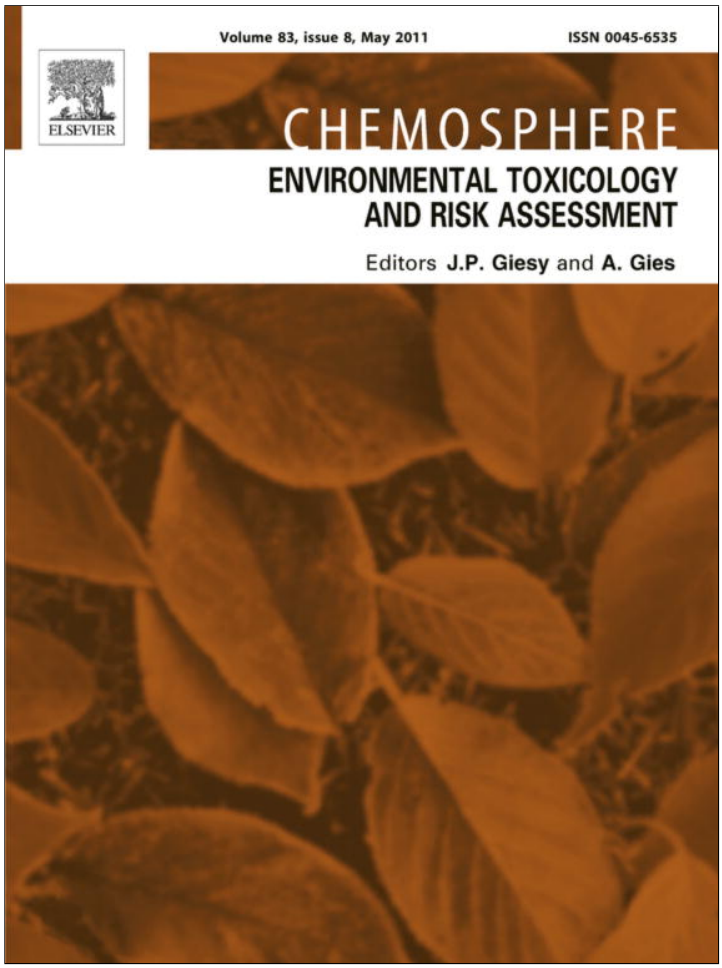

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Reversed association between levels of prostate specific antigen and levels of blood cadmium and urinary cadmium

Chin-Ching Wu [a], Yeong S. Pu [b], Hsi-Chin Wu [a], Chun-Yuh Yang [c], Yi-Chun Chen [d,*]

[a] Department of Public Health and Division of Urology, China Medical University and Hospital, Taichung 404, Taiwan
[b] Department of Urology, National Taiwan University Hospital, Taipei 100, Taiwan
[c] Department of Public Health, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[d] Department of Health Management, I-Shou University, Kaohsiung 824, Taiwan

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ABSTRACT

Prostate cancer associated with cadmium exposure may indicate a link between prostate specific antigen (PSA) and levels of blood cadmium (BCd) and urinary cadmium (UCd). Thus, these associations were investigated. We recruited 295 men, 50 years of age and above from a health check-up program at a health center as subjects of the study. They completed a self-reported questionnaire and provided fasting samples of blood and urine for cadmium assay. The assay was performed using atomic absorption spectrophotometry. Blood samples were also collected for the assays of total cholesterol and high-density lipoprotein measures. The means of BCd and UCd increased with age and the means of all subjects were $1.19 \pm 1.04\ \mu g\ L^{-1}$ and $1.37 \pm 1.76\ \mu g\ g^{-1}$ creatinine, respectively. The PSA levels were positively associated with the lipid levels, but reversely associated with BCd and UCd levels. The multivariate logistic regression analysis showed that men with PSA $\geqslant 4.0\ ng\ mL^{-1}$ had an odds ratio (OR) of 0.4 (95% CI = 0.1–0.9) to have BCd > $0.49\ \mu g\ L^{-1}$, and an OR of 0.4 (95% CI = 0.2–1.0) to have UCd > $0.45\ \mu g\ g^{-1}$ creatinine. In conclusion, the PSA levels are reversely associated with BCd and UCd levels.

