

REVIEW

Mechanisms of Cadmium Carcinogenicity in the Gastrointestinal Tract

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Abstract

Cancer, a serious public health problem in worldwide, results from an excessive and uncontrolled proliferation of the body cells without obvious physiological demands of organs. The gastrointestinal tract, including the esophagus, stomach and intestine, is a unique organ system. It has the highest cancer incidence and cancer-related mortality in the body and is influenced by both genetic and environmental factors. Among the various chemical elements recognized in the nature, some of them including zinc, iron, cobalt, and copper have essential roles in the various biochemical and physiological processes, but only at low levels and others such as cadmium, lead, mercury, arsenic, and nickel are considered as threats for human health especially with chronic exposure at high levels. Cadmium, an environment contaminant, cannot be destroyed in nature. Through impairment of vitamin D metabolism in the kidney it causes nephrotoxicity and subsequently bone metabolism impairment and fragility. The major mechanisms involved in cadmium carcinogenesis could be related to the suppression of gene expression, inhibition of DNA damage repair, inhibition of apoptosis, and induction of oxidative stress. In addition, cadmium may act through aberrant DNA methylation. Cadmium affects multiple cellular processes, including signal transduction pathways, cell proliferation, differentiation, and apoptosis. Down-regulation of methyltransferases enzymes and reduction of DNA methylation have been stated as epigenetic effects of cadmium. Furthermore, increasing intracellular free calcium ion levels induces neuronal apoptosis in addition to other deleterious influence on the stability of the genome.

Keywords: Cadmium- gastric cancer - DNA damage repair - antioxidant enzymes

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Introduction

Cancer, a serious public health problem in worldwide, resulted from an excessive and uncontrolled proliferation of the body cells without obvious physiological demands of organs (Pasupathi et al., 2011). Cancer in both genders was one of the five major causing of mortality. It is responsible for 25% of mortality every year (Herszenyi and Tulassay, 2010). It was estimated that the number of new diagnosed cancer cases in developed countries will increase from 56% in 2008 to more than 60% in 2030 (Ferlay et al., 2008).

According to World Health Organization (WHO), cancer was the second causes of death in the developed countries and third in the developing countries in 2006 (National registration of cancer cases, 2008). It was supposed that this health problem would surpass cardiovascular disease as the first causes of death worldwide in 2010 (World Health Organization, 2007).

The gastrointestinal (GI) tract including the esophagus, stomach and intestine is a unique organ system compared with other systems in the body. It has the highest cancer

incidence and cancer-related mortality in the body (Maria, 2008). The human gastrointestinal tract consisted of many microorganisms that play a vital role in the preservation of intestinal mucosa against invasive bacteria and maintaining the balance of mucosal. It also provided the essential nutrient for cells (Pull et al., 2005). An imbalance between epithelial cell proliferation and death in the resident intestine microflora resulted in malignancy in this tract. In addition to, the increasing of cell turnover was associated with tumorigenesis (Fukata and Abreu, 2008). Gastrointestinal (GI) cancers are responsible for 20% of estimated new cancer cases and 15% of estimated death worldwide (Herszenyi and Tulassay, 2010). In Iran, gastrointestinal malignancy was one of the most prevalent cancers in both genders in 2010 (Mayer, 2005).

It was showed that both genetic and environmental factors could affect the incidence of cancers (Sonnenschein and Soto, 2008). People with special genetic polymorphism may be more susceptible to the effects of environmental exposures. For example; individuals with BRCA1, BRCA2 and p53 genetic modifications presented less are able to suppress the growth of cancer cells (Vogelstein and

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Kinzler, 2004). However, the role of environmental factors might be more important than the genetics. It has been acknowledged that environmental factors are responsible for 80% of cancer causes (Parsa, 2012). Life style habits like smoking, the consumption of alcohol, physical inactivity, unhealthy dietary habits, family history, sunlight radiation, occupational factors such as exposure to asbestos, benzene, benzidine, cadmium, nickel, arsenic, radon and vinyl chloride in the workplace, as well as therapeutic drugs, viruses and bacteria, hormonal therapy were the most serious environmental risk factors involved in the carcinogenesis (Parsa, 2012; Pasupathi, et al., 2011). In this paper, the researcher gave a brief summary about gastrointestinal cancers, followed by a comprehensive description regarding the role of cadmium as a toxic heavy metal in the carcinogenesis of gastrointestinal tract.

Esophagus Cancer, Prevalence and Risk Factors

Esophagus cancer was first reported in China over 2000 years ago as “Ye Ge” with means “hard of swallowing with blockage of the gullet and vomiting after eating” or “dysphagia and belching”. It was manifested the greater incidence in elderly population than younger (Qian, 1960).

Esophageal cancer was the 8th most common cancer worldwide and the 6th most common cause of cancer related death. Esophagus cancer is responsible for 5.5% of all malignant tumors of the GI tract (Brown and Devesa, 2002; Crane et al., 2007; Voutilainen, 2008; Kort et al., 2009). This type of gastrointestinal cancer occurred two to four-fold more in men than females, although in the area with high prevalence, it might appear with the same rates (Stathopoulos and Tsiaras, 2003).

There is high incidence of esophagus cancer in Iran. It was claimed that Iran is the most common cites of esophagus cancer worldwide (Sadjadi et al., 2010). It was estimated, of the 35,000 annual deaths occurred due to cancer in Iran, about 5,800 cases was related to esophagus cancer (Sadjadi et al., 2005).

