Polish Annals of Medicine 24 (2017) 133–137

Contents lists available at ScienceDirect

Polish Annals of Medicine

journal homepage: www.elsevier.com/locate/poamed

Original research article

The association between blood cadmium levels and the risk of gastrointestinal cancer in Tabriz, northwest of Iran

A. Ostadrahimi[a], L. Payahoo[a,*], M.H. Somi[b], S.H. Hashemzade[c], A. Esfahani[c], M. Asgharijafarabadi[d], M. Mobasseri[e], N. Samadi[f], S. Faraji[a], Y. KhajeBishak[a,*]

[a] Nutrition Research Center, Student Research Committee, Department of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Liver and Gastrointestinal Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Nutrition Research Center, Student Research Committee, Department of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Epidemiology, Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Department of Internal Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Department of Biochemistry and Laboratory Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article history:
Received 9 January 2016
Accepted 11 May 2016
Available online 23 August 2016

Keywords:
Blood cadmium
Environmental pollutant
Gastrointestinal cancer

ABSTRACT

Introduction: Cancer is a major health problem worldwide. Gastrointestinal tract malignancy is one of the most common forms of cancer around the world. Occupational exposure to the heavy metals including cadmium was defined as one of the most important environmental risk factors involved in initiation of cancer. Cadmium, a toxic and non-essential heavy metal, was classified as group 1 carcinogen.
Aim: The aim of this study was to investigate the association between blood cadmium levels and the risk of gastrointestinal cancer in cancer patients.
Material and methods: This descriptive study was carried out on 111 gastrointestinal cancer patients as cases and 111 healthy people as controls from January to October 2013 in Tabriz, northwest of Iran. The protocol of this study is approved by the Ethics Committee in Tabriz University of Medical Science. Considering inclusion criteria, participants were selected randomly and a written informed consent was filled out for each patient. Demographic data were obtained by questionnaire. Blood samples (5 mL) were collected from each patient in fasting status and analyzed by graphite furnace atomic absorption spectrophotometer (GFAAS).
Results and discussion: Blood cadmium levels were significantly higher in cancer patients compared to healthy individuals ($P = 0.037$). The results of multivariate regression model did not show significant association between the concentrations of blood cadmium and the risk of gastrointestinal cancer: $P = 0.137$, OR = 1.15 (95% CI; 0.96–1.38).
Conclusion: Our data suggest that finding individuals with high blood cadmium level and then lowering this amount can be considered as important strategy to prevent gastrointestinal cancer.

1. Introduction

Nowadays, the main reason for human morbidity and mortality have been changed from infectious to non-communicable diseases.[1] Cancer, uncontrolled growth and spread of abnormal cells, has been known as one of the leading causes of death in both developed and developing countries.[2,3] About 14.0 million new cases of cancer and 8.2 million deaths were occurred worldwide in 2012.[4] Among all kinds of malignancies, gastrointestinal tract (GI) cancer is one of the most common malignancies in both genders worldwide.[5] GI cancer is responsible for 20% of estimated new cancer cases and 15% of estimated deaths in the world.[6]

Cancer incidence is due to both genetic and environmental factors.[2] It was suggested that environmental factors accounts for 80% of cancer causes.[7] The most serious environmental risk factors which involved in carcinogenesis, are unhealthy lifestyle habits like smoking, consumption of alcohol, physical inactivity, unhealthy dietary habits and occupational factors.[6] Recently, it was shown that some trace elements have main roles in carcinogenesis. These chemical elements present in minute quantities and find naturally in environment.[8] Trace elements such as arsenic (As), cadmium (Cd), nickel (Ni), selenium (Se), and zinc (Zn), are

* Correspondence to:
E-mail addresses: llllpayahoo44@gmail.com (L. Payahoo), khajebishaky@tbzmed.ac.ir (Y. KhajeBishak).

http://dx.doi.org/10.1016/j.poamed.2016.05.004

associated with human health by various routes.[8] Many studies confirmed that cadmium could involve in most malignancies in the body. Cadmium, a toxic and non-essential heavy metal with half-life 10–30 years, has been classified as group 1 carcinogen. Carcinogenicity of cadmium in many organs such as kidney, lung, breast, liver, prostate, bladder and pancreas was manifested in many animals and human studies.[6] It was shown that cadmium develops cancer via genotoxic effects,[9] inhibition of apoptosis, DNA repair[9–11] and activation proto-oncogenes.[12,13] Human exposure to cadmium occurs through air pollution and contaminated water and food.[14] One of the most important risk factors for cancer development is the accumulation of cadmium in circulation.[15] After exposure, blood level of cadmium increases rapidly until it reaches a concentration that manifested the intensity of exposure.[16] However, when cadmium exposure stops, its levels in the blood never return to the pre-exposure concentration.[15]

We proposed that gastrointestinal cancer patients have higher levels of blood cadmium in comparison to healthy individuals. Considering the lack of study in this field in Iran, the present study was conducted to investigate blood cadmium levels in gastrointestinal cancer patients in Tabriz, Iran.

