RESEARCH COMMUNICATION

Some Mineral, trace Element and Heavy Metal Concentrations in Lung Cancer

Ufuk COBANOGLU[1], Halit DEMİR[2*], Fuat SAYIR[1], Memet DURAN[3], Duygu MERGAN[1]

Abstract

Objective: We aimed to determine the relationship between some mineral, trace element and heavy metal levels in the patients of lung cancer by measuring serum levels of copper (Cu), lead (Pb), zinc (Zn), iron (Fe), cobalt (Co), cadmium (Cd), manganese (Mn), magnesium (Mg). Methods: A total of 50 lung cancer and human health (30 lung cancer and 20 healthy human) were included in the study. Venous blood samples of each lung cancer were obtained, and serum Cu, Pb, Zn, Fe, Cd, Co, Mn, Mg levels were analysed by Atomic Absorption Spectrophotometer measurements. Results: Mg value measured in lung cancer group were lower than the control group and this was statistically significant (P<0.01). Serum Cu level was significantly lower with lung cancer compared to healthy human (P<0.01). Pb level was significantly higher than those of controls (P<0.01). The serum Zn level was significantly lower in serum of lung cancer group than controls (P<0.01). Serum Mn and Co levels were found increased in lung cancer group than controls (P<0.01). Cd value was higher in lung cancer but it was not statistically significant (p>0.01). The mean concentration of Fe in the serum of lung cancer patients was higher than in the controls, but the difference was not significant (p>0.01). There was a positive correlation between Cd and Pb level, and between Mn and Fe levels in lung cancer. There was a negative correlation between Co and Zn levels of healthy human. There was a negative correlation between Co and Mg levels of lung cancer. Conclusions: Serum Cu, Pb, Zn, Fe, Mg, Co, Mn and Cd might be play a role in the patients of lung cancers. Zn may protective as potent lung cancer. In addition, it is suggested that low levels of zinc can induce the pathogenesis of lung cancer.

Keywords: Minerals - trace elements - heavy metals - lung cancer

Asian Pacific J Cancer Prev, **11**, 1383-1388

Introduction

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.5 million deaths worldwide annually (WHO, 2007). An important feature in the aetiology of lung cancer is its strong association with cigarette smoking (Flanders et al., 2003). Trace-heavy elements play an significant role in human health and disease. Some, as Cd, are non essential but others are essential for continue of normal metabolizma functions. These elements are take office in different metabolic pathway of cell and tissues. Each of essential and nonessential trace element may be toxic if found in cell, tissue and fluids in large concentrations (Çavuşoğlu et al., 2008). Cd is known to be one of the most toxic environmental and industrial pollutants. Its industrial applications were developed based on its unique chemical and physical properties. Cd is a ubiquitous toxic heavy metal and, unlike organic compounds, it is not biodegradable and has a very long biological half-life. In spite of many studies, the mechanism of its toxicity has not yet been well elucidated and in contrast to other metals, there is no effective therapy for its poisoning (Messner et al., 2009).

Recent research seems to indicate that a low level of lead (Pb) exposure has a number of negative consequences for health. Among these consequences are impairment of the function of renal tubular cells, inhibition of sperm formation, damage to the fetus, slowing of motor nerve velocity, dysfunction of the central nervous system, and hypertension and other cardiovascular diseases (Landrigan, 1989; 1990; Meller et al., 1992).

Zn is a trace element, essential for living organisms.

*[1]Yuzuncu Yil University, Faculty of Medicine, Department of Thoracic Surgery, [2]Yuzuncu Yil University, Faculty of Science and Art, Department of Chemistry, [3]Yuzuncu Yil University, Faculty of Medicine,Department Of Pulmonary Medicine, Van. *For correspondence : halitdemir2005@yahoo.com*

More than 300 enzymes require zinc for their activity. Zn deficiency in humans is a significant worldwide problem (Prasad, 1998a; 1998b). It seems therefore that rapidly growing tumour tissue may increase the body's requirement for zinc and, when this is not supplied in the diet, lower the circulating level of the mineral (Atukorala et al., 1979).

