RESEARCH ARTICLE

Association of Cadmium but not Arsenic Levels in Lung Cancer Tumor Tissue with Smoking, Histopathological Type and Stage

Nalan Demir[1]*, Serkan Enon[2], Vugar Ali Turksoy[3], Zeliha Kayaalti[3], Seda Kaya[3], Ayten Kayi Cangir[2], Tulin Soylemezoglu[3], Ismail Savas[1]

Abstract

Background: To evaluate association of lung cancer with arsenic and cadmium levels measured in tumor tissue. Materials and Methods: Ninety-five patients with lung cancer tumor tissue obtained surgically were included in this study. Arsenic and cadmium levels were measured and levels of metals were compared among types of lung cancer and with reference to patient data. Results: The histopathologic diagnoses of the 95 cases were SCC, 49, adenocarcinoma, 28, large cell, 11 and SCLC, 1. Mean tumor arsenic and cadmium levels were 149.3±129.1μg/kg and 276.3±219.3μg/kg, respectively. Cadmium levels were significantly associated with smoking (p=0.02), histopathologic type (p=0.005), and TNM staging (r=0.325; p=0.001), although arsenic was not related to any parameter (p>0.05). There was no relation between metal levels and mortality (p>0.05). Conclusions: We found a significant association between tumor cadmium levels of patients with lung cancer and smoking, histopathologic type and staging, although there was no relation with arsenic levels.

Keywords: Lung cancer - surgical tumor tissue - arsenic - cadmium - smoking stage - histopathological type

Asian Pac J Cancer Prev, **15 (7)**, 2965-2970

Introduction

The development of lung cancer is associated with multiple factor including genetic, immunologic, and environmental factors. Although smoking is the most common cause of lung cancer, the other causes including exposure to toxic metals from environment or cigarette smoke should keep in mind. Mechanisms of metal carcinogenesis may explain with oxidative stress, DNA repair modulation and disturbances of signal transduction pathways (Beyersmann and Hartwig, 2008).

Arsenic is a potent toxicant metalloid that may exist in a number of inorganic and organic forms. The main route of exposure to inorganic arsenic compounds is drinking water and food. The International Agency for Research on Cancer (IARC) has classified inorganic arsenic as a known human carcinogen by both the inhalation and oral exposure routes (ATSDR, 2007). Occupational and environmental exposure to arsenic has been associated with lung cancer (Ferreccio et al., 2000; Heck et al., 2009). On the other hand, inadequate data present on the relationship between lung cancer and environmental low-dose arsenic exposure.

Cadmium is a toxic, bioaccumulative, non-essential and highly widespread heavy metal. The most important sources of cadmium exposure for people in the general population are air pollution, cigarette smoke and food. IARC has classified cadmium as group 1 human carcinogen, having concluded that cadmium can produce lung cancers in humans and animals exposed by inhalation (ATSDR, 2012).

Chronic exposure to arsenic and cadmium has been reported worldwide affecting nearly one hundred million people in most countries. Both of them have a long biologic half-life in humans and they are very harmful to humans because of in vivo accumulation in liver, kidney, lung and other tissues. Beside of nonneoplastic effects, the development of lung and other internal cancers such as in bladder, kidney, liver, gallbladder and breast due to chronic exposure have been well defined since 1950 (Waalkes, 2003; ATSDR, 2007; Chhabra et al., 2012; Rahim et al., 2014).

Arsenic and cadmium can be accumulated in hair, nail, skin and lung. Previous studies have identified associations between levels of arsenic and cadmium in urine, blood and hair with lung cancer, although a few of these reported on surgical tumor tissue (Diez et al., 1989; Gerhardsson and Nordberg, 1993; Mutti and Corradi, 2006). This paper adds to these publications based on the evaluation of tumor metal levels in patients with lung cancer. The objectives of this study were to determine the accumulation of arsenic and cadmium in tumor tissue obtaining surgically in patients diagnosed lung cancer, and to evaluate association of these metals and lung cancer.

