Cadmium, Sexually Transmitted Disease, and Risk for Prostate Cancer

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Abstract: *Background*: Several studies suggested that cadmium and sexually transmitted diseases (STDs) may increase risk for prostate cancer. However, these associations are not well established. The aim of this study was to investigate associations among cadmium, STDs, and risk for prostate cancer.

Methods: A community-based case-control study of 113 newly diagnosed, incident cases and 258 age and race frequency-matched community controls was conducted in the Piedmont Triad area of North Carolina. All participants completed a medical/lifestyle/dietary questionnaire, underwent anthropometrics, and provided urine samples. Urinary cadmium was used as a biomarker of lifetime cadmium body burden. Multivariable unconditional logistic regression was used to assess associations among cadmium exposure, history of STDs, and risk for incident prostate cancer.

Results: Neither cadmium nor STD exposures alone were statistically significantly associated with risk for prostate cancer (odds ratio (OR) = 0.91; 95% confidence interval (CI): 0.49-1.69; and OR=1.32; 95% CI: 0.49-3.52, respectively). However, men with high urinary cadmium who also had a history of a STD had significantly increased risk for prostate cancer (OR=9.75; 95% CI: 1.28, 74.05), an association that was stronger for advanced tumors.

Conclusions: These results suggest that cadmium and STD exposures may synergistically increase risk for prostate cancer.

Keywords: Case-control studies, cadmium, prostatic neoplasms, sexually transmitted diseases.

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer and the second most common cause of cancer death in American men [1]. Despite the high morbidity and mortality from prostate cancer, other than age, race, and family history, factors influencing risk for the disease are not clear.

There is an approximate 70-fold variation in prostate cancer incidence between populations around the world [2], and when men migrate from low to high risk countries their incidence rates approximate those of their adopted countries within a generation [3]. These findings emphasize the impact of environment on prostate cancer incidence. However, little is known about the roles of environmental risk factors in prostate cancer development. Furthermore, international differences in incidence rates for prostate are primarily related to more advanced (regional/distant spread) disease, suggesting that modifiable environmental risk factors may be most relevant to the development of clinical disease [4].

Cadmium (Cd) and its compounds are heavy metallic toxicants that have been largely used in industry until the last decade, and are widely dispersed in the environment. In addition to exposure to cadmium through occupational contact, humans are exposed to cadmium through foods and tobacco grown in soils containing cadmium. Occupational exposure to cadmium has been strongly associated with risk of lung cancer in humans [5]. In 1993 cadmium was designated a human carcinogen by the International Agency for Research on Cancer (IARC) and the US National Toxicology Program.

Experimental studies found that cadmium administration *via* different routes can induce prostate cancer in rats. Waalkes *et al.* [6] found that a single subcutaneous injection of cadmium chloride increased the incidence of prostate tumors. Oral cadmium exposure also promoted a dose-related induction of proliferative lesions, such as tumors and atypical hyperplasia, in the rat prostate [7]. However, the results of epidemiological studies are quite controversial and a possible linkage of cadmium exposure with prostate cancer is not established [8, 9]. The ambiguous epidemiological findings in some studies may be due to the difficulties of measuring cadmium exposure. Unlike cadmium in hair or nails, cadmium in urine is likely a more sensitive dosimeter of lifetime cadmium body burden [10].

Roles for sexually transmitted diseases (STDs) and/or other infectious agents associated with sexual behavior in prostate carcinogenesis have been supported by some previous studies [11, 12]. A recent meta-analysis provided evidence of a higher rate of prostate cancer in men with a history of an exposure to gonorrhea, human papillomavirus, or any STD [13]. It has been postulated that underlying hormonal factors such as androgens may contribute to the association between sexual behavior, STD and prostate cancer risk [14]. Some known or unknown infectious agent(s) associated with STD may be another underlying mechanism for prostate cancer [15].

