Cadmium exposure and prostate cancer: insights, mechanisms and perspectives

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1. ABSTRACT

Cadmium (Cd) is a metal found in group 12 (IIB) of the periodic table of elements together with zinc, a metal with which it is often conjugated in nature. Occupational exposure to Cd occurs in many industrial settings, by cigarette smoking, diet and due to environmental pollution. International Agency for Research on Cancer and other epidemiological studies suggested that Cd can lead to prostate cancer and likely to kidney and lung cancers. Although epidemiological studies seem to point towards such an association, the *in vitro* studies have not been compelling. The aim of this article is to summarize current knowledge about the association of Cd exposure and prostate cancer, that suggests that new studies to show the role of Cd in the pathogenesis of prostatate cancer.

2. INTRODUCTION

Cadmium (Cd) (atomic number= 112.4.1) is a metal belonging in group IIB of the periodic table of elements. There are 8 stable and 2 radioactive isotopes of Cd in the environment (1). Almost every Cd compound has an oxidation number of +2. Cd is slowly oxidized in moist air and forms fumes of Cd oxide when heated (1-4). Cd is commercially available in the form of powders, foils, ingots, sheets, rods and crystals. From a commercial perspective, the most important Cd salts are Cd chloride ($CdCl_2$), Cd sulphate ($CdSO_4$), Cd nitrate ($Cd(NO_3)_2$), to a lesser extent, Cd oxide (CdO) and Cd sulphide (CdS) (1, 4). The properties of resistance to corrosion and extreme temperatures, high ductility, high thermal and electric conductivity make this metal suitable for various industrial applications (5). Cd is widely distributed on the earth crust at a concentration of 0,1-1 ppm, mainly associated with zinc (Zn), lead (Pb), copper (Cu) (6). The primary mineral form of Cd is CdS, so that 3 kg of Cd are produced for each ton of Zn (0,33%) (7). Cd is mostly used for the production of nichel-Cd(Ni-Cd) (83%), minor shares are for producing pigments (8%), coatings and platings (7%), stabilizers for plastics (1,2%) and other applications (ie. ferrous alloys, seminconductors, photovoltaic devices) (0,8%) (8).

The use of Cd in batteries has raised from 8% in 1970 to 75% in 2000 (1NTP, 2004). Cdmainlyused compounds are (1, 9): Cd Chloride ($CdCl_2$): preparation of CdS, printing, galvanic, production of pigments and vacuum tubes; previously used as fungicide; Cd Hydroxide($CdOH_2$): alkaline batteries,

Table 1. Epidemiological studies in humans

Study type	Exposure type	Results	References
Retrospective	Occupational	Positive association with prostate cancer	44
Retrospective	Environmental	Positive association with prostate cancer	45
Case-control	Occupational	Slightly Positive association with prostate cancer	46
Case-control	N/A	Positive association with prostate cancer	48
Cohort	Environmental	No association with prostate cancer	50
Case-control	Environmental	Positive association with prostate lesions	51
Cross-sectional	Occupational	Positive association with DNA damage	52
Cohort	Environmental	Increased prevalence of prostate, colon rectum and pancreas cancer	57
Retrospective	Dietary	No association with prostate cancer onset	58

N/A: Non-applicable

Cd Nitrate $Cd(NO_3)_2$: colorant for glass, porcelain and photographic emulsions, Cd Oxide (CdO): zinc oxide accumulators (ZnO), heat stabilizer for plastics and alloys; Cd Sulphate ($CdSO_4$): intermediate and galvanic, Cd Stearate: lubricant and stabilizer for plastics, Cd Sulphide (CdS): pigment.

Cd is found in non-ferrous metals (Zn, Pb and Cu), in iron (Fe), steel, fossil fuels (coal, oil, gas, peat and wood), in concrete and phosphatic fertilizers (10). Cd is also produced from recycled materials such as Ni-Cd batteries, production scraps and from some residues, such as dust from electric arc furnaces containing Cd or intermediate products.

