Cigarette smoking effects on serum cadmium levels in lung cancer patients

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Abstract

Objectives: The objective of this clinical study was to evaluate the effect of smoking on serum cadmium levels and establish its relation to the development of lung cancer in the Syrian population.
Methods: Three groups were included in the study, comprising of lung cancer patients (n=40) with prior history of smoking, healthy smokers (n=23) and healthy nonsmokers (n=23). Graphite furnace atomic absorption spectrometry was used to detect the cadmium levels in serum. ANOVA test was used for comparison of serum cadmium levels between the groups.
Results: The mean smoking history was 36.6 and 34.8 years in lung cancer patients and healthy smokers respectively. Cadmium levels were higher in lung cancer patients (4.80±5.0 μg/L) compared to healthy smokers (2.06±1.04 μg/L) and healthy nonsmokers (0.87±0.43 μg/L). The difference in cadmium levels between all the groups was statistically significant ($p<0.05$).
Conclusions: Serum levels of cadmium were higher in smokers compared to non-smokers in this study, which supports the evidence that smoking is major source of cadmium exposure. In addition, the significantly higher level of cadmium in lung cancer patients with substantial smoking history is suggestive of its role in carcinogenesis.

Introduction

Heavy metals like chromium, arsenic, cadmium, lead, mercury, and manganese are present in the environment (1). Human beings are exposed to heavy metals produced by agriculture, manufacturing, pharmaceutical and mining industries via food, water, air and absorption through skin. (2). Small amount of these metals are present in the human body as trace elements and is essential for good health. However, exposure to larger amounts of these metals in environment is known to cause toxic effects in various vital organs (2). Chronic exposure of human beings to these heavy metals is also identified as a potential risk for development of malignancy.

Environmental carcinogens are one of the major causes of malignancy in humans. Among the environmental carcinogens identified, metals or metal containing compounds contribute majorly to tumorigenesis (3). EU has classified metals like arsenic, beryllium, cadmium, cobalt, chromium, nickel as carcinogen under risk categories R45 (may cause cancer) and R49 (may cause cancer by inhalation) (4). These metals, except chromium are weak mutagens, and their mechanism of carcinogenicity is unclear (5).

In 1980, cadmium and cadmium compounds were listed as anticipated human carcinogens in the first annual report on carcinogens, based on experimental animal studies. In 2000, in the revised listing, cadmium was listed as a known human carcinogen in the ninth annual report on carcinogens, based on epidemiological and mechanistic studies in humans (6). The International Agency for Research on Cancer (IARC) has also classified cadmium and its compounds as a group 1-carcinogen based on the results of epidemiological studies. The United States Environmental Protection Agency (EPA), American Conference of Industrial Hygienists (ACGIH) and National toxicology program (NTP) have also identified the role of cadmium as a potential carcinogen (7).

Cadmium is found in the earth`s crust usually in combinations with other elements (7). It is obtained as a by-product from smelting zinc, lead or copper ores. Cadmium is used for metal plating, and manufacturing of pigments, batteries and plastics. Exposure is usually through food, especially shellfish, liver and kidney meats. It is also found in soil as cadmium is present in fertilizers used for agriculture. (6)

Cadmium when absorbed in the respiratory system is known to cause damage to lungs, when absorbed through the gastrointestinal system it causes irritation leading to vomiting and diarrhea. Cadmium affects the respiratory system in human and animals by producing oxidative damage like other metal agents. In animals and humans, acute exposure to cadmium via inhalation destroys the epithelial cells of the lungs, which eventually results in pulmonary edema, tracheobronchitis and pneumonitis. Long term exposure to cadmium results in lung damage by causing decreased lung function and emphysema (6). The human body does not have an effective pathway to eliminate cadmium from the body, which leads to excessive accumulation in the body. Cadmium is primarily excreted by the kidneys. The excretion rate of cadmium is low as it remains tightly bound to metallothionein, which is reabsorbed in renal tubules. As a result of its extended biological half-life (6 to 38 years in kidney) (7) long term exposure to cadmium is known to cause kidney damage. Results from animal studies show that cadmium exposure can also lead to hypertension, liver disease, reduced iron levels in blood, and damage to brain (8).

