RESEARCH ARTICLE

Association between Urinary Cadmium and All Cause, All Cancer and Prostate Cancer Specific Mortalities for Men: an Analysis of National Health and Nutrition Examination Survey (NHANES III) Data

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Abstract

Aim: This study employed public use National Health and Nutrition Examination Survey (NHANES III) data to investigate the association between urinary cadmium (UDPSI) and all cause, all cancer and prostate cancer mortalities in men. Patients and Methods: NHANES III household adult, laboratory and mortality data were merged. The sampling weight used was WTPFEX6, with SDPPSU6 applied for the probability sampling unit and SDPSTRA6 to designate the strata for the survey analysis. Results: For prostate cancer death, the significant univariates were UDPSI, age, weight, and drinking. Under multivariate logistic regression, the significant covariates were age and weight. For all cause mortality in men, the significant covariates were UDPSI, age, and poverty income ratio. For all cancer mortality in men, the significant covariates were UDPSI, age, black and Mexican race. Conclusions: UDPSI was a predictor of all cause and all cancer mortalities in men as well as prostate cancer mortality.

Keywords: NHANES III - all cancer survival - all cause survival - prostate cancer - cadmium

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Introduction

Prostate cancer is a common cancer in men (Siegel et al., 2012). The median age of prostate cancer patients is 67 years old. There are 2.5 million prostate cancer survivors. It was estimated 241740 men were diagnosed with prostate cancer in 2012. Most prostate cancers are diagnosed at a non-metastatic stage because of prostate-specific antigen screening. The survival for prostate cancer patients is high. The relative survival of prostate cancer is 97.8% at 10 years, and 91.4% at 15 years adjusted for age, sex and race (Siegel et al., 2012).

The pathogenesis of prostate cancer is complex. There are numerous molecular factors (Dahiya et al., 1996; Shand and Gelmann, 2006) as well as environmental exposure to potentially toxic materials have been thought to be related to carcinogenesis of prostate cancer. For example, cadmium exposure has been suggested in prostate cancer pathogenesis by several population based epidemiology studies (van Wijngaarden et al., 2008) (Julin et al., 2012) (Lin et al., 2013) and laboratory studies (Aimola et al., 2012).Cadmium is ubiquitous occurring in high quality paints, batteries and is a common food contaminant. Cadmium has also been linked to pathogenesis of several other human and animal cancers (Huff et al., 2007) (Satarug, 2012). National Health and Nutritional Examination Survey (NHANES) III public use data have been used to identify potential factors associated with prostate cancer pathogenesis from factors such as dietary intakes (Cui et al., 2004), life-style (Shiels et al., 2009), dietary supplement use (Tseng et al., 2005), obesity (Rohrmann et al., 2007a) (Parekh et al., 2010) , and environmental exposure to toxins such as boron (Cui et al., 2004). Some of these factors may have led to prostate cancer carcinogenesis through their effects on sex steroids (Lacher et al., 2006) (Rohrmann et al., 2007b) (Mondul et al., 2010) (Mondul et al., 2010) (Mondul et al., 2011) and they cause increased cancer mortality (Menke et al., 2010). Limited amount is known about the association between cadmium and prostate cancer mortality.

This study attempted to use public use NHANES III data and NHANES III-linked mortality data to study the association between urinary cadmium and all cause, all cancer and prostate cancer specific mortalities in men. This study took advantage of the vastness of the NHANES III data to adjust for important socio-economic factors(Cheung, 2012) that may be cofounders.

Materials and Methods

NHANES and NHANES III

NHANES is a major program of National Center of

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Health Statistics (a part of Center of Disease Control (CDC) of United States of America) started in 1971. NHANES III is a national study based on a complex, multi-stage probability sampling design. For details of NHANES data and statistical guidance as well as their analysis examples see NHANES website (http://www.cdc.gov/nchs/nhanes.htm). NHANES studies were approved by CDC internal institutional review boards. The public use data are made available to the public and researchers. The NHANES sample weights were calculated to represent non-institutionalized general US population to account for non-coverage and non-response. These patients were interviewed at home and examined in mobile examination centers (MEC). In this study, NHANES III (conducted between1988 – 1994) household adult data file was merged with NHANES III laboratory data (for the urinary cadmium data used in this study) and the NHANES III linked cancer mortality data.