Recycling accounts for about 10-15% of Cd production in developed countries (5). The primary use of Cd, in the form of $CdOH_2$, is in the Ni-Cd battery electrodes. Ni-Cd batteries are widely used in consumer products (eg. electric wireless devices, smartphones, videocameras, laptops, portable appliances and toys) and in the railway and air sector (for ignition and emergency power supply) (11, 8). CdS compounds (Cd sulfoselenide and Cd litopone) are used as pigments in a wide spectrum of applications, such as plastics, glass, pottery, rubber, enamels, colors and fireworks (4, 12). Cd pigments range from yellow to dark-brown, have good covering properties, and are highly resistant to a wide range of environmental conditions (light, high pressure and chemicals such as hydrogen sulphide (H_2S) and sulfur dioxide (SO_2) (13, 11, 10). Cd and Cd alloys are used as coatings in iron, steel, aluminum and other non-ferrous metals. They are particularly suitable for industrial applications that require long-lasting performances *eg* aerospace industry, industrial hinges, electrical parts, automotive systems, military equipment and marine installations, due to their good resistance to corrosion in alkaline solutions, low friction coefficient, good conductive properties. Furthermore, Cd alloys are easy to weld (14, 10). Cd organic acids (Cd stearate and Cd lauryl) in combination with barium sulphate ($BaSO_4$) have been widely used in the past as heat and energy stabilizers for polyvinyl chloride (PVC) and other plastics (13, 14). Small quantities of Cd are used in various alloys to enhance thermal and electrical conductivity and increase the mechanical properties of the base alloy, such as puncture, extrudability, hardness, wear resistance, traction and hardening; or to lower the melting point. Other minor uses of Cd are Cd telluride and CdS in solar cells and other semiconductor Cd compounds in various electronic applications (15, 14, 10). Traditionally, the most common applications for Cd are: pigments, stabilizers and coatings. However, in recent years, the use of Cd for these purposes has decreased, mainly due to the specific toxicity of this metal and the introduction of Community Regulations (EU), which limit its use (5). In 2003, the EU adopted restrictions on the use of hazardous substances, prohibiting the incorporation of Cd and other heavy metals into electrical and electronic equipment (including some types of Ni-Cd batteries) (16).

2.1. Occupational and environmental exposure

Cadmium pollution can origin from either stationary or mobile sources. In particular, stationary sources are all factories such as foundries, cement factories, galvanic plants, petroleum refining or coal combustion plants and incinerators.Mobile sources are Cd exhaust fumes from vehicles and/or particles resulting from tire wear, etc. The main sources of exposure to Cd and its compounds are working environments. In these places professional exposure is due to the presence of Cd in suspended dust in the air and in fumes. The highest exposure potential occurs in the production and refining of Cd, production of Ni-Cd batteries, production of Cd pigments, formulation and production of Cd alloys, mechanical plating, Zn fusion, soldering and brazing with Cd alloys and PVC material production (1, 4, 12). In exposed workers, Cd main absorption path is

through the airways, even if accidental ingestion of dust from contaminated hands and/or through food is also possible, albeit less common (11). In Europe, between 1990 and 1993, it was estimated that over two hundred thousand workers were exposed to Cd and its compounds in occupational environments such as: construction industry (n=32,113), manufacture/processing of metal products (n=23,541), non-ferrous metals industries (n=22,290), manufacture of PVC products (n=16,493), personal and household services (n=15,004) and machinery manufacturing (n=13,266) (17). Other areas where exposure can occur include: foundries, factories for the production of commercial and industrial machinery, manufacture of motor vehicle parts, metal production for architectural and structural use, production and transformation of non-ferrous metals (except Al), manufacture of metal-working machines, iron and steel mills, production of Al alloys and their transformation, production of electrical equipment and other electrical components (12). The following data represent the main source of workers' exposure to Cd and its compounds (12):

2.1. Manufacture of batteries

Zhang *et al*. (18) studied workers exposed to Cd in a Ni-Cd battery factory in China. Based on the environmental sampling carried out during the period 1986-1992, the average concentration of Cd powders was 2.1.7 mg/m^3 (range 0.1.-32.8. mg/m^3). The average total urinary Cd concentration in 214 workers was 12.8. mg/g creatinine (range 4.0.-21.4. mg/g creatinine), the overall average concentration of Cd in the blood was 9.5. mg/L (range of 3.8. to 17.4. mg/L). These values are considered to be extremely high when compared to the working-time weighted environmental limits (TLV-TWA), according to American Conference Governmental Industrial Hygienists (ACGIH) and the Italian Association of Industrial Hygienists (AIDII), which are 0,01 mg/m^3 for Cd and 0.0.02 mg/m3 for its compounds.