1. Introduction

Compared with Western men, the risk of prostate cancer is remarkably lower in Oriental men (Hsing et al., 2000). However, the incidence of the disease in Taiwan may increase more than 4-fold in two decades (Pu, 2000). Population aging, increased dietary fat consumption, and other environmental risk exposures, play important roles in the increase of risk. Cancer screening programs, on the other hand, may have an important function in timely diagnoses of prostate cancer (Giovannucci et al., 1993; Sung et al., 1999; Schröder et al., 2009). When the environmental exposure factors were considered, only few studies were found to have shown a higher risk of prostate cancer associated with the occupational cadmium exposure. However, inconclusive results show a link with non-occupational exposures (Potts, 1965; Aronson et al., 1996; Kolonel and Winkelstein, 1997; Chen et al., 2005; Sahmoun et al., 2005; Vinceti et al., 2007). While our previous study failed to prove that higher cadmium level in the body can predict the onset of prostate cancer, it showed that higher cadmium level can serve as a predictor of advanced cancer phenotypes (Chen et al., 2009).

In prostate cancer screening, the PSA measured in the blood has been used as an effective marker for the early detection of prostate cancer (Carter et al., 2006; Andriole et al., 2009; Schröder et al., 2009). Prostate cancer patients have rising PSA levels. The link between cadmium exposure, fat consumption, and PSA levels with prostate cancer may indicate a relationship between PSA level and cadmium exposure. Limited studies have investigated whether the PSA in the blood is associated with cadmium burden in men (Zeng et al., 2004; van Wijngaarden et al., 2008; Satarug et al., 2010). This study determined and compared the BCd and UCd levels in association with PSA levels.

2. Materials and methods

2.1. Subjects and data collection

Subjects for this study were 295 men, 50 years of age and older receiving routine health examinations at a health center in Taiwan. Each subject was asked to complete a questionnaire before taking the health exam. With consent, additional fasting blood and

Abbreviations: UCd, creatinine-adjusted urinary cadmium level; UCd, urine cadmium level; BCd, blood cadmium level; OR, odds ratio; CI, confidence interval.

* Corresponding author. Tel.: +886 7 615 1100x7418; fax: +886 7 615 5150.
E-mail addresses: wucc@mail.cmu.edu.tw (C.-C. Wu), yspu@ntu.edu.tw (Y.S. Pu), wuhc@mail.cmu.edu.tw (H.-C. Wu), chunyuh@kmu.edu.tw (C.-Y. Yang), kimi@isu.edu.tw (Y.-C. Chen).

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urine specimens were collected from each person on the day of the health exam. Men with known severe diseases were excluded from recruitment. The questionnaire collected information on socio-demographic characteristics, occupational history, tobacco and alcohol use, diet, physical activity, height and weight history, medical history, and family history of prostate cancer. This study was performed with the approval of the institutional ethics committee.

Using a food frequency questionnaire, each person reported dietary intake history. The questionnaire was a validated instrument and had been used in previous studies (Sung et al., 1999; Chen et al., 2005). In brief, the questionnaire contained the frequently consumed food items in Chinese families, reported at daily, weekly, or monthly frequency. Information on smoking and drinking, and other lifestyle items, were also provided. The questionnaire was validated with Cronbach's alpha values ranging from 0.75 to 0.84.

2.2. Specimen collection and cadmium analysis

Fasting urine and blood specimens were collected at the scheduled health check-up appointment. A cadmium-free sterile plastic cup attached to a plastic tube with a cone-like bottom was used to collect the urine sample. Pre-screened cadmium-free heparin tubes were used to collect 2–3 mL blood specimens. Specimens were stored at 4 °C if analysis will be performed within a week after the collection of sample. Samples were stored at −20 °C for specimen analysis, which will be performed at a later time. Urine creatinine was determined and used to normalize urine cadmium levels.