2. Aim

The aim of this study was to investigate the association between blood cadmium levels and the risk of gastrointestinal cancer in cancer patients.

3. Material and methods

This comparative study was carried out from January to October 2013 in Tabriz, northwest of Iran. The sample size was calculated by using G-Power software, setting α-error probability at 0.05, power (1-β-error probability) at 0.95% according to the similar study.[17] Finally, 111 gastrointestinal (esophagus, gastric, colon, rectum) cancer patients as a case group and 111 healthy people as a control group were allocated.

All participants were recruited from Imam Reza Hospital, the largest hospital in northwest of Iran. The protocol of this study was approved in the Ethics Committee in Tabriz University of Medical Sciences (No 5/4/2787). The patients for this study were aged between 30 and 70 with confirmed GI cancer.

Individuals with kidney diseases, anemia, pregnant women, historical gastric surgery and consumption of zinc, iron, calcium and selenium supplements were not included in the study.

After explanation the nature of the study, participants completed a written consent form. Demographic data including age, gender, type of cancer, smoking and anthropometric measurements were collected by questionnaire. Weight was measured using a Seca scale (Seca, Hamburg, Germany) in kilograms with precision of 0.1 kg with light clothes. Height was measured using a stationmaster (Seca) in meters with precision of 1.0 mm without shoes and BMI was calculated, as weight (in kilograms) divided by the square of height (in meters). Blood samples (5 mL) were collected after 12 h fasting state and frozen in −70 °C until analysis.

We applied dry ashing digestion method to prepare samples for measuring cadmium. Samples were ashed in electric furnace at 550 °C (Excition, Tehran, Iran) and then residues digested in HCl.[18] A Varian 240 AAFF graphite furnace atomic absorption spectrophotometer (GFAAS) was used for measuring of blood cadmium concentration. Cadmium was measured in 228.8 nm wavelength. The GFAAS standard curve was obtained by standard soluble (5 μg/L, 15 μg/L and 30 μg/L) and the concentration of cadmium was adjusted for bloodcreatinine level.

3.1. Statistical analysis

The data were analyzed by SPSS software (v. 16:0, Shikagho, IL, USA). Quantitative data were reported as mean ± standard deviation (SD) and qualitative data presented as frequency (percentage). Normality of data was assessed using Kolmogorov–Smirnov test. Independent-sample *t*-test was applied to compare difference between the study groups. Analysis of variance (ANOVA) test was used for comparison of differences in blood cadmium and type of cancer. Chi-square test was used to examine differences in qualitative variables in both groups. Univariate and multiple regression models were conducted to determine odds ratio (OR) of blood cadmium risk and GI cancer. Confounding factors defined as age, gender and smoking status. Statistical significance was considered as $P < 0.05$.

4. Results

Mean ages of participants were 58.67 ± 9.93 years in cancer patients and 52.03 ± 12.16 in healthy individuals ($P < 0.001$). In total, 55% of patients were males; however, about 40% of healthy people were males. About 27% of cases and 18% and controls patients were smoking cigarettes. There were no significant difference in the smoking status ($P > 0.05$). About 36.9% of patients had stomach cancer and 11.7% of them had esophagus cancer. Demographic characteristics of participants are shown in Table 1.

The results showed that blood cadmium levels in cancer patients were significantly higher than in healthy individuals ($P = 0.037$). Table 2 depicts the concentration of blood cadmium in both case and control groups, separately.

Blood cadmium concentration in females was higher than in males with exception on gastric cancer, however, there was no significant differences between two groups ($P > 0.05$). The mean concentration of blood cadmium in smokers was higher than in non-smokers; however this difference was not significant (2.67 ± 1.84 vs 2.25 ± 1.62, respectively). Fig. 1 depicts the blood cadmium differences in both genders.

Based on the results of simple logistic regression (unadjusted OR's), blood cadmium concentration, sex and age were significantly related to cancer incidence ($P < 0.05$); males had the odds of cancer incidence 76% more than females. With an increase in age and blood cadmium concentration in one year and 1 μg/L the odds of cancer incidence increased 5% and 18%, respectively.