The admissible Cd value in the urine is 5 μg/g creatinine and 5 μg/L in the blood. A study conducted in 2004 examined the cumulative exposure to CdOH$_2$ in Ni-Cd batteries workers in the United Kingdom (n=926 male workers) from 1947 to 2000. Personal sampling revealed Cd concentrations of 0.8.8-3.9.9 mg/m^3 from 1969 to 1973. Interestingly, the values measured from 1989 to 1992 were much lower (range 0.0.24-0.1.2 mg/m^3). Similarly, the results of environmental monitoring with fixed samplers demonstrated a significant exposure to Cd in workers who had operated in the period 1954-1963 (range 0.3.5-1.2.9 mg/m^3), compared to 1989-92 (Range, 0.0.02-0.0.3 mg/m^3) (19).This indicates that, over the years, the introduction of safety and health standards in workplaces and the use of safer manufacturing

systems has allowed a progressive reduction of exposure risk in workplaces.

2.1.1. Cd recovery

Professional exposure to Cd compounds (CdO, CdS and CdSO$_4$) was studied in male workers (n=571) of a Cd recovery facility in the United States between 1940 and 1982. Estimated exposure to airborne particles containing Cd ranged from 0.2. (in the reservoir area) to 1.5. mg/m^3 (in the furnace areas) before 1950, and 0.0.2 (in the tank area) to 0.6. mg/m^3 (nearby ovens) for the period 1965-1976 (20).

2.1.2. Production of Cd alloys

Occupational exposure to Cd fumes was studied in 347 workers in a Cu-Cd alloy production plant, in 624 workers working near Cu-Cd alloy processing and in 521 workers in Fe and brass, in foundries in England and Wales, from 1922 to 1980. Based on a review of 933 Cd air-samplers between 1951-83 (697 fixed samples and 236 personal samplers), the cumulative Cd exposures were estimated at 600 μg/m^3 for the period 1926-1930, decreasing to 56 μg/m^3 since 1980 (21).

2.1.3. Foundry

Professional exposure to Cd was studied in 1,462 male employees in a UK foundry between 1972 and 1991. Annual average exposures were highlighted in the main processing areas. Average air levels were considered: low in refining and mixing areas (range of mean 0.0.05-0.0.08 mg/m^3), moderate in sintering areas and in ovens (ranges ranging from 0.0.4 to 0.0.8 mg/m^3) (22).

2.1.4. Vehicle manufacturing industry

Wang *et al*. (23) assessed the exposure of 82 metal welders and 51 operators in two automotive production plants in China. The average Cd concentration in the blood of welders was 3.5.4 mg/L (range 0.2.-12.5. mg/L), significantly higher compared to the control group hematic Cd concentration, which was of 0.7.9 mg/L (range 0.1.-4.8. mg/L).

2.1.5. Other activities related with Cd exposure

Yassin and Martonik (24) calculated the prevalence and average urinary Cd levels for all US workers based on data collected from 11,228 workers (age 18-64) who participated in the third edition of the National Health and Nutrition Examination Survey (NHANES III) (25). For all workers, urinary Cd levels were between 0.0.1-15.5.7 mg/L, with an average of 0.3.0 mg/L (0.2.8 μg/g creatinine). The prevalence of high levels of Cd in urine was reported on the basis
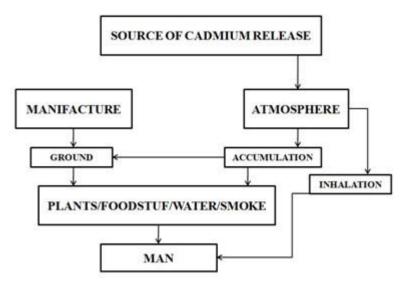
Figure 1. Sources of cadmium release and exposure.

