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Cadmium and cancer of prostate and testis

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Abstract

Cancer of the prostate is an important and potentially fatal disease in humans but the etiology is yet undefined. Cadmium and cadmium compounds are known to be human carcinogens based on findings of increased risk to lung cancer among exposed workers, but a relationship between cancer of the prostate and/or testis in humans is unclear in spite of suggestive results in rats. Parenteral administration or oral exposure to cadmium can result in proliferate lesions and tumors of the prostate in rats. The ability of cadmium to produce neoplasms in the prostate of rats is atypically dose-related and only occurs in rats at doses below the threshold for significant testicular toxicity. Testicular androgen production is essential for the maintenance of the prostate and prostate tumors. The rat testis may also develop tumors if cadmium is given parenterally at high doses. Subsequent to testicular hemorrhagic necrosis, there will be loss of testosterone production and hyperplasia and neoplasia of testicular interstitial cells, thought to be a response to trophic hormone release from the pituitary. The pathogenesis of prostatic cadmium carcinogenesis might include aberrant gene expression resulting in stimulation of cell proliferation or blockage of apoptosis. Activation of transcription factors such as the metallothionein gene and activation of some proto-oncogenes may enhance cell proliferation with damaged DNA. Suppression of DNA repair would add to the population of cells with damaged DNA. Chemically induced apoptosis can be blocked by cadmium, facilitating aberrant cell accumulation.

Human prostate cancer

Cancer of the prostate is one of the most common cancers in men. Worldwide, it kills about 200,000 men annually. In the United States, there are about 190,000 new cases each year and about 30,000 deaths (American Cancer Society 2003). It is the second most common internal cancer accounting for about 33% of cancer in men; lung is the most common cancer in both men and women. Lifetime probability of a male developing prostate cancer is about 1 in 6 compared to about 1 in 2 for all sites. A great advancement has been the understanding that prostate cancer is hormonally driven by testosterone. The pioneering work of Dr Huggins and his colleagues at the University of Chicago in 1941 showed that the growth of metastatic prostate cancer can usually be retarded for a time by castration or administration of estrogens or both, leading to the assumption that androgens play a causal role. This awareness has had a great impact on treatment and survival from prostate cancer. Only 15 or 20 years ago, one third of clinically diagnosed cases of prostate cancer were lethal, but survival has greatly improved. Today, the probability of surviving prostate cancer in the United States is now about 95%. Early diagnosis by routine examinations and the testing of older men for Prostate Specific Antigen (PSA) has enhanced survival. Other factors increasing survival include improved surgical techniques and newer forms of hormonal therapy. A United States National Cancer Institute clinical trial for the prevention of prostate cancer found that the drug finisteride (Proscar®) reduced the prevalence of prostate cancer by 24.8% over a 7 year period. This drug is an inhibitor of 5-alpha-reductase, and blocks the conversion of testosterone to dihydrotestosterone, the primary active androgen in the prostate (Thompson *et al.* 2003). The effectiveness of this drug confirms hormonal nature of prostate cancer and the specific importance of testosterone.

The link between cadmium exposure and prostate cancer in humans is presently not clear. However, cadmium has been accepted by the International Agency for Research in Cancer as a Category 1 (human) carcinogen based primarily on reports of cadmium as a pulmonary carcinogen. For instance, in a study of occupational cadmium exposure in a smelter in Colorado by Strayner *et al.* (1992) a positive association between cadmium exposure and lung cancer was found. The earliest report of an association between cadmium exposure and prostatic cancer was by Potts (1965). He identified 4 deaths from prostate cancer in 74 workers from two nickel-cadmium battery plants in the United Kingdom who had been exposed to cadmium for at least 29 years. Three other reports of occupational exposures to cadmium from England, the United States and Sweden were combined into a single cohort by Elinder *et al.* (1985) and showed a significant association between risk from occupational exposure to cadmium and prostate cancer. The validity of combining data from different exposure settings might be questioned. Several other studies have failed to find any significant increase in prostate cancer and occupational exposure to cadmium.

