Biol Trace Elem Res (2010) 134:180–187
DOI 10.1007/s12011-010-8636-y

Selenium and Cadmium Levels and Ratios in Prostates, Livers, and Kidneys of Nonsmokers and Smokers

Jutta Schöpfer · Gustav Drasch · Gerhard N. Schrauzer

Received: 20 November 2009 / Accepted: 29 January 2010 /
Published online: 20 February 2010

Abstract Cadmium (Cd) from cigarette smoke, environmental, and nutritional sources accumulates in the human prostate where it interacts with selenium (Se) in a manner suggesting the formation of a 1:1 Cd–Se–protein complex. At low Cd exposures and adequate Se status, this interaction may be beneficial as it results in the detoxification of Cd. At higher exposures, Cd may weaken or abolish the anticarcinogenic effects of Se and increase prostate cancer risk. In some older men and especially in smokers, Cd levels in prostates reach levels in stoichiometric excess over Se, which may be the reason why heavy smokers are at higher risk of developing lethal forms of prostate cancer. In the liver and the kidneys, Cd accumulates as well, but in these organs, Cd is efficiently sequestered through metallothionein formation. In the prostate, this mode of detoxification is not available or less efficient, causing Cd to interact with Se and to increase prostate cancer risk.

Keywords Cadmium · Selenium · Prostate · Liver · Kidneys · Smokers · Nonsmokers

Introduction

Cadmium (Cd) has been classified as a group 1 human carcinogen [1]. It is also registered specifically as a prostate cancer risk factor [2], as it accumulates in the prostate, where it promotes oxygen radical production, alters steroid hormone metabolism, stimulates the growth of human prostate epithelial cells, and induces their malignant transformation [3–7].

J. Schöpfer · G. Drasch
Institut für Rechtsmedizin, Ludwig-Maximillians Universität, Munich, Germany

J. Schöpfer
e-mail: jutta.schoepfer@med.uni-muenchen.de

G. N. Schrauzer
Biological Trace Element Research Institute, Chula Vista, CA 91914, USA

G. N. Schrauzer (✉)
Department of Chemistry and Biochemistry, University of California, San Diego, CA, USA
e-mail: gschrauzer@ucsd.edu

There is evidence that selenium (Se) interacts with Cd in vivo, reducing its toxicity [8]. However, as Se is metabolically inactivated in the process, Cd at sufficiently high levels of exposure also abolishes the anticarcinogenic effects of Se [9]. Relevant within this context is our recent paper [10] in which we showed that the Se/Cd ratios in the prostates of 129 men aged 15–99 years declined with age in a manner suggesting the formation of a 1:1 Cd–Se complex and more rapidly in smokers than nonsmokers. However, whereas in most of the nonsmokers, the Se/Cd ratios remained >1, in the prostates of close to one half of the 35 smokers older than 40 years, Se/Cd ratios <0.9 were observed [10], indicating the presence of Cd in stoichiometric excess over Se. Under these conditions, Cd would be expected to not only abolish the anticarcinogenic effects of Se but also to allow the promoting, transforming, and cocarcinogenic properties of Cd to manifest themselves, which could explain why smokers are at higher risk of developing lethal forms of prostate cancer [11, 12]. However, as much of absorbed Cd passes through the liver and is ultimately deposited in the kidneys, it seemed of interest to examine whether Cd also interacts with Se also in these two organs. We therefore determined the levels of Cd and Se in the livers and kidneys of the 129 men and compared them with the corresponding levels of these elements in their prostates.

Materials and Methods

Autopsy Cases

Postmortem samples of 129 men aged 15–99, who died from accidental fatalities or a sudden nonmalignant illness, were obtained from the autopsy sample collection of the Institute of Forensic Medicine, University of Munich, Germany. Anamnestic data (smoking habits, illnesses, professions) were obtained from relatives, medical documents, or police officers. All individuals were Germans, had their permanent residence in Southern Bavaria, and had not been occupationally exposed to Cd or Se.

Autopsy Samples

Three different organ tissues (prostate liver, kidney) and urine, excluding samples of corpses with signs of decomposition or posttraumatic changes, were removed from every subject, all less than 48 h after death.

All tissue and urine samples were placed native into polyethylene bags and were immediately deep-frozen and kept at −20°C until they were analyzed.