Considering that smoking is one of the major sources of cadmium, this factor entered to simple logistic regression and the results showed that smokers had the odds of cancer incidence 67%

Table 1
Demographic characteristics of participants ($n = 222$).

Variables	Cases ($n = 111$)	Controls ($n = 111$)	P
Age, year	58.67 ± 9.93	52.03 ± 12.16	**0.001***
Gender, n (%)			
Male	61 (55.0)	45 (40.9)	**0.044****
Female	51 (45.0)	65 (59.1)	
Type of cancer, n (%)			
Esophagus	13 (11.7)		
Stomach	41 (36.9)	–	
Colon	39 (35.2)		
Rectum	18 (16.2)		
Smoking statue, n (%)			
Yes	30 (27.0)	21 (18.2)	0.116**
No	81 (73.0)	90 (81.8)	
Weight, kg	66.42 ± 9.2	69.80 ± 8.8	0.054*
BMI, kg/m^2	25.18 ± 2.7	25.69 ± 3.3	0.190*

*Independent Student's *t*-test; **χ^2 test; bold indicates significant results ($P < 0.05$).

Table 2
Cadmium levels in blood samples of participants ($n = 222$).

Variables	Cases ($n = 111$)	Controls ($n = 111$)	P	Meandiff (range)
Blood cadmium (μg)	2.57 ± 1.70	2.10 ± 1.83	**0.037***	0.46 (0.02–1.91)

Data presented as mean ± SD; *Independent-sample *t*-test; bold indicates significant results (P < 0.05).

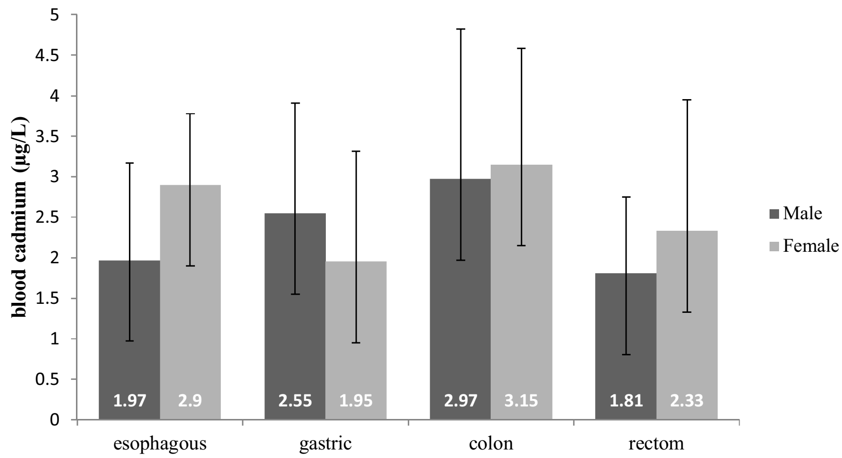

Fig. 1. Differences of blood cadmium levels in males and females.

more than non-smokers. However it was not a significant association.

Therefore, age, sex, blood cadmium and smoking status were candidates to enter in the multivariate analysis.

After adjusting (age, gender, smoking status, blood cadmium) the results showed that with an increase in blood cadmium levels in 1 μg/L the odds of cancer incidence increased 15% but it was not significant association (Table 3).

5. Discussion

Cancer is a serious public health issue worldwide.[19] Cadmium as a ubiquitous metal has not any biological role in human body.[6] Based on experimental and epidemiological studies, cadmium has been defined as a carcinogenic factor for human.[20] It is better to note that human activities result in cadmium accumulation in the body is 3–10 times more than natural.[21]

