Original Article
Middle East Journal of Cancer 2013; 4(2): 79-86

Evaluation of Trace Elements in Pancreatic Cancer Patients in Iran

Leila Farzin♦, Mohammad Esmail Moassesi, Fattaneh Sajadi, Mohammad Amin Ahmadi Faghih

Environmental Laboratory, Nuclear Science Research School, Nuclear Science and Technology Research Institute, Atomic Energy Organization of Iran (AEOI), Tehran, Iran

Abstract

Background: Pancreatic cancer is a major worldwide health problem. Little is known about the etiology of pancreatic cancer, which is an important cause of cancer mortality in developed countries. This study evaluates the importance of amounts of trace elements in pancreatic cancer etiology and diagnostics.

Methods: Atomic absorption spectrometry was used to estimate zinc, selenium, copper, cadmium and lead concentrations in 80 patients with pancreatic cancer admitted to various hospitals in Tehran Province over an 18-month period and in 100 control subjects.

Results: There were significantly lower levels ($P<0.001$) of zinc in patients' sera (63.12±26.45 µg/dl) compared with controls (107.05±30.23 µg/dl). The mean concentration of cadmium in patients (3.10±1.05 µg/l) was higher than in healthy subjects (1.52±0.88 µg/l; $P<0.0001$). In addition, there were significant variations in blood cadmium concentrations due to tobacco smoking in both groups ($P<0.001$). No significant differences in levels of selenium, copper and lead were observed between the two groups ($P>0.05$).

Conclusion: In this study and by analyzing data from recent major reported series, we have found that cadmium is a plausible pancreatic carcinogen. This study also suggests a significant relationship between zinc metabolism and pancreatic cancer.

Keywords: Pancreatic cancer, Trace elements, Atomic absorption spectrometry, Iran

♦Corresponding Author:
Leila Farzin, PhD
Environmental Laboratory
Nuclear Science Research School, Nuclear Science and Technology Research Institute, Atomic Energy Organization of Iran (AEOI), Tehran, Iran
Fax: +98-21-88221121
Tel: +98-912 619 2201
Email: LFarzin84@yahoo.com

Introduction

Cancer of the pancreas is an important cause of cancer mortality in developed countries and accounts for more than 28000 deaths in the United States per year. It produces few specific symptoms in its early stages and is usually detected at an advanced and incurable stage.[1,2] All types of pancreatic cancer (PC) begin when abnormal cells grow out of control within the pancreas. Exocrine

Received: February 10, 2013; Accepted: March 10, 2013

tumors comprise 95% of all PC because they begin in the exocrine cells that produce enzymes to aid in digestion. Accounting for less than 5% of all pancreatic tumors are endocrine tumors, also called neuroendocrine or islet cell tumors.

Pancreatic cancer usually occurs in the sixth, seventh and eighth decades of life and rarely in adults less than 40 years of age.[3,4] In Western countries, the incidence of PC peaks between 60-80 years of age.[5] This cancer is still the disease of elderly people in Iran, but patients are comparatively younger at the time of diagnosis than in Western countries. This may suggest that some genetic and/or environmental factors could contribute at least in part to the development of PC in Iran. In many areas of Iran, particularly in rural regions, consanguineous marriage is still common. This may cause aggregation of genetic defects that lead to PC.

In addition, in Iran where there is rapid industrial development, the amount of toxic metals that accumulate in the human body from a polluted environment is expected to increase.

Trace elements play an important role in human health and disease. It has become evident that there is an intimate relationship between trace elements and cancer. Some trace elements are known carcinogens; others appear to provide protection against cancer. The immune system (immunoglobulins, cell mediated immunity, phagocytosis complement, lysosomes, interferon, metabolic function, hormones, metabolic and respiratory alkalosis) is the natural mechanism which defends against cancer. Trace elements zinc (Zn), selenium (Se) and copper (Cu) augment this natural mechanism. They are important cofactors for several enzymes that play a role in maintaining DNA integrity. The high levels of cadmium (Cd) and lead (Pb) may be linked with a number of physiological disorders in humans. There is a growing body of scientific research that suggests Cd and Pb contribute to carcinogenesis by increasing oxidative stress.[6] Oxidative stress damages DNA and can lead to mutations which promote cancer. These heavy metals also disrupt the process of apoptosis (programmed cell death).[7] Apoptosis is vital for safe removal of sick/unhealthy cells, including those that may become cancerous.

