous epidemiology studies on the association of the highest mortality rates (1950–1989) in the United States for several cancers, including CC with usage of the Mississippi River as a source of potable water in Louisiana support the argument of a possible association between water pollution and CC risk (Cantor 1997; Goitlieb, Carr, and Clarkson 1982; Page 1976).

The second likely pathway of pesticide to people is food consumption. Residues of pesticides are reported in 78% to 85% of fruits, vegetables and grains (USDA 2015, 2016). Cyclic changes of urinary pesticide levels in the same group of people after switching from inorganic to organic food and then from organic to inorganic food in an experiment study indicates that food consumption can be a significant pathway of pesticides to people, and maybe the most significant pathway to people in non-agricultural regions (Lu et al. 2006). Given that up to 80% of the food supplies in the 48 contiguous US states, other than a few coastal states, could be local (within 100 miles of production, Zumkehr and Campbell 2015), exposure to pesticide from consumption of local food supplies can be a major source of exposure for people in the MSR floodplain (Holme et al. 2016).

Exposure to pesticide fume and dust can be an important pathway of pesticide to people in agricultural regions (Morgan et al. 2008). However, whether respiration intake is a valid pathway of pesticide that can affect colon in the general public is not certain and it is evidenced by the inconsistent result of agricultural cohort studies (Lee et al. 2007; Weichenthal, Moase, and Chan 2010). In addition, adsorptions of pesticide fume and dust by people might be similar to adsorption of mercury vapor by people, where lung and kidney have the most accumulation, instead of colon (Asano et al. 2000; Lien et al. 1983; Ye et al. 2013). More studies are needed in this aspect.

4.3. Smoking and water arsenic factors

Previous studies suggested that cigarette smoking is associated with an increasing risk of CRC (Botteri et al. 2008; Cheng et al. 2015; Liang, Chen, and Giovannucci 2009; Marley and Nan 2016). This is consistent with the significant correlations between smoking and higher CRC incidence risk ($r = 0.55$, $p = .00$) and CC mortality rates ($r = 0.57$, $p = .00$) shown in this study (Figure 3). Kentucky and West Virginia have the highest smoking prevalence rates in the United States and they also have higher CRC and CC risks than surrounding states. Increase of RRs for CC after smoking factor being filtered off indicates an independent association of CC risk and pesticide (Table 1).

Another environmental toxin that might facilitate CC risk in the MSR floodplain is the high arsenic level in both soil and water of the Mississippi embayment region (Figure 5, Pillai et al. 2010). High arsenic levels in anoxic soil condition of this region facilitate the release of the bioavailable arsenic to plants and well water (Kingsbury et al. 2014; Kleiss 2000). The release of bioavailable arsenic can be evidenced by the high arsenic level in long-grain rice of the United States at 0.26 μg As g^{-1}, the highest among data from worldwide samples reported by Williams et al. (2005). High arsenic intake was reported to be associated with variety of cancers, including lung, kidney and colon, though arsenic in organic form can be less toxic than in inorganic form (García-Esquinas et al. 2013; Martinez et al. 2011; Smith et al. 1992; Yang et al. 2008). Therefore, possible high arsenic exposure in the ME region can be a concern as well.

5. Limitation and implication of the current study

Other factors that can influence CC risks including prevalence of alcohol consumption, red meat in the diet, lack of dietary fiber, ulcerative colitis and Crohn's disease, radiotherapy for other cancers, gallstones and acromegaly (Haggar & Boushey 2009; Lansdorp-Vogelaar et al. 2015; Marley and Nan 2016; Skrzydlewska et al. 2001). Their influences on geospatial distribution of CC risk in the United States are not clear. In addition, confounding factors such as social economic conditions and comorbidities might affect the spatial distribution of CC risks (Haggar & Boushey 2009). High black population tends to be associated with high CC risk in the ME region. Industrial chemicals along the MSR in Louisiana might also contribute to water pollution (DeRouen et al. 1977; Gottlieb et al. 1981).

Though association of pesticide application and CC risk in the MSR region in this study is preliminary, given that people in the MSR floodplain, particularly the ME region of the MSR floodplain are the group that has the highest likely exposure to pesticide in the United States, results of this study call for further investigation into the association between CC and exposure to pesticide in the MSR region.

Conclusions

The results of this study show that there is a higher CRC risk in the MSR floodplain, particularly in the ME region than in the rest of the 48 contiguous US states possibly because of the historically heavy agricultural pesticide application. CRC incidence risk is about 29% higher in the MSR floodplain than the rest of the 48 contiguous states. CC mortality risk is about 33% higher in the ME region than the rest of the 48 contiguous states. About 80% of the US major crops produced and about two-thirds of all US pesticides applied in agriculture are in the MSR Basin. Historically, high levels of pesticide residues in plants, fish tissues, finished drinking water of public water supplies and private wells indicate a possible long-term low-dose exposure of people to pesticide in this region. Exposure to pesticide from local food consumption is also a likely significant source of pesticide for people. Water logged anoxic condition that favors the mobilization of bioavailable arsenic from soil into water might be a concern for facilitating the progress of CRC in the ME region as well. Geographical correlations among pesticide, diabetes and CC mortality risk are apparent in this study. However, elevated CC risk in the MSR floodplain after smoking and diabetes factors being filtered off indicates that pesticide being an independent risk factor for CC. The 15-year gap between peaks of CC incidence and insecticide application in the US might be an indicator that reduction of insecticide application is one of the main causes for recent decrease of CC incidences in the US.

Disclosure statement

The author declares that there is no conflict of interest regarding the publication of this paper.

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