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It has been hypothesized that carcinogenesis involves both initiating and promoting factors. Cadmium and infectious agents may be both genotoxic/mutagenic and mitogenic and could synergistically increase risk for prostate cancer. Herein, we report the results of a case-control study of incident prostate cancer in which urinary cadmium was used as a biomarker of lifetime cadmium exposure, and personal histories of sexually transmitted disease were ascertained as surrogate indicators of possibly harboring asymptomatic, chronic, infectious agent-induced inflammation in the prostate.

MATERIALS AND METHODOLOGY

Study Subjects

This community-based case-control study of incident prostate cancer was conducted in the Piedmont Triad area of North Carolina. The research protocol was approved by the Committee for Human Research at Wake Forest University, Winston-Salem, North Carolina. The 113 cases for the study consisted of black and white men with a pathology-documented diagnosis of prostate cancer. All cases were over 50 years old, English speaking, and newly diagnosed with first time ever prostate cancer. Cases were identified and recruited from all cases diagnosed with prostate cancer during the study period in area urology and radiation oncology practices within days of diagnosis and studied prior to initiating treatment for the disease. A total of 258 controls were recruited from the same geographic area as cases by a random selection procedure using the Polk Directory. All controls were frequency matched to cases on age and race, and had no history of prostate cancer. Participants were excluded if they had a history of a previous cancer (other than non-melanoma skin cancer), current prostate disease (e.g., symptomatic benign prostatic hypertrophy or prostatitis), previous prostate surgery, active tuberculosis, or current liver or kidney disease.

Data Collection

All participants attended a four- to five-hour study visit at the General Clinical Research Center (GCRC) at Wake Forest University, involving informed consent procedures, interview, completing a medical/lifestyle questionnaire and a Block Food Frequency Questionnaire, anthropometrics, and providing blood and spot and timed urine samples. Participants received $50 for their time and effort for participating in the study. Cadmium was measured in the spot urine samples in triplicate using continuum source atomic absorption spectrophotometry. Urinary cadmium concentration was normalized to urinary creatinine. Blinded duplicate samples were measured on ten percent of participants to assess the reliability of the assays. STD exposure was ascertained by self-report *via* the medical questionnaire in response to the question, "Have you ever been told by a doctor that you had:" any of the following diseases, one by one: "syphilis", "gonorrhea (clap)", "genital herpes", "genital warts", or "other sexually transmitted diseases". PSA data were not available since at the time of the clinical phase of this study (1994 – 1996) the National Cancer Institute (NCI) had a policy prohibiting the use of NCI funds for PSA measurements. Tumor staging by the TNM system and pathology information on cases was abstracted from hospital tumor registries. Gleason scores were not available.

Data Analysis

Descriptive comparisons of cases and controls were tabulated and analyzed using the Chi-square test for categorical variables and the *t*-test for continuous variables. Intra-class correlation analysis was used to evaluate the reliability of urinary cadmium and creatinine measurements.

Cadmium exposure was defined as urinary cadmium per mg of urinary creatinine and analyzed in the models as a two-level variable (low: $< 5.34 \times 10^{-4}$ μg/mg; high: $\geq 5.34 \times 10^{-4}$ μg/mg) based on the median value among controls. The largest initial unconditional logistic regression model was established including potential confounding and effect modifying variables (listed in the descriptive comparisons of cases and controls in Table **1**) and their cross-product terms with cadmium. The gold standard model was generated after collinearity diagnostics and backward elimination. Criteria for inclusion in the final model included biological plausibility, fit at the $p \leq 0.1$ level of statistical significance, and changing the estimated odds ratio for the primary exposure variable by $\geq 10\%$. The final full model included the main exposure variable (urinary creatinine-standardized cadmium), frequency matching variables (age and race), education, smoking status, family history of prostate cancer in a first degree relative, physical activity, vasectomy, multivitamin taking, total energy intake, body mass index (BMI), STD, and a cadmium by STD interaction term. Cigarette smoking, associated with prostate cancer in some studies [16, 17], did not meet the criteria for inclusion in the statistical models in this study. The Hosmer-Lemeshow Goodness-of-Fit test was performed to evaluate the suitability of the full model.