Beside the role of oncogene and tumor suppressor gene alternations, dietary habits specially taking hot tea, nutritional deficiency such as vitamins A, C, E, B₁₂, B₉ and B₂, family history, smoking and alcohol, the consumption of fried and grilled red meats and contaminated foods and waters with heavy metals such as cadmium, lead, copper, nickel and chromium were stated as the most important environmental risk factors influence on the incidence of esophagus cancer (Abnet et al., 2004; Islami et al., 2004; Nouarie et al., 2004; Kamangar et al., 2005; Sepehr et al., 2005; Akbari et al., 2006; Taghavi et al., 2007; Islami et al., 2008; Akbari et al., 2008; Nasrollahzadeh et al., 2008; Cross et al., 2010; Rasool et al., 2012).

Gastric Cancer, Prevalence and Risk Factors

Gastric cancer is one of the highest prevalent cancers worldwide, especially in developed countries. More than 750,000 of new gastric cancer cases reported annually in the world. With aging, the incidence of this malignancy

raised and the highest rate occurred those ages 80 years or older (in men twice than females) (Crew and Neugut, 2006; Brenner et al., 2009; Jemal et al., 2009).

Gastric cancer was the fourth most common cancer and the second important causes of cancer mortality (Parkin et al., 2001; Parkin, 2004). It was estimated, only 22% of patients with gastric cancer survived during 5 years after diagnosis (Francisci et al., 2009). In Iran, gastric cancer was more prevalence in northern and northwestern areas especially in Ardabil province (Babaei et al., 2010).

Gastric cancer was multicausal disease. Along with genetic, *Helicobacter pylori* infection, dietary factors, smoking and alcohol and occupational exposure such as cadmium, lead, etc is responsible for as the leading risk factors in its occurrence (Kelley and Duggan, 2003; Crew and Neugut, 2006; Malekzadeh et al., 2009). Consumption of salted and cured meat smoked and fired foods, pickled vegetables and nitrate added in foods were the most important dietary risk factors. In contrast, fresh and green leave vegetables, citrus fruits and vitamin C were expressed as protective dietary factors (Crew and Neugut, 2006; Pasupathi et al., 2011).

Colorectal Cancer, Prevalence and Risk Factors

Colorectal cancer was the second causes of both death and incidence in developed countries and fifth in developing countries (Stewart and Kleihues, 2003). About 1 million new cases of colorectal cancer were diagnosed and over the half of a million were died from colorectal cancer yearly. This rate was equal to approximately 8% of all cancer related mortality worldwide (Parkin et al., 2005). Due to the influence of many risk factors in the incidence of colorectal cancer, its prevalence differed at least 25-fold between countries (Stewart and Kleihues, 2003; Parkin et al., 2005).

In Iran, colorectal cancer was the third common cancer in males and fourth in females, and it was estimated that about 6.3% of all cancer death related to this malignancy (Terry et al., 2001). In Tehran, the occurrence of colorectal cancer was increased strongly by 82% during the last 30 decades (Bianchini et al., 2002).

There was sufficient evidences that beside the inherited factors (Herszenyi and Tulassay, 2010), lifestyle risk factors such as diets rich in processed foods, poor of dietary fibers, drinking of alcohol (Terry et al., 2001; Gonzalez, 2006; Kesse et al., 2006), physical inactivity (Samad et al., 2005), diabetes (Berster and Goke, 2008), obesity (Bianchini et al., 2002) and high level of toxic trace elements such as cadmium (Emre et al., 2013) had a crucial role in the incidence of colorectal cancer. It has been estimated that the proportion of dietary factors in its incidence to be up to 50% (Haggard and Boushey, 2009).

Heavy Metals and Harmful Effects on Human Health

Among the various chemical elements recognized in the nature, some of them including zinc, iron, cobalt, and copper had essential roles in the various biochemical and

physiological processes, but only in the allowed levels and the others such as cadmium, lead, mercury, arsenic, and nickel were considered as a threat for the human health especially in high and chronic levels in live-organisms (Mudgal et al., 2010; Arslan et al., 2011). Heavy metals were included as a mixed group of elements with the metallic properties and specific density of more than 5g/cm³ (Alissa and Ferns, 2011).

Toxic heavy metals might enter into the human food chain through soils, waters and air after absorbing by plants and animals and accumulated with time in the human body (Madaan and Mudgal, 2009; Malik et al., 2010; Mudgal et al., 2010). Human generally get exposed to the toxic heavy metals through the respiratory, the skin and gastrointestinal tract (Mudgal et al., 2010). In addition to the route of ingestion, toxicity of heavy metal could associate to its chemical form, dose, tissue affinity, age and sex, as well as whether, exposure was acute or chronic (Johri et al., 2010).

Recently, the concentration of heavy metals had been raised due to the various industrial or occupational human activities (Mudgal et al., 2010). In addition to, the deficiency of essential trace elements in the body could result in the increasing of toxic heavy metal accumulation in the human organs (Mudgal et al., 2010).

