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# Effects on the prostate of environmental cadmium exposure – A cross-sectional population study in China

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**Abstract**

To explore possible effects of environmental cadmium exposure on prostate in humans, and the possible relationship of serum sex hormones to occurrence of clinic signs of tissue changes in the prostate, a case-control study was undertaken in the southeast part of China in 1998. A total of 297 male volunteers from a control area and two cadmium-polluted areas were included as subjects in this study. All the subjects were required to answer a questionnaire and to undergo a complete physical examination including digital-rectal examination (DRE). Blood and urine samples were collected. Serum total prostate specific antigen (PSA), total serum testosterone (T), follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured by radioimmunoassay and enzymeimmunoassay method, respectively. The data of urinary cadmium (U-Cd) and blood cadmium (B-Cd) were obtained by atomic absorption spectrometry (AAS) as an indicator of cadmium body burden. Statistical analysis was applied to investigate a possible relation between cadmium exposure and prostate pathological changes. The results show that there is a clear dose-response relationship between cadmium exposure and the prevalence of cases with abnormal PSA. The blood cadmium content in cases with positive DRE was significantly higher than that of subjects with negative DRE ($P < 0.05$). Significant differences in the level of FSH between cases with positive DRE and the normal subjects were also noted ($P < 0.05$). These results indicate that chronic environmental cadmium exposure is associated with injuries to human prostate. A possible relationship to changes in circulating sex hormones needs further investigation.

## Introduction

Cadmium (Cd) is a toxic transition metal with a wide variety of adverse effects on humans (Nordberg 1992). There are several sources of human exposure to cadmium, including occupational exposure, environmental exposure and smoking. Now, cadmium gets increasing concern because many studies in human populations and in animals indicate that cadmium is a potential carcinogen to human prostate (Ross *et al.* 1987; Van der Gulden *et al.* 1995; Waalkes *et al.* 1992). Cadmium has been designated as a human carcinogen based on its carcinogenicity to the lung (IARC 1993; Ades & Kazantzis 1988; Sorahan 1987). Some studies (Ross *et al.* 1987; Van der Gulden *et al.* 1995) have shown a link between occupational cadmium exposure and prostate cancer, but evidence are not convincing and complete enough. There are also many other studies (Sorahan & Waterhouse 1983; Armstrong & Kazantzis 1983) which showed different results and not supported the viewpoint that cadmium exposure can result in prostate cancer. Although oc-

cupational exposure to cadmium does not appear to greatly increase the risk for prostate cancer, some evidence (West *et al.* 1991) suggest that environmental exposure to cadmium may lead to increased risk of prostate cancer in humans. In animal tests, there are enough evidence to confirm the carcinogenicity of cadmium to the prostate in rodents (Waalkes *et al.* 1999).

In our study, we try to find out whether long term low level cadmium exposure in the environment can be related to damage of the prostate or not, and provide a clue for further research on possible mechanisms of the adverse effects of cadmium to human prostate.

## Subjects and methods

### *Subject selection*

Residents of two cadmium polluted areas (located 0.5 and 12 km from a non-ferrous smelter) and a control area (40 km from the smelter) in south-east China were recruited to the present study. Cadmium from the smelter had contaminated river water used for irrigation of rice fields. Levels of Cd in rice were 2.39 mg/kg and 0.48 mg/kg in the two polluted areas and 0.05 mg/kg in the control area. Detailed background information is described elsewhere (Jin *et al.* 2002, 2004).

In our study, male healthy subjects 35 years or older were selected to ensure the long enough exposure period. The persons selected from the three areas in this study lived in similar living habits, economic situation and they were all eating the local rice as the main food. All migrants after 1961 were excluded in this study. Finally, 96 subjects from the control area, 75 from the medium polluted area, and 126 from the heavy polluted area were recruited. Each participant was required to answer questionnaires on environment and symptoms of prostate, respectively, and to give a sample of blood and urine. In this study, all subjects were asked to undergo a complete physical examination including digital rectal examination (DRE) after urine and blood samples were collected.

### *Ethical considerations*

The study was carried out with the permission of the local authority and the Ethics Committee of Shanghai Medical University and with the consent of each participating individual. It was made clear by the responsible Chinese Principal Investigator that participation was on a completely voluntary basis.