of the following ranges: ≥15 mg/L, ≥10 mg/L, ≥5 mg/L and ≥3 g/L. The prevalence of urinary Cd levels ≥5 mg/L was 0.4.2% (n=551.0.00) for levels ≥10 mg/L was 0.0.6% (n=78.4.71) and for ≥15 mg/L was 0.0.028% (n=3.9.07). The percentage of workers with high urinary Cd varied with the type of occupation and type of industry. Urinary Cd levels ≥10 mg/L were twice as high among metal-working workers as compared with workers in the manufacturing industry (0.4.5% vs. 0.2.6%). Urinary Cd levels ≥5 mg/L were 12 times higher among vehicle mechanic workers than transport workers (1.7.1% versus 0.1.4%) and 5 times higher in construction workers than agricultural ones (0.7.3% versus 0.1.4%). Figure 1 summarizes the sources of cadmium release and exposure.

2.2. Cd absorption and metabolism

Inhalation is the main route of exposure to the Cd in professional environments; less frequently, exposure to Cd can occur through ingestion of food and drinking water. Exposure to particulate matter containing Cd can lead to absorption of Cd in both animals and humans (4). In working environment, Cd and its compounds, being non-volatile, are suspended in the air in the form of thin particles.

Animal studies (26) have shown that the lung can retain up to 20% of metal particles, particularly after short-term exposure. If ingested, most of Cd passes through the gastrointestinal tract without being absorbed. Estimates of the absorption rate of Cd in humans vary from 3% to 6.5.% (27, 28). When absorbed, Cd binds to metallothionein, forming a complex Cd-metallothionein which is transferred (through the blood) mainly to the liver and kidneys (29). Metallothionein is inducible in different tissues (eg liver, kidneys, intestines, and lungs) after exposure to

various agents including cadmium (29, 30, 31). During renal transport, the Cd-metallothionein complex is readily filtered by the glomeruli and can be efficiently reabsorbed at the proximal tubules (32, 33). In tubules, a portion of the protein is rapidly degraded and Cd is released (33). Cd builds up in kidney tubules and causes damage to tubular cells, especially in proximal tubules (34). The absorbed Cd is excreted very slowly and is almost equally eliminated in urine and stools (35). It has a long biological half-life and mainly accumulates in the liver and kidneys (half-life in kidney cortical is 10 to 30 years) (36). Overall, in humans, half-life is 7-16 years (35, 37).

3. DISCUSSION

We performed a literature search over the last 50 years about the association between prostate cancer and Cd exposure. Search was performed on Medline (https://www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.scopus.com/). The terms used to perform this research included: prostate cancer, cadmium, Cd, cadmium exposure, prostate, prostate tumor. Internal references of the examined studies were also taken into account. Research articles were included in the review, except for works published in languages other than English. *In vivo* and *in vitro* studies were included. After an independent search for scientific literature by reviewers, a total of 218 papers were collected. 143 were ruled out following review of the title and the abstract and 3 studies were excluded after review of the text. Finally, 75 studies were included for review. A flowchart depicting the selection of studies is shown in Figure 2.

The toxicology and carcinogenicity of Cd and its compounds, as well as the environmental impact (2, 3, 1, 4, 38, 39), are still partially studied
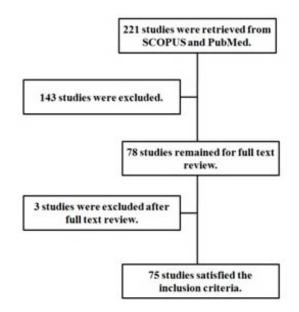
(1, 4, 11, 40, 41, 36, 42). Potts, in 1965, examined a small cohort of United Kingdom workers employed in Ni-Cd batteries and observed an increase in the incidence of prostate cancer (43). Lemen *et al*. (44) performed an epidemiological study that showed a positive correlation between workers exposure to Cd and lung and prostate cancers. A descriptive study on Cd polluted areas in Japan has shown an increase in prostate cancer mortality in two of the four studied areas (45). A case-control study conducted on a cohort of British cadmium workers showed a slightly increased odd ratio (OR) for prostate cancer, alongside an excess of mortality due to respiratory diseases and no evidence supporting a link with renal cancer (46). Nevertheless, a subsequent review of cohort studies did not confirm these results (47).

