Association between air cadmium exposure and prostate cancer aggressiveness at diagnosis

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Abstract

Background

There is conflicting evidence of a relationship between cadmium exposure and prostate cancer (PC) mortality in the general population. Since most PCs are indolent and clinically inconsequential, low grade and low stage tumors may mask an association between cadmium exposure and PC mortality.

Methods

We collected patient data from the 2010 – 2014 Surveillance, Epidemiology, and End Results (SEER). Aggressiveness at diagnosis was defined as stage categorized as either metastatic or localized and Gleason grade as high or low. The 2011 National Air Toxics Assessment database provided county-level air cadmium concentrations. We assessed the association between ambient exposure to air cadmium and PC aggressiveness at diagnosis in the US. Odds Ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression comparing the 80 th to 20 th percentile of cadmium exposure and adjusted for age at diagnosis, sociodemographic status, smoking prevalence and overall air quality at the county-level and were stratified by race and degree of urbanization by Rural-Urban Continuum Codes (RUCC). Similar OR and CI were calculated for arsenic and lead since exposure to these metals sometimes coincide with cadmium exposure as well.

Results

The study cohort consisted of 230,540 cases from 493 counties. Higher air cadmium exposure was associated with an increased likelihood of metastatic PC compared to localized PC (OR 1.02, CI 1.01 – 1.03) and higher Gleason grade at diagnosis (OR 1.01, CI 1.00 – 1.02). The strongest associations were observed in nonmetropolitan areas with urban populations of 20,000 to 250,000 (RUCC2 counties): (OR 1.26, CI 1.14 – 1.39) for metastatic vs. localized PC, and (OR 1.36, CI 1.25 – 1.49) for high vs . low grade cases although these results differed somewhat by race. Compared to arsenic and lead, cadmium tended to show stronger associations with PC aggressiveness.

Conclusion

The strongest associations between air cadmium exposure and tumor aggressiveness were found among RUCC 2 counties, areas where 40 million Americans reside. Further studies are necessary to identify air cadmium pollution sources in these communities and to rule out additional confounding factors. Air cadmium exposure in the general population may be a more important factor than previously recognized in prostate cancer progression.

Background

Environmental exposures have been shown to be associated with prostate cancer (PC) incidence. Cadmium, in particular, was suspected to be associated with PC after reported cases among workers exposed to cadmium oxide in a nickel cadmium (Ni-Cd) battery factory in the UK [1]. A later study suggested that higher exposure to cadmium fumes was linked to PC mortality although these results were not statistically significant [2]. Occupationally exposed cohorts are often small, experience high doses of cadmium, and therefore overexposed workers can die due to other complications such as lung cancer [3] and renal failure [4] before they develop PC.

However, considering levels of exposure more relevant to the general population, the relationship between cadmium and PC aggressiveness and progression remains unclear.

It is estimated that an average 60 kg individual in the US consumes roughly 18.6 µg of cadmium daily through the diet [5], although this can vary depending on the population and methods used [6][7]. Factors that affect the amount of cadmium present in crops include use of phosphate fertilizers, nearby sources of contamination, soil pH, and cultivating practices [8]. Smoking is also a major route of cadmium exposure as smokers have been found to have more cadmium deposited in their organs than non-smokers [9]. In rural areas, the ambient air concentration of cadmium is close to 0.1 ng/m^3, and in urban areas this value can vary from 0.1 ng/m^3 to 0.5 ng/m^3, but in industrial areas, these concentrations can be as high as 100 ng/m^3 [10]. The Agency of Toxic Substances & Disease Registry (ATSDR) states that the amount of cadmium inhaled in the air is negligible except near cadmium-emitting facilities which include smelters, mines, waste incinerators, coal and fossil fuel combustion plants and various manufacturing facilities [11].

Assuming most individuals inhale approximately 10 cubic meters of air per day, the amount of cadmium absorbed through the air could be a substantial amount of daily cadmium intake near cadmium-emitting facilities. Up to 50% of inhaled cadmium can be absorbed directly into the blood [12] compared to a gastrointestinal absorption rate of approximately 5% for dietary cadmium [13]. In addition, the concentration of cadmium compounds in ambient air affects the amount of cadmium that can deposit in the soil, water, and in-house dust leading to other routes of exposure [14].

For the purposes of this study, PC aggressiveness was defined in the form of stage and grade.

Stage and Gleason grade at diagnosis are the strongest predictors of PC mortality. In cases from 2008 to 2014, PC had a 5-year survival rate of 98% for all stages combined. However, metastatic PC had a 5-year survival rate of 30% [15]. Gleason tumor grade scoring system is used by pathologists to evaluate how much the cells in the cancerous tissue still resemble normal prostate tissue under the microscope. The total Gleason score can vary from 2 to 10 and inversely correlates with survival rates. In one study, patients with a total Gleason score of ≤ 6 had a 10-year survival rate of 98.4% while those with total Gleason scores of $8 \geq$ had a 10-year survival rate of 69.9% [16].