### *Blood sampling*

Blood samples (8–10 ml) were obtained randomly by venipuncture from 10:00 a.m. to 16:00 p.m., and blood sampling was not preceded by any prostatic manipulation. All the subjects were told in advance not to eat any food until the blood sampling was finished. All blood samples were collected into clean tubes, and serum was then separated and stored at $-70$ °C immediately. Any sample with hemolysis was excluded in test of PSA and sex hormones.

### *Urine sampling*

Spot urine samples were collected in acid-washed containers and were stored frozen ($-20$ °C) until analysis. Urine was assayed for cadmium after acidification with concentrated nitric acid.

### *Hormone assay*

Radioimmunoassay was applied to test the concentration of testosterone (T) in serum, and enzymeimmunoassay method was used to determine luteinising hormone (LH) and follicle stimulating hormone (FSH). The radioimmunoassay and enzymeimmunoassay methods were established according to the WHO manual (WHO 1994). The kits for testosterone (T), luteinising hormone (LH) and follicle stimulating hormone (FSH) detecting were generously provided by WHO. The intra- and inter-assay variation coefficients of the internal quality control pools for T, LH and FSH were all within 10%.

### *PSA assay*

The radioimmunoassay kits for PSA were purchased from Diagnostic Products Corporation (DPC) USA. Every operation strictly obeyed the procedure described in the manual. Then, all the samples were counted for 1 min in a gamma counter (FMJ-II gamma counter, Shanghai). The interassay coefficient was less than 10%.

### *Cadmium measurement*

Cadmium in blood, BCd and urine, UCd, was analysed by atomic absorption spectrometery including a strict quality control program (Jin *et al.* 2002).

*Table 1.* The reference values (ng/ml) of the age-specific PSA (the 90$^{th}$ percentile of PSA in each age group of low exposure group).

| Age group | N | The 90$^{th}$ percentile | Reference value (ng/ml) |
|---|---|---|---|
| 40- | 66 | 2.49 | 2.5 |
| 50- | 35 | 3.37 | 3.5 |
| 60- | 37 | 4.16 | 4.5 |
| 70- | 18 | 6.58 | 6.5 |

The life cumulative uptake of (Cai et al. 1998) cadmium was calculated based on rice consumption. The fractional uptake of cadmium (Cd-uptake) from food was assumed to be 0.05. The cumulative uptake of cadmium = daily cadmium intake (daily rice consumption * average rice Cd concentration) * weighting factor * years * 365 * 0.05. According to this formula, the average Cd-uptake for the population in this study were 23.3 (12.7–33.9), 106.8 (88.2–117.1) and 544.4 (456.8–582.5) mg in the control, moderately and highly polluted areas, respectively. The difference in Cd-uptake is statistically significant ($P < 0.001$) among these areas.

*Statistical analysis*

Statistical analysis was carried out with the statistical analysis software SPSS9.0 and Epifo6.0. Results are given as geometric mean and standard deviation. Statistical inferences are based on the different levels of significance ($P < 0.05$ or $P < 0.01$).

## Results

*Cadmium in blood and urine*

Among the subjects from control area, 98% show urinary cadmium levels lower than 5 $\mu$g/L. But in medium and high exposure area, 23% and 80.6% have urinary cadmium levels higher than 5 $\mu$g/L. It can be noted that there is only one person with urinary cadmium level lower than 2 $\mu$g/L in high exposure area. A similar distribution pattern of blood cadmium was also found. There is a close correlation ($r = 0.73$, $P < 0.01$) between the levels of urinary cadmium and blood cadmium as shown by Jin *et al.* (2002).

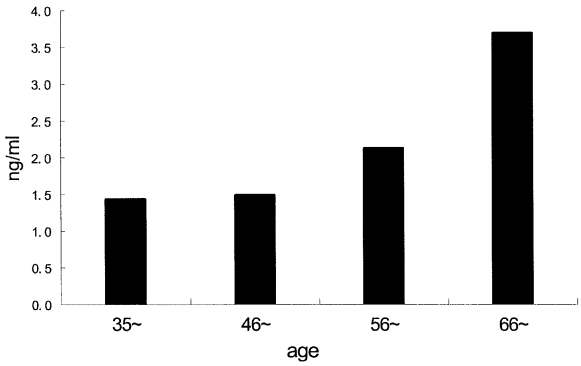


*Fig. 1.* Distribution of serum PSA levels according to age for all subjects (geometric mean).