*[1]Department of Chest Diseases, [2]Department of Thoracic Surgery, Faculty of Medicine, [3]Institute of Forensic Sciences, Ankara University, Ankara, Turkey [&]Equal contributors *For correspondence: dr.ndemir@gmail.com*

Materials and Methods

The study was approved by the local ethics committee in accordance with institutional rules and Declaration of Helsinki requirements (25.05.2009/152-4825).

Subjects

Totally, 103 patients who performed thoracic surgery due to lung mass, between the years 2009-2012, were investigated in a case-control study, prospectively. 95 patients diagnosed with lung cancer by histopathology were included to this study.

Tumor tissue collection and storage

Tumor tissue samples obtaining surgically were collected amount of 1-2 g in 95 patients who operated at the Department of Thoracic Surgery of Ankara University, following informed written consent. All of the samples prevented of the metal contamination. Fragments were put into sterile vials and immediately stored at -20°C.

Metal analysis

The analysis of tumor tissue for arsenic and cadmium was performed at the Institute of Forensic Sciences of Ankara University, Toxicology Laboratory in this study.

Arsenic and cadmium were determined by Varian AA 240 Z Zeeman Graphite Atomic Absorption Spectrometry (GFAAS) according to the analytical techniques which described clearly in previous studies (Hou et al., 2001). The concentration of metals in lung tissues, calculated as ratio between the total amount (in μg) of metals measured in the digestion solution and the weight of the digested dry tissue, is reported as μg/g dry tissue. The detection limits (LOD), calculated as 3 standard deviations of the background signal obtained on 10 white samples, for different elements (expressed as μg/g dry tissue) were: 0.00005 for cadmium; 0.001 for arsenic.

Study Design

The patient's data including demographic data, detailed history, clinical and laboratory findings were recorded by Lung Cancer Data Registry Form.

According to the smoking habits, subjects were classified into the following subgroups: currents smokers (CS), ex-smokers (ES) and non-smokers (NS). CS included even subjects who stopped tobacco smoking from no more than one year; whereas the NS group included both subjects who had never smoked and ex-smokers from at least 15 years who smoked no more than 30 pack years (PY).

Thorax computed tomography (CT), pulmonary function test (PFT), and arterial blood gas analysis (ABG) of all cases were evaluated before the operation. All patients were classified according to TNM (Tumor Node Metastasis) staging (Goldstraw et al., 2007). Patients were screened for lymph node involvement and distant metastasis by one or more diagnostic method including thorax computed tomography, abdomen CT or ultrasonography (USG), whole body bone scintigraphy and positron emission tomography (PET) before treatment. None of the enrolled patients received previous chemotherapy or radiotherapy treatments before the collecting tumor tissue.

Follow up

Patients were followed up for three years (2009-2012). Mortality was recorded in cases on every visit.

Statistical analysis

Data were assessed by using SPSS 16.0 for Windows software package. Student t and one-way ANOVA parametric tests were used for the comparison of groups in terms of metric variables and data were measured as mean±standart deviation. The chi-square test was used to compare categorical variables. In addition, case summary reports and frequency charts were used to analyze the group variables. All p values were two-tailed and a p value 95% ($p<0.05$) and 99% ($p<0.01$) were considered statistically significant.

Results

Eighty-five male and 10 female, totally 95 patients were enrolled in the study. Mean age was 60.3±8.1 years. While seventy-three patients (76.8%) were current smoker (CS), 16 of patients were ex-smoker (ES) with mean pack year was 48.7±25.6. Only 6 patients were non-smoker. Eleven patients (11.6%) had an occupational possible exposure to toxic gas and inhalation, but none of these had arsenic and cadmium exposure due to their work, directly. Five of all were history of previous cancer which developed from another organ. Among 44 patients, the most common existing comorbidities were hypertension (n=17, 17.9%) and diabetes mellitus (n=15, 15.8%).