The main sources of heavy metals exposure in addition to occupational exposure were cosmetic products like lipsticks, eye makeup and skin lightening creams (Sainio et al., 2000). The presence of lead in traditional eye cosmetics (Al-Ashban et al., 2004), mercury and lead in paint-on tattoos and hair dyeing (Lekouch et al., 2001), arsenic in Bottled Zamzam holy cadmium Water (Britain's Food Standards Agency, 2007), were reported. Tobacco plants were the other source of heavy metals (Al-Saleh et al., 2000; Ashraf, 2012).

With respect to harmful effects of heavy metals in human health, neurological and immunological disorders (Moreira and Moreira, 2004; Candelaria et al., 2006), carcinogenicity in many organs of body (Moreira and Moreira, 2004; Elst et al., 2007; Demir et al., 2011; Chhabra et al., 2012; Pirincci et al., 2013; Fasinu and Orisakwe, 2013), developmental retardation, kidney injury, endocrine disruption (Moreira and Moreira, 2004), bone metabolism disorders and skeletal deformation (Wu et al., 2001), inflammation (Umanzor et al., 2006) aging (Gonzalez-Cortijo et al., 2008) and finally death have been documented (Moreira and Moreira, 2004).

Cadmium: Background, Physico-chemical Properties

Cadmium as a ubiquitous, toxic and non-essential heavy metal (with atomic number 48) belonged to the group IIB of the periodic table (Bernard, 2008; Prins and Korach, 2008; Nordberg, 2009). Among the 90 naturally elements on the earth, cadmium was ranked 67th. Natural and human activities lead to the accumulation of cadmium in the environment. It was remarkable to note that cumulative effects of cadmium in the nature due to the human activities were 3-10 times more than the natural (Joseph, 2009).

In humans, it has identified any specific biological function for cadmium (Anetor, 2012). However, due to the specific chemical properties of cadmium, including corrosion resistance, low melting temperature, and high thermal and electrical conductivity, there were numerous applications in the various industries such as nickel-cadmium batteries, pigments, coatings, paints, and stabilizers for plastics (Nordberg, 2009; Anetor, 2012).

Absorption, Transport, Metabolism and Excretion of Cadmium

The amount of cadmium entered into the human body depended on the route of entry. It has estimated that daily intake of cadmium in uncontaminated areas was 25-60 µg/day for a 70 kg person but the rates might rise up to 61 µg/day in contaminated areas (Mudgal et al., 2010). Approximately 3-10% (average 5%) of ingested cadmium was absorbed from the gastrointestinal tract (Sahmoun et al., 2005). This rate depended on the exact dose and nutritional status (Jin et al., 2002). Some dietary factors such as protein, calcium, vitamin D and trace elements such as zinc and copper might affect on the amounts of its absorption (Godt et al., 2006; Mudgal et al., 2010). It was shown that high levels of zinc, calcium, lead, nickel, chromium and magnesium could reduce the uptake of cadmium (Nica et al., 2014). Individuals with iron deficiency for example in anemia, pregnant and reproductive age women had high affinity for the cadmium uptake (Silver et al., 2013). Dietary fiber also was the other factor affects on the cadmium uptake (Asagba, 2009).

The respiratory system was the other route of cadmium entry in the body. About 50% of inhaled cadmium is absorbed (Sahmoun et al., 2005). Smoking and tobacco as the major sources of inhalation cadmium were absorbed approximately 50% of in the human lungs (Agency for Toxic Substances and Disease Registry, 2012). Cadmium-cysteine complex was the main form of cadmium entry through the respiratory system (Zalups and Ahmad, 2003).

The last important route of cadmium exposure was dermal tissues. Cadmium could enter into the systemic blood circulation through the binding with sulfhydryl radicals of cysteine in keratinocytes and then metallothionein in skin (Fasanya-Odewumi et al., 1998). Thus, the main form of cadmium absorption through skin manifested as cadmium- metallothionein (Zalups and Ahmad, 2003).

After absorption, cadmium transported by proteins with high affinity to cadmium especially divalent metal transporter 1 (DMT1) and albumin into the different organs (Tallkvist et al., 2001; Himeno et al., 2002). Voltage-sensitive calcium channels had a major role in cellular uptake of cadmium (Hinkle et al., 1987). Cadmium excreted mainly through urine and in slight amounts in feces. With considering this, half-life of cadmium was estimated 15-20 years in humans (Zalups and Ahmad, 2003; Kayankarnna et al., 2013). Approximately 50% of the cadmium was stored in the liver and kidney organs due to their high metallothionein concentration, others including testis, spleen, heart, lungs, thymus, salivary glands, epididymis, and prostate could store cadmium in

slight amounts (Joseph, 2009).

Cadmium status varied in smokers than non smokers. Smokers had 4-5 times higher cadmium levels in blood and 2-3 times greater amounts in kidneys compared with nonsmokers. As well as, approximately 10 % of the inhaled cadmium oxide in smokers was stored in lung tissues, and about 30-40% was absorbed into systemic blood circulation (Mudgal et al., 2010). Finally, cadmium in smokers could cause a disorder with name acute respiratory distress syndromes (ARDS) (Parikh et al., 2014).