*Age specific reference values of PSA*

Prostate is the only organ that will continue to grow all through life. Because of this, the level of prostate specific antigen will increase continuously following the enlargement of the volume of prostate. In this study, we found that the level of PSA increase with age (Figure 1). To identify potential subjects with pathological changes of prostate in PSA-based mass screening, one of the most important steps is to determine the age-specific reference value of PSA. First, we calculated the 95$^{th}$ percentile of creatinine adjusted urinary cadmium from control area to be 4.49 $\mu$gCd/g creatinine. This value will be used as a cut-off value to evaluate cadmium exposure situation. All the subjects whose creatinine adjusted urinary cadmium is lower than the cut-off value (4.49 $\mu$g/g creatinine) will be defined as subjects of low-exposure, and then be classified into low-exposure group due to their low cadmium body burden. Then we calculated the 90$^{th}$ percentile of PSA of each age group in this low-exposed group. These values are listed in Table 1. From Table 1, we find that the age specific reference values we obtained are similar with values reported in a previous study (Oesterling 1993). So, in order to make our data comparable, we adopted the same age specific reference values of PSA as in Oesterling's study. The values are 2.5 ng/ml for subject whose age is under 50, 3.5 ng ml for age from 50 to 59, 4.5 ng/ml for age from 60 to 69, and 6.5 ng/ml for subject whose age is 70 or older. Based on age-specific PSA, 29 cases (10%) with positive PSA were screened out, and 4 PSAs were greater than 10 ng/ml. Cases with abnormal PSA has slightly higher cadmium body burden compared to normal subjects, but no statistical significance is found.

*Table 2.* Comparing the cadmium body burden between suspects with positive DRE and the normal subjects.

| DRE | Cadmium body burden | | | | | |
|---|---|---|---|---|---|---|
| | Cd-uptake (mg) | N | Urinary cadmium ($\mu$g/g creatinine) | N | Blood cadmium ($\mu$g/l) | N |
| + | 335.4 ± 254.5 | 10 | 2.48 (0.07–15.31) | 10 | 7.08* (2.50–31.38) | 10 |
| − | 259.3 ± 241.5 | 274 | 3.91 (0.10–42.99) | 274 | 3.08 (0.12–44.75) | 272 |

*Significantly higher than in group with DRE-.

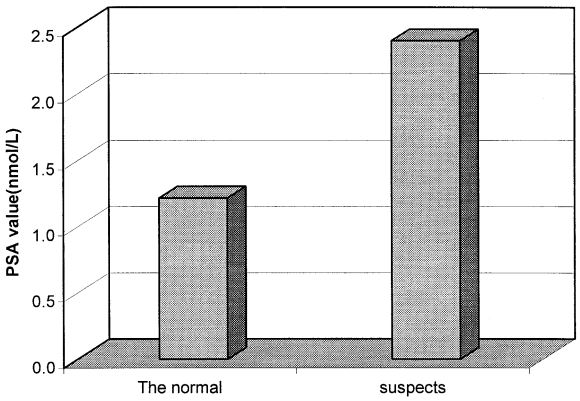


*Fig. 2.* Levels of serum PSA in cases with suspicious DRE and in the normal subjects. $^*P < 0.05$.

### *Cadmium body burden and PSA in DRE positive and negative subjects*

287 participants underwent complete physical examination. 10 were diagnosed as suspects of prostate cancer by professional physicians through digital rectal examination. All these persons were immediately suggested to undergo needle biopsy, but the results are not available to us up to now. Then, the cadmium body burden in suspects with abnormal DRE and in the normal subjects was compared. The results are listed in Table 2. It was noted that the cadmium body burden as indicated by BCd in cases with suspicious DRE is significantly higher than that of subjects with non-suspicious DRE, but there is no increase in the other estimates of body burden (Cd uptake, UCd).

Of the 10 cases with positive DRE, 3 also have positive PSA. The levels of serum PSA in suspects with abnormal DRE were higher than in normal persons. The difference is statistically significant ($P < 0.05$) (Figure 2).