NHANES III linked mortality data

NHANES III participants were followed passively until December 31, 2006 for their mortality data. Detailed information about the data and analysis guidelines are available at their website (http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes3_linkage.htm). In brief, probability matching was used to link NHANES III with National Death Index for vital status and mortality, age 90 years old was censored because they contribute little in person years. NHANES used multiple sources including the use of death certificates and with the National Death Index to ascertain vital status and cause of death.

Statistical analysis

NHANES III employed a complex sampling strategy and analysis (Ezzati-Rice and Murphy, 1995) (Lemeshow and Cook, 1999) (Graubard and Korn, 1999)(Chang et al., 2010). Matlab programs (posted on Matlab File Exchange) were developed to convert SAS files provided by NAHNES to STATA programs to download NHANES III data files for further analysis. Specialized survey software is needed for NHANES complex data analysis (Cohen, 1997). STATA 12 (College Station, TX) was among those recommended by CDC to analyze the complex NHANES data and was used in this study. The sampling weight used for urinary cadmium was WTPFEX6 because the urinary cadmium was collected in MEC, SDPPSU6 was used for the probability sampling unit (PSU) and SDPSTRA6 was used to designate the strata for the STATA survey commands. STATA scripts were written for this analysis, and will be submitted for publication separately. Univariate and multivariate logistic regressions (Jewell, 2004) were used to study the relationship between urinary cadmium and all cause, all cancer and prostate cancer death in men. The status of mortality was coded as a binary outcome (1= death, 0 = otherwise). Linearized Taylor Standard Error estimation was used. The covariates and the corresponding NHANES III codes used were: UDPSI (urinary cadmium concentration, nmol/L), MXPAXTMR (age at the MEC final examination in months), HSSEX (sex, _IHSSEX_1 = male, female as the reference group when applicable, only men were included in this study), HAM6S (weight in lbs without clothes), DMPMETRO (urban rural residence status), IDMPMETRO_2 (rural residence, urban residence was used as the reference group), DMARETHN (race and ethnicity, IDMARETHN_2 = non-Hispanic black, IDMARETHN_3 = Mexican Americans, IDMARETHN_4 = others, non-Hispanic white was used as the reference group), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption, number of hard liquor drinks per month), and HAR4S (smoking, number cigarettes per day). For STATA analyses, only the patients without missing values for all of WTPFEX6, SDPPSU6, SDPSTRA6, UDPSI, MXPAXTMR, HSSEX, DMPMETRO, HAM6S, DMARETHN, DMPPIR, HAR4S, and HAN6JS were included in this study.

Further, these additional NHANES III codes considered not eligible: UDPSI (888888), HAM6S (888), HAM6S (999), DMPPIR (888888), the numerator of DMPPIR was the midpoint of the observed family income category in the Family Questionnaire variable:HFF19R, and the denominator was the poverty threshold, the age of the family reference person, and the calender year in which the family was interviewed, HAR4S (666), HAR4S (777),

Table 1. Univariate and Multivariate Analyses of Pretreatment Predictors of Endometrial Cancers