Sources of Cadmium

Industrial products such as cadmium-nickel batteries, control rods and shields within nuclear reactors and television phosphors as well as protective coatings (electroplating) for metals like iron were the main sources of occupational contaminant of cadmium (Mudgal et al., 2010). The concentration of cadmium in near zinc/lead smelters was estimated to be to 1.16 $\mu\text{g}/\text{m}^3$ compared with 10 ng Cd/m³ in non-contaminated areas (Ursinyova and Hladikova, 2000). After the emission of cadmium into the atmosphere, soils and waters grow plants and animals rapidly uptake cadmium (Schoeters et al., 2006). Commercial sludge for fertilizing agricultural fields was the other source of cadmium (Mudgal et al., 2010).

Two groups of food pyramid including grains especially rice and wheat and vegetables especially root and leafy vegetables (such as carrots and parsnip, lettuce and spinach) were able to accumulate cadmium in high amounts and accounted for more than 80% of cadmium intake by foods (Nordberg, 2009). Meat, fish, crustaceans and fruits might be as the other source of cadmium in low amounts (Schoeters et al., 2006).

Another source of cadmium was indoor dust. It was demonstrated that the concentration of cadmium in dust particles have been higher indoors than outdoors (Rasmussen et al., 2001). Some affecting factors might be related to the traffic near home, heating with coal, city location and dampness of home (Meyer et al., 1999).

One of the main components of tobacco is cadmium. Nicotiana species is able to concentrate cadmium in their leaves independent of soil cadmium content. In smokers, inhaled cadmium could enter systemic blood circulation with average 50%. It was demonstrated that smokers have 4-5 times higher cadmium levels in blood and 2-3 times greater amounts of that in their kidneys compared to nonsmokers (Faroon et al., 2008). Besides the amounts of cadmium could absorb from foods and cigarette, heavy smokers are more than double at risk of cadmium hazards (Mudgal et al., 2010).

Common Biomarkers of Cadmium Assessment

Because of accumulation cadmium in the kidneys, the urinary cadmium serves as reliable index of long-term exposure and accumulated cadmium in the body (Orlowski and Piotrowski, 2003; Schoeters et al., 2006). While recent exposure can be assessed by blood cadmium concentration (Jin et al., 2002). Age can influence on the

internal cadmium concentrations. As well as, smoking and living in the contaminated areas are documented as the other influential factors (Schoeters et al., 2006).

The FAO/WHO Joint Expert Committee of Food Additives and Contaminants (JEFCA, 2001) has established a provisional tolerable weekly intake (PTWI) of 7 mg/kg body weight (bw) cadmium. However, recently, the European Food Safety Authority (EFSA) has lowered this range to be 2.5 $\mu\text{g}/\text{kg}/\text{bw}$ based on cadmium-induced nephrotoxicity, (EFSA, 2009).

Hazards of Cadmium on the Human Health

Cadmium, an environment contaminant, cannot be destroyed in the nature (Jarup and Akesson, 2009; Thevenod and Lee, 2013). Cadmium through the impairment of vitamin D metabolism in the kidney resulted in the nephrotoxicity and subsequently bone metabolism impairment and fragility (Jarup and Alfvén, 2004). Moreover, cadmium has toxic effects in lungs (Waalkes, 2000; Nawrot et al., 2006, Demir et al., 2014). Reproductive organs toxicity, low birth weight and premature birth were the other adverse effects of cadmium (Johnson et al., 2003). Individuals with chronic cadmium exposure had illustrated also neurological system and brain disorders (Viaene et al., 2000). Emphysema, immune system suppression and diabetes were the other reported complications of cadmium (Jin et al., 2004; Valko et al., 2005).

Cadmium and Cancer

Cadmium and its inorganic compounds were currently classified (International Agency for Research on Cancer) as a Group 1 carcinogen for human by IARC and German MAK Commission in 2004 (Hartwig, 2013).

There was strong evidence specially based on experimental studies regarding cadmium carcinogenicity (Josep, 2009). Cadmium is able to produce malignant tumors in multiple organs following long term and chronic exposure (Waalkes et al., 1999a, 1999b, 2000). Besides experimental studies, epidemiological studies have also confirmed the potential cadmium carcinogenicity (Joseph, 2009; Cobanoglu et al., 2010; Rahim et al., 2013; Cheung et al., 2014).

Review on the Scientific Literature

Beside many experimental studies (Bertin and Averbek, 2006; Giaginis et al., 2006; Waalkes et al., 1989b), carcinogenicity of cadmium also was illustrated in human studies. Kellen et al, showed that blood cadmium concentration was significantly in high level ($p < 0.001$) in patients with bladder cancer ($n=172$) compare with controls ($n=359$) (Kellen et al., 2006).

Nawrot et al, in a case-control study demonstrated the incidence of lung cancer in subjects inhabitant in high exposure area ($n=521$) was significantly higher than inhabitant in low-exposure area ($n=473$) ($p=0.026$) (Nawrot et al., 2006). Beveridge et al, reported a significant association between cadmium exposure especially in formers and non-smokers and lung cancer

occurrence (n=1598 patients with lung cancer, n=1965 controls) (p=0.046) (Beveridge et al., 2010). Kazi et al. (2008) investigation illustrated that the average cadmium levels in whole blood and scalp hair samples of male lung cancer patients (n=120) was significantly higher than controls (n=150) (p<001).

McElroy et al, reported that risk of breast cancer occurrence in cases (n=246 woman with breast cancer) was twofold compared with controls (n=254 healthy woman) (p<0.26; OR=2.29, 95%CI=1.3-4.2) and this rate was risk increased positively with increasing of urine cadmium (p=0.01) (McElroy et al., 2006). In addition to, Julin et al. (2012) in population base cohort study revealed a positively significant association between dietary cadmium intake and the risk of breast cancer in 55,987 Swedish postmenopausal women (RR=1.21, (95%CI), 1.07-1.36; p=0.020).

