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Prostate-Specific Antigen Levels in Relation to Cadmium Exposure and Zinc Intake: Results From the 2001–2002 National Health and Nutrition Examination Survey

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BACKGROUND. Cadmium exposure has been suggested as a risk factor for prostate cancer, and experimental literature suggests that the carcinogenic effect of cadmium is modified by the presence of zinc. We evaluated total prostate-specific antigen (PSA) levels in relation to urinary cadmium concentrations and dietary zinc intake.

METHODS. PSA levels were determined in 1,320 men over the age of 40 in the 2001–2002 National Health and Nutrition Examination Survey (NHANES). Urinary cadmium concentrations were measured in about one-third of the sample population, whereas dietary zinc intake was based on participants' 24-hr recall. Information on all three variables was available for 422 men in the 2001–2002 NHANES survey. We performed linear regressions to evaluate the relationships these factors after accounting for age and other covariates.

RESULTS. Little evidence for an association between cadmium and elevated PSA level was observed. However, the data provide suggestive evidence for an interaction between zinc intake and cadmium exposure (P for interaction = 0.09). Among men with zinc intake less than the median level of 12.67 mg/day, an increase in 1 μg/g creatinine cadmium exposure was associated with a 35% increase in PSA level. In contrast, among men with greater than median zinc intake, little evidence for an association between cadmium and PSA was found.

CONCLUSIONS. These findings suggest a protective effect of zinc intake on cadmium-induced prostatic injury, and may provide further rationale for investigating the impact of these factors individually and jointly on the etiology of prostate cancer. *Prostate 68: 122–128, 2008.*

KEY WORDS: **prostate-specific antigen; cadmium; zinc; epidemiology**

INTRODUCTION

Prostate cancer is a significant burden on men's health. It is the most frequently diagnosed non-cutaneous malignancy in the United States with 218,890 new cases and 27,050 deaths expected in 2007, making this the second leading causes of cancer-related mortality for American men [1]. The nature of the risk factors contributing to the development of prostate cancer remains largely unknown [2–11]. However, it has been argued that moderate risks cannot be excluded for most occupational and environmental exposures [2,12]. For example, cadmium is a potential risk factor for prostate cancer based on substantial supportive evidence from experimental studies for such an association.

Cadmium is a non-essential heavy metal that occurs naturally in zinc and lead ores and in some rock phosphate fertilizers [13–15]. Anthropogenic sources

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of cadmium have continued to rise over the past century [13,16], although commercial use of cadmium recently (2001–2004) declined by about 70% due to environmental concerns [17]. Commercially, cadmium is predominantly used in the manufacture of batteries (78%), pigments (12%), coatings and plating (8%), stabilizers for plastic (1.5%), and nonferrous alloys and other uses (0.5%) [16,17], and more than 500,000 workers are thought to be exposed to cadmium each year [16]. Emissions of cadmium into the environment occur mainly via anthropogenic activities, and have been estimated to be up to 10-fold greater than emissions from natural sources [13]. Consequently, the application of fertilizers and sewage sludge to land, industrial production of cadmium containing products, and smelter emissions has increased the uptake of cadmium in the general population [18,19]. Food crops grown on soils rich in cadmium from natural or man-made sources constitute a major source of non-occupational cadmium [20]. Therefore, the diet is the most important source of cadmium exposure in the general non-smoking population and puts everyone at risk of exposure [16,17]. Smoking typically doubles the total daily absorption of cadmium [17,19,21,22]. Approximately 3–10% of ingested cadmium, and about 50% of inhaled cadmium is absorbed into the bloodstream [23]. Cadmium accumulation occurs primarily in the liver and kidney, with the most extensive accumulation in the renal cortex (one-third to one half of total accumulation) [15]. Most of the cadmium in the liver and kidney is bound to metallothionein, an inducible metal-binding protein that functions in the homeostasis of heavy metals (e.g., zinc) and provides protection against many of cadmium's toxic effects [17,23]. Due to the renal reabsorption of the cadmium–metallothionein complex and the absence of an active biochemical mechanism for elimination, the excretion rate of cadmium is extremely slow with an estimated half-life of cadmium in the kidney between 10 and 30 years [17,19]. Approximately 0.001% of cadmium in the body is excreted per day, mostly in urine [15]. Cadmium concentration in blood and urine are commonly used as biological markers of cadmium exposure. Cadmium in blood generally reflects current exposure, whereas urinary cadmium is proportional to the concentration in the kidneys [19]. In the absence of substantial damage to the kidney, urinary cadmium is considered a good marker of both steady state exposure to cadmium as well as an indicator of total body burden [24]. Therefore, it is a useful estimate for long-term exposure [25], which can be used in epidemiological studies of cadmium carcinogenicity to more accurately evaluate dose–response associations in populations in which cadmium exposure is occurring through multiple possible pathways.