Mg deficiency can paradoxically increase the risk of, or protect against oncogenesis. Over 300 enzymes that influence the metabolism of carbohydrate, amino acids, nucleic acids and protein, and ion transport, require Mg (Seelig, 2002).

Mn is an element essential for health in trace amounts, but toxic at higher exposures. Since manganese is replacing lead in gasoline globally, evaluation of potential cancer effects is essential (Spangler and Reid, 2009). There are a few reports in the literature examining the effects of excess oral exposure of humans to manganese. In addition, information regarding the carcinogenicity (ability to cause cancer) of manganese in humans or animals is not available.

Co is a natural element found throughout the environment. Acute exposure to high levels of cobalt by inhalation in humans and animals results in respiratory effects, such as a significant decrease in ventilatory function, congestion, edema, and hemmorhage of the lung (CPHS, 1992). It may thus be important to be specific about the chemical structure of the cobalt and confounding exposures.

Cu and Fe are redox-active transition metals and can participate in single electron reactions and catalyse formation of free radicals, including the undesirable hydroxyl radicals. Fe is a relatively abundant element in the universe. It is found in the sun and many types of stars in considerable quantity. Iron nuclei are very stable. Iron is a vital constituent of plant and animal life, and is the key component of haemoglobin (Casanueva and Viteri, 2003). High intracellular ferritin concentrations are thought to be a response to the increased iron load observed in these pathologies and can effectively suppress the intracellular iron and iron-mediated cell injury (Erbaycu et al., 2007).

The aim of this study was to investigate some mineral, trace element and heavy metal concentrations in lung cancer.

Materials and Methods

Biochemical Analysis

Subjects were recruited from patients attending the outpatient clinics and those hospitalised in the ward of the Thoracic Surgery Department of Yuzuncu Yil University Hospital. The study included a total of 50 subjects (30 lung cancer and 20 healthy human). The average age of cancer patients and 54 ± 8:29, 10 (33.3%) females, 20 (66.7%) patients were male. Control group of healthy individuals who constitute 5 (25%) women, 15 (75%)' u and female patients, mean age was set at 49 ± 8.16. Venous blood samples of lung cancer were obtained from the antecubital fossa veins the lung cancer in accordance with the guidelines set out in the Declaration of Helsinki. Consent was given by family members of all the patients included in this work. The study was approved by the local ethics committee. Serum was separated by centrifugation and the samples were processed immediately. The serum samples were placed in deionised polyethylenetubes and kept at 80 oC in a deep-freeze (without thawing) until the day of study.

Determination of serum concentrations of Cu, Zn, Mg, Mn, Pb, Co, Cd, and Fe was performed by Atomic Absorption Spectrophotometer measurements, in which a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK) was used.

Statistical Analysis

The results were expressed as the mean ± standard error (SE). One-way ANOVA was used for the comparison of mean values of the groups. Then, Student-*t* test was used to determine the difference between groups. In addition, Pearson's correlation analysis was carried out to determine the relationships among the variables. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were carried out using the SPSS® statistical software package (SPSS for Windows version 13.0, SPSS Inc., Chicago, Illinois, USA).

Results

The serum levels of Cu, Zn, Fe, Mn, Pb, Mg, Co, Cd of lung cancer and healthy human are shown in Table 1.

Mg level measured in lung cancer group were lower than the control group and this was statistically significant (P<0.01) (Figure 1). Serum Cu level was significantly lower with lung cancer compared to healthy human (P<0.01) (Figure 2). Pb level was significantly higher than those of controls (P<0.01) (Figure 3). The serum Zn level was significantly lower in serum of lung cancer group than

Table 1. Serum Levels of Cu, Zn, Fe, Mn, Co, Mg, Cd and Pb of the Lung Cancer and Healthy Groups

	Lung cancer				Control			
	Mean	St. Dev.	Min.	Max.	Mean	St. Dev.	Min.	Max.
Fe (μg/dI)	2.178	1.934	0.07	6.73	1.949	0.530	1.20	2.52
Mg (μg/dI)	15.621*	2.221	9.24	17.37	18.580	0.405	18.12	19.25
Cu (μg/dI)	0.977*	0.316	0.05	1.37	1.748	0.198	1.49	2.26
Mn (μg/dI)	0.090*	0.044	0.0150	0.145	0.003	0.002	0.0002	0.0075
Zn (μg/dI)	0.539*	0.225	0.2400	0.990	2.051	0.298	1.500	2.560
Co (μg/dI)	0.078*	0.053	0.009	0.202	0.033	0.016	0.012	0.054
Pb (μg/dI)	0.177*	0.047	0.096	0.243	0.034	0.028	0.005	0.075
Cd (μg/dI)	0.035	0.008	0.020	0.048	0.025	0.028	0.001	0.075