In agreement with these results, Nagata et al, showed that odds ratios (ORs) of breast cancer according to the tertile of the creatinine-adjusted urinary cadmium levels in 153 newly diagnosed woman with breast cancer compare with 431 controls in Japan were in elevated level in highest tertile versus lowest (OR=6.05, (95%CI=2.90-12.62, p<0.01) (Nagata et al., 2013).

Strumylaite et al, investigation showed also a positively significant association between the concentrations of urine and blood cadmium in breast cancer patients (n=57) compared with controls (n=51) (Strumylaite et al., 2011). Gallagher et al, in a case-control study, observed a significant increasing trend in the risk of breast cancer by elevated urinary cadmium concentrations in cases (n=100 with breast cancer, n=98 without) living on Long Island and in US women (n=92 with breast cancer, n=2,884 without) compared controls (p=0.023 and p=0.039, respectively) (Gallagher et al., 2010).

Regarding cadmium carcinogenicity in prostate organ, there were inconsistency findings. Vinceti et al., survey demonstrated that toenails cadmium levels of patients with newly diagnosed with prostate cancer (n=40) were statically in high levels compared with controls (n=58) (OR=4.7, p=0.004) (Vinceti et al., 2007). Lee et al., demonstrated that urinary cadmium levels in 113 newly diagnosed prostate cancer patients were significantly higher than 258 as controls. However, it was stated that cadmium along with sexually transmitted diseases could increase the risk of prostate cancer (OR=9.75; 95%CI: 1.28, 74.05) (Lee et al., 2009). However, in another study, Itoh et al, found no significant association between dietary cadmium intake and breast cancer in 390 eligible matched pairs (Itoh et al., 2014). Platz et al. (2002) demonstrated no significant differences between toenail cadmium concentrations in cases (n=115 prostate cancer) compared controls (n=227 healthy age-matched).

Kriegel et al. (2005) concluded that serum cadmium levels of 31 newly diagnosed pancreatic cancer patients (n=52) were significantly in high level versus controls and odds ratio for pancreatic cancer risk was shown significant result for serum cadmium level (OR=1.12; (95%CI=1.04-1.23), p=0.008). In consistent of this study, Luckett et al, illustrated a significantly positive association between urinary cadmium concentration and the risk of

pancreatic cancer especially in 4th quartile versus the first quartile (p<0.0001) (Luckett et al., 2012). These results also were confirmed in Schwartz et al 'study (Schwartz and Reis, 2000). Table 1 was illustrated the detailed results of cadmium carcinogenicity in the experimental and human studies.

Mechanisms of Cadmium Carcinogenicity

The major mechanisms involved in the cadmium carcinogenesis could be related to the suppression of gene expression, inhibition of DNA damage repair, inhibition of apoptosis, and induction of oxidative stress (Hartwig, 2010). In addition to, cadmium through the aberrant DNA methylation (Benbrahim-Tallaa et al., 2007; Huang et al., 2008), endocrine disruption (Benbrahim-Tallaa et al., 2007) and cell proliferation can cause carcinogenicity in the tissues (Huang et al., 2008).

The formation of reactive oxygen species (ROS), interference with anti-oxidative enzymes, inhibition of DNA repair enzymes, deregulation of cell proliferation and suppressed apoptosis were documented as the other carcinogenicity mechanisms of cadmium in body organs (Waalkes, 2003). Figure 1 was presented the mechanisms of cadmium carcinogenicity in the body organs.

Cadmium Toxicity

Cadmium toxicity was first recognized in the nineteenth century. Large amounts and long-term exposure with cadmium in the village's water supply of Toyama city, Japan manifested as Itai-itai disease. Most important clinical features of Itai-itai disease were renal dysfunctions, bone disorders including osteomalacia and osteoporosis, skeletal deformations and multiple fractures, femoral and back pain especially in postmenopausal women, immune system defects and apathies. Moreover, abnormality in the urine glucose, calcium, and amino acids levels was reported. Exposure to the large amounts of cadmium especially in zinc mine located in the upper areas of a river had severe consequences on the health and mortality rate (Oudeh et al., 2002; Inaba et al., 2005). Today, the important sources of cadmium toxicity in human are those involved in handling, assembling and