Most Cd in the body is bound to metallothioneins, low molecular weight proteins that function in the homeostasis of essential metals, such as Zn.[8,9] The Cd-metallothionein complex is distributed to various tissues and organs and is ultimately reabsorbed in kidney tubuli.[10] Because the body has no mechanism for the excretion of Cd, it accumulates in tissues. In humans, the largest amount of Cd is deposited in the kidneys and liver, followed by the pancreas and lungs.

The toxicity of Pb results from its avidity for the sulfhydryl group of proteins and various enzymes, which leads to jeopardy of their function. Lead binds hemoglobin in red blood cells and slowly accumulates in the soft tissues and skeleton.

The advent of atomic absorption spectrometry (AAS) techniques has provided more accurate determinations of low levels of trace elements in human body fluids. In this study, we have assessed serum Zn, Se, Cu, Cd and Pb levels in PC patients compared to subjects from the same region in Iran, using AAS. We have also examined the contributions of age, sex and smoking status to overall risk for PC. Although the sample size in this study is small, it is our hope that these initial data will act as a springboard for larger, more in-depth studies that will analyze the relationship between these elements and PC in a more detailed fashion.

Materials and Methods

Patients and controls

Between February 2010 and August 2011, 80 newly diagnosed patients with adenocarcinoma of the pancreas (exocrine PC) from various hospitals of Tehran Province were recruited to participate in this study. PC patients (group I) consisted of 34 women and 46 men, whose ages ranged from 37 to 80 years. No patients with chronic pancreatitis were included in this study. Group II (controls) were composed of 100 healthy subjects, 45

Table 1. Characteristics of the study population [n (%)].

Characteristics	Group I	Group II	*P*-value
Age (years)			
<60	37 (46.25)	49 (49)	0.42
≥60	43 (53.75)	51 (51)	
Sex			
Male	46 (57.5)	55 (55)	0.52
Female	34 (42.5)	45 (45)	
Smoking			
Yes	24 (30)	25 (25)	0.40
No	56 (70)	75 (75)	
Occupation			
Housewife	17 (21.25)	28 (28)	
Industrial	30 (37.5)	33 (33)	0.30
Professional	33 (41.25)	39 (39)	

females and 55 males. The age of these volunteers ranged from 35 to 79 years.

We used an interviewer administered questionnaire, which included questions about age, lifetime occupational and smoking histories. There were no significant differences between the PC patients and the control subjects in terms of age, sex, smoking status or occupation, as shown in Table 1. The donors belonged to a middle socio-economic status with urban dietary habits. Information was also collected about family history of PC. The purposes of the study had been previously explained to all volunteers. A written informed consent was obtained from the participants in this study. The present Study is approved by IRB (Institutional Review Board).

To avoid effects of concurrent infections on Zn, Se, Cu, Cd and Pb concentrations, individuals who had an infection as recently as one month before the study were excluded.

Sample preparation and analytical methods

Blood samples were collected in the early morning, into plastic tubes that contained lithium heparin (Vacuette, Geiner Labortechnik, Kremsmünter, Austria). A portion of the blood was used for the measurement of Cd and Pb concentrations; the remainder was centrifuged at 3000 g at room temperature to determine serum Zn, Se and Cu levels. The samples were stored at-20 ºC until trace element analysis.[11]

Special care was taken to avoid any contamination with metals during the blood sampling, storage and analysis. All laboratory ware including pipette tips and autosampler cups were cleaned thoroughly with detergent and tap water, rinsed with distilled water, soaked in dilute nitric acid then rinsed thoroughly with deionized distilled water. All chemicals used were of analytical grade for spectroscopy (Merck, Germany).

A Varian model AA-220 atomic absorption spectrometer, equipped with a deuterium lamp for background correction was used for all experiments. Adapted temperature program, appropriate sample dilution and other analytical features of the method have been described elsewhere.[12,13]

Statistics

Statistical evaluation was carried out by using the SPSS 11.5 version for Windows. Summary statistics (n, mean, standard deviation) were calculated. Values were statistically compared using one-way analysis of variance (ANOVA) taking into account sex, age and smoking as a grouping variable. All results were expressed as mean±SD and statistical significance was defined as $P<0.05$.

Results

The results obtained from determination of Zn, Se, Cu, Cd and Pb levels in two groups, according to sex, age and smoking status are given in Table 2.