The carcinogenic mechanism of Cadmium is not clearly understood. Few studies conducted illustrate that non-genotoxic cadmium act via epigenetic mechanism (9). Cell proliferation due to induction of reactive oxygen species (ROS) and alteration of DNA methylation seem to be responsible for the process of carcinogenesis (10). Prolonged exposure to cadmium disrupts the DNA methylation and enhances DNA Methyl transferase activity (11). This leads to the generation of abnormal or misfolded-proteins, mutagenesis, changed cell signaling and apoptosis. Another mechanism responsible for cadmium carcinogenesis is thought to be through translational machinery pathways. Cadmium is shown to induce the over expression of the cellular proto-oncogene eEF1A2.Aberrant regulation of the expression of the translational control proteins (eIF3 and eEF1δ) is known to induce transformation and tumoriogenesis (12).

Cadmium is also found in tobacco plants as they have a tendency to accumulate cadmium from fertilizers present in soil. Additionally, cigarette smoking is another source of cadmium exposure. Compared to nonsmokers, smokers have twice the amount of cadmium in their body. It has been estimated that tobacco smokers are exposed to 1.7µg cadmium per cigarette, about 10% is inhaled while smoking cigarettes. Absorption of cadmium is dependent on the size of the particle and the water solubility. Almost 50% of the cadmium inhaled via cigarette smoke can be absorbed through lungs into systemic circulation as cadmium particles in smoke are very small (6). Cadmium levels in the body can be detected in blood, urine, hair, or nail. Blood cadmium reflects recent exposures to cadmium. Urinary cadmium reflects the total body burden of cadmium, however when renal damage occurs it leads to increased excretion rate, which makes urinary cadmium level an inaccurate reflection of body burden (7). The national geometric mean serum cadmium level for adults is 0.47µg/L. Geometric mean serum cadmium levels for smokers was reportedly three times (1.58µg/L) the normal cadmium level (6).

Epidemiologic studies conducted during 1950s have demonstrated carcinogenic effects of tobacco smoke on lungs, which is also recognized by public health and regulatory agencies since mid-1960s. Geographical and temporal patterns of tobacco consumption is reflected in lung cancer due to tobacco smoking, which is the major cause of lung cancer in most of the human population. Risk of lung cancer due to tobacco smoking is dependent on average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern (13).

Tobacco smoking in various forms in various regions is associated with lung cancer. In western countries smoking cigars, cigarillos and pine, Europe: cigarettes, cigars and pipe, India: bidis, and China: water pipes are associated with lung cancer (13). In Syrian Arab republic health profile by WHO in 2006, it was observed that 42.9 % males were tobacco smokers which was higher than the Eastern Mediterranean region (32.0%) (14). To assess the effect of tobacco smoking and its relation to lung cancer in Syrian region, we evaluated cadmium levels in lung cancer patients with history of smoking in the present study. Similarly cadmium levels for healthy smokers and non-smokers were also evaluated. The study is designed to establish a correlation between smoking, cadmium and lung cancer in the Syrian population.

Material and Methods

Study population: This was a cross-sectional, observation study designed to compare the levels of cadmium between lung cancer patients, healthy smokers and healthy nonsmokers conducted at the Bairouni university hospital between February 2010 and March 2011. The lung cancer patients, healthy smokers and healthy nonsmokers were included in the study based on their willingness to participate. All patients and volunteers were from in and around the city of Damascus belonging to the same race. Patients with lung cancer of different histology from Bairouni university hospital were considered for serum sampling. Appropriate sampling techniques were employed to ensure inclusion of volunteers from across the city population.

The study was approved by the ethics committee at Damascus university and informed consent was obtained from the patients and volunteers prior to participation in the study. Vital information including age, gender and years of smoking were collected from all patients and volunteers after they provided written informed consent. Additional information on the type of lung cancer was collected for patients. Random blood samples were collected for the assessment of cadmium without any prior preparation. Every patient and volunteer who participated in the study provided blood which was drawn from the antecubital vein. Whole blood samples collected in ethylenediaminetetraacetic acid (EDTA) dry tubes were allowed to clot for 30 minutes, and then centrifuged at speed 3000 rpm for 10 minutes. Serum was extracted and stored till test day. All samples were analyzed at the Damascus university laboratory and Bairouni University Hospital Laboratories.