Biochemical Separation and Estimation of Cadmium and Selenium

Tissue Digestion

From 0.5 to 1 g of tissue was digested in a mixture of 65% HNO_3, 30% H_2O_2, and ultrapure water in a high-pressure microwave system. Cd and Se were determined using atomic absorption spectrometry with the graphite furnace technique and longitudinal AC Zeeman effect background correction. Precision and accuracy of the methods used for Cd and Se determinations were tested using standard reference material no. 186 (pig kidney) distributed by Promochem BCR.

Cd and Se concentrations in the tissue samples are expressed in micrograms per gram wet weight.

Urine

Tests for the main nicotine metabolite cotinine were run in the urine samples by competitive enzyme immunoassay (Cotinine Micro-Plate EIA, Ora Sure Technologies Inc., USA)

Results

Figures 1 and 2 show the Se and Cd concentrations in the prostates of the nonsmokers and smokers, Figs. 3 and 4 the levels of these elements in the kidneys, and Figs. 5 and 6 in the livers of smokers and nonsmokers as a function of age, with the corresponding concentration—age functions inserted.

Based on the analytical results obtained, all subjects of the present study were exposed to Cd and, as would be expected, the smokers among them more so than the nonsmokers.

Figure 1 shows that the polynomial Cd-age curve does not cross the least-squares fitted Se-age line, indicating that nonsmokers maintain an excess of Se over Cd in their prostates over their entire lifespan. Although this excess is diminishing with age, levels of Cd in excess over Se were seen in only three of our 61 nonsmokers; one of them was the oldest of our subjects; at 99 years of age, his prostate was not significantly enlarged, appeared normal on histological examination, and its Se content of 1.77 µmol/kg was close to average, but its Cd content was with 3.42 µmol/kg, the highest among the nonsmokers of our study. Conceivably, he was a former smoker, or he had been exposed to other sources of Cd during his lifetime. However, his age was not responsible for the high Cd value since the prostate of our second oldest nonsmoker, aged 96, contained the same amount of Se, but only 1.2 µmol Cd/kg.

The lowest Cd values, of 0.11 µmol/kg, were measured in the prostates of two nonsmokers, one of whom was the youngest of our subjects, aged 15 years, the other was 41 years old, and in the prostates of both, the observed Se contents of 2.65 and 1.5 µmol/kg indicate the presence of Se in substantial excess over Cd. Low levels of Cd levels were also

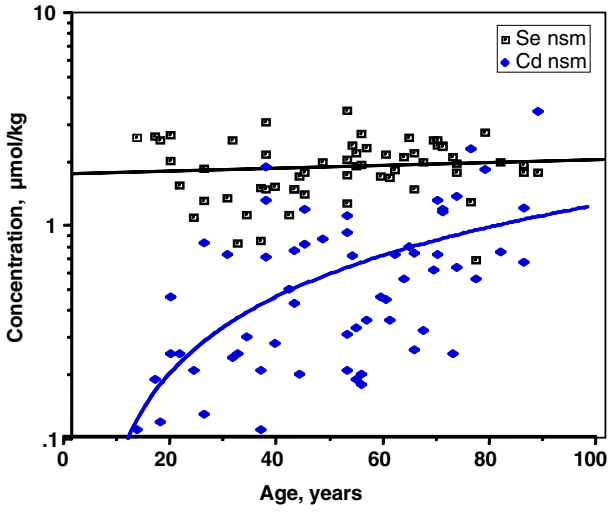

Fig. 1 Selenium and cadmium in the prostates of nonsmokers

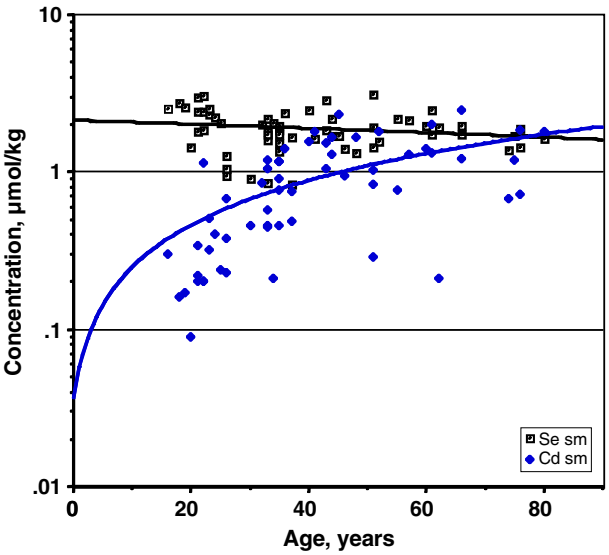

Fig. 2 Selenium and cadmium in the prostates of smokers

measured in the prostates of other nonsmokers, demonstrating that, under favorable circumstances, excessive Cd exposures can be avoided.