Vinceti *et al*. (48), in a case-control study on hospitalized patients with prostate cancer, measured the concentration of Cd accumulated in the toe nails of patients and observed a dose-response relation between Cd exposure and prostate cancer risk. Using increased urinary excretion of β2-microglobulin (β2M) as a marker of Cd toxicity, an increase in cancer incidence and mortality was observed in a Cd polluted area (relative risk (RR), 2.5.8, 95% CI: 1.2.5 (49, 50). The authors concluded that there was a significant association between β2M urinary excretion and cancer mortality, but there was neither a significantly increased standardized incidence ratio of cancer, nor a relevant relationship between urinary β2M and cancer incidence rate (49, 50). A case-control study conducted in 1998 in South East China examined 297 male volunteers, which included two groups living and operating in Cd-polluted areas and a control group. Serum total prostate specific antigen (PSA), total

serum testosterone (T), follicle stimulating hormone (FSH) and luteinizing hormone (LH) values were registered. Urinary Cd (U-Cd) and blood Cd (B-Cd) were also evaluated. The results showed a clear dose-response relationship between Cd exposure and the prevalence of abnormal values of PSA (51). These results suggested that chronic Cd exposure might be associated with prostate lesions in humans (6). Studies conducted on workers exposed to Cd, cobalt (Co) and Pb, reported a positive correlation between Cd concentrations in air and blood and DNA damage (single stranded and interrupted) (52-55).

Sahmoun *et al*. (56) examined the literature on prostate cancer and exposure to Cd published between 1966 and 2002, reporting a positive association in 3 of 4 descriptive studies, in 5 of 10 case-control studies and 3 of 11 cohort studies. The authors concluded the review indicating the limits of these studies, especially regarding the issues related to a poor assessment of exposure, which could be a critical factor for the validity of the studies. When they limited their review to 4 cohorts of Ni-Cd battery workers only (where the exposure assessment was more accurate), they calculated a standardized mortality rate (SMM) of 1.2.6 (95% CI: 0.8.3-1.8.4) for prostate cancer. A recent epidemiological study examined a population exposed to heavy metals such as Cd, As and Pb in their living environment, due to the proximity of glasswork plants. The results of the study showed an increase in the prevalence of gastrointestinal tract cancer, including colon, rectum and pancreas in both genders and of prostate cancer in men (57). A retrospective study evaluated dietary cadmium intake in a population of 26,778 men who had been enrolled in the Danish Diet, Cancer and Health

cohort. These subjects were administered a 192 item semi-quantitative questionnaire and Cd exposure was calculated basing on mean Cd content in food. Following statistical analysis, the results showed no association between dietary Cd intake and prostate cancer onset, even after correction for smoking habits, BMI, Zn or Iron (Fe) intake (58). Studies carried out to assess the risk of cancer in cohorts of workers exposed to Cd are often affected by: the size of the workers' cohorts, usually too small for long term studies; lack of previous data on Cd exposure, particularly for non-US plants; inability to examine and define a cumulative exposure gradient in different studies (12). In addition, cigarette smoking is considered a confounding factor in relation to the assessment of the risk of lung cancer among workers exposed to Cd and this data was only directly addressed in US studies (12). Cigarette smoke is an important source of Cd exposure. Smoking subjects have an absorbed dose of Cd that is twice as high as that of non-smokers (6).