*: (p<0.01)

Table 2. Correlations Between Variables in Lung Cancer Group (r)

	Fe	Mg	Cu	Mn	Zn	Co	Pb	Cd
Fe (μg/dI)	1							
Mg (μg/dI)	-0.027	1						
Cu (μg/dI)	-0.093	0.317	1					
Mn (μg/dI)	0.446*(a)	-0.028	-0.021	1				
Zn (μg/dI)	-0.217	0.307	0.125	0.090	1			
Co (μg/dI)	-0.042	-0.470*(b)	0.060	0.094	-0.078	1		
Pb (μg/dI)	0.243	-0.105	0.326	0.439	0.128	-0.003	1	
Cd (μg/dI)	-0.122	0.013	0.378	0.172	0.018	0.130	0.496*(b)	1

*: p<0.05; a: positive correlation; b: negative correlation

Table 3. Correlation Between Variables in Healthy Group (r)

n =10	Fe	Mg	Cu	Mn	Zn	Co	Pb	Cd
Fe (μg/dI)	1							
Mg (μg/dI)	0.052	1						
Cu (μg/dI)	0.250	-0.075	1					
Mn (μg/dI)	0.008	0.048	0.046	1				
Zn (μg/dI)	0.045	0.338	0.127	0.368	1			
Co (μg/dI)	0.107	0.082	-0.389	-0.628	-0.684*(b)	1		
Pb (μg/dI)	-0.123	0.308	-0.175	0.552	0.253	-0.376	1	
Cd (μg/dI)	0.456	0.128	0.410	-0.096	0.389	-0.166	-0.130	1

*: p<0.05; a: positive correlation; b : negative correlation

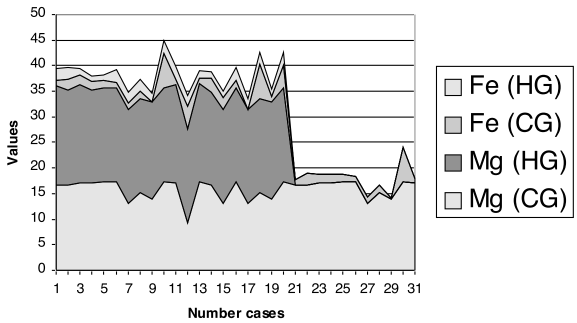

Figure 1. Fe and Mg Levels (Healty Group and Cancer Group)
*HG (Healthy Group); **CG (Cancer Group)

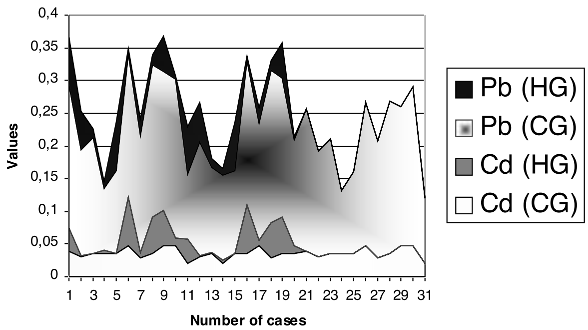

Figure 3. Pb and Cd Levels (Healty Group and Cancer Group)
*HG (Healthy Group); **CG (Cancer Group)

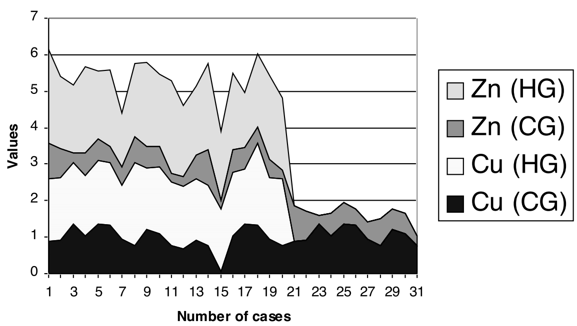

Figure 2. Zn and Cu Levels (Healty Group and Cancer Group)
*HG (Healthy Group); **CG (Cancer Group)