In this study, blood cadmium concentration in gastrointestinal cancer patients was significantly higher than in controls. Many epidemiological and clinical studies were reported high level of cadmium in cancer patients.[22] Kellen et al. reported that cadmium concentration of bladder cancer patients ($n = 172$) were significantly higher than controls ($n = 359$) ($P < 0.001$). Individuals with bladder malignancy were at risk of cancer 5.7 times more than controls (OR = 5.7; 95%CI = 3.3–9.9).[22] In another study, Strumylaite et al. showed a positively significant association between the concentrations of blood cadmium in breast cancer patients ($n = 57$).[23] Kriegel et al. showed that serum cadmium concentration in pancreatic cancer patients was significantly higher than in controls (11.1 ± 7.7 ng/mL vs 7.1 ± 5.0 ng/mL, respectively; $P = 0.012$).[16] In Nagata et al. investigation, OR of breast cancer in newly diagnosed woman with breast cancer ($n = 153$) according to the tertile of the creatinine-adjusted urinary cadmium levels were in higher levels than controls (OR = 6.05; 95%CI = 2.90–12.62; $P < 0.01$).[24] Gallagher et al. manifested a significant increasing trend in the risk of breast cancer by elevating urinary cadmium levels in cases compared controls (100 patients with breast cancer, 98 without breast cancer and 92 with breast cancer, 2884 without breast cancer, respectively) living on Long Island and US population ($P = 0.023$, $P = 0.039$, respectively).[25] Lee et al. demonstrated that urinary cadmium levels in 113 newly diagnosed prostate cancer patients were significantly higher than controls. It had been stated that cadmium beside sexually transmitted diseases could increase the risk of prostate cancer (OR = 9.75; 95%CI = 1.28–74.05).[26] Luckett et al. showed a significantly positive association between urinary cadmium concentration and the risk of pancreatic cancer was illustrated ($P < 0.001$).[27] These results also were consistant with another study by Schwartz et al.[28]

Regarding cadmium carcinogenicity, many molecular and cellular mechanisms have been proven. Cadmium through induction of DNA damage, genetic instability and suppression of DNA repair system, results in mutation and cancer occurrence.[29] Induction of oxidative stress through production of reactive oxygen species,[30] aberrant DNA methylation,[21,31] interaction with anti-oxidative enzymes[32] are the other mechanisms which are involved in carcinogenicity of cadmium.

In this study, there was no association between age and gender variables with blood cadmium concentration. In agreement of our

Table 3
Odds ratio and confidence interval of blood cadmium in gastrointestinal cancer patients.

Variables	Unadjusted		Adjusted*	
	OR (95% CI)	P	OR (95% CI)	P
Blood cadmium, μg/L	1.18 (1.10–1.40)	**0.037**	1.15 (0.96–1.38)	0.138
Age, year	1.05 (1.02–1.08)	**<0.001**	1.05 (1.02–1.08)	0.051
Sex				
Female	1			
Male	1.76 (1.03–3.00)	**0.037**	1.23 (0.66–2.28)	0.508
Smoking				
No	1			
Yes	1.66 (0.87–3.16)	0.118	1.24 (0.60–2.56)	0.561

Adjusted for age, gender, smoking status, blood cadmium; * *P* for logistic regression; bold indicates significant results ($P < 0.05$).

study, Kellen et al. showed that the concentration of blood cadmium in bladder cancer patients ($n = 172$) vs controls ($n = 359$) did not increase by age.[17] In another study, Nordberg et al. reported that in elderly people ($n = 804$) with mean age of 87 years, there was no association between blood cadmium levels and age in both genders.[33] González-Estecha et al. showed that in 951 participated subjects (231 men and 720 women), there was a positively significant correlation between females but not males and blood cadmium levels. However, no significant association between blood cadmium levels and age was reported ($r = 0.063$; $P = 0.071$).[34]

In contrast of our study, dell'Omo et al. demonstrated that in 434 people (208 females and 226 males) residents of Umbria, a population in central Italy, there was a significant correlation in non-smokers but not in smokers ($r = 0.15$, $P = 0.014$; $r = 0.07$, $P = 0.35$, respectively) between blood cadmium levels and age.[35] Olsson et al. showed that blood cadmium levels of 105 southern Sweden people increased with age in males comparing with females.[36]

The association between blood cadmium, age and gender has been showed controversial results. It was stated that blood cadmium mainly serves as a recent exposure index; however, it acts as a reliable reflector of cadmium in body.[17] Many studies were manifested that females had significantly more cadmium levels than males due to more absorption of dietary cadmium especially when iron deficiency appears. During iron deficiency, transporter of cadmium is up regulated, thus more amounts of cadmium will be absorbed.[37]

Smoking is another source of cadmium exposure.[17] Cadmium content in one cigarette is estimated to be 0–6.67 mg.[38] Plants such as cereal grains, potatoes and tobacco absorb cadmium through soils. Cadmium in tobacco plant specially accumulates in leaves.[38] However, cadmium content of tobacco differs depending on type of soil and its composition.[39] However, in our study the level of blood cadmium in smokers was higher than non-smokers, but between blood cadmium levels and smoking there was not significant correlation. In agreement of our study, dell'Omo et al. manifested that the blood cadmium levels of 434 individuals (94 smokers, 177 non-smokers) resident in Umbria, a population in Central Italy, in smokers were higher than non-smokers.[35] Olsson et al. also showed that the blood cadmium levels of 105 southern Sweden people (26 smokers, 79 non-smokers) in smokers were higher than non-smokers.[36]

Due to low number of smoking subjects participated in this study, there were some difficulties in interpretation of cadmium level and smoking correlation.