The etiology of prostate cancer in humans is certainly complex and may include age, race, occupational, environmental and lifestyle factors as well as interactions between genes and the environment. The prevalence of prostate cancer is much less among Japanese and Hong Kong Chinese than among residents of the Unites States. However, Japanese migrating to the United States have a prevalence rate similar to native born Americans which seems to emphasize the role of the environment and lifestyle. The Background Document for Cadmium of the National Toxicology Program of the United States Report on Carcinogenesis, (NTP,1999), states that there is some epidemiological evidence for a possible relationship between cadmium and human prostate cancer from case control studies (Van der Gulden 1995) and geographic distribution studies, (Shigematsu *et al.* 1982; Bako *et al.* 1982), but the document summarizes a number of epidemiological studies of occupational exposures to cadmium that did not find a relationship between cadmium and prostate cancer (NTP 1999). While providing some evidence of a relationship between exposure to cadmium and prostate cancer, the evidence is not definitive. A systematic review of recent epidemiological data by Verougstraete *et al.* (2003), of environmentally exposed populations did not find an increased relative risk of cancer.

Experimental prostate cancer

Several recent studies have shown that chronic exposure to cadmium by several different routes of administration can produce tumors of the prostate. This effect is dose-dependent and also dependent on cadmium effects on other tissues, particularly the testis. Waalkes *et al.* (1988) showed that a single subcutaneous injection of cadmium chloride over a wide range of doses in rats showed that over two years prostate tumor incidence was elevated at doses below the threshold for significant testicular toxicity, but the prostate tumor response was lost at the higher, testopathic doses. As in humans, prostate cancer in rats is hormonally driven. Testicular androgen production is essential for the growth and maintenance of the prostate and prostate tumors. The rat testes are extremely sensitive to cadmium-induced tumorgenesis. When given at sufficiently high parenteral doses, cadmium rapidly induces severe testicular hemorrhagic necrosis (Goering *et al.* 1995; Waalkes *et al.* 1997). This is followed by the occurrence of testicular interstitial cell tumors. It is suggested that testicular necrosis, testicular atrophy and loss of androgen production stimulates the production of leuteotrophic hormone releasing hormone by the hypothalamus (Waalkes *et al.* 1997). This, in turn, stimulates release of leuteotrophic hormone by the pituitary gland and subsequent over-stimulation of remnant interstitial tissue in the testes resulting in tumor formation (Waalkes *et al.* 1997). Even though interstitial cells of the testes are the primary producers of androgens in the males, after cadmium treatment these cells become dysfunctional (Waalkes *et al.* 1997). Therefore, it is thought that testicular toxicity by cadmium is responsible for the loss of prostatic tumors production by high dose cadmium in rats. Oral cadmium exposure can also induce a dose-related induction of proliferative lesions (tumors and atypical hyperplasia) in the rat prostate (Waalkes *et al.* 1991). In this study at higher doses of oral cadmium a similar loss of prostatic response occurred (Waalkes *et al.* 1991). Oral cadmium exposure can also result in interstitial cell tumors in the rat testes, indicating probable testicular dysfunction (Waalkes & Rehm 1992). Cadmium treatment can also enhance the appearance of chemically induced prostate tumors in rats (Shirai *et al.* 2003).

Modification of cadmium -induced prostate and testicular tumors by zinc

Zinc can have an important impact on cadmium-induced carcinogenesis. Excess zinc appears to facilitate cadmium-induced prostate cancer by preventing testicular toxicity and maintaining testosterone production (Waalkes *et al.* 1989). On the other hand, dietary zinc deficiency reduces the carcinogenic potential of cadmium in the prostate by enhancing cadmium toxicity to the testis resulting in testicular and prostatic atrophy and a decrease in testosterone secretion (Waalkes & Rehm 1992). Induction of prostate atrophy would likely counter any proliferative effects of the metal in this organ. The selective antagonism by zinc of the carcinogenic effect of cadmium suggests that zinc may act at a variety of important binding sites, including sites potentially important in gene regulation or enzyme activity (Waalkes *et al.* 1991). For example, zinc can induce the synthesis of the metal-binding protein metallothionein, which reduces many of the adverse effects of cadmium (Klaassen *et al.* 1999).