The increased environmental pollution by cadmium has raised concerns about its effects on the health of the general population [14,15,20]. Historically, the first site suspected to be associated with occupational exposure to cadmium was the prostate [26], although recent epidemiological studies have not strongly supported such an association. Nevertheless, several interesting leads have emerged, and experimental studies strongly suggest that cadmium can cause cancer of the prostate [27–29]. It is likely that the effect of cadmium on prostate cancer is complex and potentially dose-dependent, and may be modified by exposure to zinc [28,29]. We examined the relationship between prostate-specific antigen (PSA), urinary cadmium, and dietary zinc intake in a nationally representative sample of U.S. males over the age of 40. We hypothesized that we would observe a positive association between urinary cadmium and PSA levels given that elevated PSA levels are indicative of prostatic epithelial damage. It should be noted, however, that cadmium, as an inductor of PSA expression, may also result in elevated PSA levels independent from other processes [30].

MATERIALS AND METHODS

Study Population

We evaluated the association between urinary cadmium concentrations and PSA levels in the 2001–2002 NHANES public use data file [31]. This is the first NHANES survey in which PSA levels were determined in men over the age of 40 [32]. Levels of total and free PSA were measured in 1,320 eligible men after excluding men who reported having any of the following conditions: current infection or inflammation of the prostate gland, rectal exam in the past week, prostate biopsy in the past month, cystoscopy in the past month, history of prostate cancer, or had missing data on any of these eligibility criteria [33]. In the heavy metal exposure examination of this survey, cadmium levels were measured based on a single spot urine collection in a one-third randomly selected subset of the 2001–2002 NHANES study population age 12 and older ($n = 2,804$). Urinary cadmium levels were available in about one-third of the 1,320 eligible men. Thus, after merging the heavy metals and PSA datasets a total of 437 men with both PSA and urinary cadmium levels were available for analysis.

Explanatory Variables

Urinary cadmium levels were measured with inductively coupled plasma-mass spectrometry (ICP-MS) after correction for interference from molybdenum oxide, and were subsequently adjusted for urinary

creatinine levels according to the formula described by Paschal et al. [24]. Zinc intake was calculated based on 24-hour recall from the NHANES dietary survey in 2001 and the integration of two nationwide dietary intake surveys (U.S. Department of Agriculture's Continuing Survey of Food Intakes by Individuals (CSFII) and NHANES) in 2002, in combination with a food table listing micronutrient levels for individual food items (no biological markers of zinc were available) [31]. For those for whom dietary zinc intake estimates were available (n = 422), about 66% reported that the amount of food they ate during the 24 hr period was about average. Almost 12% reported that they ate much more than usual and 22% reported that they ate much less than usual during the study period. Additionally, we considered zinc intake from dietary supplements (see below). Other covariates considered include age (continuous or categorical; 40–59, 60–69, 70–79, and 80+), race (white, black, other), education (<high school, high school, >high school), body mass index (BMI; <25, 25–29, 30+) and smoking status (dichotomous: ever, never; continuous: duration of smoking in years).

