Cadmium Exposure and Cancer Mortality in the Third National Health and Nutrition

Examination Survey Cohort

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Abbreviations:
NHANES III: Third National Health and Nutrition Examination Survey
uCd: urine creatinine-corrected cadmium concentration
NCHS: National Center for Health Statistics
NDI: National Death Index
BMI: Body mass index
aHR: adjusted hazard ratio
95%CI: 95% confidence interval
py: pack-years (cigarette smoking)

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Abstract

Objective: This study examined prospective data from the Third National Health and Nutrition Examination Survey (NHANES III) cohort to investigate the relationship between cadmium exposure and cancer mortality, and the specific cancers associated with cadmium exposure, in the general population.

Methods: Vital status and cause of death through December 31, 2006 were obtained by the National Center for Health Statistics for NHANES III participants. Cadmium concentration of spot urine samples was measured, and corrected for urine creatinine. Weighted Cox proportional hazards regression with age as the time metric was applied to estimate sex-specific adjusted hazard ratios (aHRs) of mortality associated with uCd for all cancers and the cancers responsible for the most deaths in the US. Estimates were stratified by smoking history and adjusted education, body mass index, and race.

Results: uCd was associated with cancer mortality (aHR per 2-fold higher uCd (95%CI), men: 1.26 (1.07-1.48)); women: 1.21 (1.04-1.42)). In men, mortality from lung, pancreatic cancer and non-Hodgkin lymphoma was associated with uCd; an association with leukemia mortality was suggested. In women, associations were suggested with mortality due to lung cancer, leukemia, ovarian, and uterine cancer, but evidence was weaker than in men.

Conclusions: Cadmium appears to be associated with overall cancer mortality in men and women, but the specific cancers associated differ between men and women, suggesting avenues for future research. Limitations of the study include the possibility of uncontrolled confounding by cigarette smoking or other factors, and the limited number of deaths due to some cancers.

<u>What this paper adds</u>

- Laboratory evidence demonstrates that cadmium is a carcinogen in animals, and some epidemiological studies support an association between occupational and environmental cadmium exposure and cancer in humans.

- Prospective epidemiological studies in the general population of environmental cadmium exposure and cancer are limited.

- Using data from NHANES III, a cohort representative of the US population, the results of this study suggest that cadmium exposure, assessed by urinary cadmium concentration, was associated with all-cancer mortality in men and women.

- Cadmium exposure, independent of cigarette smoking, was most strongly associated with lung cancer, non-Hodgkin lymphoma, and pancreatic cancer mortality in men. In women, the associations of urinary cadmium with mortality from specific cancers were less clear.

Cadmium, a heavy metal, is classified as a human carcinogen[1]. Evidence of cadmium's carcinogenic potential comes from animal studies, which have been extensively reviewed[1-4]. Epidemiological studies of workers exposed to cadmium have found strongest evidence of increased lung cancer risk[5, 6], although controversy remains[7, 8]. Less is known about the long-term carcinogenic potential of cadmium exposure in the broader population and for other organs, but evidence suggests that cadmium is associated with lung[9], breast[10], and endometrial[11] cancer and may contribute to excess total cancer mortality[12].

The general population is primarily exposed to cadmium due to agricultural practices or industrial releases that result in contaminated soil. Crops such as leafy vegetables, pulses, grains, and tobacco accumulate cadmium from the soil, leading to human exposure[3]. Cadmium has also recently emerged as a contaminant of consumer goods[13].

In this analysis, we have examined data from the Third National Health and Nutrition Examination Survey (NHANES III), representative of the US population, linked to national death records, through December 31, 2006. We investigated urine cadmium concentration, a marker of long-term cadmium exposure[14, 15], in association with overall cancer mortality and mortality due to the cancers responsible for the most deaths in the US.

Materials and Methods

NHANES III and urine cadmium measurement. The NHANES III (1988-1994) comprised interviews and examinations of a stratified sample representative of the non-institutionalized US population. The survey structure, content, and laboratory procedures of NHANES III have been detailed[16, 17].

Spot urine samples collected from participants were assayed for cadmium and creatinine as described[16, 17]. Cadmium concentration (μg) was divided by creatinine (g) to correct for variation in hydration and reported as creatinine-normalized urine cadmium (uCd, μg/g).