Prior population studies have primarily focused on dietary cadmium intake and PC incidence and mortality. However initially, the focus was on cohorts that were occupationally exposed to cadmium by inhaling it in factories. We therefore aim to study the relationship between air cadmium exposure and PC stage and grade at diagnosis in an ecologic manner using a large representative population-based sample of PCs in the entire United States.

Methods

Outcome data

Clinical and pathological data was collected from the Surveillance, Epidemiology, and End Results (SEER) for reported PC cases diagnosed from 2010 to 2014 [17]. PC stage at diagnosis was categorized as either metastatic or localized using TNM staging. Tumor grade was categorized 6 and below (low grade) and 8 and greater (high grade). When comparing high grade *vs.* low grade cases, Gleason scores of 7 were excluded as they denote an

intermediate score. SEER recorded the county of residence of these PC patients as well. The county of residence is used for linking exposure data.

Exposure data

Air cadmium exposure data was collected from the 2011 National Air Toxics Assessment (NATA) which was developed by the Environmental Protection Agency (EPA) to estimate concentrations of air toxics in the United States [18]. Since arsenic and lead are known causal agents of PC [19][20] and individuals that are exposed to cadmium in the air often are simultaneously exposed to arsenic and lead, we retrieved airborne lead and arsenic exposure data from NATA as we considered these metals covariates. At various point emission sources, cadmium, lead and arsenic particulate matter were collected on high quality filter paper as part of the 2011 National Emissions Inventory. Metals were dissolved in hot acid for extraction and were analyzed using inductively coupled plasma/mass spectrometry [21][22]. The total exposure concentration of cadmium compounds in the air was a county-level metric calculated by the EPA through models using weighted averages of air cadmium concentration levels measured at these various point emission sources. In this study, we utilized quintiles of cadmium exposure concentration for ease of interpretation. QGIS open source software was used to construct a map of the US to display air cadmium exposure concentration by quintile at the county-level to visualize regions in the US that have higher amounts of air cadmium than others (Fig. 1).

Covariates

Indices for overall air quality and sociodemographic status at the county-level were obtained from the EPA [23]. These indices represent two domains of five that are part of the Environmental Quality Index (EQI) which encapsulates many environmental factors into a single score. The air quality index assesses the concentrations of hazardous air contaminants. Likewise, the index for sociodemographic status considers education levels, socioeconomics, and reports of violent crime at the county-level. Since preliminary analyses found that worse environment quality scores are associated with increased risk of a PC case of being metastatic compared to localized, we adjusted for county-level EQI scores for sociodemographic status and air quality in our logistic regression models.

Air cadmium concentrations are included in the computation of the air domain index score. To address potential collinearity, we calculated models without and with the EQI air domain score for comparison. Since lead and arsenic is often present in the air with cadmium, these metals were considered covariates as well.

Demographic data such as county of residence, age at diagnosis, self-reported race and ethnicity were obtained from the SEER database for each patient.

Because smoking is a strong confounder of the amount of cadmium an individual is exposed to, we adjusted for smoking prevalence at the county-level. Annually, the Centers for Disease Control and Prevention administers a survey called the Behavioral Risk Factor Surveillance System (BRFSS) through random telephone calls in which it asks respondents whether they are current smokers. Smoking prevalence data from 2011 was used which was represented as percentage of adults in each county who were current smokers. For this study, the BRFSS data was retrieved online from CountyHealthRankings.org [24].

The USDA classifies all counties in the US using nine Rural-Urban Continuum Codes (RUCC). We grouped the 9 RUCC codes into 4 categories which have been previously used for public health analyses: RUCC category 1

represented all metropolitan counties (original RUCC codes 1, 2, and 3). RUCC category 2 included counties with original RUCC codes 4 and 5 (nonmetropolitan counties with an urban population of 20,000 to 250,000). Original RUCC codes 6 and 7 (nonmetropolitan counties with an urban population of 2,500–19,999) were grouped into RUCC category 3. Lastly, RUCC category 4 consisted of original RUCC codes of 8 and 9 which are completely rural counties with populations of less than 2,500 [25]. Cases were stratified by their RUCC category code for further analysis. RUCC 1, 2, 3, and 4 used subsequently will refer to the category codes as defined above.

Statistical analysis

Odds Ratios (OR) and 95% confidence intervals (CI) assessing the relationship between county-level air cadmium exposure concentration and PC stage and grade at diagnosis were calculated using multivariable logistic regression models. Analyses were adjusted for age at diagnosis, county-level sociodemographic index, county-level smoking prevalence and county-level air quality index and were stratified by RUCC category. Cases were also stratified by race within each RUCC category. OR included all cases but were calculated comparing the 80th *vs*. 20th percentile of cadmium exposure for ease of interpretation. We calculated similar 80th *vs*. 20th percentile OR for lead and arsenic for comparison as well. All statistical analyses were performed using MATLAB (MathWorks, Natick, MA), with $p < 0.05$ or 95% CI of OR not crossing 1.0 to be considered significant. The incidence of aggressive PC was assessed in each RUCC category to understand whether there was a difference in risk of metastatic and high grade PC at diagnosis in any of the RUCC county types.