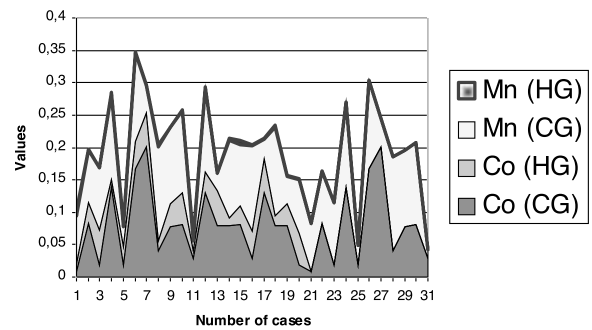

Figure 4. Mn and Co Levels (Healty Group and Cancer Group)
*HG (Healthy Group); **CG (Cancer Group)

controls (P<0.01) (Figure 2). Serum Mn and Co levels were found increased in lung cancer group than controls (P<0.01) (Figure 4). Cd value was higher in lung cancer but it was not statistically significant (p>0.01) (Figure 3). The mean concentration of Fe in the serum of lung cancer patients was higher than in the controls, but the difference was not significant (p>0.01) (Figure 1)(Table 1). There was a positive correlation between Cd and Pb level, and between Mn and Fe levels in lung cancer (Table 2). There was a negative correlation between Co and Mg levels of lung cancer (Table 2). There was a negative correlation between Co and Zn levels of healthy human (Table 3).

Discussion

Lung cancer is the most frequent cancer type around the world and a continuously growing health problem (Spiro and Porter, 2002). Lung cancers can arise in any part of the lung, but 90%-95% of cancers of the lung are thought to arise from the epithelial, or lining cells of the larger and smaller airways (bronchi and bronchioles); for this reason, lung cancers are sometimes called bronchogenic carcinomas or bronchogenic cancers (WHO, 2007). Carcinogenic elements may act as either genotoxic or epigenetic carcinogens (Stavrides, 2006; Huff et al., 2007; Navarro Silvera and Rohan, 2007). Metal containing dust from either polluted environments or cigarette smoke is a well-acknowledged risk factor for the development of cancer (Bradley and Golden, 2006; De Palma et al., 2008). Most studies have not given information on an number of relevant confounders by Cd. Physiological doses of Cd increase endothelial permeability by DNA damage-induced inhibition of endothelial proliferation and cell death induction, which is inhibited by zinc (Messner et al., 2009). Pb and Cd are established toxic and carcinogenic metals (Nawrot et al., 2002). The link between environmental cadmium exposure and lung cancer has been not explained by differences in age, sex, smoking, or occupational exposure to cadmium, therefore, there is less information about environmental exposure to cadmium. A doubling of soil cadmium has been linked with a 57% increased risk of lung cancer (Nawrot et al., 2006). Cd value was higher in lung cancer but it was not statistically significant (Table 1). Although (Cd) is an important and common environmental pollutant and has been linked to cancer diseases, it is little known about its effects in of lung cancer. The researchers conclude that environmental exposure to cadmium increases the risk of lung cancer. They warn that pollution that occurred in the past, and that may be continuing in some areas, continues to pose a health hazard. Level of Cd was similar to that reported in a previous study study (Nawrot et al., 2006). New research suggests that cadmium is one of the critical ingredients causing emphysema, and even low-level exposure attained through second-hand smoke and other means may also increase the chance of developing lung disease (WHO, 2007; Messner et al., 2009).

Literature data about Pb are more controversial. The element was found to be 1-2 orders of magnitude higher than controls in the lung tissue of exposed workers (Baumgardt et al., 1986), but an accumulation of pulmonary Pb in lung cancer patients has not been definitely demonstrated , as well as its relationship with tobacco smoke (Adachi et al., 1991).