Vital status. NHANES III participants ages ≥17 years (N=9,388 men; 10,636 women) were traced for mortality through December 31, 2006 by the National Center for Health Statistics (NCHS), following validated procedures[12, 18]. In brief, participants were matched to death certificates, the National Death Index (NDI), Social Security Administration records, and Centers for Medicare and Medicaid Services records using probabilistic algorithms. Cause of death was ascertained from the NDI and death certificates, recoded from ICD-9 to ICD-10 by NCHS if necessary, and was unavailable for 69 of 5,360 deaths in the cohort.

We sequentially excluded participants who reported prior cancer diagnosis other than non-melanoma skin cancer (N=780), without measured uCd (N=2,738) or complete information for other analysis variables (N=815), or who died of cancer within 1 year of baseline (N=18). Follow-up time for remaining participants (N=7,455 men and 8,218 women) was calculated from the date of NHANES III interview to death, or 31 December 2006.

Statistical Analysis. Sex-specific Cox regression was applied to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI) for death from all cancers and individual cancers associated with uCd, included in regression models as a single logarithmic term or parameterized as sex-specific quartiles. The quartile cut-off values of uCd in the US adult population were determined separately for men and women age ≥17 years without non-melanoma skin cancer diagnosis prior to baseline.

NHANES III protocols included extensive questions covering tobacco use[17]. Individuals who reported smoking ≥100 cigarettes total, no longer smoking cigarettes, and smoking no cigarettes within the previous 5 days were considered former smokers. All others were current smokers. Pack-years (py) of cigarette smoking was calculated from self-reported average number of cigarettes smoked per day (assuming 20 cigarettes / pack) and total number of years smoked; a single period of cessation or higher rate of smoking, if reported, was accounted for in the calculation.

Cox regression was stratified by smoking history (never smoker; former smoker and <20 py; former smoker and ≥20 py; current smoker and <20 py; current smoker and ≥20 py), allowing different baseline hazard functions for each group; and adjusted for baseline body mass index (BMI, linear), race/ethnicity (non-Hispanic white; all others), and education (<12 y; ≥12 y). Results were not materially changed after further adjustment for years since smoking cessation (former smokers), an additional linear term for py, use of oral tobacco, cigar smoking, tobacco pipe smoking, prevalent diabetes, family income, occupation or industry[19], and, among women, parity, (baseline) menopausal status, or restriction to post-menopausal women (not shown). Age (months) was the time variable for analysis, with participants entering risk sets at the time of interview. Stata 11 (StataCorp, College Station, TX) survey data analysis features to account for the sampling structure of NHANES III, following NCHS analytic guidelines[17]. Taylor linearization method was employed to estimate standard errors.

The proportional hazards assumption underlying Cox regression was checked graphically for adjustment variables in the final model. Possible violation of proportional hazards for smoking history motivated stratification; no important violations were found for other variables. For uCd, we also examined models including explicit interactions between age and uCd but found no statistically significant interactions.

Results

Follow-up for mortality averaged 13.4 and 13.8 years for men and women, respectively; 420 men and 303 women died of cancer. Geometric mean uCd for NHANES III participants included in this study was 0.252 µg/g (95%CI: 0.235 – 0.271 µg/g) in men, and 0.352 µg/g (95%CI: 0.327 - 0.379 µg/g) in women.

Each two-fold increase in uCd was associated with a 26% (95%CI: 7 – 48%) and 21% (95%CI: 4 - 42%) higher adjusted hazard of cancer death among men and women, respectively (Table 1). Adjusted hazard of death from all cancers was 70% (95%CI: 20%-140%) higher for men, and 34% (95% CI: -3 to 85%) for women, for individuals in the uppermost quartile uCd than for those in the lower three quartiles.

Among men, the association between uCd and mortality from lung cancer was statistically significant (Table 1). Of 23 deaths from pancreatic cancer in men, 17 occurred among men in the upper quartile of uCd (aHR (95%CI): 7.25 (1.77-29.80)). Similarly, 9 of 11 NHL deaths occurred among men in the upper quartile of uCd (aHR(95%CI): 25.83 (3.93-169.6)). Associations of uCd with mortality from lung, uterine and ovarian cancer in women, and with mortality from leukemia in both sexes, were also suggested.