Results

The study cohort consisted of 230,540 PC cases from 493 counties reported by SEER which was used to compare risk of metastatic PC compared to localized PC (Table 1). When comparing high vs low Gleason grade risk, patients with a Gleason Score of 7, an intermediate score, were eliminated leaving 130, 317 cases for analysis (Table 1). Roughly 76% of the cohort was White and 16% was Black although exact race proportions slightly varied by RUCC county type (Table 1). The largest number of patients were found in RUCC 1 with less patients found in RUCC 3, then RUCC 2, and lastly in RUCC 4 (Table 2). Most patients also had PC that was of low stage and low grade: 92% of patients had localized cancer (8% metastatic) (Table 1) and 70% low Gleason grade score (30% high Gleason score) which remained fairly consistent among the RUCC county types (Table 1).

Table 1
Cohort descriptives of prostate cancer cases obtained from Surveillance, Epidemiology, and End Results (SEER).

Cohort Descriptors	No. of Cases (%) within cohorts of 2 measures of prostate cancer aggressiveness									
	Metastatic vs Localized Cohort (n = 230,540)					High vs Low Gleason Grade Cohort [a] (n = 130,317)				
	All RUCC	RUCC 1	RUCC 2	RUCC 3	RUCC 4	All RUCC	RUCC 1	RUCC 2	RUCC 3	RUCC 4
Race										
White	174,182 (76)	152,523 (74)	7,931 (75)	12,613 (84)	1,520 (59)	98,726 (76)	86,592 (75)	4,486 (81)	6,303 (86)	1,345 (94)
Black	36,802 (16)	34,998 (17)	1,204 (11)	2,092 (14)	536 (21)	19,714 (15)	18,017 (16)	691 (12)	936 (13)	70 (5)
Other	11,767 (5)	10,795 (5)	934 (9)	105 (1)	358 (14)	6,923 (5)	6,628 (6)	249 (4)	41 (1)	5 (0.3)
Unknown	7,789 (3)	6,986 (3)	469 (4)	156 (1)	143 (6)	4,954 (4)	4,749 (4)	112 (2)	78 (1)	15 (1)
Tumor Aggressive Type										
Aggressive	17,318 (8)	15,194 (7)	869 (9)	1,209 (8)	205 (8)	39,112 (30)	34,230 (30)	1,900 (34)	2,470 (34)	687 (36)
Non-Aggressive	213,160 (92)	190,054 (93)	8,911 (91)	13,751 (92)	2,352 (92)	91,205 (70)	81,756 (70)	3,638 (66)	4,888 (66)	1,228 (64)

[a] Cases with Gleason Score 7 were excluded from analysis as they represent an intermediate score.

Overall, higher levels of air cadmium exposure concentration were associated with an increased likelihood of a PC case being metastatic (OR 1.02, CI 1.01–1.03) and having high Gleason grade at diagnosis (OR 1.01, CI 1.00–1.02) (Table 2). The strongest associations were observed in RUCC category 2 counties: those in nonmetropolitan areas with urban populations of 20,000 to 250,000 (Table 2). These adjusted odds ratios for the 80th *vs*. 20th percentile of cadmium exposure were: (OR 1.26, CI 1.14–1.39) for metastatic *vs*. localized cases and (OR 1.36, CI 1.25–1.49) for high *vs*. low Gleason score cases respectively.

Table 2
Odds ratios for aggressive prostate cancer for cases from Surveillance, Epidemiology and End Results (SEER).

Measure of Aggressiveness	County Type	Case Descriptives		OR (95% CI)	
		No. of Counties (%)	No. of Patients (%)	Unadjusted	Adjusted
Metastatic vs Not	All	493 (100)	230,540 (100)	1.030 (1.021, 1.040)	1.017 (1.005, 1.030)
	RUCC 1	209 (42)	205,302 (89)	1.077 (1.057, 1.097)	1.021 (1.000, 1.043)
	RUCC 2	47 (10)	9,783 (4)	1.277 (1.167, 1.397)	1.258 (1.139, 1.389)
	RUCC 3	172 (35)	12,898 (6)	0.982 (0.920, 1.048)	0.971 (0.896, 1.052)
	RUCC 4	65 (13)	2,557 (1)	0.852 (0.700, 1.038)	0.905 (0.721, 1.134)
High vs Low Gleason Grade	All	493 (100)	130,317 (100)	1.000 (0.985, 1.017)	1.011 (1.001, 1.021)
	RUCC 1	209 (42)	115,986 (89)	1.022 (1.007, 1.037)	1.007 (0.990, 1.025)
	RUCC 2	47 (10)	5,538 (4)	1.371 (1.269, 1.482)	1.364 (1.250, 1.489)
	RUCC 3	172 (35)	7,358 (6)	1.038 (0.990, 1.089)	1.098 (1.036, 1.164)
	RUCC 4	65 (13)	1,435 (1)	0.878 (0.765, 1.007)	1.056 (0.900, 1.240)
OR: Odds Ratio					
CI: Confidence Interval					

Generally, unadjusted and adjusted odds ratios were similar (Table 2). In the RUCC category subgroups, adjusted odds ratios for cases comparing high *vs*. low Gleason grade tended to be larger (RUCC 2, 3, 4) than for metastatic *vs*. not, but roughly equal for RUCC 1 (Table 2). In RUCC 4, adjusted odds ratios were not statistically significant for both metastatic and high Gleason grade PC. For RUCC 3, cadmium was associated with high Gleason grade at diagnosis but not for metastatic PC, and in RUCC 1, cadmium was associated with metastatic PC but not with high Gleason grade. Lastly, in RUCC 2, adjusted odds ratios were statistically significant and the largest among all RUCC categories for both metastatic PC and high Gleason grade at diagnosis (Table 2).