Fe phyiological essential, but biochemically dangerous. Although Fe is an essential nutritional element for all life forms, it is known that excess Fe and Fe deficiency also lead to oxidative DNA damage (Ames, 2001). Also, it was proposed that low iron levels could play a role in the prevention of infection and cancer (Weinberg, 1990). The researchers report that risk of lung cancer increased with increasing iron and calcium uptake (both dietary and supplementary). In the bloodstream another multicopper ferroxidase, ceruloplasmin (Cp), oxidizes Fe (II) to Fe (III), thereby facilitating the loading of Fe (III) onto transferrin for delivery to peripheral organs via transferrin receptor-mediated endocytosis (Andrews, 2000; Hellman and Gitlin, 2002; Kaplan, 2002). The mean concentration of Fe in the serum of lung cancer patients was higher than in the controls, but the difference was not significant (Table 1). It has been reported that there is a statistically significant increase in serum Fe levels in patients with lung cancer compared with benign inflammatory lung disease. Level of Fe was similar to that reported in a previous study (Masiak and Herzyk, 1984).

Zn plays an important role in nucleic acid and protein synthesis and tumour growth is retarded in zinc deficient rats (Piccinini et al., 1996; Mahabir et al., 2006). Furthermore, zinc deficiency increased the lipid peroxidation in various rat tissues, whereas the zinc supplementation corrected the impairment (Shaheen and El-Fattah, 1995; Ozdemir and Inanc, 2006). Zn concentrations in the blood serum of Carcinoma planoepitheliale patients do not deviate from normal values, whereas those of carcinoma anaplasticum and adenocarcinoma subjects are significantly increased (Masiak and Herzyk, 1984). Several laboratory and human studies have found that high levels of supplemental zinc taken over extended periods of time may result in decreased copper absorption in the intestines and copper deficiency. However, some studies in humans suggest that high dietary zinc may not interfere with the actual tissue or plasma concentrations of copper (Araya et al., 2006). Serum zinc level (SZL) was measured in groups of lung cancer patients. In the present study, it was found that the level of serum Zn decreased in lung cancer patients (Table 1). Level of Zn was similar to that reported in a previous study (Atukorala et al., 1979). Decreased gastrointestinal absorption and tissue-specific absorption of Zn may be have contributory effects.

The effect of Mg on cancer produced by tumor transplants, or by chemicals, has depended on the time Mg supplementation or deficiency was induced, relative to exposure to oncogens (Collery et al., 1981). Optimal Mg intake may be prophylactic against initiation of some neoplasms. Since cancer cells have high metabolic requirements, it is not indicated (alone) in the treatment of cancer (Collery et al., 1981). It has recently been shown that Mg supplementation inhibited the increased DNA synthesis of the colon epithelium, excess proliferation of which had been chemically induced in rats; it was suggested that this effect might be related to Mg suppression of oncogen-induced large bowel carcinogenesis (Mori et al., 1992). In our study, serum Mg level decreased in lung cancer compared to controls (Table 1).

Mn is naturally ubiquitous in the environment. Manganese is essential for normal physiologic functioning in humans and animals, and exposure to low levels of manganese in the diet is considered to be nutritionally essential in humans. Chronic effects of Mn reported in humans from inhalation exposure to manganese are respiratory effects such as an increased incidence of cough, bronchitis, dyspnea during exercise, and an increased susceptibility to infectious lung disease. No studies are available regarding cancer in humans from oral exposure to manganese (CPHS, 1992). Serum Mn level was found higher lung cancer compared to controls in this study (Table 1).

Co is an essential element in humans, as a constituent of vitamin B12. Human studies are inconclusive regarding inhalation exposure to cobalt and cancer, and the one available oral study did not report a correlation between cobalt in the drinking water and cancer deaths (CPHS, 1992). Compared to the reference tissue material, Co and Se occur at increased concentrations, while Fe contents show decreased values in the tumor tissue. In the case of Au, Rb and Zn no significant changes are observed (Masiak and Herzyk, 1984). In one study on workers that refined and processed cobalt and sodium, an increase in deaths due to lung cancer has found for workers exposed only to cobalt (CPHS, 1992). Only one study investigated the effects of exposure to cobalt salts. The initial study reported an increased risk of lung cancer among cobalt production workers, but a follow-up study of the same workers found no increased risk of cancer (Moulin et al., 1998). Interpretation of this finding is limited by the small number of exposed workers who developed cancer. In the present study, it was found that the level of serum Co increased in lung cancer patients (Table 1). This finding agrees with that reported in our study (Masiak and Herzyk, 1984). In agreement with previous literature, we measured very low levels of Co and the element was not significantly higher in non small cell lung cancer (NSCLC) patients (Garcia et al., 2001).