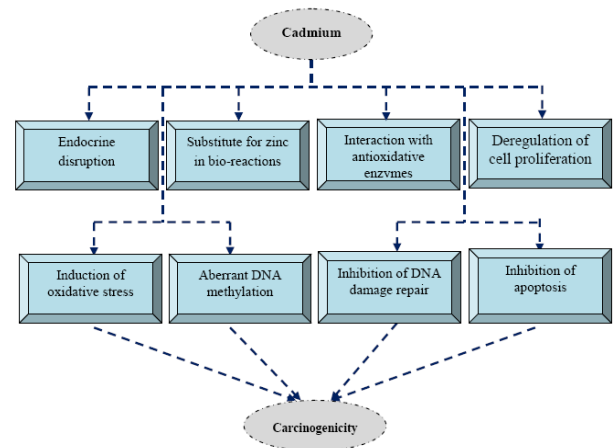


Figure 1. Mechanisms of Cadmium Carcinogenicity in the Body Organs

Table 1. Experimental and Human Studies of Cadmium Carcinogenicity

Reference	Type of cancer	Design	Case/control	Results
<i>In vitro</i> studies				
Waalkes et al., 1999	Prostate	Injection of CdCl ₂ as a single injection (with doses 0, 1, 2, 4, 8, 16, 32 μ mol/kg)	n= 30 Noble (NBL/ Cr) rats in each group	-Lower doses of cadmium (<4 μ mol/kg) resulted in a clear dose-related increase in proliferative lesions -Cadmium induced proliferation lesions in the dorsolateral prostate of Noble rats.
Waalkes et al., 2000	Tumorigenic cells	Injection of CdCl ₂ once a week for 18 weeks (with doses 0, 10, 20, or 30)	n= 30 Wistar n= 30 Fischer rats	-Multiple cadmium exposures resulted in the enhance of metastatic potential of the ensuing tumors and the more rapid incidence of more highly aggressive tumors.
Monsefi et al., 2008	-	Control,	Male adult Balb/c mice	-The sperm count, sperm motility,
		low dose (Ld) with 23 mg/kg, and high dose (Hd) with	nine animals in each	sperm maturity, and the level of testosterone decreased significantly in the high dose administered group.
		50 mg/kg of Cadmium chloride		-The number of newborns and their weights and crown rump lengths reduced.
		in 0.5 mL distilled water for 45 days		-Cadmium accumulation in testis and middle of the quadriceps femoris muscle was significantly higher in animals receiving 50 mg/kg cadmium chloride.
<i>In vivo</i> studies				
Platz et al., 2002	Prostate	Case-control	n=115 cases n=227 controls	-No significant differences between toenail cadmium concentrations in cases controls (p>0.05). -Serum cadmium levels of cases were significantly in high level than controls.
Kriegel et al., 2005	Pancreatic	Case-control	n= 31 cases n=52 controls	-Odds ratio for pancreatic cancer risk was significant for serum cadmium level (OR=1.12; (95%CI=1.04-1.23), p=0.008).
McElroy et al., 2006	Breast	Case-control	n=246 cases n=254 controls aged 20 - 69	-Twofold risk of breast cancer in cases compared with controls (p<0.26 μ g/g; OR = 2.29, 95%CI=1.3- 4.2).
Nawrot et al., 2006	Lung	Case-control	n=521 cases n= 473 controls	-Incidence of lung cancer in cases inhabitant in high exposure area was significantly higher than controls inhabitant in low-exposure area (p=0.026).
Vinceti et al., 2007	Prostate	Case- control	n=40 cases n=58 controls aged 43- 83	toenails cadmium levels of cases were statically high than controls.
Kellen et al., 2007	Bladder	Case- control	n=172 cases n=359 controls above 50 years	-Cadmium concentration was significantly high in cases compare with controls (p<0.001).
Kazi et al., 2008	Lung	Case- control	n=120 cases n=150 controls ranged 40-70 years	-The average cadmium levels in whole blood and scalp hair samples of cases was significantly higher than controls (p<0.01).
Li et al., 2009	Prostate	Case-control	n=113 cases n=258 controls	-Urinary cadmium levels along with sexually transmitted diseases increased the risk of prostate cancer (OR=9.75; 95% CI: 1.28, 74.05).
Beveridge et al., 2010	Lung	Case-control	n=1598 cases n=1965 controls	-There was a significant association between cadmium exposure especially in former and non-smokers and lung cancer occurrence (p=0.046).
Gallagher et al., 2010	Breast	Case-control	n=100 cases n=98 controls in Long Island women and n=92 cases n=2884 controls	-A significant trend in breast cancer risk by elevated urinary cadmium concentrations (p=0.023 and p=0.039, respectively).

Strumylaite et al., 2011	Breast	Case-control	n=57 cases n=51 controls	-There was a positive and significant association between the concentration of urine and blood cadmium in cases compared with controls.
Julin et al., 2012	Breast	Cohort	n=55987 Swedish postmenopausal women	-There was a positively significant association between dietary cadmium intake and the risk of breast cancer in women participated in the study (RR=1.21, (95%CI), 1.07-1.36, p= 0.020).
Luckett et al., 2012	Pancreatic		n= 69 cases n=158 controls (older than 20 years of age)	-There was a significantly positive association between urinary cadmium concentration and the risk of pancreatic cancer especially in 4th quartile versus the first quartile (p<0.0001).
Nagata et al., 2013	Breast	Case-control	n=153 cases n=431 controls	odds ratios (ORs) of breast cancer risk according to the tertile of the creatinine-adjusted urinary cadmium level in were in elevated level in highest tertile versus lowest tertile (OR = 6.05, (95 % CI= 2.90-12.62, p<0.01) .
Itoh et al., 2014	Breast	Case-control	n=390 cases n= 390 controls	no significant association between dietary intake of cadmium and breast cancer in 405 eligible matched pairs.

dismantling mobile phones, computer circuit boards, and batteries (Schoeters et al., 2006). Toxicity of cadmium was exert through the effect on the functions of cells in different organs such as the respiratory tract, the urinary, cardiovascular, gastrointestinal and nervous systems and bones. These toxic effects induced degeneration or even transmutation of cells (Zarros et al., 2008).