In RUCC 2, there is a trend that suggests that cadmium has a stronger association with metastatic PC (Fig. 2) and higher Gleason grade (Fig. 3) when compared to arsenic (metastatic *vs*. non-metastatic: 1.13, 1.08–1.18, high *vs*. low Gleason grade: 1.12, 1.08–1.17) and lead (metastatic *vs*. not: 1.00, 0.96–1.04, high *vs*. low Gleason grade: 1.05, 1.02–1.08). Odds ratios among the three metals do not seem to be different in RUCC 3 and 4 (Fig. 2 and Fig. 3). Any difference between the three metals in RUCC 1 and when all counties are combined seems to be small (Fig. 2 and Fig. 3). For this reason, we focused our attention on studying RUCC category 2.

We also calculated OR and CI without the air quality index score as a covariate to check for overadjustment. The results did not differ with and without the air quality score in the model (results not presented). In addition, simply being in RUCC 2 does not explain higher incidence of aggressive PC. The percentage of patients that have aggressive PC is roughly the same in all 4 RUCC categories. For metastatic PC this percentage varies from 7.4–8.8% and for higher Gleason grade from 29.5–35.9% (Table 1**)**.

To help understand the associations found in each of these counties, the cohort was stratified by race. Focusing on RUCC 2, comparing the 80th *vs*. 20th percentile of metastatic *vs*. localized PC, the odds ratio for White was (OR: 1.35, CI 1.20–1.52) and for Black (OR: 1.04, CI 0.72–1.52). For 80th *vs*. 20th percentile for high *vs*. low Gleason score, odds ratio for White was (OR: 1.33, CI 1.13–1.57) and for Black (OR: 0.98, CI 0.58–1.66) (Fig. 4).

Discussion

Overall, air cadmium exposure was significantly associated with high tumor grade and metastatic PC at diagnosis (Table 2) among a large national cohort in the US. In RUCC 3 and 4, these odds ratios tended not to be statistically significant, and for RUCC 1 they were not very large (Fig. 2 **and** Fig. 3**)**. In RUCC 2, among the three metals, odds ratios were observed to be the largest among cadmium which suggests exposure to air cadmium is more important than exposure to arsenic and lead (Fig. 2 **and** Fig. 3**)**. In RUCC 1, 3, and 4, the results suggest that the adjusted odds ratios are similar among the three metals (Fig. 2 **and** Fig. 3).

Previous literature on the topic of association between cadmium overburden and PC aggressiveness fall into two categories: mortality as endpoint and biomarkers of aggressiveness at diagnosis.

For the first category (mortality as endpoint), meta-analyses literature surveys showed no statistically significant evidence of an association between cadmium exposure and PC mortality in the general population [26][27]. However, mortality by itself, may not be a sufficient method to evaluate tumor aggressiveness for at least three reasons: (1) inaccuracy of death certificates and other methods of quantifying cause-related mortality, (2) differences in treatments, and (3) attenuation of the potential effect of environmental toxicants such as cadmium when the large majority of patients has an indolent disease such as PC.

Only a few papers addressed the second category (signs of aggressiveness at diagnosis). In an aged-matched study in four hospitals in Taiwan with 234 PC cases, patients with higher serum and urinary cadmium levels had significantly higher stage and Gleason grade, suggesting that high cadmium body burden could affect tumor aggressiveness [28]. Among a large Danish cohort of 26,778 men (1,567 cases) followed prospectively for 13 years, there was no comparison between cases with high dietary cadmium vs. low dietary cadmium for the ratio of aggressive to non-aggressive cases, but the incidence of either of these two types of PC cases was not increased in men with high cadmium dietary exposure when analyzing these subtypes separately [29]. In Sweden, another large prospective study that also used food frequency questionnaires to estimate the amount of cadmium daily ingestion discovered a rate ratio (RR) of 1.29 (CI: 1.08–1.53) for localized cases and RR of 1.14 (CI: 0.86–1.51) for advanced cases when comparing tertiles of dietary cadmium after 10.8 years of follow up. However, there was no cross-comparison of aggressive with non-aggressive PC cases [30]. An earlier population-based study of 358 patients showed a tendency for higher incidence of aggressive PC in men in the upper quartile of dietary cadmium when compared to men in the lower quartile of the patient population: OR = 1.8 (CI: 0.7–4.7) for men < 68 years old, and OR = 1.5 (CI: 0.6–3.7) for men 68 years old and above [31]. The strongest association was found for the

entire (non-aggressive, intermediate aggressiveness and aggressive PC tumors) patient population that was > 67 years old, OR = 1.8 (CI: 1.1–3.1).