Unconditional logistic regression with the gold standard model was used to assess the associations between cadmium exposure and STD history and risk of prostate cancer controlling for all potential confounding variables simultaneously. The same final model was used to assess associations of cadmium exposure with different stages of prostate cancer; cases were categorized as having localized (confined within the prostate gland) or advanced (extension beyond the prostate capsule and/or regional/distant spread) disease according to the TNM tumor staging system, and then both case groups were compared to all controls. The full model without cadmium or STD was used to assess the respective associations of STD and cadmium with incident prostate cancer. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). The cut-point for statistical significance was 0.05 for all analyses.

RESULTS

Of 203 case subjects who were initially found to be eligible, 113 (55.7%) were interviewed. Attrition was because of refusal or non-response (34.3%), inability to come for the study visit (6.0%), or cases eventually refused or did not pass final eligibility assessed during the study visit (4.0%). Of the 877 eligible control subjects, 258 were interviewed (29.4%). Again, attrition was because of refusal or non-response (66.6%), or controls eventually refused or did not pass final eligibility during the study visit (4.0%). Among 371 participants, 30 did not answer the questions on STDs, and cadmium results were not available (e.g., insufficient urine volume) on 20 participants, thus leaving 321 participants avail-

Table 1. Characteristics of Men Diagnosed with Incident Prostate Cancer and Controls, Piedmont Triad Area, North Carolina, U.S., 1994-1996

Characteristics	Cases (n = 113)		Controls (n = 258)		P Value*
Age (years)**	66.1	(7.5)	67.0	(7.6)	0.87
Race (%)					
Black	15.0		14.3		
White	84.1		85.3		0.85
Education (%)					
< High school	23.9		16.3		
High school	44.2		50.0		
≥ College	31.9		33.7		0.22
1° relative with prostate cancer (%)	21.2		15.1		0.02
Currently smoke (%)	13.3		9.3		0.26
Physical activity (%)					
Light	31.0		29.1		
Moderate	53.1		57.8		
Vigorous	14.2		9.7		0.41
BMI (kg/m^2)	27.0	(3.9)	27.3	(3.7)	0.46
Vasectomy (%)	23.0		26.0		0.55
Total energy intake (kcal/day)	2,106	(1,058)	1,827	(641)	0.01
Take multivitamins (%)	69.0		76.0		0.13
History of STD (%)	13.3		8.9		0.22
Urinary cadmium/creatinine ($\mu g/mg \times 10^{-4}$)	6.74	(7.3)	6.61	(5.9)	0.87

BMI, body mass index; STD, sexually transmitted disease.

* Two sided *p*-values from Chi-square test for categorical variables and two-sample *t*-test for continuous variables; for categorical variables that were not normally distributed, non-transformed values shown but p-*values* based on variables transformed to meet normality assumptions.

** Mean (standard deviation) presented unless otherwise indicated.

able for analyses involving STDs and cadmium jointly. Intra-class correlation coefficients for the reliability of the cadmium and creatinine measurements on the blinded duplicate urine samples were 0.78 and 0.99, respectively.

Selected characteristics of all cases and controls are summarized in Table **1**. The frequency matching variables, age and race, were well balanced between the cases and controls. Cases were more likely to have a family history of prostate cancer in a first degree relative and higher total energy intake. Urinary creatinine-standardized cadmium in the study population ranged from zero to 40 $\mu g/mg \times 10^{-4}$, and neither mean levels (Table **1**) nor the frequencies of men with values above and below the median level in controls ($5.34\ \mu g/mg \times 10^{-4}$) differed between cases and controls ($p = 0.61$).

Of the 113 cases, all had adenocarcinoma of the prostate for which tumor grade and TNM stage was available on 101; of these, 30 percent had localized and 70 percent had advanced disease, and 6.8 percent of tumors were well differentiated, 79.6 percent were moderately differentiated, and 13.6 percent were poorly differentiated. There were no significant differences in concentrations of cadmium by tumor grades and stages (data not shown).