Few studies have managed to extrapolate the effects of confounding factors arising from co-exposure to other substances such as As and Ni (12). Ju-Kun *et al*. (59), in a recent meta-analysis, assessed the correlation between Cd exposure and the risk of prostate cancer. The results suggest that Cd exposure is a risk factor for prostate cancer in occupational settings, especially in high doses. These results were particularly consistent because of the large sample size of the analysis, even though the authors recognized the possible limitations consequent to the influence of publication bias or the influence of confounding factors. On the other hand, Chen *et al*. (60) performed a meta-analysis of cohort and case-control studies among general and occupational populations exposed to Cd and found no sufficient evidence to support a positive association between Cd exposure and prostate cancer. In 2012, the International Agency for Research on Cancer (IARC) stated that the data regarding Cd exposure and the risk of prostate cancer are suggestive of an association, but the results are still inconsistent (12). Animal experimental studies clearly demonstrate that Cd and its compounds can induce the onset of both benign and malignant tumors through different routes of exposure(1, 4, 41, 42, 61-68). *In vivo* studies conducted on rats administered oral $CdCl_2$ showed prostate hyperplasia development (65) and increased incidence of large cell lymphoma, leukemia, prostate and testicular tumors (69, 70). Waalkes *et al*. (64) studied Nobel rats poisoned with drinking water containing Cd and noted the onset of proliferative lesions of prostate and kidneys. Overall, Cd exposure has proven to causes tumors of the hematopoietic system (leukemia and lymphoma), sarcoma and adrenal, liver, lung, kidney, pancreas, pituitary gland, prostate and testes cancer in laboratory animals (1, 36). Oral administration of $CdCl_2$ caused prostate cancer and/or preneoplastic lesions in Wistar rats and in Noble rats (69, 63). In

rats, inhalation of various compounds of Cd ($CdCl_2$, CdO, CdS) and endotracheal administration of $CdCl_2$ induce pulmonary tumors (12).

$CdCl_2$ induces proliferative lesions and testicular tumors in rats after subcutaneous or oral administration (12). The pathogenic mechanisms on Cd toxicity have been studied on various experimental models. In laboratory animals, Cd causes tumors in many tissues: therefore, the mechanism of carcinogenicity is likely to be multifactorial (6). In rodents, Cd salts administration results in an increased number of micronuclei and chromosomal aberrations. In mammalian cells, *in vitro*, Cd compounds induce DNA breaks and chromosomal aberrations (36, 70). Soluble and insoluble Cd compounds determine genetic toxicity through indirect mechanisms such as oxidative stress, inhibition of DNA repair systems, alteration of cell proliferation and of tumor suppressor functions (71). An experimental study combined evidence of *in vitro* cell cultures and mice models to clarify the role of autophagy in the development of Cd-induced prostate cancer (72). The authors tested the effects of Psoralidinon Cd-transformed prostate epithelial cells (CTPE). CTPE cells normally exhibit a highly aggressive and invasive behavior, but showed an overall decrease in growth and expression of pro-survival signaling proteins after treatment. These results were also tested on xenograft models *in vivo* (72)*.*

CdS induces the formation of hydrogen peroxide in polymorphonucleated leukocytes in humans; $CdCl_2$ induces superoxide production in rat and human phagocytes (73). Antioxidant agents and antioxidant enzymes (74 - 76) suppress the induction of DNA strand breaks and chromosomal aberrations determined by Cd in mammalian cells. Since Cd does not undergo physiological reduction reactions, the higher production of reactive oxygen and oxidative cell damage can be due to the inhibitory effect of Cd on antioxidant enzymes and DNA repair systems (75, 76). Cd is co-mutagenic and increases the mutagenesis caused by ultraviolet radiation, alkylation and oxidation, in mammalian cells. These effects are a consequence of Cd-mediated inhibition of various types of DNA repair mechanisms such as nucleotide excision, mismatch repair and the elimination of thepre-mutagenic DNA base alteration 7,8-dihydro8-oxoguanine (77).