*Table 3.* Chi-square test for trend between adjusted urinary cadmium and prevalence of the cases with abnormal serum PSA (based on the age-specific reference of PSA).

| Urinary Cadmium ($\mu$g/g creatinine) | PSA + | PSA − | percentage | Crude OR* | 95%CI |
|---|---|---|---|---|---|
| 0- | 5 | 71 | 6.6% | 1.00 | |
| 2- | 7 | 92 | 7.1% | 1.08 | 0.33-3.54 |
| 5- | 7 | 43 | 12.1% | 2.31 | 0.69-7.73 |
| 10- | 7 | 37 | 15.6% | 2.69 | 0.80-9.06 |
| 20- | 3 | 13 | 18.8% | 3.28 | 0.70-15.43 |

*OR = odds ratio.
$X^2 = 5.15$, $P < 0.05$.

*Table 4.* Chi-square test for trend between estimated cadmium uptake and prevalence of the cases with abnormal serum PSA (based on the age-specific reference of PSA).

| Cd-uptake (mg) | PSA + | PSA − | percentage | Crude OR* | 95% CI |
|---|---|---|---|---|---|
| 0- | 4 | 92 | 4.2% | 1.00 | |
| 50- | 9 | 66 | 12.0% | 3.14 | 0.93-10.63 |
| 150- | 15 | 106 | 12.4% | 3.25 | 1.04-10.14 |

*OR = odds ratio.
$X^2 = 3.959$, $P < 0.05$.

### *Prevalence of abnormal PSA*

According to adjusted urinary cadmium and estimated cadmium uptake, all the subjects with negative PSA and the cases with positive PSA (according to age-specific PSA references) are subdivided into different cadmium body burden groups. Chi-square analysis for trend is applied to determine the possible relation between cadmium body burden and the prevalence of suspicious prostate cancer due to the level of serum PSA. The result shows that the prevalence of cases with positive PSA increase with the cadmium body

*Table 5.* Comparing the concentration of serum testosterone (T), follicle stimulating hormone (FSH), and luteinizing hormone (LH) between cases with positive PSA or abnormal DRE and the normal subjects.

| | | n | T (nmol/l) | FSH(IU/l) | LH(IU/l) |
|---|---|---|---|---|---|
| PSA | + | 29 | 10.96 | 9.77 | 9.55 |
| | | | (3.28-29.52) | (3.02-38.19) | (2.86-39.32) |
| | − | 266 | 10.47 | 8.51 | 7.58 |
| | | | (0.23-35.01) | (1.29-63.22) | (0.92-48.09) |
| DRE | + | 10 | 12.88 | $15.85^{**\blacklozenge}$ | $12.16^{*}$ |
| | | | (7.23-17.06) | (4.98-45.76) | (2.75-30.09) |
| | − | 277 | 10.47 | 8.31 | 7.59 |
| | | | (0.23-33.34) | (1.71-50.70) | (0.92-48.09) |

$^{*}P < 0.05$, $^{**}P < 0.01$
$^{\blacklozenge}P < 0.05$, after controlling the confounding effect of age, BMI by covariance analysis.

burden (Tables 3 and 4). No similar trend is found in blood cadmium (not shown).

*Sex hormones*

It is interesting to note (Table 5) that the levels of serum testosterone (T), follicle stimulating hormone (FSH) and luteinizing hormone (LH) are all higher in cases with suspicious DRE or with abnormal PSA than that of corresponding sex hormones in normal subjects. Statistically significant differences are noted only in FSH and LH between cases with suspicious DRE and the normal subjects. After controlling the confounding effects of age and BMI, a significant difference can only be observed in FSH for the subjects with abnormal DRE.

## Discussion

The introduction of prostate-specific antigen (PSA) testing in 1986 revolutionized the management of patients with prostate cancer. Normally, only low level of PSA presents in the blood stream, and the most common upper limit value of PSA in use to screen prostate cancer is 4 ng/ml. It is always the case that increased serum concentrations will indicate some kinds of prostatic pathology, including prostate cancer. The specificity of PSA is considered good compared with many other tumor markers, but furthering improvement is needed.