Our study had some limitations. The first was impossibility of measuring other trace elements such as zinc and iron that can affect absorption and accumulation of cadmium in the body. We also did not examine cadmium level in foods and soil. Small sample size for each type of cancer is another limitation for our study.

6. Conclusions

In this study, we showed that the concentration of cadmium in blood samples of gastrointestinal patients were in high levels than controls. Considering many adverse effects of cadmium as a toxic and pollutant metal in the nature, it needs more attention to find the major sources of cadmium exposure in northwest of Iranian population. Future studies are needed to investigate other mechanisms related to the cadmium carcinogenicity and other factors that affect cadmium levels in gastrointestinal cancer incidence.

Conflict of interest

There was no conflict of interest.

Acknowledgments

The authors thank the Vice Chancellor for Research (VCR) of Tabriz University of Medical Sciences (TUOMS), Nutrition Research Center and Department of Internal Medicine for supporting this study. This is a part of a database from thesis entitled "Evaluation of the dietary habits, urinary and blood cadmium of some gastrointestinal cancer patients with healthy people."

References

1. Babaei M, Mousavi S, Malek M, et al. Cancer occurrence in Semnan Province, Iran: results of a population-based cancer registry. *Asian Pac J Cancer Prev*. 2005;6(2):159–164.
2. Rathod CP, Dhawale SC, Kshirsagar RV. Recent trends in screening and evaluation methods of anticancer drugs. *IAJPR*. 2012;2(5):506–515.
3. Cui XB, Peng H, Li S, et al. Prognostic value of PLCE1 expression in upper gastrointestinal cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*. 2014;15(22):9661–9666.
4. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359–E386.
5. Gao SR, Li LM, Xia HP, Wang GM, Xu HY, Wang AR. Clinical observation on recombinant human endostatin combined with chemotherapy for advanced gastrointestinal cancer. *Asian Pac J Cancer Prev*. 2015;16(9):4037–4040.
6. Bishak YK, Payahoo L, Osatdrahimi A, Nourazarian A. Mechanisms of cadmium carcinogenicity in the gastrointestinal tract. *Asian Pac J Cancer Prev*. 2015;16(1):9–21.
7. Parsa N. Environmental factors inducing human cancers. *Iran J Public Health*. 2012;41(11):1–9.
8. Navarro Silvera SA, Rohan TE. Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes Control*. 2007;18(1):7–27.
9. McMurray CT, Tainer JA. Cancer, cadmium and genome integrity. *Nat Genet*. 2003;34(3):239–241.
10. Waalkes MP, Rehm S, Cherian MG. Repeated cadmium exposures enhance the malignant progression of ensuing tumors in rats. *Toxicol Sci*. 2000;54(1):110–120.
11. Shimada H, Shiao YH, Shibata M, Waalkes MP. Cadmium suppresses apoptosis induced by chromium. *J Toxicol Environ Health A*. 1998;54(2):159–168.
12. Zheng H, Liu J, Choo KA, Michalska AE, Klaassen CD. Metallothionein-I and-II knock-out mice are sensitive to cadmium-induced liver mRNA expression of c-junandp53. *Toxicol Appl Pharmacol*. 1996;136(2):229–235.
13. Abshire MK, Buzard GS, Shiraishi N, Waalkes MP. Induction of c-myc and c-jun proto-oncogene expression in rat L6 myoblasts by cadmium is inhibited by zinc preinduction of the metallothionein gene. *J Toxicol Environ Health*. 1996;48(4):359–377.
14. Nawrot T, Plusquin M, Hogervorst J, et al. Environmental exposure to cadmium and risk of cancer: a prospective population-based study. *Lancet Oncol*. 2006;7(2):119–126.
15. Alfvén T, Järup L, Elinder CG. Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. *Environ Health Perspect*. 2002;110(7):699–702.
16. Kriegel AM, Soliman AS, Zhang Q, et al. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta region of Egypt. *Environ Health Perspect*. 2006;114(1):113–119.
17. Kellen E, Zeegers MP, Den Hond E, Buntinx F. Blood cadmium may be associated with bladder carcinogenesis: the Belgian case–control study on bladder cancer. *Cancer Detect Prev*. 2007;31(1):77–82.
18. Welna M, Szymczycha-Madeja A, Pohl P. Quality of the trace element analysis: sample preparation steps. In: Akyar I, ed. *Wide Spectra of Quality Control*. INTECH; 2011. Chapter 4 http://www.intechopen.com/books/wide-spectra-of-quality-control/quality-of-the-trace-element-analysis-sample-preparation-steps.
19. Palanisamy Pasupathi SP. Chronic tobacco smoking and gastric cancer: a review. *Int J Curr Biomed Pharm Res*. 2011;1:48–66.
20. Hogervorst J, Plusquin M, Vangronsveld J, et al. House dust as possible route of environmental exposure to cadmium and lead in the adult general population. *Environ Res*. 2007;103(1):30–37.
21. Joseph P. Mechanisms of cadmium carcinogenesis. *Toxicol App Pharmacol*. 2009;238(3):272–279.
22. Il'yasova D, Schwartz GG. Cadmium and renal cancer. *Toxicol Appl Pharmacol*. 2005;207(2):179–186.
23. Strumylaite L, Bogusevicius A, Ryselis S, et al. Association between cadmium and breast cancer. *Medicina (Kaunas)*. 2008;44(6)415–420 [in Lithuanian].
24. Nagata C, Nagao Y, Nakamura K, et al. Cadmium exposure and the risk of breast cancer in Japanese women. *Breast Cancer Res Treat*. 2013;138(1):235–239.
25. Gallagher CM, Chen JJ, Kovach JS. Environmental cadmium and breast cancer risk. *Aging (Albany NY)*. 2010;2(11):804–814.
26. Li J, Bostick RM, Ward KC. Cadmium, sexually transmitted disease, and risk for prostate cancer. *Open Epidemiol J*. 2009;2:14–19.