For analyses, we prepared 100 μL of blood mixed with 900 μL of matrix modifier [0.2% nitric acid, 0.5% Triton®-X-100, and 0.2% $(NH_4)_2HPO_4$], or 100 μL of urine mixed with 200 μL of matrix modifier [2.5% $NH_4H_2PO_4$ and 1.25% $Mg(NO_3)_2$] (Feustel et al., 1982). The BCd and UCd levels in specimens, quality control samples, and standards with matrix modifier were determined using Perkin-Elmer Model 5100 PC atomic absorption spectrometer equipped with Zeeman background correction. Reference blood samples were obtained from NYCOMED PHARMA AS, Oslo, Norway. Urinary cadmium analysis was verified using the Inter-Laboratory Comparison Program, Le Centre de Toxicology du Québec (Sainte-Foy, QC, Canada). The spike tests showed recovery rates of 100.7 ± 3.5% for urine analysis and 100.7 ± 3.6% for blood analysis. Urinary creatinine was used to adjust urine cadmium levels. The health check-up program provided information on PSA, as well as on biochemical examinations, including total cholesterol (TC), low-density lipoprotein cholesterol (LDLC), and high-density lipoprotein cholesterol (HDLC) of each participant. PSA was measured by microparticle enzyme immunoassay (MEIA) using Abbott IMx (Abbott Laboratories, Abbott Park, IL, USA). TC, HDLC, and LDLC were measured by automatic biochemical analyzer (HITACHI 7150, Tokyo, Japan) and TC was quantified by peroxidase method; HDLC was quantified by HDLC direct method. LDLC was calculated by Friedewald's equation (Friedewald et al., 1972).

2.3. Statistical analyses

Levels of PSA, TC, HDLC, LDLC, and TC in relation to HDLC ratio among participants were compared by age (50–59, 60–69, and 70 and above years) with means ± standard deviations (SD), medians, and 5th–95th percentiles. Wilcoxon rank-sum test was used to assess the differences. Categorical distributions of BCd and UCd in quartile levels, and the median-cut TC, HDLC, and LDLC levels as well as TC-to-HDLC ratio were compared between normal and abnormal PSA levels (<4 vs. ⩾4 ng mL^{-1}). The categorical distributions were tested using Chi-square. We also used the logistic regression analysis to measure whether the abnormal PSA (⩾4 ng mL^{-1}) was associated with BCd and UCd levels.

3. Results

3.1. Study subjects

A total of 295 men aged 50 years and older participated in this survey, with 177 (60%) of subjects never drunk, 82 (27.8%) men smoked, 72 (24.4%) men quitted smoking, and 139 (47.1%) men never smoked (data not shown).

3.2. PSA distributions of study subjects

Table 1 showed that both mean and median levels of PSA were higher in men aged 60 years and above than in men aged 50–59 years. There were only 24 men with the PSA levels of ⩾4.0 ng mL^{-1}. The prevalence for men with PSA levels of ⩾4.0 ng mL^{-1} increased from 6.3% for those in the 50–59 years of age, to 8.7% in men 60–69 years of age and to 13.3% in men aged 70 years and above. TC and TC-to-HDLC ratio decreased as age

Table 1
Levels of prostate specific antigen (PSA), lipids, and cadmium in blood and urine by age.