Restriction to never-smokers generally attenuated the associations between uCd and cancer mortality, although the substantially fewer number of cancer deaths resulted in less precise estimates (Table 1). uCd remained associated with lung and pancreatic cancer death among never-smoking men. Among never-smoking women, uCd was inversely associated with risk of lung cancer death, but remained directly associated with mortality from all non-respiratory

cancers combined; risk of uterine cancer death also did not change substantially after restriction to never-smokers.

Discussion

We observed associations between uCd and cancer mortality in men and women. In addition, with 6 additional years of follow-up compared to a previous report from this cohort[12], we examined specific cancers responsible for the excess risk of cancer mortality. The association of uCd with total cancer mortality and with mortality from specific cancers was in general stronger in men than in women. In men, much of the excess risk was associated with lung cancer death, in both smokers and never-smokers, consistent with the results from a Belgian population-based prospective study[9].

Our observation of an association between uCd and pancreatic cancer death in men is consistent with limited previous epidemiological evidence from occupational cohorts[20]. Because cigarettes are a major source of cadmium among smokers[3] and a cause of pancreatic cancer[21], we restricted analysis to never-smokers, but the association of uCd with pancreatic cancer mortality remained. Thus, our results add to evidence that cadmium exposure is a possible cause of pancreatic cancer, independent of smoking.

Despite supporting evidence from animals[4], to our knowledge cadmium has not been previously linked to NHL in humans[22]. NHL has not been not strongly associated with cigarette smoking[23]; our results therefore suggest further avenues of research into the etiology of NHL.

uCd has been associated with breast cancer incidence[10, 24], but our results do not support a relationship with breast cancer mortality. We observed some evidence of a relationship between

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uCd and uterine corpus and ovarian cancer death. One prior study of estimated dietary

cadmium and ovarian cancer risk found no association[25]. However, within the same cohort,

dietary cadmium was associated with endometrial cancer risk[11]. These prior studies were

motivated by laboratory evidence that cadmium can be estrogenic[26, 27]. Overall, our study

results support further investigation of the role of cadmium in hormonal cancers in women.

Our results suggesting elevated risk of cancer mortality among the general population are

somewhat surprising when directly compared to equivocal results from studies of occupational

cohorts[8, 20], who are presumably more highly exposed to cadmium. However, our use of uCd,

a specific measure of absorbed cadmium dose[1, 14, 15, 28], may have increased the

sensitivity of our study and previous similar studies[9, 12] in comparison to occupational studies

that employ other exposure assessment methods[8]. Moreover, the "healthy worker bias,"

incomplete follow-up resulting in survival selection, and small numbers of deaths limit

occupational studies of cadmium and cancer[1, 8].

Of course, our study also has important limitations that must be considered. There were

relatively small numbers of deaths from some cancers, especially among non-smokers.

Combined with the relatively large number of comparisons made in our study, we expect that

some of the statistically significant associations observed resulted from Type I errors. In

addition, NHANES III follow-up data include cancer mortality but not incidence. Therefore, our

results pertain to fatal cancers, and may thus differ from the results of studies of cancer

incidence. Finally, although we controlled for tobacco use, residual confounding remains

possible, and we were limited in our ability to control for other potential sources of confounding

including occupational exposures.

The strengths of this study include its prospective design, setting within a well-documented cohort with nearly complete follow-up designed to be representative of the US population. In addition, urine cadmium reflects accumulation in the kidneys, and is considered a measure of long-term cadmium exposure, especially in populations exposed non-occupationally to cadmium[1, 3, 14, 15, 28]. uCd takes years to decrease substantially after cessation of exposure [15, 29], and therefore likely comprises an accurate ranking of internal cadmium dose, minimizing misclassification of exposure in our analysis.

Overall, these results add evidence in support of the hypothesis that exposure to cadmium is a cause of excess cancer death in the US population. Our results also shed light on the specific cancers which may be associated with environmental cadmium exposure. However, because of important limitations, these results should be viewed with caution and, perhaps, as hypothesis-generating. More data are needed to clarify the relationship between cadmium exposure and cancer in the general population.