27. Luckett BG, Su LJ, Rood JC, Fontham ET. Cadmium exposure and pancreatic cancer in south Louisiana. *J Environ Public Health*. 2012;2012:180186.
28. Schwartz GG, Reis IM. Is cadmium a cause of human pancreatic cancer? *Cancer Epidemiol Biomarkers Prev*. 2000;9(2):139–145.
29. Filipic M, Fatur T, Vudrag M. Molecular mechanisms of cadmium induced mutagenicity. *Hum Exp Toxicol*. 2006;25(2):67–77.
30. Hartwig A. Cadmium and cancer. *Met Ions Life Sci*. 2013;11:491–507.
31. Benbrahim-Talla L, Liu J, Webber MM, Waalkes MP. Estrogen signaling and disruption of androgen metabolism in acquired androgen-independence during cadmium carcinogenesis in human prostate epithelial cells. *Prostate*. 2007;67(2):135–145.
32. Waalkes MP. Cadmium carcinogenesis. *Mutat Res*. 2003;533(1–2):107–120.
33. Nordberg GF. Historical perspectives on cadmium toxicology. *Toxicol Appl Pharmacol*. 2009;238(3):192–200.
34. González-Estecha M, Trasobares E, Fuentes M, et al. Blood lead and cadmium levels in a six hospital employee population PESA study, 2009. *J Trace Elem Med Biol*. 2011;25:S22–S29.
35. dell'Omo M, Muzi G, Piccinini R, et al. Blood cadmium concentrations in the general population of Umbria, central Italy. *Sci Total Environ*. 1999;226(1):57–64.
36. Olsson M, Bensryd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. Cadmium in blood and urine–impact of sex, age, dietary intake, iron status, and former smoking–association of renal effects. *Environ Health Perspect*. 2002;110(12):1185–1190.
37. Kim DW, Woo HD, Joo J, et al. Estimated long-term dietary exposure to lead, cadmium, and mercury in young Korean children. *Eur J Clin Nutr*. 2014;68(12):1322–1326.
38. Dguimi HM, Debouba M, Ghorbel MH, Gouia H. Tissue-specific cadmium accumulation and its effects on nitrogen metabolism in tobacco (*Nicotiana tabaccum*, Bureley v. Fb9). *CR Biol*. 2009;332(1):58–68.
39. Zaprjanova P, Dospatliev L, Angelova V, Ivanov K. Correlation between soil characteristics and lead and cadmium content in the aboveground biomass of Virginia tobacco. *Environ Monit Assess*. 2010;163(1–4):253–261.