	Age, years			*p*-Value[a]
	50–59	60–69	70+	
PSA (ng mL^{-1})				
n	143	104	45	0.02
Mean ± SD	1.38 ± 1.73	1.86 ± 2.03	1.83 ± 1.73	
Median	0.9	1.15	1.01	
5th–95th percentile	0.3–4.3	0.4–5.8	0.4–5.8	
>4.0, %	6.3	8.7	13.3	
Total cholesterol (mg dL^{-1})				
n	144	105	45	0.04
Mean ± SD	217.1 ± 37.6	208.9 ± 40.7	201.8 ± 27.8	
Median	216.5	210	203.5	
5th–95th percentile	159–284	147–272	156–247	
<130, >200, %	62.5	57.1	52.2	
HDL cholesterol (mg dL^{-1})				
n	141	99	46	0.29
Mean ± SD	45.9 ± 12.1	47.6 ± 11.0	47.3 ± 11.9	
Median	44	47	46	
5th–95th percentile	30–71	33–70	31–70	
⩽35, %	17.7	12.1	15.2	
LDL cholesterol (mg dL^{-1})				
n	141	99	46	0.06
Mean ± SD	129.0 ± 27.9	137.7 ± 35.3	141.9 ± 33.0	
Median	133.5	135	142	
5th–95th percentile	82–172	72–196	95–205	
⩾160, %	26.2	26.3	13.0	
TC/HDL_C ratio[b]				
n	141	99	46	0.02
Mean ± SD	4.95 ± 1.28	4.55 ± 1.19	4.49 ± 1.11	
Median	4.7	4.5	4.45	
5th–95th percentile	3–7.2	3–7	3..2–6.9	
<3.0, >5.7, %	35.5	17.1	15.2	
Blood cadmium (ug L^{-1})				
n	142	105	46	0.48
Mean ± SD	1.16 ± 1.10	1.18 ± 0.89	1.33 ± 1.15	
Median	0.8	0.88	0.92	
5th–95th percentile	0.13–3.35	0.19–3.01	0.27–3.62	
Urine cadmium (ug Cd^{-1} g^{-1} cre.)				
n	144	105	46	0.13
Mean ± SD	1.24 ± 1.92	1.44 ± 1.47	1.67 ± 1.82	
Median	0.86	1.11	1.06	
5th–95th percentile	0.10–3.32	0.12–3.44	0.09–5.96	

[a] Wilcoxon rank-sum test.
[b] Total cholesterol to HDL cholesterol ratio.

Table 2
Associations between prostate specific antigen (PSA) and blood cadmium, urine cadmium, and lipid.

	PSA, ng mL^{-1}		*p*-Value
	<4 *n* (%)	≧4 *n* (%)	
Blood cadmium (ug L^{-1})			
BCd ≦ 0.493	63 (23.4)	10 (41.7)	0.26
0.493 < BCd ≦ 0.843	69 (25.6)	5 (20.8)	
0.843 < BCd ≦ 1.413	69 (25.6)	4 (16.7)	
BCd > 1.413	68 (25.3)	5 (20.8)	
Urine cadmium (ug Cd^{-1} g^{-1} cre.)			
UCd ≦ 0.45	64 (23.6)	10 (41.7)	0.20
0.450 < UCd ≦ 0.945	69 (25.5)	5 (20.8)	
0.945 < UCd ≦ 1.73	68 (25.1)	6 (25.0)	
UCd > 1.73	70 (25.8)	3 (12.5)	
Total cholesterol (mg dL^{-1})			
≦210	136 (50.2)	11 (45.8)	0.68
>210	135 (49.8)	13 (54.2)	
HDL cholesterol (mg dL^{-1})			
≦45	136 (50.2)	18 (75.0)	0.02
>45	135 (49.8)	6 (25.0)	
LDL cholesterol (mg dL^{-1})			
≦137	143 (52.8)	10 (41.7)	0.181
>137	135 (49.8)	14 (58.3)	
TC/HDL_C ratio			
≦4.6	154 (56.8)	5 (20.8)	0.001
>4.6	117 (43.2)	19 (79.2)	

Table 3
Odds ratio and 95% confidence interval for elevated prostate specific antigen with significant association with blood cadmium.