On the evaluation of thorax CT, tumor diameters of all patients were varied 2 to 11 cm. The most common localization of tumor was right upper lobe (n=28, 29.5%). The diagnosis of patients was confirmed by the samples obtained from surgical resection material (n=58, 61.1%), mucosal biopsy and/or brushing taken with bronchoscopy (n=24, 25.2%), and transthoracic needle biopsy (n=13, 13.7%).

The histopathologic diagnoses were squamous cell carcinoma (SCC) (n=49, 51.6%); adenocarcinoma (n=28, 29.5%); large cell (n=11, 11.6%); and small cell lung cancer (SCLC) (n=1, 1.1%). Six cases (6.3%) were not defined to the cell type and they were accepted as non-small cell lung cancer (NSCLC). Seven cases of female patients (n=10) were adenocarcinoma, while 48 of male patients (n=85) had squamous cell lung cancer.

When we evaluated to the patients according to the TNM staging, the most common stage was stage IB (n=52, 54.7%). Two cases (2.1%) with cranial and bone metastasis on admission. While 46 cases (48.4%) were treated with the combination of surgery and adjuvant chemotherapy (CT), 42 cases (44.2%) were treated only surgically. The combination of surgery and radiotherapy (RT) was given to 4 cases (4.2%). Neo-adjuvant CT and then surgery were administered to one case (1.1%). One case was taken only CT, one case was also treated with RT-CT combination (Table 1).

In tumor tissue obtaining surgically of cases, mean

Table 1. Patient Characteristics on Admission

	n	%
Sex (F/M)	10-85	10.5/89.5
Mean age, year	60.3±8.1	
Smoking habits		
Current smoker	73	76.8
Ex-smoker	16	16.8
Non-smoker	6	6.3
Mean pack-year	48.7±25.6 (3-150)	
Occupational exposure	11	11.6
Previous cancer history	5	5.3
Co-morbidities		
Hypertension	17	17.9
Diabetes mellitus	15	15.8
Atherosclerotic cardiac disease	11	11.6
Hyperlipidemia	6	6.3
Cardiac failure	3	3.2
Chronic obstructive pulmonary disease	3	3.2
Tumor localization		
Right lung		
Upper lobe	28	29.5
Hilar	11	11.6
Mid lobe	17	17.9
Lower lobe	6	6.3
Left lung		
Upper lobe	16	16.8
Hilar	11	11.6
Lower lobe	6	6.3
Diagnostic methods		
Surgical material	58	61.1
Fiberoptic bronchoscopy	24	25.2
Transthoracic needle biopsy	13	13.7
Histopathologic diagnosis		
SCC	49	51.6
Adenocarcinoma	28	29.5
Large cell	11	11.6
NSCLC	6	6.3
SCLC	1	1.1
TNM staging		
IA	5	5.3
IB	52	54.7
IIA	1	1.1
IIB	12	12.6
IIIA	15	15.8
IIIB	7	7.4
IV	2	2.1
Treatment		
Surgery	42	44.2
Surgery+ chemotherapy and/or radiotherapy	51	53.7
Chemotherapy and/or radiotherapy	2	2.1

arsenic and cadmium levels were found as 149.3±129.1 (37.6-1012.3) μg/g and 276.3±219.3 (26.8-965.4) μg/g, respectively. When the arsenic and cadmium levels were compared, statistically significant correlation was not found (r=0.057; p=0.585).

After the smoking habits stratified, cadmium levels were found higher in CS and ES than NS, it was statistically significant (p=0.02); however, there was no a significant association between arsenic and smoking status (p=0.09). When the patients were evaluated for possible occupational metal exposure during past working activity, no significant differences were found among these patients and others for metal levels (p>0.05).