Unlike other studies of dietary cadmium that were interested in comparing the incidence of PC of varying aggressiveness separately [29][30][31], we calculated the odds ratio comparing the probability of aggressive to nonaggressive PC to understand the role cadmium may play in PC progression as this is an important measure of outcomes. In addition, our results support the findings that PC patients with higher cadmium levels have higher stage and Gleason grade [28]. Lastly, since the absorption of dietary cadmium is relatively low compared to the absorption of cadmium inhaled into the body, our results may provide a more comprehensive assessment of environmental exposure to cadmium.

One of the many difficulties in assessing the risk imposed by excess cadmium in the diet is to separate cadmium intake (which is heavily dependent on the ingestion of bread and potatoes) from adiposity, which is a well-known risk factor for PC aggressiveness and mortality [32]. Our findings support the idea that it is important to consider the relationship between environmental factors and the stage of cancer. Since we found the strongest associations to be in RUCC category 2 counties, follow-up studies should be conducted in these areas to further investigate the relationship of environmental exposure to air cadmium and PC. This could lead to future studies to identify modifiable sources of high cadmium emission. RUCC 2 counties are especially important because approximately 40 million Americans [25] live in these areas with a substantial portion of them subject to high cadmium exposure.

Since the ATSDR has indicated that air exposure to cadmium is only substantial near cadmium-emitting facilities, our hypothesis is that many cadmium-emitting facilities such as factories and mines tend to be in RUCC 2 counties which have populations of 20,000 to 250,000. Individuals in RUCC 2 counties might be closer to sources of cadmium pollution in the air than individuals living in other categories of RUCC counties. We hypothesize that these cadmium-emitting facilities are present in RUCC 1, 3 and 4 counties, but their effect is diluted. Since RUCC 3 and 4 counties consist of mostly rural areas, it is possible that residents tend to live in more spread-out areas away from urban activity and air pollution, so most individuals would not be impacted. On the other hand, RUCC 1 counties are metropolitan counties with a high number of residing individuals. Because facilities that emit air cadmium might only exist in some neighborhoods, overall negative effects among the RUCC 1 cohort might not be observed because only a portion of the population would be exposed.

To identify the sources of high air cadmium exposure for each of the counties with high incidence of metastatic and high grade cancer at diagnosis is beyond the scope of this paper, but an important task. Every year, the US Census Bureau obtains industry size by number employed at the county-level through the American Community Survey. This data is available publicly through an interactive website called Data USA, as a collaboration between Deloitte and MIT Learning Group [33]. By comparing known sources of cadmium from the ATSDR to the list of all industries in each county in the upper two quintiles of air cadmium concentration in RUCC2 counties, some possible sources of cadmium exposure could be identified. Putative sources include smelters, mining and quarrying, waste incinerators, coal and fossil fuel power plants, and factories for manufacturing equipment and nickel-cadmium batteries.

The association between environmental cadmium exposure and diseases can be traced to contamination of drinking water, food sources and/or by inhalation of airborne cadmium in the work environment, cigarettes, and ambient air. In areas where city water cadmium levels are regulated and food is shipped from other areas, disease

associations may be more accurately traced to dangerous air cadmium levels than in local water and soil. A previous study analyzing air quality and advanced PC stage prompted us on this investigation. Future studies that look at the link between cadmium or other environmental agents and PC should also consider the stage and grade of PC at diagnosis. The effect of cadmium on aggressiveness of PC is of particular interest since PC has high incidence, but by comparison with most other types of cancer, PC has a relatively low rate of progression to more aggressive disease [34].

Also of interest would be to understand the biological mechanisms of action of cadmium on cancer progression. Most of the literature addresses the effect of cadmium on the initiation and promotion of PC, with little attention to progression of already established malignancy (an increase in genomic instability, tumor growth and metastasis).

The few articles that do focus on low, nanomolar cadmium concentrations suggest that cadmium may act as a hormone disruptive agent and activator of signal transduction pathways that promote cell growth [35][36], but other possible mechanism(s) may also contribute. Most of the mechanism-driven studies in the literature utilize micromolar range *in vitro* concentrations of free, unbound cadmium salts that may not be relevant to PC as such concentrations of free cadmium rarely, if ever reach the prostate.

Studying the stage and grade score of PC at diagnosis eliminated any confounding factors that may be related to differences in treatment. Possible limitations include that the SEER database only contains data from 11 states, and it does not record if PC patients relocated from one county to another. Previous epidemiological studies have shown it is very challenging to estimate an individual's amount of cadmium intake, absorption, and retention in the prostate. In this study, using county-level cadmium exposure concentrations, it is impossible to assess a specific individual's exposure to air cadmium and its absorption. In addition, cadmium exposure concentration could vary throughout the county as well, which means that different individuals living in the same county could be exposed to different amounts of air cadmium. Lastly, it is also possible that our calculated odds ratios are affected by other factors in addition to the presence of cadmium that are not accounted for in our model, such as body mass index (BMI), waist-to-hip ratio, and physical activity. The main limitation of our study, in common with most epidemiological studies, is its observational nature.