Blood Cadmium Analysis: To determine the level of cadmium in the serum, Perkin Elmer Graphite Furnace Atomic Absorption Spectrometry (GFAAS) was used. The blood samples were diluted in a 1:20 ratio with matrix modifier (0.2% nitric acid, 0.5% Triton X-100, and 0.2% ammonium phosphate) which was mixed with the equal volume of (0.2% ammonum phosphate, 1% Ammonium pyrrolidine dithiocarbanate, 1ml Hcl, methyl isobutyl ketone) solution. The floating organic phases were transferred into pyrolytic-coated partitioned tubes. Cadmium quantification was based on the measurement of light absorbed at 228.8 nm. The operating parameters for working elements in the spectrometer were set as recommended by the manufacturer.

Statistical analysis: The study had no pre-specified sample size calculation as there was no hypothesis testing involved in the study. The statistical analysis was performed using SPSS 19 software. Statistical analysis was performed after all patients had completed the study participation. Descriptive analysis was used; continuous data were summarized by mean, standard deviation, median and range. Categorical data were displayed as counts and percentage.

To evaluate the level of cadmium in serum, mean and standard deviation were calculated. ANOVA test was performed to analyze the difference in cadmium blood concentration between the 3 groups. Least significant difference (LSD) test was performed to compare the statistical difference between the groups.

Results

Study Population

The study enrolled 40 lung cancer patients with prior history of smoking cigarettes from Bairouni hospital between February 2010 and March 2011. Healthy volunteers including 23 smokers and 23 nonsmokers from Damascus city were also enrolled in the study. Lung cancer patient with a mean age of 59±11.8 years were comparatively elder to healthy smokers and nonsmokers (Table 1). Mean years of smoking in lung cancer group was 36.6 years compared to 34.8

years in healthy smoker group. Majority of patients in both the groups smoked 20 cigarettes per day (23 in lung cancer patients and 12 in healthy smokers). All three groups in the study were comparable with similar demographic features.

The lung cancer patients were classified based on the histology, staging and the performance status measured by ECOG scale (Table 2). Majority of patients were with stage IV squamous cell carcinoma or adenoacrcinoma and performance status of 2 and 3 on ECOG scale.

Cadmium in the Serum

The cadmium level as assessed by GFAAS, in patients with lung cancer was 4.8±5 μg/L, which was higher than healthy smokers (2.06±1.04 μg/L) and healthy nonsmokers (0.87±0.43 μg/L). The highest blood level of cadmium was 28.64 μg/L, 6.24 μg/L and 1.82 μg/L in lung cancer patients, healthy smokers and healthy nonsmokers respectively (Table 3). ANOVA test performed between the 3 groups demonstrated significant difference (<0.05). Further LSD test was used for the analysis between the groups. There was a statistically significant difference in the mean serum cadmium level between lung cancer patients and healthy smokers (p=0.005), lung cancer patients and healthy nonsmokers (p=0.0001) and between healthy nonsmokers and smokers (p=0.0001), as presented in Table 3.