In this case-control study, we observed a significant difference in both Zn and Cd levels between the patient (P<0.001) and control (P<0.0001) groups. Zinc level was 63.12±26.45 µg/dl in PC patients, which was statistically lower than controls (107.05±30.23 µg/dl). The mean concentration of Cd in patients (3.10±1.05 µg/l) was higher than in healthy subjects (1.52±0.88 µg/l). There was a nonsignificant difference in Se, Cu and Pb levels observed between both groups.

Taking into consideration the sex of the subjects, we observed a significant decrease in serum Zn levels in female PC patients compared to males (P<0.01). In addition, when the subjects were divided into two age groups, there appeared to be a significant increase (P<0.05) in blood Cd levels of patients older than 60 years.

As shown in Table 2, there were significant variations in blood Cd concentrations due to tobacco smoking in patients and healthy subjects. Among all subjects, we observed a general tendency for blood Cd to increase significantly with tobacco consumption (P<0.001). In addition, the Pb concentration in the control group increased with smoking (P<0.0001).

Discussion

Worldwide, there are more than 10 million new cancer cases each year and cancer is the cause of approximately 12% of all deaths.[14] A large number of epidemiologic studies have been undertaken to identify potential risk factors for cancer, amongst which the association with trace elements has received considerable attention.

In this study, we compared the levels of each of the trace elements noted above between PC patients and healthy controls. There was a significant increase (P<0.0001) in blood Cd in PC patients compared with controls. Our findings agreed with earlier studies that suggested significantly higher Cd levels in cases compared to controls.[15-17] The strongest suspicion of an association between Cd exposure and PC has been reported in Louisiana.[18,19] Whereas, Zn levels were found to be statistically lower in patients compared to controls. This result agreed with results reported elsewhere.[20-22]

The pancreas is a secretory tissue with unusual Zn requirements. Thus it must tightly regulate Zn metabolism through the integration of Zn import, sequestration and export mechanisms. Recent findings indicate that this tissue utilizes Zn for basic cellular processes but also requires Zn for unique cellular needs. In addition, abundant Zn is transported into the secretary pathway and a large amount is subsequently secreted in a tightly regulated manner for unique biological processes. There is a growing body of information implicating Zn dysregulation in the pathogenesis of PC.[23,24]

Zinc participates in the regulation of cell proliferation in several ways; it is essential to enzyme systems that influence cell division and proliferation. Recent studies have shown that zinc availability is also important for tumor growth and progression because zinc is a critical component for many enzymes, which are involved in hypoxia, angiogenesis, cancer cell proliferation and metastasis of cancer.[25,26] High Zn concentrations are toxic to cells; therefore, cells have evolved a complex system to maintain the balance of Zn uptake, intracellular storage and efflux.[27,28] Two solute-linked carrier (SLC) gene families have been identified in Zn transport, SLC30, which encodes for Zn transporter (ZnT) proteins, and SLC39, which encodes for ZIP proteins.[28-30] They appear to have opposing roles in cellular Zn homeostasis. ZnT transporters reduce intracellular Zn availability by promoting Zn efflux from cells or into intracellular vesicles, whereas ZIP transporters increase intracellular Zn availability by promoting extracellular Zn uptake and vesicular Zn release into the cytoplasm.

It has been observed that ZIP4 was substantially overexpressed in 94% of clinical pancreatic

Table 2. Concentrations of trace elements according to sex, age and smoking status.

		Se	Cu	Zn	Cd	Pb
		Serum (µg/dl)	Serum (µg/dl)	Serum (µg/dl)	Blood (µg/l)	Blood (µg/l)
Total	Cases	9.25±2.14	87.14±19.57	63.12±26.45*	3.10±1.05**	157.16±51.40
	Controls	10.06±2.59	91.17±20.11	107.05±30.23*	1.52±0.88**	145.21±46.13
Males	Cases	8.02±2.54	86.33±19.10	67.47±25.10***	3.19±0.97	148.33±53.08
	Controls	8.97±2.68	90.78±20.14	109.11±29.33	1.50±0.89	146.82±46.09
Females	Cases	10.91±2.43	88.24±19.73	57.23±29.41***	2.98±1.10	169.11±50.31
	Controls	11.39±2.60	91.65±19.97	104.53±32.08	1.54±0.87	143.24±46.20
Age						
<60 years	Cases	9.10±1.99	89.05±19.44	63.97±25.88	2.51±1.08****	160.55±49.97
	Controls	9.92±2.15	90.54±21.05	109.21±29.78	1.54±0.85	144.80±46.18
≥60 years	Cases	9.38±2.27	85.50±19.67	62.39±28.12	3.61±0.97****	154.24±52.10
	Controls	10.19±2.29	91.78±19.89	104.97±31.56	1.50±0.90	145.60±46.11
Smoking	Cases	9.15±1.89	86.63±19.33	55.22±27.13	4.06±1.08*	167.36±54.38
	Controls	9.97±2.44	92.88±20.57	98.23±30.12	2.11±0.93*	166.24±45.14**
Non-smoking	Cases	9.29±2.03	87.36±20.02	66.51±26.25	2.69±1.04*	152.79±50.07
	Controls 1	0.09±2.50	90.60±19.94	109.99±30.25	1.32±0.87*	138.2±46.23**