In present study, there is a clear positive trend between PSA and age shown in Figure 2. This finding is consistent with previous reports (Stamey *et al.* 1987; Collins *et al.* 1993; Oesterling *et al.* 1993). PSA is mainly synthesized in and secreted from epithelium of prostate tissue, and prostate volume increases with age. But in Collins's study (Collins *et al.* 1993), it seemed that age and prostate volume influence the serum PSA concentration independently. So they were the first to suggest evaluating the sensitivity and specificity of PSA by adjusting for volume and age in the diagnosis of prostate cancer. The recommended age-specific reference ranges for serum PSA from the study of Oesterling *et al.* (1993) were adopted in this study. The US Food and Drug Administration has approved the use of serum PSA testing, combined with digital rectal examination (DRE), as an aid in the detection of prostate cancer in men aged 50 years and older.

In this study, DRE-based screening detected 10 persons as suspected prostate cancer patients. Among the 10 suspects of prostate cancer, 3 (30%) also have abnormal PSA and others (70%) were below the corresponding upper limit according to the age-specific PSA. It seems that the results of DRE were not consistent with that of PSA. But the serum PSA level in cases with suspicious DRE was significantly greater than that of the normal subjects. These results suggest that as a screening method for prostate cancer, PSA or DRE, were independently useful in screening out cases suspected to have prostate tumor. Because no data of needle biopsy was available, further comments about the efficiency of DRE and PSA can not be made. In this study, it was noted that the prevalence of cases with abnormal PSA increased with cadmium body burden (Table 3). It may be of interest in this context to note that in a parallel study on the same population (Zeng *et al.* 2004) an increasing trend of high serum testosterone values was found in relation to urinary Cd. There was however no statistically significant increase in average testosterone level with UCd. It was found in the present study that the BCd, but not UCd in cases with positive DRE was significantly higher than that of subjects with negative DRE (Table 2). These results indicate that cadmium exposure, to some extent, may be related to effects of prostate, including changes that are considered indicative of cancer.

Interesting to note (Table 5) that after adjustment for age and BMI, there is a statistically significant increase in FSH in DRE positive persons. Cadmium-induced alteration of sex hormones might thus play a role in the occurrence and development of the prostate cancer. But futher studies are needed concerning such a possible effect. Prostate is stimulated to grow and

is maintained in size and function by the presence of serum testosterone. A normal function of the hormonal axis beginning with a rhythmic release of LHRH (LH releasing hormone) by the hypothalamus followed by a pulsate secretion of LH and FSH from the testes and is responsible for normal prostate growth and function (Frick & Aulitzky 1991). But at the same time, testosterone plays an important role in the etiology of prostate cancer. Animal models suggest that androgens may act as promoters in preclinical prostate cancer. In men with benign prostate hyperplasia, androgen deprivation of the prostate leads to reduction in prostate size (Bardin *et al.* 1991). In addition, Hsing & Comstock (1993) reported that cases of prostate cancer had higher circulating testosterone than controls. Moreover, they found that the mean serum level of testosterone was lower in men with latent prostate cancer than those with the clinically overt cancer. In one study in rats (Waalkes *et al.* 1992), it appears that cadmium produces prostatic tumors if testicular support is maintained because tumors are observed only with doses of cadmium below the threshold for induction of testicular degeneration and dysfunction or when such degeneration is prevented by zinc. Similar findings were also reported by Shirai *et al.* (1993). The tissue of prostate will atrophy after cadmium-induced testicular degeneration.

The underlying mechanisms by which cadmium may induce prostate cancer remain obscure. In view of the cumulative properties of cadmium, prostate is a critical organ where cadmium will enter and be stored due to the long half-life of cadmium in human body. In a recent study (Brys *et al.* 1997), an increasing Cd content and a decreasing Zn content were found in tissues of human prostate neoplasm compared to normal tissue. Zeng *et al.* (2003) also found increased Cd content and decreased Zn as well as changes in metallothionein levels in prostate tissue of rats orally exposed to Cd.

In conclusion, our population-based study in the southeast part of China found that long term environmental cadmium exposure was associated with injuries to human prostate. A possible relationship to changes in circulating serum sex hormones needs further investigation.

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## References

Ades AE, Kazantzis G. 1988 Lung cancer in a non-ferrous smelter: The role of cadmium. *Br J Ind Med* **45**, 435.

Armstrong BG, Kazantzis G. 1983 The mortality of cadmium workers. *Lancet* **1**, 1425.

Bardin CW, Swerdloff RS, Santen RJ. 1991 Androgens: Benefits. *J Clin Endocrinol Metab* **73**, 4–7.