Cu is a mineral found in trace amounts in all tissues in the body. Although only a small amount is needed, copper is an essential nutrient that plays a role in the production of hemoglobin, myelin, collagen, and melanin. In one clinical study that followed over 1,600 patients with lung cancer found that dietary zinc and copper intakes are associated with reduced risk of lung cancer (Araya et al., 2006). An increased mean serum copper level has been found in 149 patients with lung cancer when compared with 19 healthy people and 23 patients with non-malignant lung diseases (Huhti et al., 1980). Some studies have shown that increased serum Cu in tumour cells or lung epithelial lining fluid of individuals with lung cancer (Diez et al., 1989; Mahabir et al., 2006), but in the present study, it was found that the level of serum Cu decreased in lung cancer patients (Table 1). Our findings do, however, differ from those reported by Atukorala et al. It is confirmed that serum copper levels play an important role in indicating the stage of lung cancer development. Serum copper determinations importanable in assessing the clinical stage in lung cancer.

In conclusion, Zn may protective as potent lung cancer. It is suggested that low levels of zinc can induce the pathogenesis of lung cancer.

References

Adachi S, Takemoto K, Ohshima S, et al (1991). Metal concentrations in lung tissue of subjects suffering from lung cancer. *Int Arch Occup Environ Hlth*, **63**, 193-7.

Ames BN (2001). DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. *Mutat Res*, **475**, 7-20.

Andrews NC (2000). Iron homeostasis: Insights from genetics and animal models. *Nat Rev Genet*, **1**, 208-17.

Araya M, Pizarro F, Olivares M, et al (2006). Understanding copper homeostasis in humans and copper effects on health. *Biol Res*, **39**,183-7.

Atukorala S, Basu TK, Dickerson JW, et al (1979). Vıtamın A, zınc and lung cancer. *Br J Cancer*, **40**, 927-31.

Baumgardt B, Jackwerth E, Otto H, et al (1986). Trace analysis to determine heavy metal load in lung tissue. A contribution to substantiation of occupational hazards. *Int Arch Occup Environ Hlth*, **58**, 27-34.

Bradley TP, Golden AL (2006). Tobacco and carcinogens in the workplace. *Clin Occup Environ Med*, **5**, 117-37.

Casanueva E, Viteri FE (2003). Iron and oxidative stress in pregnancy. *J Nutr*, **133**, 1700-8.

Cavusoglu, K, Cakir AS, Kurtman Ç (2008). Radyoterapi gören akciger kanseri hastalarin plazma iz element duzeylerindeki degisimin belirlenmesi. *FU Sag Bil Derg*, **22**, 211-22.

Cobalt Public Health Service (1992). U.S. Department of health and human services, Atlanta, GA.

Collery P, Anghileri LJ, Coudoux P, et al (1981). Magnesium and cancer: clinical data. *Magnesium Bull*, **3**, 11-20.

De Palma G, Goldoni M, Catalani S, et al (2008). Metallic elements in pulmonary biopsies from lung cancer and control subjects. *Acta Biomed*, **1**, 43-51.

Dìez M, Cerdàn FJ, Arroyo M, et al (1989). Use of the copper/zinc ratio in the diagnosis of lung cancer. *Cancer*, **63**,726-30.

Erbaycu A, Uçar H, Gülpek M, et al (2007). The contribution of serum ferritin, iron, iron binding capacity and bronchoalveolar lavage ferritin levels in differential diagnosis of lung cancer from benign pulmonary diseases. *Int J Hematology Oncology*, **7**, 127-37.

Flanders WD, Lally CA, Zhu BP, et al (2003). Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: results from cancer prevention study ii1. *Cancer Res*, **63**, 6556-62.