	PSA ≧ 4 ng mL^{-1} Odds ratio (95%CI)
Age, year	
50–59	1.0
60–69	1.7 (0.6–4.6)
70+	2.9 (0.9–9.0)
TC/HDL_C ratio	
≦4.6	1.0
>4.6	5.9 (2.1–16.7)
Blood cadmium (ug L^{-1})	
BCd ≦ 0.493	1.0
BCd > 0.493	0.4 (0.1–0.9)

Table 4
Odds ratio and 95% confidence interval for elevated prostate specific antigen with more significant association with urine cadmium.

	PSA ≧ 4 ng mL^{-1} Odds ratio (95%CI)
Age, year	
50–59	1.0
60–69	1.7 (0.6–4.6)
70+	2.7 (0.9–8.5)
TC/HDL_C ratio	
≦4.6	1.0
>4.6	5.4 (1.9–15.1)
Urine cadmium (ug Cd^{-1} g^{-1} cre.)	
UCd ≦ 0.45	1.0
UCd > 0.45	0.4 (0.2–1.0)

increased ($p = 0.04$ and $p = 0.02$, respectively). Means of both BCd and UCd levels increased with age but were not significant. For all men, the means ± SDs of BCd and UCd were 1.19 ± 1.04 μg L^{-1} and 1.37 ± 1.76 μg g^{-1} creatinine, respectively.

3.3. Relationships between blood cadmium and urine cadmium

Men with PSA levels of ⩾4.0 ng mL^{-1} were more likely to have lower BCd (⩽0.49 μg L^{-1}) and lower UCd (⩽0.45 μg g^{-1} creatinine), but the differences were not significant in the quartiled distributions of the BCd and UCd levels (Table 2). Likewise, no significant correlations between abnormal PSA and TC and between abnormal PSA and LDLC were observed. However, men with abnormal PSA were more likely to have HDLC ⩽ 45 mg dL^{-1} and more likely to have TC-to-HDLC ratio > 4.6. The multivariate logistic regression analysis showed that men with PSA ⩾ 4.0 ng mL^{-1} had an odds ratio of 0.4 (95% CI = 0.1–0.9) to have BCd > 0.49 μg L^{-1}, and 0.4 (95% CI = 0.2–1.0) to have UCd > 0.45 μg g^{-1} creatinine (Tables 3 and 4).

4. Discussion

Although the benefit of prostate cancer screening is still debatable, PSA has been used as a routine biological tumor marker in prostate cancer detection (Smith et al., 1997; Thompson et al., 2004). With the US Food and Drug Administration approval, the PSA test along with the digital rectal examination has become an effective procedure for the early detection of the tumor (Andriole et al., 2009; Schröder et al., 2009). Among the 126,462 PSA-based tests in the European Randomized Study of Screening for Prostate Cancer, 16.2% were positive for ages between 50 and 74 years (Schröder et al., 2009). Only 8.1% of the PSA tests in our study were positive, reflecting that Asian men are at lower risk of the tumor.

Among the etiologic factors associated with prostate cancer, cadmium contribution is relatively rarely studied, particularly for the general population because of low level of exposure and variation in the body burden. The prostate is one of the organs responsible for cadmium deposition (Satarug et al., 2010). High level of cadmium exposure has been considered as a factor that can induce prostate cancer. It is possible that an elevated PSA may be associated with higher cadmium exposure. However, limited evidence to establish this association exists.

van Wijngaarden et al. (2008) have used the 2001–2002 US National Health and Nutrition Examination Survey (NHNES) data to evaluate the association between PSA levels and UCd concentrations. They found no significant association among men with higher zinc intake. However, the PSA level increased with the increase of cadmium intake of men with low zinc intake. In general, higher zinc burden in the human body may compete with cadmium intake and deposit. The BCd level is probably low when zinc burden is high in the human body.

Another study conducted in China found that PSA level increased when the cadmium intake and UCd concentration increased among men living in areas with different exposures to cadmium from river water (Zeng et al., 2004). They also found that men with positive digital rectal exam had higher BCd levels but lower UCd levels. Our study shows that PSA levels are reversely associated with both BCd and UCd levels. Those with abnormal PSA (⩾4.0 ng mL^{-1}) had an odds ratio of 0.4 associated with elevated BCd and UCd.