For these reasons, follow-up studies should be conducted using state and local registries to use more precise concentrations of air cadmium exposure. The EPA publishes air toxic concentration data for census blocks and tracts, areas that are smaller than counties. These exposure concentrations might provide more information about the link between the distance of a patient's address of residence to a cadmium-emitting source and PC aggressiveness at diagnosis. Lastly, studies should consider accounting for an individual's occupation as well, as these might affect the amount of an individual's exposure to air cadmium.

Conclusion

Instead of addressing the effect of environmental cadmium on PC incidence and mortality, we studied cadmium effect on PC aggressiveness. Higher cadmium air exposure concentration was associated with advanced stage and higher grade of PC at diagnosis with the strongest associations observed in RUCC category 2 counties (nonmetropolitan counties with an urban population of 20,000 to 250,000). Since air cadmium is not conventionally considered a major route of cadmium exposure except in occupational settings, further studies should be conducted to investigate the effect of this form of cadmium intake, and how it relates to PC

aggressiveness. Similar analyses could be undertaken to investigate other metals, pollutants, and environmental risk factors in PC aggressiveness. Better understanding of the possible role of cadmium in PC progression could lead to prevention and therapeutic interventions to decrease body cadmium overburden or to block cadmium effect. The effects of air cadmium in the general population may be a more important factor than previously recognized.

Abbreviations

ATSDR
Agency of Toxic Substances and Disease Registry
BMI
Body mass index
BRFSS
Behavioral Risk Factor Surveillance System
CI
Confidence interval
EPA
Environmental Protection Agency
EQI
Environmental quality index
NATA
National Air Toxics Assesment
OR
Odds ratio
PC
Prostate cancer
RR
Rate ratio
RUCC
Rural-Urban Continuum Codes
SEER
Surveillance, Epidemiology, and End Results

Declarations

Ethics approval and consent to participate

Data is available in public databases; ethics approval is not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no potential conflicts of interest.

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Authors' contributions

Conceptualization: V.V., M.R.A., J.S.J., and A.K.B.; Data Curation: V.V., M.R.A., J.S.J., and A.K.B.; Formal Analysis: V.V. and A.K.B.; Methodology: M.R.A., and J.S.J.; Writing – original draft: V.V. and A.K.B.; Writing – review and editing: V.V., M.R.A., J.S.J., and A.K.B. All authors agree to the final manuscript.