Table 1. Estimated adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) of cancer mortality associated with creatinine-corrected urine cadmium (uCd; μg cadmium per g creatinine).

	Men							Women						
	per 2-fold uCd			Q1-3**	Q4 (>0.580 μg/g)			per 2-fold uCd			Q1-3**	Q4 (>0.819 μg/g)		
	Deaths	aHR	95%CI	Deaths	Deaths	aHR	95% CI	Deaths	aHR	95%CI	Deaths	Deaths	aHR	95% CI
Entire Population														
All Cancer	420	1.26	(1.07-1.48)	160	260	1.70	(1.20-2.40)	303	1.21	(1.04-1.42)	136	167	1.34	(0.97- 1.85)
Lung	131	1.81	(1.49-2.21)	19	112	3.22	(1.26-8.25)	76	1.21	(0.79-1.84)	19	57	1.82	(0.99- 3.33)
All cancers except lung	289	1.07	(0.90-1.27)	141	148	1.30	(0.87-1.95)	227	1.21	(1.05-1.39)	117	110	1.19	(0.84- 1.69)
Prostate	54	1.06	(0.71-1.57)	30	24	1.34	(0.75-2.38)							
Breast	1			1	0			42	1.08	(0.91-1.28)	30	12	0.58	(0.34- 0.98)
Colon and rectum	49	0.90	(0.60-1.35)	30	19	0.84	(0.37-1.94)	22	1.06	(0.62-1.81)	10	12	0.80	(0.19- 3.39)
Pancreas	23	1.51	(0.85-2.70)	6	17	7.25	(1.77-29.80)	14	1.03	(0.72-1.48)	8	6	1.24	(0.58- 2.63)
Liver	14	0.89	(0.74-1.08)	8	6	0.51	(0.20-1.32)	9	1.14	(0.84-1.54)	3	6	1.21	(0.40- 3.61)
Leukemia	10	1.93	(0.72-5.19)	4	6	1.86	(0.31-11.13)	13	1.29	(0.97-1.71)	5	8	1.67	(0.55- 5.07)
Non-Hodgkin's Lymphoma	11	2.53	(1.72-3.71)	2	9	25.83	(3.93-169.6)	11	0.90	(0.49-1.66)	7	4	0.67	(0.16- 2.90)
Ovary								13	1.41	(0.86-2.29)	6	7	2.40	(0.66- 8.69)
Uterine corpus								7	1.48	(1.09-2.00)	4	3	1.03	(0.23- 4.62)
Never-smokers														
All cancers	87	1.14	(0.87-1.49)					131	1.00	(0.84-1.19)				
Lung	5	2.16	(1.39-3.36)					8	0.57	(0.33-0.97)				
All cancers except lung	82	1.11	(0.84-1.45)					123	1.14	(1.00-1.29)				
Prostate	18	0.90	(0.71-1.14)											
Breast	0							22	1.03	(0.85-1.24)				
Colon and rectum	18	0.95	(0.73-1.24)					9	0.81	(0.63-1.03)				
Pancreatic	5	3.95	(1.94-8.04)					8	0.84	(0.55-1.29)				
Liver	5	0.99	(0.79-1.24)					6	1.37	(1.19-1.58)				
Leukemia	3	1.63	(0.53-4.98)					8	1.13	(0.86-1.48)				
Non-Hodgkin's Lymphoma	3	1.93	(0.46-8.07)					8	1.18	(0.65-2.15)				
Ovary								10	1.32	(0.75-2.31)				
Uterine corpus								4	1.63	(1.06-2.51)				

* Adjusted for age (as the time axis in Cox regression; months), smoking history (never; former with <20 pack-years; former with ≥20 pack-years; current with <20 pack-years; current with ≥20 pack-years), body mass index (linear continuous variable), education (<12 years, ≥12 years), and race (non-Hispanic white, other); HRs and 95% CIs were estimated accounting for the NHANES III survey design.

**uCd quartiles cut-off values (μg/g): 0.153, 0.297, 0.580 (men) and 0.210, 0.418, 0.819 (women). Note that a 2-fold increase in uCd corresponds approximately to quartile boundaries.

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Human Subjects Research:

This research used only publicly available, de-identified data and is therefore not categorized as human-subjects research.

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