When the cases with SCLC and NSCLC exclude from the statistical analysis due to small number cases and indefinite diagnosis, in the remaining 88 cases with non-small cell lung cancer, the comparison of histopathologic type and metal levels were showed that arsenic and cadmium levels were higher in patients with squamous and large cell lung cancer than other types of lung cancer. While arsenic levels were found no associated with lung cancer type (p=0.34), cadmium levels were significantly different according to the histopathologic type of lung cancer (p=0.005) (Table 2).

Cadmium levels were significantly associated with lung cancer TNM staging of cases, statistically (p=0.007). Nonetheless, there was no significant difference for arsenic levels. At the result of this finding, TNM staging were found more associated with cadmium levels than arsenic. When the cases were subdivided into the two groups (Group I: Stage IA, IB, 2A, 2B, and Group II: Stage 3A, 3B, 4, and extensive stage for SCLC), the comparison of the two groups was shown that cadmium levels were significantly higher in group II than group I (p=0.001). Although arsenic levels were also high at group II as cadmium, there was no remarkably difference, statistically (p=0.140) (Table 3).

Finally, the mean survival time was 586.6±316.1 (4-1318) days. Mortality was seen in 10, 15 and 20 cases

Table 2. The Evaluation of the Relationship between Smoking Status and Histopathologic Diagnosis of Cases with Lung Cancer and Tissue Arsenic and Cadmium Levels

	Arsenic levels	Cadmium levels
All cases (n:95)	149.3±129.1	276.3±219.3
Smoking Status		
Non-smoker (n=6)	312.4±358.6	132.9±127.8
Ex-smoker (n=16)	159.6±89.4	330.9±245.1
Current smoker (n=73)	129.0±93.1	266.4±209.1
p	0.09	0.02
Histopathology		
SCC (n:49)	137.6±104.6	319.2±239.1
Adenocarcinoma (n:28)	174.5±178.3	176.6±155.3
Large cell (n:11)	115.9±49.1	389.0±217.3
p	0.343	0.005

Table 3. The Comparison of the TNM Staging and Arsenic and Cadmium Levels in Tumor Tissue Samples of Cases with Lung Cancer

Stage	Arsenic levels	Cadmium levels
Stage IA (n=5)	115.8±44.5	276.3±219.3
Stage IB (n=52)	137.2±99.8	224.9±162.1
Stage IIA (n=1)	163.3	501.3
Stage IIB (n=12)	146.1±70.6	311.1±234.2
Stage IIIA (n=15)	196.9±234.4	390.6±235.1
Stage IIIB (n=7)	124.2±100.8	491.1±370.9
Stage IV (n=2)	267.1±291.5	250.1±185.5
SCLC (n=1)	195.1	72.6
p	0.75	0.007
Groups		
I (IA, IB, 2A, 2B)	137.6±91.2	234.0±178.6
II (3A, 3B, 4, extensive stage)	182.1±199.6	394.8.6±277.2
p	0.14	0.001

Table 4. The Relationship of Tissue Arsenic and Cadmium Levels of Cases with Lung Cancer and Mortality on Three Years Follow-Up in All Cases

	Tumor arsenic levels	Tumor cadmium levels
Living patients (n=76)	138.5±91.5	264.4±206.9
Exitus (n=19)	192.4±222.9	324.0±264.3
p	0.104	0.291

during the six months, 1 and 3 years follow-up. In present study mortality rate was 20.0% (n=19) in a following period for three years. Both of metal levels were no different according to the survival, statistically (Table 4).

Discussion

Human exposure to arsenic and cadmium is common because of their wide spread use in industry and their environmental persistence. Many large epidemiologic studies over the past 50 years have been well defined an increased lung cancer risk in arsenic and cadmium-exposed population, to date. However, chronic poisoning among the general population to these metals by inhalation or oral route is also keep in mind for development of lung cancer beside of occupational exposure (Jarup, 2003).