As shown in Table **2**, neither urinary cadmium nor a history of STD exposures individually was statistically significantly associated with risk for prostate cancer. However, as shown in Table **3**, higher cadmium exposure was statistically significantly associated with a nearly 10-fold increase in incident prostate cancer among those with a history of a sexually transmitted disease.

Multivariable-adjusted associations between cadmium exposure and prostate cancer stratified by tumor stage and STD history are shown in Table **4**. Among those with a history of a sexually transmitted disease, higher cadmium exposure was statistically significantly associated with a 19-fold increased risk for advanced prostate cancer. Because of the insufficient sample size an association between cadmium exposure and localized prostate cancer could not be meaningfully assessed. Among those without a history of a sexually transmitted disease, no association was found between cadmium and either localized or advanced disease.

DISCUSSION

The findings from this study suggest that higher cadmium exposure combined with a history of a sexually transmitted disease may increase risk for prostate cancer—especially advanced prostate cancer. There is substantial

Table 2. Multivariable-Adjusted Associations[*] of Incident Prostate Cancer with Urinary Cadmium and History of Sexually Transmitted Disease

	n (Cases/Controls)	OR	95% CI	*p* Value[**]
Urinary cadmium/creatinine (μg/mg X 10^{-4})				
< 5.34 X 10^{-4}	53/122	1.00		
≥ 5.34 X 10^{-4}	49/127	0.91	0.49, 1.69	0.77
History of STD				
No	90/213	1.00		
Yes	15/23	1.32	0.49, 3.52	0.58

OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease.
[*] Two sided *p*-values from Wald Chi-square test by unconditional logistic regression.
[**] Without interaction of cadmium and STD.

Table 3. Multivariable-Adjusted Associations[*] of Urinary Cadmium with Incident Prostate Cancer According to History of Sexually Transmitted Disease

		n (Cases/Controls)	Urinary Cadmium/Creatinine		95% CI	*p* value[**]
			Low OR	High OR		
History of STD	No	90/213	1.00	0.65	0.32, 1.32	0.23
History of STD	Yes	15/23	1.00	9.75	1.28, 74.05	0.03

OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease.
[*] With interaction of cadmium and STD.
[**] Two sided *p*-values from Wald Chi-square test by unconditional logistic regression.

Table 4. Multivariable-Adjusted Associations[*] of Urinary Cadmium with Incident Prostate Cancer According to TNM Tumor Stage and Sexually Transmitted Disease History

Tumor Stage	STD History	*n* (Cases/Controls)	Urinary Cadmium/Creatinine		95% CI	*p* value[**]
			Low OR	High OR		
Localized	-	25/213	1.00	1.01	0.31, 3.25	0.99
	+	1/23	---	---	---	---
Advanced	-	53/213	1.00	0.66	0.27, 1.59	0.36
	+	14/23	1.00	19.54	1.54, 247.30	0.02

OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease.
[*] With interaction of cadmium and STD.
[**] Two sided *p*-values from Wald Chi-square test by unconditional logistic regression.
--- Indicates no result available because of insufficient sample size.

biological plausibility for these findings. Carcinogenesis is a multi-step process involving initiating and promoting factors. Cadmium and infection-related inflammation may act in this manner. The mechanism of carcinogenesis by cadmium may involve epigenetic or indirect genotoxic effects resulting in activating proto-oncogenes, enhancing cell proliferation, blocking apoptosis, and hindering DNA repair [18]. Likewise, inflammation from STD-associated infectious agents is another potential mechanism for prostate carcinogenesis. Recently, a novel virus was found in human prostate tumors [15], suggesting that viral-induced inflammation may increase risk for prostate cancer. Sexual contact may be the source of this or another yet to be identified virus. It is well known that inflammation influences the pathogenesis of cancers by inflicting cell and genomic damage, triggering restorative cell proliferation to replace damaged cells, and elaborating a portfolio of cytokines that promote cell replication, angiogenesis and tissue repair [19]. Chronic or recurrent inflammation is linked to the development of several human cancers such as liver, esophagus, stomach, large intestine, and urinary bladder cancers [19].