Brys M, Nawrocka AD, Mielos E, Zydek C, Barecki A, Krajewska WM. 1997 Zinc and cadmium analysis in human prostate neoplasms. *Biol Trace Elem Res* **59**, 145–152.

Cai S, Yue L, Jin T, Nordberg GF. 1998 Cadmium and renal dysfunction: Dose response in a population living in an area contaminated by irrigation water. *WHO Bull* **76**, 153–159.

Collins GN, Lee RJ, McElvie GB. 1993 Relationship between prostate specific antigen, prostate volume and age in the benigh prostate. *Br J Urol* **71**, 445.

Frick J, Aulitzky W. 1991 *Physiology of the prostate*. Infection. Suppl 3, 115–117.

Hsing AW, Comstock GW. 1993 Serological precursors of serum hormones and risk of subsequent prostate cancer. *Epidemiol Biomarkers Prev* **2**, 27–32.

IARC. 1993 *IARC Monographs on the evaluation of carcinogenic risks to humans Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry* Lyon, France: IARC; Vol. 58.

Jin T, Nordberg M, Frech W, Dumont X, Bernard A, Ye T, Kong Q, Wang Z, Li P, Lundstrom N, Li Y, Nordberg G. 2002 Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad) *BioMetals* **15**, 397–411.

Jin T, Wu X, Tang Y, Nordberg M. Bernard A, Ye T, Kong Q, Lundstrom NG, Nordberg GF. 2004 Environmental epidemiological study and estimation of benchmark dose renal dysfunction in a cadmium polluted area in China. *BioMetals* **17**: 525–530.

Nordberg GF, Herber RF, Alessio L. 1992 *Cadmium in the human environmental: toxicity and carcinogenicity*. Lyon: IARC Scientific Publications; No. 118.

Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Pansen LA, Girman CJ, Lieber MM. 1993 Serum prostate-specific antigen in a community-based population of healthy men: Establishment of age-specific reference ranges. *JAMA* **270**, 860.

Ross RK, Shimizu H, Paganini-Hill A, Honda G, Henderson BE. 1987 Case-control studies of prostate cancer in blacks and whites in southern California. *JNCI* **78**, 869.

Shirai T, Iwasaki S, Masui T, Mori T, Kato T, Ito N. 1993 Enhancing effect of cadmium on rat ventral prostate carcinogenesis induced by 3,2′-dimithyl-4-aminobiphenyl. *Jpn J cancer Res.* **84**, 1023–1030.

Sorahan T, Waterhouse JAH. 1983 Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. *Br J Ind Med* **40**, 239.

Sorahan T. 1987 Mortality from lung cancer among a cohort of nickel-cadmium battery workers. *Br J ind Med* **44**, 803.

Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. 1987 Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* **317**, 909–916.

Van der Gulden, Kolk JJ, Berbeek AL. 1995 Work environment and prostate cancer risk. *Prostate* **27**, 250–257.

Waalkes MP, Rehm S, Perantoni AO, Coogan TP. 1992 Cadmium exposure in rats and tumours of the prostate. In: Nordberg GF, Herber RFM, Alessio L, eds. *Cadmium in the Human Environment: Toxicity and Carcinogenicity*. Lyon: IARC Scientific Publications; Vol. **118**, 391–400.

Waalkes MP, Anver M, Diwan BA. 1999 Carcinogenic effects of cadmium in the noble (NBL/Cr) rat: induction of pituitary, testicular, and injection site tumors and intraepithelial proliferative lesions of the dorsolateral prostate. *Toxicol Sci* **52**, 154–161.

West DW, Slattery ML, Robison LM, French TK, Mahoney AW. 1991 Adult dietary intake and prostate cancer risk in Utah: A case-control study with special emphasis on aggressive tumors. *Cancer Cause Control* **20**, 85.

Zeng X, Jin T, Zhou Y, Nordberg GF. 2003 Changes of serum sex hormone levels and MT mRNA expression in rats orally exposed to cadmium. *Toxicology* **186**, 109–118.

Zeng X, Jin T, Buchet JP, Jiang X, Kong Q, Ye T, Bernard A, Nordberg GF. 2004 Impact of Cadmium Exposure on Male Sex Hormones: A Population-Based Study in China. *Environ Res* (in press).