The traditional approach is based on the determination of toxic metals and their metabolites in biologic samples such as urine, human blood, and hair. The lungs are target organs of several metals by inhalation. Because of their low solubility in the alveolar regions of the lungs, these poorly soluble compounds have a long residence time in the lungs (Mutti and Corradi, 2006). According to this, the determination of metal levels in lung cancer tissue can allow the definition of relationship between metal exposure and lung cancer. This study was aimed to evaluate the relation of lung cancer and arsenic and cadmium levels in tumor tissue obtaining surgically.

Currently, the elevation of arsenic and cadmium in tumor tissue of cases with lung cancer have been demonstrated at previous studies, although another studies showed that there were no different in autopsies for metal levels between lung cancers and other cases (Adachi et al., 1991). While most of studies performed in post-mortem samples of cases had exposure history or not, only few studies which evaluated tissue samples obtaining during surgical intervention have observed in literature ((Díez et al., 1989; Gerhardsson and Nordberg, 1993). Long half-life values were observed for these elements, especially in lung tissue. The present study was also confirmed to the elevation of arsenic and cadmium levels in tumor tissue of cases with lung cancer. This findings indicates that cadmium have a long biological half-time.

De Palma et al. evaluated the levels of cadmium and some metallic elements in lung tissue biopsies from cancerous and unaffected tissues in 45 NSCLC patients and 8 control subjects undergoing surgery. As an unexpecting result, this study demonstrated that the unaffected lung tissue was more representative than the cancerous tissue of the pulmonary content of metallic elements (Palma et al., 2008). In contrast to this, another study performed by Zhu et al. analyzed trace element contents in benign lung tissue, lung cancer tissue and paracancerous tissue of patients with lung cancer, and the contents of cadmium and other elements including lead (Pb), chromium (Cr), manganese (Mn), cuprum (Cu) and zinc (Zn) in cancer tissues were found higher than those in paracancerous tissues (Zhu et al., 2004). Our study was conducted in lung cancer tissue as similar to these studies. However, paracancerous tissue samples were not obtained, and not compared to the cancerous tissue according to the metal levels.

Whereas occupational exposure is well described risk factor for arsenic and cadmium exposure ('t Mannetje et al., 2011); there was no found a relation between occupational history and metal levels of cases in this study, because of any cases had occupational history including arsenic and/or cadmium poisoning. The relationship of smoking and lung cancer have been known very long time (Doll and Hill, 1950). When the association of toxic metals and smoking is overviewed, tobacco smoke is a main factor affecting the concentration levels of cadmium, lead, and to a lesser extent nickel in the lung tissues of NSCLC patients. Particularly, cadmium elevation in blood, urine and tissue of smokers had been described previously (Gerhardsson and Nordberg, 1993; De Palma et al., 2008). Cigarette smoke contains measurable amounts of cadmium, and passive smokers living in the same households as smokers have significantly higher blood cadmium levels (Wysowski et al., 1978). Nonetheless, never smokers have also been lung cancer due to environmental risk factors and carcinogenic effects of metals were seen among non-smokers (Samet et al., 2009). As similar to previous studies, cadmium levels were showed significantly higher in tumor tissue obtained from current smokers in present study. Additionally, our result was compatible with earlier studies which showed the association of smoking and cadmium levels from Turkey (El-Agha and Gokmen, 2002). When smoking is taking into account as a source of cadmium, this may be accepted as an expecting result.

According to the histopathology of lung cancer, a few studies evaluating to association of tumor metal levels and lung cancer type have been observed in literature. Guo et al showed that the carcinogenicity of arsenic on lungs is also cell type-specific. Arsenic a result of this study including 37.290 lung cancer patients, squamous cell and small cell carcinomas appeared to be related to arsenic ingestion, but not adenocarcinoma (Guo et al., 2004).

In present study, in cases with squamous and large cell lung cancer, metal levels especially cadmium were found higher in tumor tissue than other histopathologic type; however, this result may be due to small number of cases had other histopathologic type including to the study.