Outcome and Covariates	NHANES III Code	Category	Value	Std Dev.	95% Confidence Interval
Prostate cancer death (n=98)*			0.0029	0.0013	0.00026 - 0.0055
Urinary cadmium: SI (nmol/L)	UDPSI		8.22	0.26	7.69 - 8.75
Age in months at MEC exam	MXPAXTMR		474.9	5.74	463.36 - 486.43
Sex	HSSEX	Men = 1	9,401		
		Women = 2	10,649		
Weigh without clothes -lbs	HAM6S		177.97	1.45	175.07 - 180.88
Rural/urban code	DMPMETRO	Urban = 1	9,979		
based on USDA code		Rural = 2	10,071		
Race-ethnicity	DMARETHN	Non-Hispanic white = 1	8,483		
	Non-Hispanic black = 2		5,486		
	Mexican American = 3		5,306		
	Other = 4		775		
Poverty Income Ratio (unimputed income)	DMPPIR		2.75	0.079	2.59 - 2.91
Hard liquor - times/month	HAN6JS		3.93	0.52	2.88 - 4.98
Cigarettes smoked per day	HAR4S		20.99	0.58	19.84 - 22.16

*Prostate cancer death = 1, Otherwise = 0

HAR4S (888), HAR4S (999), HAN6JS (888), HAN6JS (999). A total of 31,981 subjects were excluded, and 2,013 were eligible for this study.

Results

There were 20024 cases in NHANES III linked mortality data file included in this study. 13,944 cases were not available in the public use file to protect the privacy of youth subjects. 26 cases in the NHANES III linked dataset did not have mortality data. All cause mortality (5,291 deaths out of 33994 subjects), all cancer mortality (using ucod_113 codes 017 to 037, 1,117 deaths were counted out of 33,994 subjects), and prostate cancer specific death (ucod_113 033, 98 deaths were counted out of 33,994 subjects) were used as the binary outcomes for this analysis. The NHANES III adult data file and the NHANES III linked mortality file were merged according to the SEQN number provided by NHANES III to uniquely identify the cases. Table 1 shows the demographic, socioeconomic and other unvariables used in this study. Urinary cadmium has a mean 8.22 nmol/L. The mean age was 474.9 months for the included cases. Of the 20050 adults available in NHANES III, there are 9401 men, 10649 women. Their mean weight was 177.97 lbs. There were 9979 urban and 10071 rural residents according to the USDA designation. There were 8483 non-Hispanic whites, 5486 non-Hispanic blacks, 5306 Mexican Americans and 775 cases of other race and ethnicity. The un-imputed poverty income ratio mean was 2.75. On average the men drank 3.93 hard liquor drinks per month, they on average smoked 20.99 cigarettes per day. For this study, there were 2013 eligible subjects with complete data.

Table 2 shows the univariate logistic regression of covariates for NHNAES III linked prostate cancer specific death. The odds ratios (95% confidence intervals) were respectively: urinary cadmium concentration, nmol/L, 1.033 (1.0059- 1.063); age in months at the MEC examination, 1.01 (1.007 - 1.014); weight in lbs without clothes, 0.97 (0.94 - 0 .99); USDA urban rural residence status, 0.33 (0.051 - 2.14); race-ethnicity, 0.41 (0 .12 - 1.45); poverty income ratio, 1.075 (0.74 - 1.55); number of liquor drinks per month, 1.01 (1.0025 - 1.018); and number of cigarettes per day, 1.011 (0.99-1.04). The urinary cadmium concentration was a significant predictor of prostate cancer mortality. All the univariables were used in the multivariate analysis so as not to miss potentially important predictors.

Table 3 shows the multivariate logistic regression of covariates of NHANES III linked prostate cancer specific death. The beta coefficients (95% confidence interval) were respectively: urinary cadmium concentration, (nmol/L) -0.0063 (-0.092 - 0.079); age in months at the MEC examination, 0.0094 (0.0056 – 0.013); weight in lbs without clothes, -0.03 (-0.062 - 0 .0012); USDA rural residence (urban residence used as the reference), -1.63 (-3.49 - 0.24), black race (non-Hispanic white used as the reference), -0.72 (-3.13 -1.68); Mexican American race and others were dropped from the analysis because

Table 2. Univariate Logistic Regression of Covariates for NHANES III Linked Prostate Cancer Specific Death