Garcia F, Ortega A, Domingo JL, et al (2001). Accumulation of metals in autopsy tissues of subjects living in tarragona county, spain. *J Environ Sci Hlth A Tox Hazard Subst Environ Eng*, **36**, 1767-86.

Hellman NE, Gitlin JD (2002). Ceruloplasmin metabolism and function. *Annu Rev Nutr*, **22**, 439-58.

Huff J, Lunn RM, Waalkes MP, et al (2007). Cadmium-induced cancers in animals and in humans. *Int J Occup Environ Hlth*, **13**, 202-12.

Huhti E, Poukkula A,Uksila E (1980). Serum copper levels in patients with lung cancer. *Respiration*, **40**, 112-6.

Kaplan J (2002). Mechanisms of cellular iron acquisition: Another iron in the fire. *Cell*, **111**, 603-6.

Landrigan PJ (1989). Toxicity of lead at low dose. *Br Jn Ind Med*, **46**, 593-6.

Landrigan PJ (1990). Lead in the modem workplace. *Am J Public Hlth*, **80,** 907-8.

Mahabir S, Spitz MR, Barrera SL, et al (2006). Dietary zinc, copper and selenium, and risk of lung cancer. *Int J Cancer*, **120**, 1108-15.

Masiak M, Herzyk D (1984). Behaviour of microelements in lung cancer patients. *Fresenius J Analytical Chemistry*, **317**, 661-2.

Meller L, Tage S, Kristensen TS (1992). Blood lead as a cardiovascular risk factor. *Am J Epidemiol*, **136**, 1091-100.

Messner B, Knoflach M, Seubert A, et al (2009). Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. *Arterioscler Thromb Vasc Biol*, **29**, 1392-4.

Mori H, Morishita Y, Yoshimi N, et al (1992). Effect of magnesium hydroxide on methylazoxymethanol acetate-induced epithelial proliferation in the large bowels of rats. *Cancer Lett*, **62**, 43-8.

Moulin JJ, Wild P, Romazini S, et al (1998). Lung cancer risk in hard-metal workers. *Am J Epidemiol*, **148**, 241-8.

Navarro Silvera SA, Rohan TE (2007). Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes Control*, **18**, 7-27.

Nawrot TS, Thijs L, Den Hond EM, et al (2002). An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. *J Hum Hypertens*, **16**, 123-31.

Nawrot T, Plusquin M, Hogervorst J, et al (2006). Environmental exposure to cadmium and risk of cancer: a prospective population-based study. *Lancet Oncol*, **7**, 119-26.

Ozdemir G, Inanc F (2005). Zinc may protect remote ocular injury caused by intestinal ischemia reperfusion in rats. *Tohoku J Exp Med*, **206**, 247-51.

Piccinini L, Borella P, Bargellini A, et al (1996). A case-control study on selenium, zinc, and copper in plasma and hair of subjects affected by breast and lung cancer. *Biol Trace Elem Res*, **51**, 23-30.

Prasad AS (1998a). Zinc deficiency in humans: a neglected problem. *J Am Coll Nutr*, **17**, 542-3.

Prasad AS (1998b). Zinc in human health: an update. *J Trace Elem Exp Med*, **11**, 63-87.

Seelig MS (2002). Epidemiology of water magnesium evidence of contributions to health. The magnesium web site, http://www.mgwater.com/epidem.shtml.

Shaheen AA, El-Fattah AA (1995). Effect of dietary zinc on lipid peroxidation, glutathione, protein levels and superoxide dismutase activity in rat tissues. *Int J Biochem Cell Biol*, **27**, 89-95.

Spangler JG, Reid JC (2009). Environmental manganese and cancer mortality rates by county in north carolina: an ecological study. *Biol Trace Elem Res*, **1**, 8415-9.

Spiro SG, Porter JC (2002). Lung cancer-where are we today? Current advances in staging and nonsurgical treatment. *Am J Respir Crit Care Med*, **166**, 1166-96.

Stavrides JC (2006). Lung carcinogenesis: pivotal role of metals in tobacco smoke. *Free Radic Biol Med*, **41**, 1017-30.

Weinberg ED (1990). Cellular iron metabolism in health and disease. *Drug Metab Rev*, **22**, 531-9.

WHO (2007). Cancer world health organizasion.