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Figures

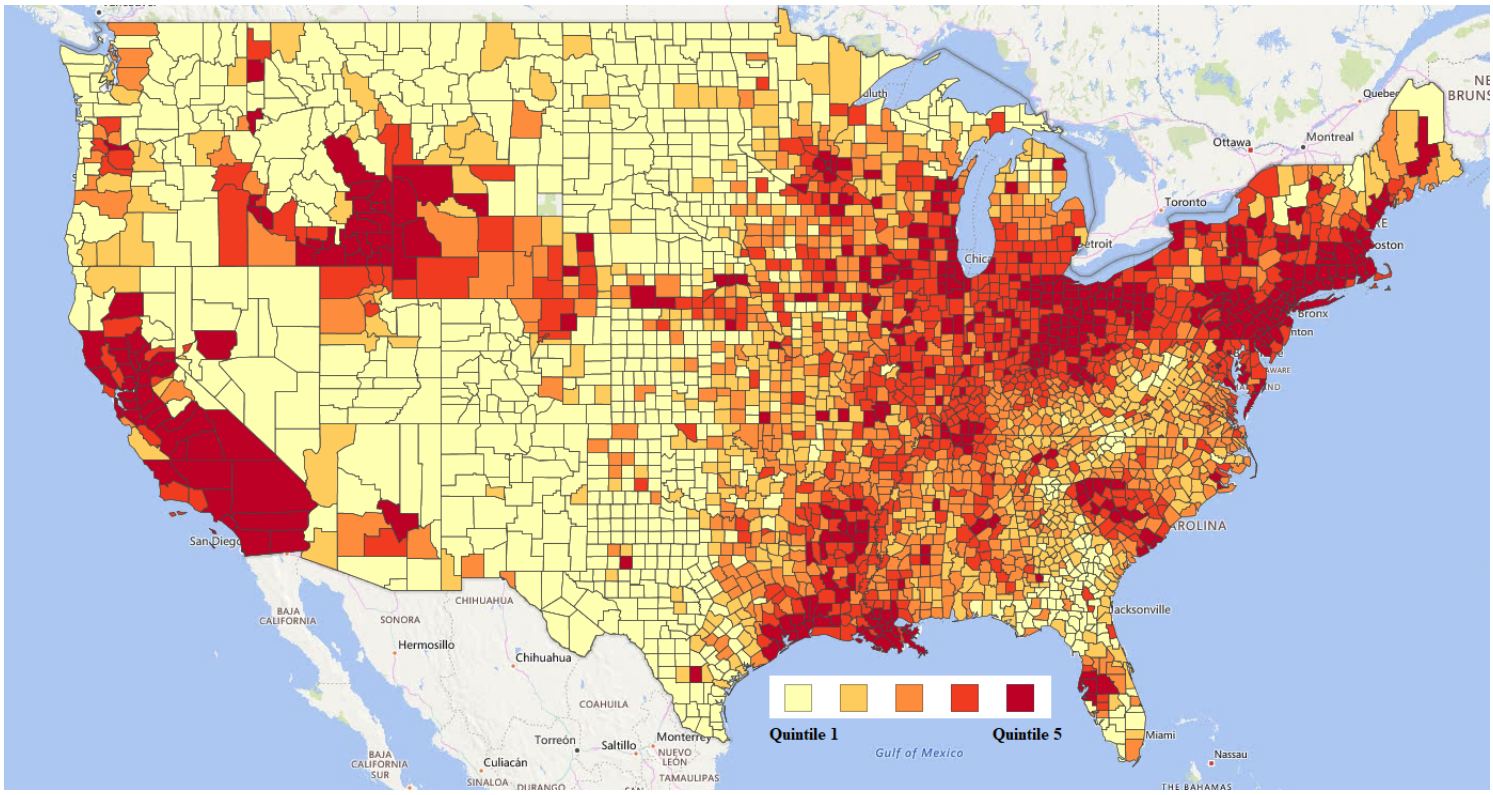

Figure 1

County-level air cadmium exposure concentration in the US by quintile.

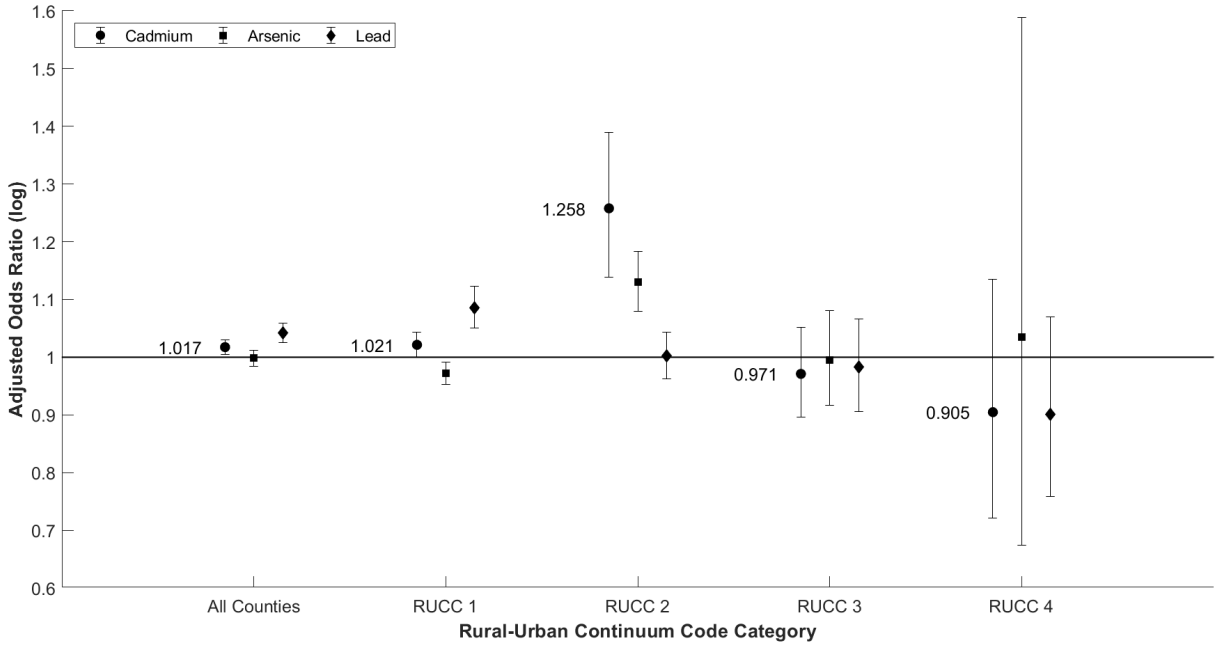

Figure 3

Adjusted odds ratios for metastatic vs. localized prostate cancer for the 80th vs 20th percentile of metal exposure concentration (OR, 95% CI) among 230, 540 cases collected from the Surveillance Epidemiology and End Results (SEER), a nationally representative cohort in the US.