Low Cd concentrations do not seem to generate oxidative damage, but they effectively inhibit DNA oxidative damage repair in mammalian cells (78, 79). In the process of nucleotide excision, Cd interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway (77, 79). In human cell extracts, Cd has shown to inhibit DNA-mismatch repair (80). In addition, Cd inhibits 8-oxo-dGTPase in human and *E. coli* cell cultures (81). This inhibitory effect grows with the concentration

of Cd and could explain the induction of the 8-oxo-dG into DNA which has been observed in other studies (82). The molecular mechanism of inactivation of DNA repair proteins involves Cd-induced displacement of Zn from Zn-finger structures. The removal of Zinc, in fact, alters the function of some DNA repair proteins such as *PigmentousXeroderma A* (XPA) group, required for nucleotide-excision and Formamido-Pyrimidine-DNA-glycosylase (FPG), which is involved in E. coli base excision (83).

Cd inhibits the function of 8-oxoguanine-DNA-glycosylase (hOGG1), which is essential in DNA repair mechanisms. Although hOGG1 does not contain Zn-binding structures within its molecular structure, inhibition of its function is due to its down regulation resulting from decreased DNA binding of the SP1 transcription factor, which contains Zn-finger structures (84). Finally, Cd induces a conformational change in the Zn domain of p53 protein. Thus, in addition to directly inhibiting repair proteins, Cd causes a down regulation of the genes involved in DNA repair *in vivo* (85). Like other metals, Cd can show atomic/molecular mimicry of essential nutrients (86). In other words, it can compete with essential nutrients for sites that are important in gene regulation, enzyme activity and/or maintenance of genomic stability (36, 87, 88). The role of connexin 43 (Cx43) and of androgen receptor activation in the development of prostate cancer in Cd exposed subjects has been evaluated in a recent study. The authors noted that changes in Cx43 are involved in the enhanced proliferation of human prostate epithelial cells exposed to low doses of Cd. They also hypothesized that Cd could induce cell proliferation through endocrine-disrupting effects and added flutamide (and androgen receptor antagonist) to their cell cultures. After treating with flutamide, Cd did not seem to exert any effect on cell proliferation or Cx43 expression (89). Numerous studies have shown that Zn reduces the carcinogenic effect of Cd in some sites (such as lung, testes and injection sites), but not all (*eg* prostate) (36).

The impact of Cd on DNA repair mechanisms may be particularly relevant in Cd "adapted" cells. This metal, in fact, induces several genes to tolerance to several reactive oxygen species, in particular those that code for metallothionein, synthesis and function of glutathione, catalase and superoxide dismutase (75). These modifications allow cell survival at chronically high concentrations of Cd (90). Taking into account the impact of Cd on DNA repair and the contextual tolerance and toxicity of this metal, there is a greater chance of inducing further critical mutations (61). Several mechanisms could potentially contribute to Cd-induced carcinogenesis. Direct DNA binding seems to be of lesser importance, and mutagenic responses are weak. Compelling evidence emerges from disorders in DNA repair mechanisms and onco-suppressive proteins that lead to chromosomal

damage and genomic instability (6). Other reported effects include changes in DNA methylation patterns as well as interactions with signal transduction processes that may contribute to the alteration of cell growth regulation (6). A recent study used CTPE cells to evaluate whether KRAS gene overexpression could play a role in the pathogenesis of Cd-induced prostate cancer. This experiment was conducted basing on previous knowledge, which reported the ability of As to transform human prostate epithelial cells (RWPE-1) into neoplastic cells, with KRAS playing a pivotal role in this process (91). Cd showed an even greater capacity of transforming RWPE-1 into neoplastic cells, and silencing of KRAS did markedly reduce malignant hallmarks such as hypersecretion of MMP-2, colony formation and cell survival, albeit it did not reverse the malignant phenotype. The authors concluded that KRAS gene plays a key role in the development and maintenance of Cd-induced prostatic cancer (92).