Statistical Analysis

First, we conducted a descriptive analysis to estimate average and median creatinine-adjusted urinary cadmium levels (UCD_{CR}) and PSA concentrations across categories of age, race, education, body mass index, and smoking status. Furthermore, we evaluated median PSA concentrations across quartiles of cadmium and zinc exposure. Subsequently, in a linear regression PSA levels (transformed with natural logarithm) were predicted as a function of UCD_{CR} (continuous), age (continuous), race, education, BMI, smoking status (dichotomous; adjustment for smoking duration yielded similar results (data not shown), and therefore additional smoking metrics such as pack-years were not considered), and zinc intake (dichotomous based on median dietary intake of 12.67 mg/day, and continuous). Other regression models included a product term of UCD_{CR} (continuous and dichotomous based on a median of 0.31 μg/g) and dietary zinc intake (dichotomous) to evaluate the impact of a possible interaction on PSA levels. Zinc intake from supplements in the past 30 days was also combined with dietary intake in another dichotomous variable, where individuals above the median dietary intake *or* with recent zinc intake from supplements were considered exposed while those below the median dietary zinc intake and not taking supplemental zinc were considered unexposed. Findings did not materially differ from those considering dietary intake only (data not shown), therefore these results are not discussed further. All statistical analyses were done in SAS version 9.2 (SAS Institute, Cary, NC) using the SURVEYMEANS and SURVEYREG procedures which incorporated the appropriate sample weights (WTSH M2YR), and stratum and PSU variables (SDMVSTRA and SDMVPSU, respectively).

RESULTS

PSA levels increased substantially with age from a median of 0.80 ng/ml in men aged 40–59 to 2.20 ng/ml among men over the age of 80 (data not shown). Median PSA levels were slightly higher among black men, and somewhat lower among overweight/obese men and ever smokers. Univariate analyses demonstrated no consistent increase in median PSA level across quartiles of cadmium (0.8, 0.8, 0.8, and 1.0 ng/ml, respectively) or zinc exposure (0.9, 0.9, 0.8, and 0.9 ng/ml, respectively). Table I shows the results of the multiple linear regression analysis of log-transformed PSA concentrations. Little evidence for an association between cadmium and elevated PSA level was observed with and without adjustment for zinc intake, and in the absence of considering an interaction with zinc intake. Similarly, there was little correlation between zinc intake (continuous or dichotomous) and PSA level. Evaluation of urinary cadmium concentrations or zinc intake by quartiles of exposure in relation to PSA levels did not change these observations (data not shown).

On the other hand, the data provide suggestive evidence for an interaction between zinc intake and cadmium exposure (P for interaction = 0.09 and 0.07 for continuous and dichotomous cadmium variable, respectively). Among men with zinc intake less than the median level of 12.67 mg/day, an increase in 1 μg/g creatinine of UCD_{CR} is associated with a 35% (i.e., $e^{\beta} = e^{0.30}$) increase in PSA level. Alternatively, PSA levels in men with low zinc intake and UCD_{CR} levels above the median are 22% (i.e., $e^{0.20}$) greater as compared to men with low zinc intake and UCD_{CR} levels below the median. In contrast, among men with greater than median zinc intake, little evidence for an association between cadmium and PSA was found.

DISCUSSION

The prostate is believed to be a target organ for cadmium deposition, in addition to the kidney and liver [34,35]. Several studies have shown that cadmium can induce tumors and preneoplastic lesions of the prostate in rats after injection or oral administration [28,29]. The cadmium effect in these studies was reported to be dose-dependent at doses below the threshold for significant testicular toxicity [29]. At sufficiently large doses, cadmium induces testicular

TABLE I. Linear Regression Models for the Association Between Levels of Creatinine-Adjusted Urinary Cadmium, Zinc Intake and PSA Levels (Natural Logarithm): National Health and Nutrition Examination Survey 2001–2002*

	Cadmium + zinc[a]		Cadmium–zinc interaction[b]		Cadmium–zinc interaction[c]	
Variable	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Intercept	−1.38 (0.26)	<0.0001	−1.34 (0.30)	0.0004	−1.23 (0.27)	0.0004
Creatinine adj. Cd (μg/g)	0.0065 (0.15)	0.97	0.30 (0.21)	0.18	0.20 (0.15)	0.20
Zinc intake (mg/day)[c]	0.0070 (0.0043)	0.13	0.23 (0.16)	0.19	0.15 (0.15)	0.35
Creatinine adj. Cd × zinc intake (interaction)	—	—	−0.64 (0.35)	0.087	−0.34 (0.17)	0.070
Age (years)	0.027 (0.0045)	<0.0001	0.026 (0.0043)	<0.0001	0.025 (0.0042)	<0.0001
Race/ethnicity[d]						
Black	0.34 (0.16)	0.052	0.30 (0.17)	0.087	0.30 (0.17)	0.094
Other	0.049 (0.13)	0.71	0.025 (0.14)	0.86	0.011 (0.13)	(0.94)
Education level[e]						
High school	0.030 (0.13)	0.83	0.057 (0.13)	0.66	−0.011 (0.12)	0.93
>High school	0.051 (0.13)	0.70	0.061 (0.12)	0.63	0.019 (0.11)	0.87
Ever smoked	−0.29 (0.050)	<0.0001	−0.30 (0.047)	<0.0001	−0.33 (0.070)	0.0003
Obesity						
25–29	−0.34 (0.12)	0.012	−0.31 (0.12)	0.019	−0.33 (0.11)	0.011
30+	−0.14 (0.16)	0.41	−0.12 (0.16)	0.48	−0.14 (0.16)	0.39