Inflammation in the prostate derived from a STD-associated exposure may promote the development of prostate cancer initiated by high cadmium exposure. A similar phenomenon has been observed in hepatic carcinogenesis. Dietary exposure to aflatoxin B1 (AFB1) and chronic hepatitis B virus (HBV) infection are synergistic risk factors for hepatocellular carcinoma. Like cadmium, aflatoxins have been demonstrated to be carcinogenic in many experimental models and are classified as carcinogenic in humans by the International Agency for Research on Cancer (IARC) [20].

Like STD infectious agents, HBV is a common contagious virus. Several large cohort studies found a synergistic interaction between AFB1 exposure and the HBV carrier state in hepato-carcinogensis [21, 22]. Synergism between the human papilloma virus (HPV) and cigarette smoking has also been observed for cervical cancer [23], and between H. pylori and nitrates for stomach cancer [24]. Such evidence supports the plausibility of prostate tumorigenesis by the combined exposures of cadmium and STD infection.

The carcinogenic potential of cadmium in prostate cancer is clearly established from experiments in animals [6]. However, the epidemiological evidence is still inconclusive [25]. Similarly, the epidemiologic association between prostate cancer and a history of STD is not well defined. Consistent with several other epidemiological studies, we did not find any statistically significant associations between cadmium exposure or a history of STD and prostate cancer alone [10, 25]. However, we did find a synergistic association of cadmium exposure and a history of STD with incident prostate cancer, especially advanced prostate cancer. To our knowledge, this is the first study to investigate an interaction between such potential prostate cancer initiating and promoting exposures. Our findings suggest the need for investigating possible relationships among cadmium exposure, infection/inflammation, and prostate cancer in larger, preferably prospective studies.

This study has several strengths and limitations. One strength of the study also contributed to its primary limitation: the time-consuming, in-person data collection procedures yielded high quality information and biological samples, but also harmed the consent rate, which may have biased the results. Other strengths of the study included the community-based design and studying cases within days of diagnosis and before initiation of treatment. Like most case-control studies, this study also has well-known potential and inherent limitations, such as possible recall biases and ambiguous temporal relationships. However, in this study recall biases were likely minimized by studying cases immediately after diagnosis and before initiation of treatment, and in any case would not have affected urinary cadmium levels. Temporal ambiguity appears to be a minimal threat to the validity of our findings since it seems likely that acquiring a sexually transmitted disease and lifetime accumulations of cadmium preceded prostate cancer in our cases. History of STDs likely was under-reported because of the sensitivity of divulging such information, but likely biased associations toward the null. A further limitation of this study is that no prostate biopsies were done on controls to rule out sub-clinical prostate cancer and reduce possible case-control status misclassification. However, if some controls did have prostate cancer, this would have tended to bias our results toward the null. Another limitation of this study was the small sample size, which restricted our ability to investigate interactions by stratified analyses. Because of the small number of participants with a history of sexually transmitted diseases, it was not possible to identify which type of STD, if any, was most responsible for modifying the cadmium-prostate cancer association.

CONCLUSIONS

In summary, consistent with the hypothesis that cancers are caused by a combination of initiating and promoting factors, risk of incident prostate cancer was statistically significantly associated with persons who had higher cadmium exposures plus a history of STD exposure, but neither alone. Our findings also suggest that these potentially synergistic exposures may be more related to advanced disease. However, the biologically plausible synergistic interaction between cadmium and STD needs to be further investigated in larger, preferably prospective studies.

ABBREVATIONS

AFB1 = Aflatoxin B1

BMI = Body mass index

Cd = Cadmium

CI = Confidence interval

HBV = Hepatitis B virus

IARC = International Agency for Research on Cancer

OR = Odds ratio

STD = Sexually transmitted disease

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