Cadmium has multiple effects on cells and induces various mutations in the genome resulted in gene instability which may play an important role in the development of cancer (Slebos et al., 2006; Kamaleshwar et al., 2009). This pollutant toxic metal affects on the cell cycle progression, proliferation, differentiation, DNA replication and repair, as well as apoptotic pathways (Dong et al., 2001; Fang et al., 2002; Yang et al., 2004; Oh and Lim, 2006).

Cadmium toxicity and genotoxicity was likely due to several indirect mechanisms such as interaction with DNA and proteins, by generating reactive oxygen species, impairing the cellular antioxidant defense system, altering gene expression, interfering with signal transduction, activating cellular proto-oncogenes such as c-fos, c-myc, and c-jun (Garrett et al., 2002; Misra et al., 2003; Joseph et al., 2004), inhibiting DNA repair mechanisms, suppressing apoptosis event in various cell types and epigenetic changes in DNA methylation patterns (Waisberg et al., 2003; Hartwig, 2010). In mammalian cells, cadmium could activate cyclin D and cyclin E expression by activation of some transcription factors (Deckert, 2005). Besides, proteins such as hemoxygenase1 that activate by stress and have crucial role in the production of IL-10 and TNF- α were induced by cadmium (Croute et al., 2005). Several genes involved in the stress response to pollutants or toxic metals also can influence by cadmium (Bertin and Averbek, 2006).

Interaction of Cadmium with Antioxidant Enzymes and Inducing Oxidative Stress

Oxidative stress was classified as the effectiveness molecular basis of cadmium toxicity (Rani et al.,

2014). In physiological processes, cadmium could not participate directly in redox reactions, but it could manifest the carcinogenicity effects through oxidative stress-related reactions (Liu et al., 2009). Cadmium through substitution with copper, zinc and iron in various proteins, and increasing the cellular amount of free redox-active metals could induce oxidative stress (Dorta et al., 2003). Enhanced oxidative stress might initiate tumor development by mutagenesis and deregulate cell growth and promote tumor growth depending on dose and the time of interference (Hartwig, 2010).

On the other hand, cadmium through the interference with the antioxidant enzymes activity such as catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase mainly due to the thiol groups (Stohs et al., 2001; Valko et al., 2005; Gavanji et al., 2013) participated in the induction of oxidative stress (Stohs et al., 2001; Valko et al., 2005). Also, the ability of cadmium in affecting on the oxidative damage in DNA was documented. It could be involved in the induction of cellular proliferation, inhibition of the apoptotic mechanisms and blocking of the DNA repair mechanisms (Zarros et al., 2008).

The production of various reactive oxygen species (ROS) such as hydrogen peroxide, superoxide and hydroxyl radicals by cadmium of depletion of glutathione and protein-bound sulfhydryl groups was reported in many studies (Stohs et al., 2001; Khan et al., 2013). ROS might be involved in cadmium-induced genotoxicity. It was illustrated long-term exposure to cadmium could affect on the lipid peroxidation reactions and inhibited activity of superoxide dismutase as one of the strongest antioxidant enzymes (Patra et al., 1999).

Effects of Cadmium on the DNA Repair Systems

DNA repair pathways removed the most of deleterious errors damage caused by normal metabolic activities and environmental factors occurred in cell cycle. If the DNA repair systems were inactivate and ineffective,

the accumulation of DNA damage could result in the development of many chronic diseases such as cancer (Giaginis et al. 2006). Mismatch repair, base excision repair and nucleotide excision repair accounted for the main components of DNA repair systems (Mudgal et al., 2010).

Mismatch Repair

Mismatch repair (MMR) system involves in the stability of genome through repairing base-base mismatches and insertion/deletion loops during DNA replication, as well as, mismatches in heteroduplexes (HDNA) that were formed as result of sequence heterologies during recombination (Modrich and Lahue, 1996). Other DNA damages occurred through normal intracellular metabolism physical and chemical agents from the environment can repair by MMR. These mismatches showed a mutagenic and tumorigenic potential. MMR involved various proteins, which recognize, excise and repair mismatched bases by resynthesis. The MMR machinery played an important role in DNA damage recognition but also activates cell cycle checkpoints and apoptotic pathways after detection of damages (Bertin and Averbeck, 2006). Besides correcting replication errors, the MMR system was also implicated in other cellular processes such as recombination, activation of cell cycle checkpoints, and apoptosis. Following alkylation damage MMR- proficient cells, in contrast to MMR-deficient cells, arrested at the G2/M cell cycle checkpoint and, if the damage was extensive, induce apoptosis (Bellacosa, 2001).

In humans, six functional MMR genes have been recognized (Hsieh, 2001; Marti et al., 2002). Defects in MMR activity resulted in genetic instability, which was assumed to promote tumorigenesis and increase incidence of different type of cancers in organs (Boland, 2000). Cadmium is a mutagen that inhibits mismatch repair by reducing the capacity for MMR of small misalignments and base-base mismatches. Cadmium may inhibit MMR already at low concentrations such as 5 μ M (Jin et al., 2003). Cadmium is able to sufficiently suppress the MMR system to abrogate the G2 cell cycle checkpoint arrest following alkylation damage (Bertin and Averbeck, 2006). This toxic element may escape G2 arrest and/or apoptosis following DNA damage, thus continuing proliferation of cells with genetic changes, the hallmark of cancer cells (Bertin and Averbeck, 2006). The MMR system also plays a key role in cell killing in response to alkylating agents, and MMR deficient cells are about 100 times more resistant to the cytotoxicity of alkylating agents (O'Brien and Brown, 2006; Hsieh and Yamane, 2008).