Previous analysis of lung cancer mortality in these metals identified excess lung cancer mortality. According to the Third National Health and Nutrition Examination Survey (NHANES III), cadmium appears to be associated with overall cancer mortality in men and women (Adams et al., 2012). Another study was also showed that cadmium was an independent factor effecting mortality in lung cancer (Park et al., 2012). Arsenic exposition is also related mortality in patients with lung cancer compared with the

controls (Nakadaira et al., 2002). However Sorahan et al. were not found a relation between cadmium exposure and lung cancer mortality (Sorahan and Esmen, 2004). This study was not showed a relation between cadmium and arsenic levels in tumor tissue and mortality in lung cancer cases.

Heavy metals contamination of groundwater, surface water, air and foods has been described in previous studies from Turkey. It is major public health hazard in Turkey as it has been in the world (Akbulut and Tuncer, 2011). Recent studies in Turkey generally worked in the lung, kidney and liver autopsy samples for the determination of metal levels (Kayaalti et al., 2010). Although the association of toxic metals exposure and lung cancer have been well defined in previous studies from most of countries (Ferreccio et al., 2000; Sorahan et al., 1995), there is few report showing the association of tumor tissue metal levels and lung cancer from Turkey. Çobanoglu et al. were conducted a study in 50 cases (30 lung cancer and 20 healthy human) from Turkish population and they were observed that cadmium value was higher in lung cancer but it was not statistically significant (Cobanoglu U et al., 2010). However, arsenic levels were not measured in this study. Limitation of this study is the number of cases was restricted with operated patients at a single center. Thus the very few cases with small cell lung cancer were included to study. Another limitation was that tissue samples of control group without lung cancer were not obtained for this study. Other limitation was that the past environmental exposure dose of arsenic and cadmium for each patient was unknown.

In conclusion, this study showed that tumor cadmium levels were more related with lung cancer type and smoking history than arsenic. Larger studies are necessary for the evaluation of toxic metal levels' affects to lung tissue in cases with lung cancer. The recognition of toxic metal exposure in patients diagnosed lung cancer by measurements of metal levels in affecting lung tissue is important, thus it can lead to actions to reduce exposure. In order to protect public health for possible polluting toxic elements, it is important to know the concentrations of these elements in the human body.

Acknowledgements

This work was financially supported by T. R. Prime Ministry State Planning Organization and Research Fund of Ankara University (Grant number 2003K1201902).

References

Adachi S, Takemoto K, Ohshima S, Shimizu Y, Takahama M (1991). Metal concentrations in lung tissue of subjects suffering from lung cancer. *Int Arch Occup Environ Health,* **63**, 193-7.

Adams SV, Passarelli MN, Newcomb PA (2012). Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. *Occup Environ Med*, **69**, 153-6.

Akbulut NE, Tuncer AM (2011). Accumulation of heavy metals with water quality parameters in Kızılırmak River Basin (Delice River) in Turkey. *Environ Monit Assess*, **173**, 387-95.

ATSDR. Toxicological profile for arsenic. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2007.

ATSDR. Toxicological profile for cadmium. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 2012.

Beyersmann D, Hartwig A (2008). Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol*, **82**, 493-512.

Chhabra D, Oda K, Jagannath P, et al (2012). Chronic heavy metal exposure and gallbladder cancer risk in India, a comparative study with Japan. *Asian Pac J Cancer Prev*, **13**, 187-90.

Cobanoglu U, Demir H, Sayir F, Duran M, Mergan D (2010). Some mineral, trace element and heavy metal concentrations in lung cancer. *Asian Pac J Cancer Prev*, **11**, 1383-8.

De Palma G, Goldoni M, Catalani S, et al (2008). Metallic elements in pulmonary biopsies from lung cancer and control subjects. *Acta Biomed*, **79**, 43-51.

Diez M, Arroyo M, Cerdan FJ, et al (1989). Serum and tissue trace metal levels in lung cancer. *Oncology*, **46**, 230-4.