[a]Creatinine adjusted Cd levels and dietary zinc intake included as continuous variables.
[b]Creatinine adjusted Cd levels included in the model as a continuous variable; zinc included as a dichotomous variable based on a median intake of 12.67 mg/day.
[c]Creatinine adjusted Cd levels included in the model as a dichotomous variable based on a median of 0.305 μg/g; zinc included as a dichotomous variable.
[d]Reference = non-Hispanic whites.
[e]Reference = <high school.
*Four hundred twenty-two observations included in the analysis due to missing zinc values.

hemorrhagic necrosis resulting in decreased testosterone secretion and consequently the loss of androgen production. It has been postulated that this observation could explain the loss of prostatic tumor response at substantially elevated dose levels of cadmium in rats [27,28]. Interestingly, cadmium has also been shown to be associated with neoplastic transformation of human prostate epithelial cells [36]. In a study of 11 normal human prostate samples, 16 benign prostatic hyperplasia samples and 7 prostate cancer samples, increased cadmium levels of 0.73 (±0.12) ppm were reported in cancer tissues as compared to 0.40 (±0.10) ppm in normal tissues [37]. Current mechanistic evidence for a role of cadmium in prostate carcinogenesis suggests the involvement of epigenetic or indirect genotoxic mechanisms [29]. For instance, cadmium exposure may result in resistance to chemically induced apoptosis [38], abrogated DNA repair [39], and the activation of proto-oncogenes or genes associated with cell proliferation [29,40].

It is important to consider an individual's exposure to cadmium and zinc simultaneously which is particularly relevant in human populations where dietary intake and occupational exposure may involve concurrent exposure to both compounds [16,41]. Zinc stimulates the bioavailability of metallothioneins (MT) which increase the binding of cadmium, thereby reducing the bioavailability of cadmium and its toxicological effects [28]. In our data there was a weak but statistically significant ($P < 0.01$) inverse correlation between dietary zinc intake and creatinine adjusted urinary cadmium levels ($r = -0.15$ for untransformed variables, $r = -0.20$ for log transformed variables). Additionally, zinc may antagonize or enhance cadmium-induced prostate carcinogenesis via its dose-dependent effect on testicular androgen production [28,29]. Interestingly, prostatic zinc levels have been observed to be higher in men with prostate cancer in comparison to men without malignancy. Whether this finding is causative, resultant or merely an unrelated association is unknown [42].

We observed a positive correlation between urinary cadmium levels and PSA levels after the interaction with zinc was taken into account. That is, a cadmium effect on PSA levels was only observed when dietary zinc intake levels were low, which supports the potential impact of zinc on cadmium-induced prostatic cellular injury. Given the recent evidence implicating cadmium itself as an androgen receptor ligand and inducer of androgen associated gene transcription,

however, a direct role for cadmium in our study as an inductor of PSA expression cannot be excluded [30]. These findings from experimental and observational studies illustrate that the effect of cadmium on prostate cancer is complex and potentially dose-dependent, and may be modified by exposure to zinc. Further investigation in humans is needed to provide further insight into these mechanisms.