The other interactions of cadmium with MMR was related to the ATP binding and hydrolysis of MMR enzymes by cadmium resulted in the reducing of DNA binding activity and thus the ability to discriminate between mismatched and matched DNA base pairing in isolated systems (Lutzen et al., 2004; Giaginis et al., 2006; Wieland et al., 2009).

Base Excision Repair

The other DNA repair system is base excision repair

(BER), which allows the restoration of base damage and removes of different types of endogenous single strand breaks in DNA damage, including oxidative DNA base modifications like 8-oxoG arising from normal cellular metabolism and genotoxic agents such as ultraviolet A radiation, X-rays and alkylating agents (Memisoglu and Samson, 2000; Nilsen and Krokan, 2001). This process generates a basic (AP) site, which is further processed in a multistep process with slight differences depending on the type of damage (de Boer and Hoeijmakers, 2000; Christmann et al., 2003; Hakem, 2008; Camenisch and Naegeli, 2009). BER mainly corrects non-bulky lesions produced by alkylation, oxidation or deamination (Memisoglu and Samson, 2000; Nilsen and Krokan, 2001).

BER involves two distinct pathways, which both are initiated by a DNA glycosylase. In the "short patch" pathway, a single base replacement is catalyzed by DNA polymerase β (Pol β), AP endonuclease, DNA ligase III and XRCC1. In the "long patch" pathway, 2- 8 nucleotides are removed along with the damaged nucleotide (Frosina et al., 1996).

According to the effect of cadmium on this pathway, low concentrations of cadmium disturbed the repair of oxidative DNA base damage induced by visible light as well as DNA alkylation damage in mammalian cells (Fatur et al., 2003). Cadmium exposure inhibits and modifies certain proteins of BER such as formamidopyrimidine glycosylase (Bertin and Averbeck, 2006). In addition to direct interactions with DNA repair proteins, cadmium may disturb DNA repair processes via interaction with zinc containing transcription factors (Vercesi et al., 1997). Specifically, Cadmium inactivates a series of proteins, involved in the first step of BER. Moreover, Cadmium is able to suppress additional steps of BER, such as polymerization and ligation of DNA strand breaks, inactivating proteins such as DNA Pol β , PARP and Ligase I (Giaginis et al., 2006).

Nucleotide Excision Repair (NER)

NER is the most important DNA repair system involved in the removal of structurally unrelated bulky base adducts and DNA distorting lesions including those from ultra-violet (UV)-induced cyclobutane pyrimidine dimers (CPDs), (6-4) photoproducts (6-4 PP) and some chemical mutagens such as cisplatin and the polycyclic aromatic hydrocarbon carcinogen which cause significant helical distortions and block transcription and replication processes (Costa et al., 2003; Mitchell et al., 2003). At least 30 different proteins and enzymes are required in the steps of mammalian cell cycle. Most of them are involved in the damage recognition and the incision at both sides of the lesion, followed by the repair polymerization leading to the displacement of the damaged oligonucleotide and finally the ligation of the repair patch (Hartwig, 2010).

Cadmium exposure interferes with different steps of NER. Cadmium exposure has inhibitory effect on the protein with name xeroderma pigmentosum A (XPA). This protein consists of 273 amino acids, which involves in the recognition of DNA impairments induced by many environmental agents. After exposure DNA binding capacity of XPA is strongly diminished (Hartwig et

al., 2002). The main mechanism may be related to the displacement of zinc by cadmium in the zinc finger structures. XPA may also relate to the other NER proteins (Bertin and Averbeck, 2006).

Cadmium Genotoxicity and the Influence on P53 Protein

The p53, tumor suppressor protein, is one of the most important mediators of cell cycle that arrest and apoptosis in response to genotoxic stress (Anetor, 2012). The inactivation of p53's function is documented as a key factor in the development of tumor and the alternation of DNA damage response. This may result in genome instability and cancer occurrence (Spike and Wahl, 2011). It was showed that cadmium can have effect on the both structure and function of p53 through different mechanisms such as apoptosis (Ho, 2004; Urani et al., 2014). Cadmium can bind to thiol groups as well as substitute with zinc in structure of P53. These functions result in the impairment and decreasing the ability of cells to respond to DNA lesions (Anetor, 2012).

Beside the harmful effects of cadmium on the P53, many studies were documented that cadmium can result in epigenetic changes in effects on human and experimental cell lines (Waalkes, 2003; Lauwerys and Hoet, 2006; Martinez-Zamudio and Ha, 2011; Wang et al., 2012).

Cadmium affects multitude cellular processes of genes, including signal transduction pathways, cell proliferation, differentiation, and apoptosis (Saedi et al., 2013). The down regulation of methyltransferases enzymes and the reduction of DNA methylation have been stated as one of the effects of the cadmium on the epigenetic (Doi et al., 2011). As well as, increasing the intracellular free calcium ion levels inducing neuronal apoptosis was stated as the other deleterious effect of cadmium on the stability of genome (Xu et al., 2011).

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