On the other hand, in the prostates of more than half of the smokers, Cd was present in excess over Se; these probably were from the heavy smokers among our subjects. The prostate of our oldest smoker, aged 80, contained Cd and Se at the levels of 1.82 and 1.62 µmol/kg, consistent with Fig. 2, which shows that the Se-age function crosses that of Cd at 78 years.

The levels of Se in the prostates of our subjects ranged from 0.69 to 3.49 µmol/kg, reflecting primarily their different dietary Se intakes. High levels of Cd in the prostates tend to be associated with lower Se concentrations. Thus, we previously reported [10] that the prostates of the men of the present study with the highest Cd contained significantly less Se

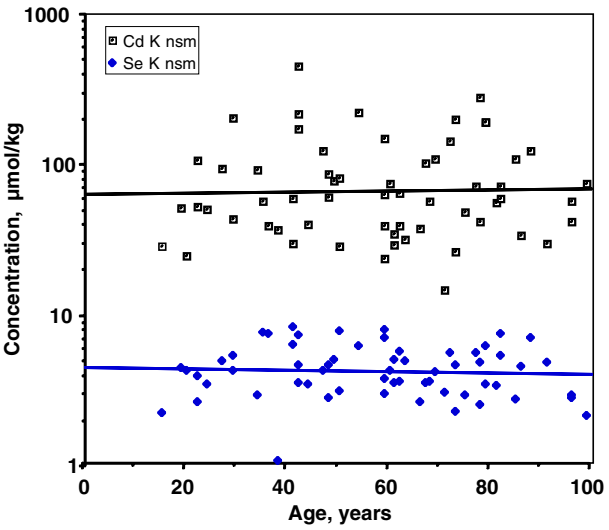

Fig. 3 Selenium and cadmium in the kidneys of nonsmoker

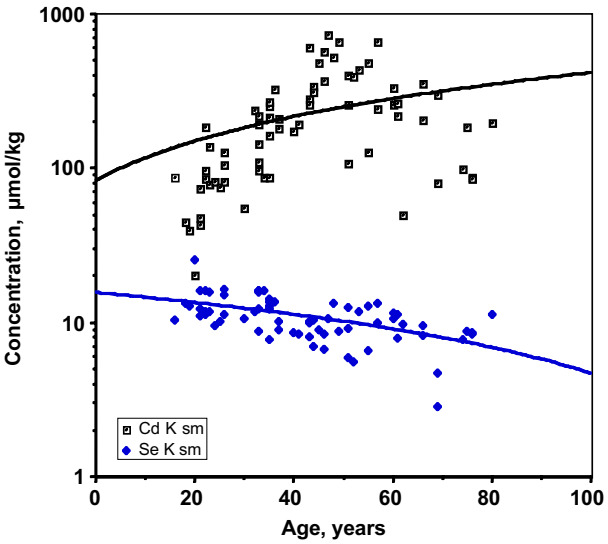

Fig. 4 Selenium and cadmium in the kidneys of smokers

than the prostates of the men with the lowest Cd levels. Comparing Fig. 2 with Fig. 1, it may be seen that the Se in the prostates of the smokers also declines with age, while the opposite is true for the nonsmokers. Evidently, in smokers, less Se reaches the prostate because some of the circulating Se is trapped by inhaled Cd, causing it to be deposited in other organs, most likely in the lungs.

In the kidneys of both the nonsmokers and smokers, Cd was found to be present in close to 20-fold excess over Se (see Figs. 3 and 4). In the nonsmokers, the average Cd concentration was 63 µmol/kg, ranging from 15 to 500 µmol/kg, and the average Se concentration was 4.5 µmol/kg, ranging from 1 to 8 µmol/kg; the levels of the two elements showed no dependence on age (see Fig. 3). The observed average Cd concentration of 240 µmol/kg in the kidneys of the smokers was close to four times that of the nonsmokers and ranged from 11 to 750 µmol/kg. The average Se content was with 10.4 µmol/kg twice as