Values represent the mean±SD for patients (n=80) and controls (n=100). Asterisks denote the significance of differences between groups (* P<0.001; ** P<0.0001; *** P<0.01; **** P<0.05).

adenocarcinoma specimens compared with surrounding normal tissues. The localization of ZIP4 to the cell membrane of pancreatic β-cells suggests that ZIP4 participates in Zn import into the cells. The increased expression of ZIP4 is strongly associated with the pathology of PC by facilitating increased intracellular Zn accumulation[23,31] and proliferation of PC cells.[24] Thus, decreased Zn concentrations in the serum of PC patients can be linked to increased expression of ZIP4.

Currently, there is a marginal increase in exposure to Cd in daily life. Cadmium is a known human carcinogen. This toxic element accumulates in the body over time because there are no specific mechanisms for its removal. The half-life of this metal in the body ranges from 10 to 30 years, with an average of 15 years.[32]

Cadmium can induce the activation of several oncogenic and tumor suppressor proteins known to be overexpressed in human PC, such as ras proteins and the p53 protein.[33-35] Cadmium also induces expression of the c-fos oncogene,[36] which is increased in many PCs and inhibits the function of the p53 tumor suppressor protein.[37,38] Finally, Cd can enhance the initiation of carcinogenesis induced by other carcinogens, such as dimethylnitrosamine and hepatitis B, and inhibit DNA repair.[39-42] Cadmium is one of the most potent agents known to induce transdifferentiation of the pancreas.[43] Transdifferentiation or metaplasia is a change from one differentiated cell type to another. Because the process of metaplasia involves cellular dedifferentiation, proliferation, and ultimately redifferentiation, agents that induce metaplasia (such as Cd) may place cells at increased risk for neoplasia.[44,45]

In summary, Cd can cause the transdifferentiation of pancreatic cells, increase the synthesis of pancreatic DNA and regulate the expression of oncogenes that are implicated in pancreatic carcinogenesis. Thus, Cd is a plausible pancreatic carcinogen.

Cigarette smoking is a significant source of Cd. One cigarette contains 1–2 µg of Cd46 and inhaled Cd is absorbed much more efficiently than ingested Cd.[47] Measurement of Cd in the blood of the PC and control groups has shown significantly higher levels in smokers than non-smokers.

An insignificant difference in Se, Cu and Pb levels was observed between the two groups in the current study, although some of findings have shown decreased bodily levels of Se17 or increased Pb and Cu concentrations in PC patients

compared to controls.[17,20] According to the study published in the Gut journal 17, people whose diets include high amounts of the mineral selenium may have a lower risk of pancreatic cancer.

While our findings need to be replicated in independent studies, they suggest the role of trace elements in PC pathogenesis and justify further research.

Acknowledgements

The authors thank all colleagues for their assistance.

Funding/Support

Nuclear Science and Technology Research Institute (Tehran, Iran).