Prostate Cancer Death	Odds Ratio	Linearized Std. Err.	t	P>t	95% Conf. Interval	
UDPSI	1.033868	0.0140766	2.45	0.018	1.005963	1.062546
MXPAXTMR	1.010344	0.0016664	6.24	0.000	1.007001	1.013698
HAM6S	0.967583	0.0127422	-2.50	0.016	0.942312	0.993532
DMPMETRO	0.328984	0.3066419	-1.19	0.239	0.050547	2.141173
DMARETHN	0.410973	0.2576265	-1.42	0.162	0.116604	1.448479
DMPPIR	1.075254	0.1971421	0.40	0.694	0.743871	1.554264
HAN6JS	1.010184	0.0037956	2.70	0.010	1.002585	1.017840
HAR4S	1.011542	0.0118272	0.98	0.331	0.988051	1.035591

*Prostate Cancer Death: 0=alive or death not related to prostate cancer, 1=death from prostate cancer. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: UDPSI (urinary cadmium concentration, nmol/L), MXPAXTMR (age at the MEC final examination), HAM6S (weight in lbs without clothes), DMPMETRO (urban rural residence status, DMARETHN (race and ethnicity, non-Hispanic white used as the reference group), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), and HAR4S (smoking). n = 2013 samples

Table 3. Multivariate Logistic Regression of Covariates for NHANES III Linked Prostate Cancer Specific Death

Prostate Cancer Death	Odds Ratio	Linearized Std. Err.	t	P>t	95% Conf. Interval	
UDPSI	-0.006296	0.0425848	-0.15	0.883	-0.09197	0.079373
MXPAXTMR	0.009405	0.0018726	5.02	0.000	0.00564	0.013172
HAM6S	-0.030313	0.0156781	-1.93	0.059	-0.06185	0.001227
IDMPMETRO_2	-1.625318	0.9274945	-1.75	0.086	-3.49120	0.240560
IDMARETHN_2	-0.724826	1.193694	-0.61	0.547	-3.12623	1.676577
IDMARETHN_3/4	0 (omitted)					
DMPPIR	-0.004108	0.1790808	-0.02	0.982	-0.36437	0.356156
HAN6JS	-0.002386	0.0050383	-0.47	0.638	-0.01252	0.007749
HAR4S	-0.001661	0.0108049	-0.15	0.878	-0.02339	0.020076
Cons	-5.817202	3.741419	-1.55	0.127	-13.34397	1.709563

*The NHANES III codes used were: UDPSI (urinary cadmium concentration, nmol/L), MXPAXTMR (age at the MEC final examination), HAM6S (weight in lbs without clothes), IDMPMETRO_2 = rural residence, urban residence used as the reference group), IDMARETHN_2 = non-Hispanic black, IDMARETHN_3 = Mexicans, IDMARETHN_4 = others, non-Hispanic white used as the reference group), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), and HAR4S (smoking). n = 2013 samples

Table 4. Multivariate Logistic Regression of Covariates for NHANES III Linked All Cause Mortality

Indicator Death	Odds Ratio	Linearized Std. Err.	t	P>t	95% Conf. Interval	
UDPSI	1.028538	0.0097212	2.98	0.005	1.009186	1.048260
MXPAXTMR	1.009011	0.0005979	15.14	0.000	1.007811	1.010214
HAM6S	1.003023	0.0026099	1.16	0.252	0.997792	1.008282
IDMPMETRO_2	1.009713	0.1872049	0.05	0.959	0.695644	1.465578
IDMARETHN_2	1.368866	0.3120686	1.38	0.175	0.865756	2.164345
IDMARETHN_3	0.687764	0.2166494	-1.19	0.240	0.365191	1.295268
IDMARETHN_4	0.683063	0.3515887	-0.74	0.463	0.242793	1.921695
DMPPIR	0.754508	0.0531005	-4.00	0.000	0.655000	.8691316
HAN6JS	1.009652	0.0052799	1.84	0.072	0.999097	1.020318
HAR4S	1.004818	0.0086289	0.56	0.578	0.987626	1.022308
Cons	0.001218	0.0008118	-10.07	0.000	0.000319	0.004649