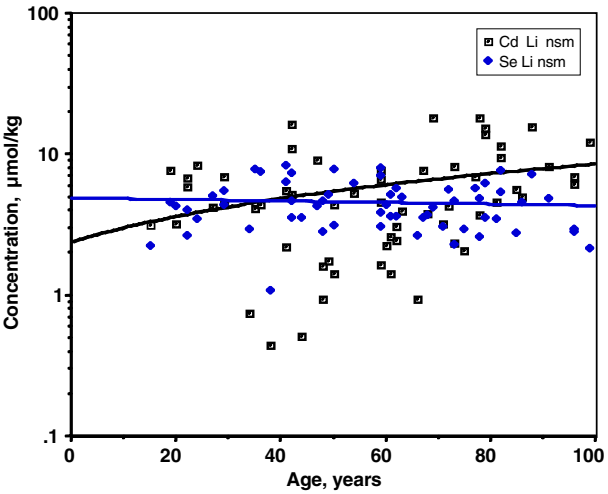

Fig. 5 Selenium and cadmium in livers of nonsmokers

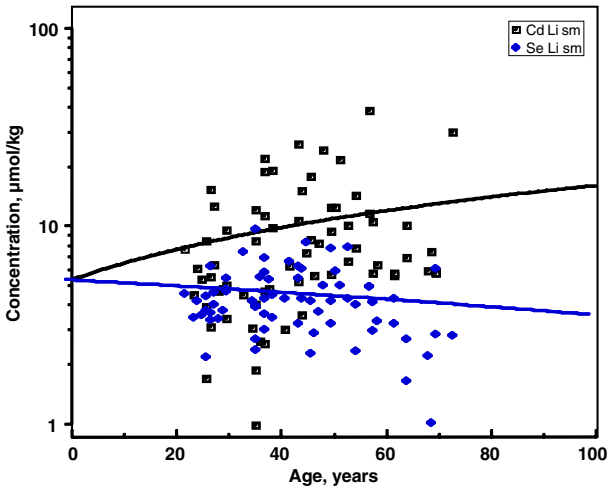

Fig. 6 Selenium and cadmium in livers of smokers

high as in the nonsmokers and ranged from 2.7 to 10.5 µmol/kg. Evidently, some of the inhaled Cd interacts with Se or selenoproteins and causes it to be deposited in the kidneys. This appears to occur to a greater extent in younger than in older smokers since kidney Se declined with age, while Cd increased. We interpret this as a sign of an increased production of metallothionein (MT) in response to the continuing influx of Cd from the inhaled cigarette smoke. However, this effect is relatively small since doubling the kidney Cd concentration causes only an about 10% decline of its Se content. The key conclusion to be drawn is that in the kidneys, MT efficiently sequesters Cd, a detoxification mechanism that is not available or efficient in the prostate, wherein MT production is highly variable due to genetic and other factors. This is important since, in general, a low MT expression has been shown to be associated with higher prostate cancer risk [13]. In accord with this conclusion are the results of a recent study which demonstrated a significantly lower MT expression in patients with prostate cancer than in controls with BPH [14].

The levels of Cd and Se in the livers of the nonsmokers and smokers are shown in Figs. 5 and 6. The average Se level of 11 µmol/kg of the livers of the smokers is approximately twice that of the livers of the nonsmokers, reflecting their higher Cd exposure. The individual Cd levels increase with age, while those of Se decline again more so in the smokers than the nonsmokers (see Fig. 6). The absence of a direct correlation between the Cd and Se levels is attributable to the fact that most of the Cd is efficiently MT-sequestered in the liver, and thus, only little of it is available for interactions with Se. In normal subjects, Cd would therefore not be expected to promote liver carcinogenesis. Indeed, Cd is not considered a strong liver cancer risk factor—it could even be protective since in a study with C3H/HeN mice, dietary Cd inhibited spontaneous hepatic carcinogenesis [15]. The underlying mechanism for this effect could be the ability of Cd at low levels to induce of MT biosynthesis [16]. The finding that low levels of Cd could prevent some forms of liver cancer is of interest in view of previously reported inverse associations between the age-corrected liver cancer mortalities in 19 countries and the estimated per capita Cd intakes [17]. The view that Cd could also have beneficial physiological functions is in line with results of animal experiments by Schwarz and Spallholz [18] and by Anke et al. [19], demonstrating positive growth effects of Cd at low dietary levels. Studies of Anke et al. are still ongoing and recently [20] led to a proposal of

a daily Cd requirement of humans of <3 μg. As the Cd requirement is substantially less than the current Cd intakes of the populations of most countries, Cd excess poses a problem, not Cd deficiency, although these findings should caution against pursuing a "zero-tolerance" policy for Cd.