The median BCd level in our study sample was slightly higher than those of Italian men (0.84 μg L^{-1} vs. 0.7 μg L^{-1}) with occupational exposure, but significantly higher than those of Swedish men (Baecklund et al., 1999; dell'Omo et al., 1999). The median UCd level in our sample was also higher than the mean value measured for 22,162 American men (0.94 μg g^{-1} creatinine vs. 0.48 μg g^{-1} creatinine) (Paschal et al., 2000). These ecological variations reflect environmental exposure differences. In our study population, the main source of cadmium exposure is from smoking. Further analysis showed that men who smoked had an odds

ratio of 3.2 (95% CI = 1.7–6.2) to have higher BCd, and an odds ratio of 2.5 (95% CI = 1.2–1.5) to have higher UCd, after controlling for age, occupation, alcohol drinking, contents of blood calcium and blood iron, and intake of fishes and shell fishes (data not shown).

Animal study has shown that cadmium is a carcinogen for rats. Our previous study failed to prove that cadmium can predict the occurrence of prostate cancer (Chen et al., 2009). The possibility of PSA level being associated with cadmium burden in humans was not supported by the findings of the study. Approximately, 41.7% of men with PSA greater than 4 ng mL^{-1} have both the BCd and UCd at lower quartiles. The elevated PSA is significantly associated with low BCd and low UCd. Instead, we found a significant negative association between PSA and HDLC. Men with HDLC greater than the median value of 45 mg dL^{-1} are less likely to have the PSA > 4.0 ng mL^{-1}. These findings indicate that high HDLC has a negative association with PSA, but levels of cadmium in blood and urine are reversely associated with PSA.

5. Conclusions

This study suggests that an elevated HDLC level has a negative association with PSA. PSA levels are also reversely associated with BCd and UCd levels. Further studies need to investigate the impact of cadmium to prostate.

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References

Andriole, G.L., Grubb, R.L., Buys, S.S., Chia, D., Church, T.R., Fouad, M.N., Gelmann, E.P., Kvale, P.A., Reding, D.J., Weissfeld, J.L., Yokochi, L.A., Crawford, E.D., O'Brien, B., Clapp, J.D., Rathmell, J.M., Riley, T.L., Hayes, R.B., Kramer, B.S., Izmirlian, G., Miller, A.B., Pinsky, P.F., Prorok, P.C., Gohagan, J.K., Berg, C.D., PLCO Project Team, 2009. Mortality results from a randomized prostate-cancer screening trial. N. Engl. J. Med. 360, 1310. doi:10.1056/NEJMoa0810696. PMID 19297565.

Aronson, K.J., Siemiatycki, J., Dewar, R., Gerin, M., 1996. Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. Am. J. Epidemiol. 143, 363–373.

Baecklund, M., Pederden, N.L., Bjorkman, L., Vahter, M., 1999. Variation in blood concentrations of cadmium and lead in the elderly. Environ. Res. Sec A 80, 222–230.

Carter, H.B., Ferrucci, L., Kettermann, A., Landis, P., Wright, E.J., Epstein, J.I., Trock, B.J., Metter, E.J., 2006. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J. Natl. Cancer Inst. 98, 1521–1527.

Chen, Y.C., Lin, R.S., Pu, Y.S., Chiang, C.I., Lai, M.K., Sung, J.F.C., 2005. Diet, vegetarian food and prostate cancer in Taiwan. Brit. J. Cancer 93, 1057–1061.

Chen, Y.C., Pu, Y.S., Wu, H.C., Wu, T.T., Lai, M.K., Yang, C.Y., Sung, F.C., 2009. Cadmium burden and the risk and phenotype of prostate cancer. BMC Cancer 9, 429. doi:10.1186/1471-2407-9-429.

dell'Omo, M., Muzi, G., Piccinini, R., Gambelunghe, A., Morucci, P., Fiordi, T., Ambrogi, M., Abbritti, G., 1999. Blood cadmium concentrations in the general population of Umbria, central Italy. Sci. Total Eniviron. 226, 57–64.