The epidemiological literature regarding the association between cadmium exposure and prostate cancer has been extensively reviewed [2,12,21,23]. Recently, Sahmoun et al. [23] described the results of 10 case–control studies (some population-based, some nested within an occupational cohort) and 11 cohort studies. They reported that although some of the highest levels of exposure have been found in the nickel–cadmium battery industry [23], cohort studies of workers in this industry showed mortality rates slightly greater but largely consistent with expected rates. Four case–control studies are of particular interest because they reported associations by tumor aggressiveness, used biological exposure markers, or described exposure-response trends [41,43–45]. Two of these studies reported some evidence for an association between indicators of cadmium exposure and the risk of aggressive or extraprostatic tumors but not when all tumors were combined [41,43]. A recent small study observed an excess but statistically imprecise risk in the highest quartile of toenail cadmium concentration based on 40 patients newly diagnosed with prostate cancer [45]. Another study found an elevated but imprecise risk with self-reported frequent occupational exposure [44]. Platz et al. [43] in their recent study did not find a statistically significant interaction between cadmium and zinc. They also used toenail concentrations of cadmium which one might surmise is likely an improvement over methods of exposure assessment employed in some other studies such as self-reported exposure or occupational levels assigned by an industrial hygienist [41,44]. However, the authors acknowledged that the physiological determinants of toenail cadmium and its usefulness to estimate cumulative exposure are unknown [24,25]. Furthermore, with only 115 cases, their study likely did not have sufficient statistical power to detect interactions. It should be noted that none of these studies relied on urinary cadmium levels, which has been considered the gold standard for long-term exposure [46].

Thus, despite some suggestive findings, previous epidemiological studies do not provide conclusive evidence for cadmium exposure playing a role in prostate carcinogenesis. However, several methodological limitations (e.g., lack of biological exposure markers or information on tumor aggressiveness) in most of these studies have likely hampered the ability to detect noteworthy associations. Interestingly, a cross-sectional study in New Zealand found a significant positive association between blood cadmium levels and elevated PSA while no correlation was found with blood zinc levels [12]. Therefore, it remains uncertain whether typical environmental exposure to cadmium is a risk factor for prostate cancer and whether zinc intake inhibits or facilitates the potential cadmium effect. Parent and Siemiatycki recently concluded in a review of occupational risk factors for prostate cancer that ''apart from the equivocal epidemiological evidence, there are other reasons to continue to pay attention to cadmium as a possible risk factor,'' citing evidence from the experimental literature clearly supporting this hypothesis [23]. Sahmoun et al. [23] reached a similar conclusion, and argued that additional occupational cohort studies are unlikely to be productive. These authors suggested that case–control studies using urinary cadmium as an exposure biomarker may resolve some of the discrepancies between experimental and observational studies [47].

The results of the present study should be viewed in light of several limitations. First, we evaluated cadmium exposure in relation to PSA levels which are mostly a measure of prostatic injury or inflammation and not necessarily indicative of malignancy. Although the PSA test is easy to administer, reproducible, inexpensive, and its cancer detection capability is superior to that of digital rectal exam alone [48], its utility as a screening tool is limited. PSA levels fluctuate over time [49,50], and PSA sensitivity and specificity have been shown to be suboptimal given a false negative rate of up to 15% and a false-positive rate of about 33%, respectively [51,52], which is why many professional medical societies have been reluctant to endorse the widespread use of PSA testing for prostate cancer screening [53]. Nevertheless, it has recently been suggested that PSA levels are best viewed as a continuous biomarker for prostate cancer risk. Secondly, the effective sample size for our analysis was quite small possibly resulting in inadequate power to detect statistically significant effects or interactions. Despite the limited sample size our findings were strongly indicative of an interaction between cadmium and zinc in the etiology of prostatic injury. Furthermore, zinc intake was based on 24-hr recall which may not be representative of long-term and perhaps more etiologically relevant zinc levels. Indeed, only two-third of men in our study reported that their dietary intake was about average. Finally, our models only explained about 15% of the variability in PSA levels despite the inclusion of well-established covariates, which demonstrates the difficulty of predicting this parameter. Importantly, this study does have several strengths including the use of biomarkers of exposure

and outcome, consideration of a variety of potential confounders, and the ability to generalize to the male U.S. population due to the nationally representative sample examined in the NHANES survey.

CONCLUSION

In conclusion, our findings appear to suggest a protective effect of zinc intake on cadmium-induced prostatic injury, which may provide further rationale for investigating the impact of these factors individually and jointly in the etiology of prostate cancer.

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