*IndicatorDeath: 0=alive, 1=dead. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: UDPSI (urinary cadmium concentration, nmol/L), MXPAXTMR (age at the MEC final examination), HAM6S (weight in lbs without clothes), IDMPMETRO_2 = rural residence (urban residence used as the reference group), IDMARETHN_2 = non-Hispanic black, IDMARETHN_3 = Mexicans, IDMARETHN_4 = others, non-Hispanic white used as the reference group, DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), and HAR4S (smoking). n = 2013 samples

Table 5. Multivariate Logistic Regression of Covariates for NHANES III Linked All Cancer Mortality

Indicator Death	Odds Ratio	Linearized Std. Err.	t	P>t	95% Conf. Interval	
UDPSI	1.014961	0.008031	1.88	0.067	0.998949	1.031230
MXPAXTMR	1.007829	0.000809	9.72	0.000	1.006205	1.009456
HAM6S	0.999609	0.004793	-0.08	0.935	0.990023	1.009287
IDMPMETRO_2	1.061413	0.329264	0.19	0.848	0.569046	1.979801
IDMARETHN_2	1.794595	0.398750	2.63	0.011	1.148276	2.804702
IDMARETHN_3	0.209665	0.096089	-3.41	0.001	0.083473	0.526633
IDMARETHN_4	1.610268	1.192635	0.64	0.523	0.363499	7.133346
DMPPIR	0.898719	0.081240	-1.18	0.243	0.749431	1.077746
HAN6JS	0.995364	0.003905	-1.18	0.242	0.987547	1.003243
HAR4S	1.021113	0.011702	1.82	0.074	0.997867	1.044901
Cons	0.000393	0.000466	-6.62	0.000	0.000036	.0042479

*IndicatorDeath: 0=alive, 1=dead. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: UDPSI (urinary cadmium concentration, nmol/L), MXPAXTMR (age at the MEC final examination), HAM6S (weight in lbs without clothes), IDMPMETRO_2 = rural residence, urban residence used as the reference group, IDMARETHN_2 = non-Hispanic black, IDMARETHN_3 = Mexicans, IDMARETHN_4 = others, non-Hispanic white used as the reference group, DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), and HAR4S (smoking). n = 2013 samples

there were no prostate cancer death associated with them once the analysis was adjusted for the weights, sampling probability and stratification (Table 3); poverty income ratio, -0.0041 (-0.36 - 0.36); number of liquor drinks per month, -0.0024 (-0.013 - 0 .0077); number of cigarettes per day, -0.0017 (- 0.023 - 0.02).

From multivariate logistic regression of covariates and NHANES III linked all cause mortality in men, the odds ratios (95% confidence intervals) were respectively: urinary cadmium concentration, nmol/L, 1.029 (1.0091 - 1.048); age in months at the MEC examination, 1.009 (1.008 - 1.01); weight in lbs without clothes, 1.003 (0.10 - 1.0083); USDA rural residence, urban residence used as the reference, -1.01 (0.70 - 1.47); black race, non-Hispanic white was used as the reference, 1.37 (0.87 - 2.16); Mexican American race, 1.37 (0.87 - 2.16) and other race-ethnicity 0 .68 (0.24 - 1.92); poverty income ratio, 0.75 (0.66 - 0.87); number of liquor drinks per month, 1.0097 (0.10 - 1.02), and number of cigarettes per day, 1.0048 (0.99 - 1.02). The urinary cadmium was significantly associated with all cause specific death in men (Table 4).