Conclusions

Cd obtained from cigarette smoke, foods, and other sources accumulates in the prostate where it interacts with Se and selenoproteins, causing the inactivation of bioactive Se in the prostate. This interaction is expected to increase prostate cancer risk especially of heavy smokers, as their prostates have more Cd than the prostates of nonsmokers and frequently contain Cd even in stoichiometric excess over Se. In addition, the excessive accumulation of Cd in the prostates could also be the reason why heavy smokers develop lethal forms of prostate cancer with higher incidence than nonsmokers. In organs such as the kidneys and the liver, the levels of Cd also tend to exceed those of Se, but in these organs, Cd is efficiently sequestered by metallothioneins, a mode of Cd detoxification not available or efficient in the prostates.

References

1. National Toxicology Program (2007) Eleventh report on carcinogens. National Toxicology Program, Washington, DC
2. Agency for Toxic Substances and Disease Registry (1997) Division of Toxicology, Agency for Toxic Substances and Disease Registry, Public Health Service. U.S. Department of Health and Human Services, Atlanta
3. Jamba L, Nehru B, Bansal MP (1997) Selenium supplementation during cadmium exposure: changes in antioxidant enzymes and the ultrastructure of the kidney. J Trace El Exp Med 10:233–242
4. Vinceti M, Venturelli M, Sighinolfi C, Trerotoli P, 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
5. Benbrahim-Tallaa L, Lio J, Webber NN, Waalkes MP (2007) Estrogen signaling and disruption of androgen metabolism in acquired androgen-independence during cadmium carcinogenesis in human prostate epithelial cells. Prostate 67:135–145
6. Achanzar WE, Diwan BA, Liu J, Quader ST, Webber MM, Waalkes MP (2001) Cadmium-induced malignant transformation of human prostate epithelial cells. Cancer Res 61:455–458
7. Zeng X, Jin T, Jiang X, Kong Q, Ye T, Nordberg GF (2004) Effects on the prostate of environmental cadmium exposure—a cross-sectional population study in China. Biometals 17:559–566
8. Bremner I (1978) Cadmium toxicity. World Ref Nutr Diet 32:165–197
9. Schrauzer GN (2008) Interactive effects of selenium and cadmium on mammary tumor development and growth in MMTV-infeced female mice. A model study on the roles of cadmium and selenium in human breast cancer. Biol Trace El Res 123:27–34
10. Drasch G, Schöpfer J, Schrauzer GN (2005) Selenium/cadmium ratios in human prostates. Biol Trace El Res 103:103–107
11. Coughlin SS, Neaton JD, Sengupta A (1996) Cigarette smoking as a predictor of death. Am J Epidemiol 143:1002–1006
12. Plaskon LA, Penson DF, Vaughan TL, Stanford JL (2003) Cigarette smoking and risk of prostate cancer in middle-aged men. Cancer Epidemiol Biomarkers Prev 12(7):604–609
13. Klaassen CD, Liu J, Diwan BA (2009) Metallothionein protection of cadmium toxicity. Toxicol Appl Parmacol 238:215–220
14. Lee JD, Wu SM, Lu LY, Yang YT, Jeng SY (2009) Cadmium concentration and metallothionein expression in prostate cancer and benign prostatic hyperplasia of humans. J Formosan Medical Ass = Taiwan yi zhi 108:554–559

15. Nichiyama S, Onosaka S, Okudaira M, Yamamoto H, Tanaka K (2003) Dietary cadmium inhibits spontaneous hepatocarcinogenesis in C3H/HeN nice and hepatitis in A/J mice but not in C57/Bl6 mice. Toxicol Appl Pharmacol 186:1–6
16. Gaddipati JP, Rajeshkumar NV, Grove JC, Maharaj SVM, Centeno JA, Maheshwari RK, Jones WB (2003) Low-dose cadmium exposure reduces human prostate cell transformation in culture and upregulates metallothionein and MT-IG mRNA. Nonlinearity Biol Toxicol Med 1:199–212
17. Schrauzer GN, White DA, Schneider CA (1977) Cancer mortality correlation studies. IV. Associations with dietary intakes and blood levels of certain trace elements, notably Se-antagonists. Bioinorg Chem 7:35–56
18. Schwarz K, Spallholz T (1976) Growth effects of small cadmium supplements in rats maintained under trace element-controlled conditions. Abstr Fed Proc 35:255
19. Anke M, Hennig A, Groppel B, Partschfeld M, Grün M (1978) The biochemical role of cadmium. In: Kirchgessner M (ed) Proceedings of the third international symposium on trace element metabolism in man and animals. Technische Universitat Munchen, Freising-Weihenstephan, pp 450–548
20. Anke M, Dorn W, Müller M, Seifert M (2005) Recent progress in exploring the essentiality of the ultratrace element cadmium to the nutrition of animals and man. Biomed Res Trace Elem 16:198–202