References

1. Rosenberg L. Treatment of pancreatic cancer. *Int J Pancreatol* 1997;22(2):81-93.
2. Flanders TY, Foulkes WD. Pancreatic adenocarcinoma: Epidemiology and genetics. *J Med Genet* 1996;33(11): 8890-8.
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics. *CA Cancer J Clin* 2009;59(4):225-49.
4. Zhang J, Dhakal I, Yan H, Phillips M, Kesteloot H. SEER Cancer Registries. Trends in pancreatic cancer incidence in nine SEER Cancer Registries, 1973-2002. *Ann Oncol* 2007;18(7):1268-79.
5. Belyaeva EA, Dymkowska D, Wieckowski MR, Wojtczak LJ. Mitochondria as an important target in heavy metal toxicity in rat hepatoma AS-30D cells. *Toxicol Appl Pharmacol* 2008;231(1):34-42.
6. Yeo TP, Hruban RH, Leach SD, Wilentz RE, Sohn TA, Kern SE, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26(4):176-275.
7. Rana SV. Disorders of apoptosis may play a critical role in some of the most debilitating metal-induced afflictions including hepatotoxicity, renal toxicity, neurotoxicity, autoimmunity and carcinogenesis. Metals and apoptosis: Recent developments. *J Trace Elem Med Biol* 2008;22(4):262-84.
8. Hamer DH. Metallothioneins. *Annu Rev Biochem* 1986;55:913-51.
9. De Lisle RC, Sarras MP, Hidalgo J, Andrews GK. Metallothionein is a component of exocrine pancreas secretion: Implications for zinc homeostasis. *Am J Physiol* 1996;271 (4 Pt 1):C1103-10.
10. Ohta H, Cherian MG. Gastrointestinal absorption of cadmium and metallothionein. *Toxicol Appl Pharmacol* 1991;107(1):63-72.
11. Arcasoy A, Canatan D, Sinav B, Kutlay L, Nurgul O, Muhtar S. Serum zinc levels and zinc binding capacity in thalassemia. *J Trace Elem Med Biol* 2001;15(2-3):85-7.
12. Farzin L, Moassesi ME, Sajadi F, Amiri M, Shams H. Serum levels of antioxidants (Zn, Cu, Se) in healthy volunteers living in Tehran. Biological trace element research. *Biol Trace Elem Res* 2009;129(1-3):36-45.
13. Farzin L, Amiri M, Shams H, Ahmadi Faghih MA, Moassesi ME. Blood levels of lead, cadmium, and mercury in residents of Tehran. *Biol Trace Elem Res* 2008;123(1-3):14-26.
14. Navarrov Silvera SA, Rohan TE. Trace elements and cancer risk: A review of the epidemiologic evidence. *Cancer Causes Control* 2007;18(1):7-27.
15. Kriegel AM, Soliman AS, Zhang Q, El-Ghawalby N, Ezzat F, Soultan A, et al. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta Region of Egypt. *Environ Health Perspect* 2006;114(1):113-9.
16. Schwartz GG, Reis IM. Is cadmium a cause of human pancreatic cancer? *Cancer Epid Biomark Prevent* 2000;9(2):139-45.
17. Amaral1 AFS, Porta M, Silverman DT, Milne RL, Kogevinas M, Rothman N, et al. Pancreatic cancer risk and levels of trace elements. *Gut* 2012;61(11):1583-8.
18. Blot WJ, Fraumeni JF Jr, Stone BJ. Geographic correlates of pancreas cancer in the United States. *Cancer* 1978;42(1):373-80.
19. Tchounwou PB, Abdelghani AA, Pramar YV, Heyer LR, Steward CM. Assessment of potential health risks associated with ingesting heavy metals in fish collected from a hazardous-waste contaminated wetland in Louisiana. *Rev Environ Health* 1996;11(4):191-203.
20. Fabris C, Farini R, Del Favero G, Gurrieri G, Piccoli A, Sturniolo GC, et al. Copper, zinc and copper/zinc ratio in chronic pancreatitis and pancreatic cancer. *Clin Biochem* 1985;18(6):373-5.
21. Costello LC, Levy BA, Desouki MM, Zou J, Bagasra O, Johnson LA, et al. Decreased zinc and downregulation of ZIP3 zinc uptake transporter in the