Feustel, A., Wennrich, R., Steiniger, D., Klauss, P., 1982. Zinc and cadmium concentration in prostatic carcinoma of different histological grading in comparison to normal prostate tissue and adenofibromyomatosis (BPH). Urol. Res. 10, 301–303.

Friedewald, W.T., Levy, R.I., Fredrickson, D.S., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18, 499–502.

Giovannucci, E., Rimm, E.B., Colditz, G.A., Stampfer, M.J., Ascherio, A., Chute, C.C., Willett, W.C., 1993. A prospective study of dietary fat and risk of prostate cancer. J. Natl. Cancer Inst. 85, 1571–1579.

Hsing, A.W., Tsao, L., Devesa, S.S., 2000. International trends and patterns of prostate cancer incidence and mortality. Int. J. Cancer 85, 60–67.

Kolonel, L., Winkelstein, W.J., 1997. Cadmium and prostatic carcinoma. Lancet 2, 566–567.

Paschal, D.C., Burt, V., Caudill, S.P., Gunter, E.W., Pirkle, J.L., Sampson, E.J., Miller, D.T., Jackson, R.J., 2000. Exposure of the US population aged 6 and older to cadmium: 1988–1994. Arch. Environ. Contam. Toxicol 38, 337–383.

Potts, C.L., 1965. Cadmium proteinuria – the health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8, 55–61.

Pu, Y.S., 2000. Prostate cancer in Taiwan: epidemiology and risk factors. Int. J. Andrl. 23 (Suppl. 2), 34–36.

Sahmoun, A.E., Case, L.D., Jackson, S.A., Schwartz, G.G., 2005. Cadmium and cancer: a critical epidemiologic analysis. Cancer Invest. 23, 256–263.

Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. Environ. Health Perspect. 118, 182–190.

Schröder, F.H., Hugosson, J., Roobol, M.J., Tammela, T.L., Ciatto, S., Nelen, V., Kwiatkowski, M., Lujan, M., Lilja, H., Zappa, M., Denis, L.J., Recker, F., Berenguer, A., Määttänen, L., Bangma, C.H., Aus, G., Villers, A., Rebillard, X., van der Kwast, T., Blijenberg, B.G., Moss, S.M., de Koning, H.J., Auvinen, A., ERSPC Investigators, 2009. Screening and prostate-cancer mortality in a randomized European study. N. Engl. J. Med. 360, 1320–1328.

Smith, D.S., Humphrey, P.A., Catalona, W.J., 1997. The early detection of prostate carcinoma with prostate specific antigen: the Washington University experience. Cancer 80, 1853–1856.

Sung, J.F.C., Lin, R.S., Pu, Y.S., Chen, Y.C., Chang, H.C., Lai, M.K., 1999. Risk factors for prostate cancer in Taiwan: a case-control study in a Chinese population. Cancer 86, 484–492.

Thompson, I.M., Pauler, D.K., Goodman, P.J., 2004. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. N. Engl. J. Med 350, 2239–2246.

van Wijngaarden, E., Singer, E.A., Palapattu, G.S., 2008. Prostate-specific antigen levels in relation to cadmium exposure and zinc intake: results from the 2001–2002 National Health and Nutrition Examination Survey. Prostate 68, 122–128.

Vinceti, M., Venturelli, M., Chiara, S., Paolo, T., Bonvicini, F., Ferrari, A., Bianchi, G., Serio, G., Bergomi, M., Vivoli, G., 2007. Case-control study of toenail cadmium and prostate cancer risk in Italy. Sci. Total Environ. 373, 77–81.

Zeng, X., Jin, T., Jiang, X., Kong, Q., Ye, T., Nordberg, G.F., 2004. Effects on the prostate of environmental cadmium exposure – a cross-sectional population study in China. Biometals 17, 559–565.