Doll R, Hill AB (1950). Smoking and carcinoma of the lung. Preliminary report. *Br Med J*, **2**, 739-48.

El-Agha O, Gokmen IG (2002). Smoking habits and cadmium intake in Turkey. *Biol Trace Elem Res*, **88**, 31-43.

Ferreccio C, Gonzalez PC, Milosavjlevic SV, Marshall GG, Sancha AM, et al (2000). Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology*, **11**, 673-79.

Gerhardsson L, Nordberg GF (1993). Lung cancer in smelter workers--interactions of metals as indicated by tissue levels. *Scand J Work Environ Health*, **19**, 90-4.

Goldstraw P, Crowley J, Chansky K, et al (2007). The IASLC lung cancer staging project: proposals for the revision of TNM staging groupings in the forthcoming (seventh) edition of the TNM classification of the malignant tumours. *J Thorac Oncol*, **2**, 706-14.

Guo HR, Wang NS, Hu H, Monson RR (2004). Cell type specificity of lung cancer associated with arsenic ingestion. *Cancer Epidemiol Biomarkers Prev*, **13**, 638-43.

Heck JE, Andrew AS, Onega T, et al (2009). Lung cancer in a U.S. population with low to moderate arsenic exposure. *Environ Health Perspect*, **117**, 1718-23.

Hou J, Chen G, Wang Z (2001). Simultaneous determination of trace cadmium and arsenic in grains using atomic absorption spectrophotometry. *Guang Pu Xue Yu Guang Pu Fen Xi*, **21**, 387-90.

Jarup L (2003). Hazards of heavy metal contamination. *Br Med Bull*, **68**, 167-82.

Kayaalti Z, Mergen G, Soylemezoglu T, et al (2010). Effect of metallothionein core promoter region polymorphism on cadmium, zinc and copper levels in autopsy kidney tissues from a Turkish population. *Toxicol Appl Pharmacol*, **245**, 252-5.

Mutti A, Corradi M (2006). Recent developments in human biomonitoring: non-invasive assessment of target tissue dose and effects of pneumotoxic metals. *Med Lav*, **97**, 199-206.

Nakadaira H, Endoh K, Katagiri M, Yamamoto M (2002). Elevated mortality from lung cancer associated with arsenic exposure for a limited duration. *J Occup Environ Med*, **44**, 291-9.

Park RM, Stayner LT, Petersen MR, Finley-Couch M, Hornung R, et al (2012). Cadmium and lung cancer mortality accounting for simultaneous arsenic exposure. *Occup Environ Med*, **69**, 303-9.

Rahim F, Jalali A, Tangestani R (2013). Breast cancer frequency and exposure to cadmium: a meta- analysis and systematic review. *Asian Pac J Cancer Prev*, **14**, 4283-7.

Samet JM, Avila-Tang E, Boffetta P, et al (2009). Lung cancer

in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res*, **15**, 5626-45.

Sorahan T, Esmen NA (2004). Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. *Occup Environ Med*, **61**, 108-16.

Sorahan T, Lister A, Gilthorpe MS, Harrington JM (1995). Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med*, **52**, 804-12.

't Mannetje A, Bencko V, Brennan P, et al (2011). Occupational exposure to metal compounds and lung cancer. Results from a multi-center case-control study in Central/Eastern Europe and UK. *Cancer Causes Control*, **22**, 1669-80.

Waalkes M.P (2003). Cadmium carcinogenesis. *Mutat Res*, **533**, 107-20.

Wysowski DK, Landrigan PJ, Ferguson SW, et al (1978). Cadmium exposure in a community near a smelter. *Am J Epidemiol*, **107**, 27-35.

Zhu X, Zhang S, Jiang Y, Li H (2004). Analysis of seven trace element contents in benign lung tissue, lung cancer tissue and paracancerous tissue of patients with lung cancer. *Zhongguo Fei Ai Za Zhi*, **7**, 222-5.