development of pancreatic adenocarcinoma. *Cancer Biol Ther* 2011;12(4):297-303.
22. Costello LC, Zou J, Desouki MM, Franklin RB. Evidence for changes in RREB-1, ZIP3, and zinc in the early development of pancreatic adenocarcinoma. *J Gastrointest Cancer* 2012;43(4):570-8.
23. Jayaraman AK, Jayaraman S. Increased level of exogenous zinc induces cytotoxicity and up-regulates the expression of the ZnT-1 zinc transporter gene in pancreatic cancer cells. *J Nutr Biochem* 2010;22(1):79-88.
24. Li M, Zhang Y, Liu Z, Bharadwaj U, Wang H, Wang X, et al. Aberrant expression of zinc transporter ZIP4 (SLC39A4) significantly contributes to human pancreatic cancer pathogenesis and progression. *Proc Natl Acad Sci* 2007;104(47):18636-41.
25. Juhasz M, Chen J, Lendeckel U, Kellner U, Kasper HU, Tulassay Z, et al. Expression of carbonic anhydrase IX in human pancreatic cancer. *Aliment Pharmacol Ther* 2003;18(8):837-46.
26. Garcea G, Doucas H, Steward WP, Dennison AR, Berry DP. Hypoxia and angiogenesis in pancreatic cancer. *ANZ J Surg* 2006;76(9):830-42.
27. Kim BE, Wang F, Dufner-Beattie J, Andrews GK, Eide DJ, Petris MJ. Zn2+-stimulated endocytosis of the m ZIP4 zinc transporter regulates its location at the plasma membrane. *J Biol Chem* 2004;279(6):4523-30.
28. Liuzzi JP, Cousins RJ. Mammalian zinc transporters. *Annu Rev Nutr* 2004;24:151-72.
29. Guerinot ML. The ZIP family of metal transporters. *Biochem Biophys Acta* 2000;1465:190-8.
30. Eide DJ. The SLC39 family of metal ion transporters. *Pflugers Arch* 2004;447(5):796-800.
31. Li M, Zhang Y, Bharadwaj U, Zhai QJ, Ahern CH, Fisher WE, et al. Down-regulation of ZIP4 by RNA interference inhibits pancreatic cancer growth and increases the survival of nude mice with pancreatic cancer xenografts. *Clin Cancer Res* 2009;15:5993-6001.
32. Jin T, Lu J, Nordberg M. Toxicokinetics and biochemistry of cadmium with special emphasis on the role of metallothionein. *Neurotoxicology* 1998;19(4-5):529-35.
33. Yamada-Okabe T, Doi R, Yamada-Okabe H. Normal and transforming Ras are differently regulated for posttranslational modifications. *J Cell Biochem* 1996;61(2):172-81.
34. Voeller HJ, Wilding G, Gelmann EP. v-rasH expression confers hormone-independent in vitro growth to LNCaP prostate carcinoma cells. *Mol Endocrinol* 1991;5(2):209-16.
35. Ruggeri B, Zhang SY, Caamano J, Di Rado M, Flynn SD, Klein-Szanto AJ. Human pancreatic carcinomas and cell lines reveal frequent and multiple alterations in the p53 and Rb-1 tumor-suppressor genes. *Oncogene* 1992;7(8):1503-11.
36. Wang Z, Templeton DM. Induction of c-fos proto-oncogene in mesangial cells by cadmium. *J Biol Chem* 1998;273(1):73-9.
37. Soon Lee C, Charalambous D. Immunohistochemical localisation of the c-fos oncoprotein in pancreatic cancers. *Zentralb Pathol* 1994;140(3):271-5.
38. Meplan C, Mann K, Hainaut P. Cadmium induces conformational modifications of wild-type p53 and suppresses p53 response to DNA damage in cultured cells. *J Biol Chem* 1999; 274(44):31663-70.
39. Wade GG, Mandel R, Ryser HJ. Marked synergism of dimethylnitrosamine carcinogenesis in rats exposed to cadmium. *Cancer Res* 1987;47(24 Pt 1):6606-13.
40. Sell S, Illic Z. Dietary cadmium may enhance the progression of hepatocellular tumors in hepatitis B transgenic mice. *Carcinogenesis* 1994;15(9):2057-60.
41. Beyersmann D, Hechtenberg S. Cadmium, gene regulation, and cellular signalling in mammalian cells. *Toxicol Appl Pharmacol* 1997;144(2):247-61.
42. Nocentini S. Inhibition of DNA replication and repair by cadmium in mammalian cells. Protective interaction of zinc. *Nucleic Acids Res* 1987;15(10):4211-25.
43. Waalkes MP, Cherian MG, Ward JM, Goyer RA. Immunohistochemical evidence of high concentrations of metallothionein in pancreatic hepatocytes induced by cadmium in rats. *Toxicol Pathol* 1992;20(3 Pt 1):323-6.
44. Parsa I, Longnecker DS, Scarpelli DG, Pour P, Reddy JK, Lefkowitz M. Ductal metaplasia of human exocrine pancreas and its association with carcinoma. *Cancer Res* 1985;45(3):1285-90.
45. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE. Increased cell division as a cause of human cancer. *Cancer Res* 1990;50(23):7415-21.
46. Goyer RA. "Toxic Effects of Metals." In: Casarett and Doull's Toxicology: The Basic Science of Poisons.

5th ed. Edited by Klaassen CD, Amdur MO and Doull J. New York, NY. McGraw Hill. 1996:691-736.

47. Friberg L. Cadmium and the kidney. *Environ Health Perspect* 1984;54:1-11.