In vitro, Cd can induce neoplastic transformation in a variety of cells, including epithelial cells of the human prostate, demonstrating its oncogenic properties (36). Furthermore, studies have proven that this metal has a broad spectrum of cell and molecular, both genetic and epigenetic effects, (36, 87, 93), that could affect all phases of the carcinogenic process (94, 95). Waisberg *et al*. (93) examined different studies, reporting that the carcinogenicity of Cd seems to be mediated by the production of reactive oxygen species. Actually, Cd - as well as other toxicants (2) - induces the production of hydroxyl radicals, superoxide anions, nitric oxide and hydrogen peroxide. It also increases levels of lipid peroxidation in the liver, liver mitochondria of rats and rat hepatocyte cultures. Cd is not a Fenton metal and induces the formation of reactive oxygen species through indirect mechanisms (93). In experimental models, Cd induces many biochemical changes, including aberrant gene expression and signal transduction, E-caderine dysfunction (which plays a pivotal role in tumor proliferation processes), inhibition of DNA methylation, DNA repair and death interruption cell line (93).

Cd modifies the expression of several genes related to carcinogenesis, including intermediate genes of early response such as c-fos, c-jun, and c-myc; stress response genes such as metallothionein and heat-shock genes; glutathione and related protein genes; transcription and transduction factors (93). In non-cytotoxic concentrations, Cd inhibits DNA repair including mismatch repair, nucleotide excision and base excision. Inhibition of DNA repair, combined with an increase in oxidative stress, causes DNA damage, cell cycle arrest, mutagenesis and genomic instability, leading to cancer or cell death (87). The biochemical alterations induced by Cd may play a role in all phases of carcinogenicity (initiation, promotion and progression). For example: 1) induction of oxidative stress in combination with decreased DNA repair can lead to genomic damage and

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gene mutations, causing preneoplastic lesions (96, 97); 2) gene expression alterations and signal mechanisms, combined with the inhibition of DNA methylation, induce proto-oncogenes, resulting in cell proliferation; 3) E-caderine dysfunction interrupts cell adhesion and causes tumor progression (93). Furthermore, Cd seems to alter the apoptotic processes. In cultured cells, Cd exposure causes a dose-dependent increase in apoptotic cells. In some experimental systems, the increase in cell death is associated with an increase of p53 protein and mRNA levels; while in other cell lines, Cd induced apoptosis is p53-independent and linked to the production of reactive oxygen species. However, the induction of apoptosis is unlikely to protect cells against malignant transformation, as some studies have found that only a small fraction of Cd exposed cells undergo apoptosis, while the remaining cells may acquire apoptotic resistance (93). In addition, cells in which Cd induces neoplastic transformation (*eg*: prostate cells, lung epithelial cells and rat hepatocites) acquire resistance to apoptosis (97 - 99). Apoptosis resistance allows accumulation of critical or preneoplastic mutations (93, 36).

4. CONCLUSIONS

In conclusion, several studies demonstrate a close relationship between exposure to Cd and proliferative lesions ending with prostate cancer (61- 64, 66). *In vitro* studies performed on human prostate cells have also shown the role of Cd in inducing malignancies (36). These findings suggest starting off further, more effective studies meant to analyse the effects of Cd exposure on humans, which may occur either at work or casually. Up to date, present epidemiological studies have several limits, as they cannot detect clear effects on man. This depends on many confounding factors such as cigarette smoking and the co-exposure to other ores and /or pollutants (100, 101, 102). Whereas, animal studies seem to highlight a relationship between Cd exposure and human prostate cancer (6). Some case-control and ecological studies suggest the association between Cd exposure and prostate cancer (104, 105, 48). The use of biomarkers to assess Cd exposure such as Cd urinary excretion and blood and serum Cd levels, can help cope with some of these limitations (6). Therefore, there is enough evidence in human beings of Cd and Cd compounds lung carcinogenicity (12). Positive associations have been observed between exposure to Cd and its compounds and kidney and prostate cancers. Ju-Kun *et al*., (59), in a recent literature meta-analysis, evaluated the correlation between Cd exposure and prostate cancer risk. Results suggested that Cd represents a risk factor of prostate cancer in professional categories exposed to high concentrations of Cd. These observations, together with a quantity of *in vivo* tests seem to suggest a probable carcinogenic role of Cd in inducing prostate cancer. Further studies still need to be carried out, which will have to take into due account the limitations of the previous ones that, until now, have not allowed to clarify the carcinogenic role of Cd in prostate cancer.

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