Mechanisms for cadmium carcinogenesis

Cadmium may be genotoxic and mutagenic at high doses (Waalkes 2000), but cadmium does not form stable DNA adducts and is not likely to induce indirect oxidative DNA damage because it is not a redox active metal. Therefore, cadmium carcinogenesis is most likely the result of epigenetic or indirect genotoxic mechanisms. There is evidence suggesting that aberrant gene expression resulting in increased cell proliferation or blockage of apoptosis may provide possible mechanisms of carcinogenesis.

It has been shown that cadmium given in the drinking water to Noble (MNBL/Cr) rats at multiple dose levels for 52 weeks resulted in an increase in proliferative lesions of the ventral and dorsolateral lobes of the prostate. There was a clear dose-response at lower levels of exposure. The lesions were described as intraepithelial hyperplasia with occasional areas of atypical epithelial cells without stromal invasion. At higher doses, prostate proliferate lesions declined to control levels. This paradoxical dose response is thought to be related to decrease in testosterone secretion due to testicular damage at the higher cadmium dose levels (Waalkes *et al.* 1999).

More recently, it has been shown that *in vitro* exposure to cadmium can induce malignant transformation of human prostate epithelial cells (Achanzar *et al.* 2001) and that cadmium exposed cells exhibit altered expression of important apoptotic regulators as well as resistance to chemically-induced apoptosis (Achanzar *et al.* 2002). It is suggested that acquisition of apoptotic resistance in prostate cells by cadmium exposure may impact tumor initiation, progression, and, potentially, eventual chemotherapeutic intervention. Other factors that may contribute to cadmium-induced carcinogenesis include up regulation of mitogenic signaling, and perturbed DNA repair resulting in indirect genotoxicity. Cadmium can inhibit DNA repair (Hartwig 1998), which could be an indirect source of mutational events. Cadmium can activate transcriptional factors that normally require zinc, such as with the metallothionein gene system (Klaassen *et al.* 1999). Cadmium can also activate some proto-oncogenes or genes associated with cell proliferation, such as *c-myc* or *c-jun*, in cells and in animals, (Abshire *et al.* 1996: Zheng *et al.* 1996).

Poirier and Viasova (2002) suggest abnormal methyl metabolism may have a role in cadmium toxicity including inappropriate gene expression and carcinogenicity. Both zinc and cadmium were found to inhibit methyl transferase in nuclear extracts from both control and methyl-deficient rats. The inhibitory activity of cadmium was greater than that of zinc regardless of whether the nuclear extracts were from the methyl deficient rats or control animals. In rats liver cells transformed by cadmium, the metal initially causes a loss of DNA methylation and inhibition of DNA methyltransferase activity (Takiguchi *et al.* (2003).

Summary and conclusions

The role of cadmium in human prostate cancer is not definitive but cadmium can induce prostate cancer in rodents. Prostate cancer in rats, like human prostate cancer, is driven by testosterone. The pathogenesis of cadmium-induced prostate cancer involves the effect of cadmium on the testis manifested by a positive dose response with low doses of cadmium but not with high doses. High doses of cadmium produce testicular degeneration reducing testosterone production. Zinc excess inhibits prostate cancer probably by induction of metallothionein. Zinc deficiency depresses cadmium-induced prostate cancer second-

ary to testicular toxicity and reduction in secretion of testosterone.

Cadmium is poorly mutagenic suggesting that epigenetic or non-genotoxic mechanisms are involved. Possible mechanisms include activation of transcription factors that require zinc. Cadmium can enhance cell proliferation with damaged DNA and activated proto-oncogenes. Also, blockage of chemically induced apoptosis by cadmium facilitates aberrant cell accumulation.

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