Table 5 shows the multivariate logistic regression of covariates of NHANES III linked all cancer mortality. The odds ratios (95% confidence intervals) were respectively: urinary cadmium concentration, nmol/L, 1.015 (1.00 - 1.03); age in months at the MEC examination, 1.0078 (1.0062 - 1.0095); weight in lbs without clothes, 1.00 (0.99 - 1.0093); USDA rural residence, urban residence was used as the reference, 1.061 (0.57 - 1.98); black race, non-Hispanic white was used as the reference group, 1.79 (1.15 - 2.80); Mexican American race, 0.21 (0.083 - 0.53); other race-ethnicity, 1.61 (0.36 – 7.13); poverty income ratio, 0.90 (0.75 - 1.078); number of liquor drinks per month, 1.00 (0.99 - 1.003); and number of cigarettes per day, 0.012 (0.10 - 1.04). The urinary cadmium is significantly associated with all cancer specific death in men (Table 5).

Discussion

Cadmium is a known human carcinogen (Huff et al., 2007) (Satarug, 2012), it has been linked to prostate cancer in several studies (van Wijngaarden et al., 2008) (Julin et al., 2012) (Lin et al., 2013). Cadmium exposure is common and has been related to pathogenesis of several human and animal cancers (Huff et al., 2007) (Satarug, 2012). In human, cadmium has been strongly linked to prostate cancer pathogenesis by population based epidemiology studies (van Wijngaarden et al., 2008) (Julin et al., 2012) (Lin et al., 2013) and laboratory studies (Aimola et al., 2012). This study used public use National Health and

Nutrition Examination Survey (NHANES III) data to investigate the association between urinary cadmium and all cause, all cancer, and prostate cancer mortalities in men. This study included 20050 adults (Table 1). The NHANES III data file was linked to NHANES III laboratory data and NHANES III linked mortality data files. For univariate logistic regression, the odds ratio (95% confidence intervals (C.I.)) for urinary cadmium concentration, nmol/L, was 1.033 (1.0059- 1.063) and was statistically significant; in addition, age, 1.01 (1.007 - 1.014), weight, 0.97 (0.94 - 0 .99) and drinking, 1.01 (1.0025 - 1.018), were also significant univariate predictors of prostate cancer death (Table 2). However, under multivariate logistic regression, the beta coefficients (95% C.I.) with significant p values only included age, 0.0094 (0.0056 – 0.013); and weight, -0.03 (-0.062 - 0 .0012). Literature has supported that prostate cancer mortality is linked to obesity (Strom et al., 2006). The lack of significance of urinary cadmium as a predictor of prostate cancer death under multivariate analysis was probably due to strongly confounding socio-economic variables, and there were relatively few prostate cancer deaths. To increase the number of cancer deaths to improve the power of the analysis, all cancer death was used in further analysis.

Since there were only 98 cases (before adjusting for the survey design) of prostate cancer related mortality in the NHANES III adult data linked to NHNAES III mortality data, to see if the effects of cadmium exposure would become more evident when more deaths were included, this study also investigated the effect of cadmium exposure on all cause (Table 4) and all cancer (Table 5) mortalities in men. For all cause mortality in men, the significant multivariate odds ratios (95% C.I.) were respectively: urinary cadmium concentration, 1.029 (1.0091 - 1.048); age, 1.009 (1.008 - 1.01); weight, 1.003 (0.10 - 1.0083); poverty income ratio, 0.75 (0.66 - 0.87); drinking, 1.0097 (0.10 - 1.02), and smoking, 1.0048 (0.99 - 1.02). For all cancer mortality in men, the significant odds ratios (95% C.I.) were respectively: urinary cadmium concentration, 1.015 (1.00 - 1.03); age, 1.0078 (1.0062 - 1.0095); black race, non-Hispanic white was used as the reference group, 1.79 (1.15 - 2.80); Mexican American race, 0.21 (0.083 - 0.53); and smoking, 0.012 (0.10 - 1.04). The effects of racial disparities (Cheung, 2012) and the adverse effects of smoking and drinking (Rothman et al., 2008) on cancer treatment outcomes have been reported and are supported by this study.

Taken together, this study showed that cadmium exposure as surrogated by urinary cadmium concentration was a significant predictor of prostate cancer mortality. In addition, positive correlations were found between cadmium exposure, age, weight and socioeconomic disparities and all cause and all cancer mortalities.

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