Discussion

The objective of this study was to evaluate the effects of cigarette smoking on serum cadmium levels between lung cancer patients, healthy smokers and healthy nonsmokers. It is known that smoking cigarettes increases the serum cadmium levels (15). Similarly, in present study, serum cadmium levels were higher in healthy smokers compared to healthy nonsmokers. We observed that, compared to healthy nonsmokers, serum cadmium levels were higher in lung cancer patients, which is similar to studies conducted in past. (15, 16, 17). Difference in level of serum cadmium between smokers and nonsmokers was observed in different regions which is comparable to present study as in Syria (smokers 4.8 μg/L vs nonsmokers 0.87μg/L), Italy (3.1 μg/L vs 1.6 μg/L) (18), and China (2.61 μg/L vs 0.94 μg/L) (19). This difference could be due to ethnic difference or the type and amount of tobacco in cigarettes (16). These higher cadmium levels could be attributed solely to cadmium inhaled from cigarettes, as cadmium levels in healthy nonsmokers are below 1 μg/g (0.87 μg/g) which is within the normal range. Hence, no other factors seem to be responsible for higher cadmium levels apart from smoking. One of the known risk factors for lung cancer is smoking and cigarette smoke constitutes approximately 70% of total cadmium present in cigarette (16). Previous study reported 3 fold (20) increase of cadmium accumulation in alveolar macrophages for smokers compared with that for nonsmokers, while another study reported seven fold increase (23). If the amount of tobacco present in cadmium is removed; risk of lung cancer due to cigarette smoking will be reduced by 10% (21). Epidemiological studies estimated that 0.2% to 1.6% smoking induced lung cancer deaths can be attributed to cadmium inhaled via cigarette smoke. However, according to rodent data 13% to 47% of smoking induced deaths could be due to cadmium (22). The present study reported similar observations, where serum cadmium levels in patients with lung cancer were higher than healthy smokers and nonsmokers and are comparable to another study conducted in Pakistan where the lung cancer patients who continued smoking had 34.2 to 67.2% increase in cadmium levels than lung cancer patients who stopped smoking. (17). These observations were also supported by a study which reported that inhaled cadmium caused up to 9% of lung cancer in humans and could be >40% in animals (20). There were certain limitations in the study, low sample size being one of them. Due to low sample size it was difficult to establish a correlation between years of smoking and serum cadmium levels. IARC has evaluated presence of 55 carcinogens in cigarette smoke with carcinogenicity evidence in laboratory animals or humans; these were not considered while evaluating the relationship between serum cadmium levels and smoking. Data was not collected for other factors known to influence serum cadmium levels like diet, presence of manufacturing unit in the vicinity etc.

In conclusion, high serum levels of cadmium in smokers compared to nonsmokers in this study further supports evidence that smoking is major source of cadmium exposure. In addition, the significantly higher level of cadmium in lung cancer patients with substantial smoking history is suggestive of its role in carcinogenesis.

Tables

Table 1: Age and years of smoking

Groups	Lung Cancer	Healthy Smoker	Healthy Nonsmoker
N	40	23	23
Age (years)			
Mean±SD	59.5±11.8	54.0-13.9	55.2-14.6
Range	31-80	26-77	25-80
Years of Smoking			
Mean±SD	36.6±12.02	34.82±12.64	NA
Range	12-60	10-65	NA
Cigarettes/ day			
0-20	23	12	NA
20-40	8	8	NA
40-60	7	3	NA
60-80	2	0	NA

Table 2: Cancer grading and classification

Histology	Staging	ECOG Performance Status	Number n (%)
Squamous Cell Carcinoma (SCC)	IV	3	10 (25)
Squamous Cell Carcinoma (SCC)	IIIb	2	7 (17.5)
Squamous Cell Carcinoma (SCC)	IIIA	2	3 (7.5)
Adenocarcinoma (ADK)	IV	3	9 (22.5)
Adenocarcinoma (ADK)	IIIA	2	1 (2.5)
Adenocarcinoma (ADK)	IIB	2	3 (7.5)
Small Cell Lung Cancer (SCLC)	Localized	2	5 (12.5)
Small Cell Lung Cancer (SCLC)	IV	2	2 (5)
Total			40 (100)

Table 3: Cancer grading and classification

Group (I)	Serum Cadmium (µg/L)		LSD test between groups			
	(mean±SD)	(Range)	Group (J)	MD(I)-MD(J)	SD	P-value
Lung Cancer	4.8±5	1.63-28.64	**Healthy Smokers**	2.75	0.82	0.005
Healthy Smokers	2.06±1.04	1.08-6.24	**Healthy Nonsmokers**	1.18	0.23	0.0001
Healthy Nonsmokers	0.87±0.43	0.02-1.82	**Lung Cancer**	3.93	0.80	0.0001

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