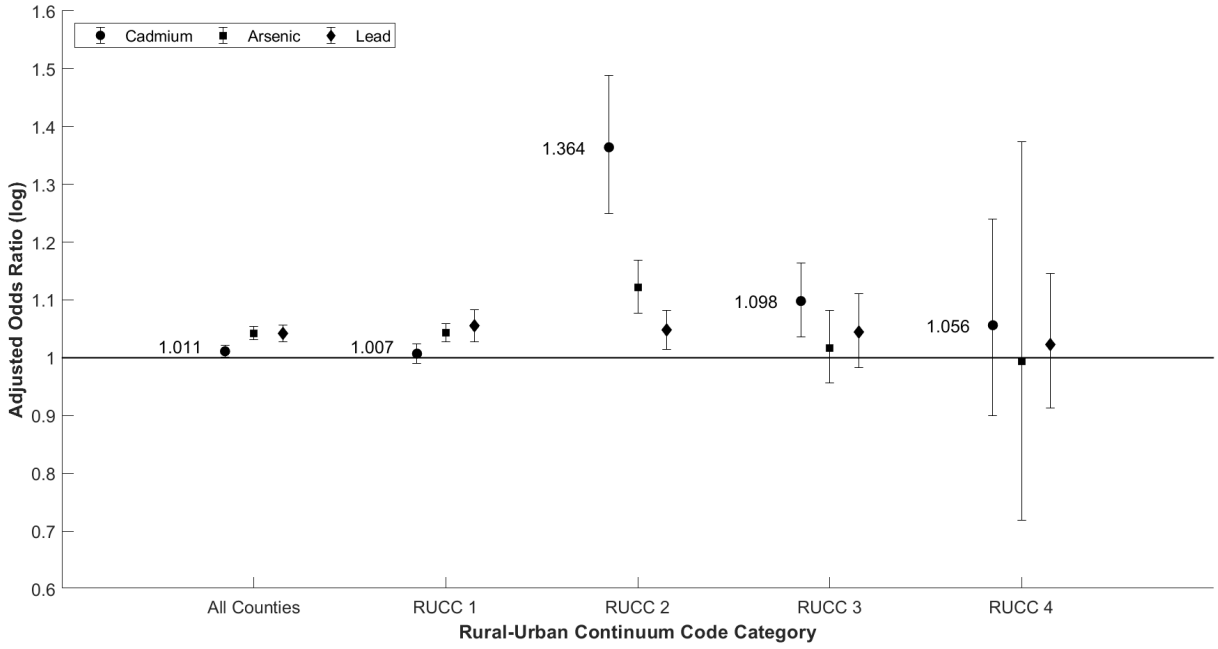

Figure 5

Adjusted odds ratios for high vs. low Gleason grade prostate cancer for the 80th vs 20th percentile of metal exposure concentration (OR, 95% CI) among 130,317 cases collected from the Surveillance Epidemiology and End Results (SEER), a nationally representative cohort in the US.

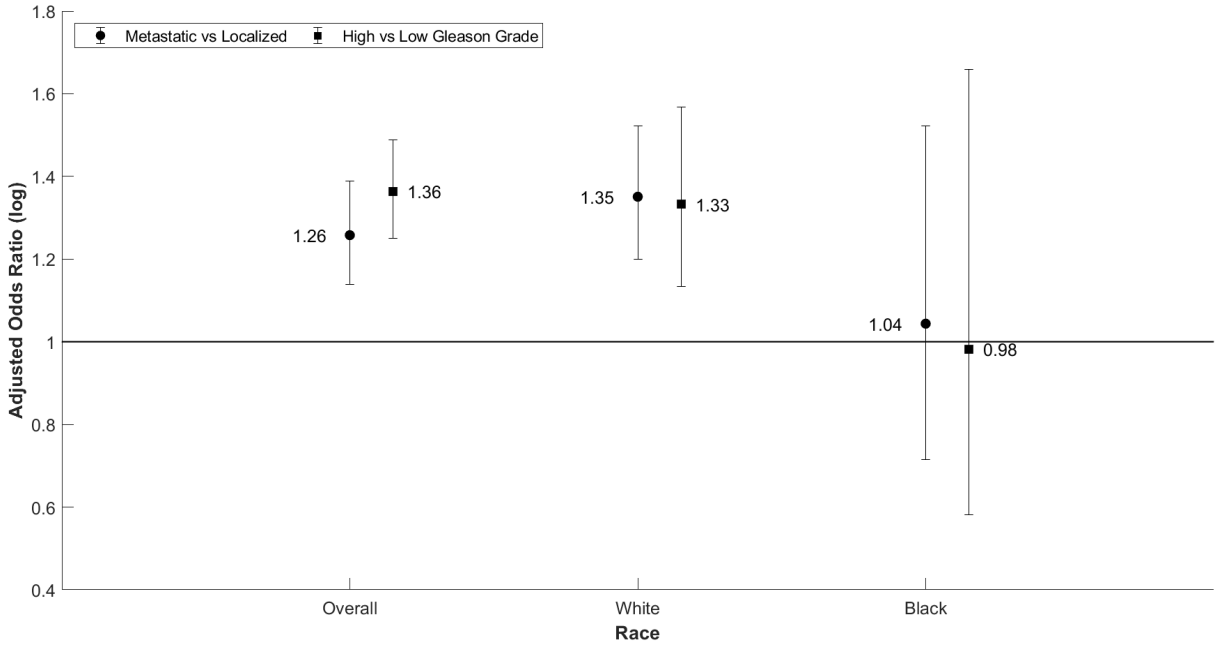

Figure 7

Adjusted odds ratios for aggressive prostate cancer for the 80th vs 20th percentile of cadmium exposure concentration (OR, 95% CI) by race in RUCC 2 counties.