

Human lung cancer and hexavalent chromium exposure

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Submitted: 2009-07-21 Accepted: 2009-09-01 Published online: 2009-10-20

Key words: lung cancer types; chromium exposure; survival; onset age

Neuroendocrinol Lett 2009; 30(Suppl 1): 182-185 PMID:20027168 NEL300709A31 ©2009NeuroendocrinologyLetters • www.nel.edu

Abstract

OBJECTIVE: Workers chronically exposed to hexavalent chromium have higher incidence of lung cancer. Our study investigates incidence of lung cancer types, age at onset of the disease and survival time among chromium exposed workers (smelters, tapers, crane operators) in comparison to non-exposed persons.

METHODS: 64 chromium exposed workers and 104 male controls with diagnosed lung cancer were analysed. The average exposure time among workers was 16.71 ± 10.02 (S.D.) years (range 1- 41 years).

RESULTS: Chromium exposure significantly decreases the age at the onset of the disease by 3.51 years (62.20 ± 9.08 years in exposed group and 65.71 ± 10.50 years in control; $P=0.018$). Small cell lung carcinoma (SCLC) forms 25.0 % of all cases in chromium exposed workers and 16.34% in non exposed individuals. No correlation was found between the age at the diseases onset and time of exposure. The mean survival time in exposed group was 9.03 ± 12.73 month, in control 12.14 ± 21.94 month, but this difference was not significant ($P=0.473$).

CONCLUSION: Occupational exposure to chromium was identified as an important risk factor of lung cancer, decreasing the age at the diseases onset. Higher percentage of SCLC was found in chromium exposed individuals.

INTRODUCTION

Lung cancer is the world's leading cause of cancer death. It is primarily due to the inhalation of carcinogens and high accessible to prevention by diminishing exposures to lung carcinogens.

Smelters are regularly exposed to higher levels of chromium at the workplace in comparison with the non-exposed individuals; respiratory tract being the major route of exposure. Based on "in vitro" and animal data as well as on epidemiological (Furst & Haro, 1969; Fraumeni, 1975; Maltoni, 1976; Ohsaki *et al.* 1978; Hill & Ferguson, 1979;

Davies et al, 1991; Wise *et al.* 2008) and cytogenetic studies in humans (IARC, 1990), IARC has classified hexavalent chromium as a carcinogen of the group I.

Entering cells, chromium induces formation of reactive intermediates, resulting in enhanced oxidative stress (Leonard *et al.* 2004). Oxidative stress caused by chromium and many other substances has cyto- and genotoxic effect (Halasova *et al.* 2001; Miadokova *et al.* 2006; Reiter *et al.* 2008; Horvathova *et al.* 2008). The reduction of Cr(VI) to Cr(V) is required for the induction of DNA damage and mutations (Quievryn *et al.* 2002). During Cr(VI) reduction, a diverse range of genetic lesions are generated including Cr-DNA binary (mono) adducts, Cr-DNA ternary adducts, DNA protein crosslinks, bi-functional (DNA interstrand crosslinks) adducts, single-strand breaks and oxidized bases. Some forms of Cr damage, such as DNA interstrand crosslinks, present physical barriers to DNA replication/transcription and, thus, likely promote a terminal cell fate such as apoptosis or terminal growth arrest. Other lesions, such as ternary DNA adducts, are potentially pre-mutagenic (O'Brien *et al.* 2003). Cr(VI) exposure elicits a classical DNA damage response within cells including activation of the p53 signaling pathway and cell cycle arrest or apoptosis (Ceryak *et al.* 2004; Bae *et al.* 2009).

Further information is needed regarding the potential involvement of oxygen radicals in chromium genotoxicity, the specific DNA repair pathways activated by chromium and the complex signaling mechanisms involved in the cellular response to Cr(VI). These pertinent issues must be considered in relation to the potential role that each plays in the induction of human respiratory tract cancer by particulate Cr(VI) compounds.

The present study is a logical continuation of our preceding studies in which increased chromosomal aberrations as well as higher incidence of lung cancer were found in workers directly exposed to chromium only, not in the group exposed to its environmental level (Halasova *et al.* 2001; Halasova *et al.* 2005).

Our present study is focused on investigation of incidence of lung cancer types, age at onset of the disease and survival time among chromium exposed workers (smelters, tapers, crane operators) in comparison to non-exposed persons.

SUBJECTS AND METHODS

Subjects and sampling. The data of the Department of Pathology of Dolny Kubin Hospital and of the Slovak National Cancer Register over 1985–2005 have been analyzed (278 men diagnosed for lung cancer).

To the present study were selected the cases with clear histopathological lung cancer types only (168 cases). According to chromium exposure two groups were formed. The first - exposed group consists of 64 formerly workers of works of reffochromium alloys with diagnosed lung cancer. The average time of exposure

was 16.71 ± 10.02 years. The control group contains 104 men with diagnosed lung cancer. These men have been never exposed nor to chromium neither any other known carcinogen.

Presented research was performed in accordance with requirements of the Ethical Commission for Research.

Exposure data. Chromium analysis in soil and air was made in the vicinity of the works. The samples were examined by atomic absorption spectrometry (Varian spectrophotometer AA 30 - P). The mean all-shift concentrations of total chromium in the air of the smelting plant were $0.03\text{--}0.19 \text{ mg m}^{-3}$, the values of hexavalent chromium were between $0.019\text{--}0.03 \text{ mg m}^{-3}$. The mean concentrations of total chromium in the air in the environment surrounding the works and in the control area ($0.0113 \text{ } \mu\text{g m}^{-3}$) did not reach the hygienic norm ($0.01\text{--}0.0117 \text{ } \mu\text{g m}^{-3}$). In the soil, in a distance of 200m from the works, the chromium content was 137 mg kg^{-1} , which is slightly exceeding the hygienic norm (100 mg kg^{-1}). The chromium content in the soil from wider distance and from the control area was below the hygienic norm (60.2 mg kg^{-1} and 46.0 mg kg^{-1} , respectively).

Statistical analysis. The found differences were tested by t-test using Program Instat.

RESULTS

The results of the age at the onset of the disease and survival time are present in **Table 1**. Chromium exposure significantly decreases the age at the onset of the disease by 3.51 years (62.20 ± 9.08 years in exposed group and 65.71 ± 10.50 years in control; $P=0.018$). No significant correlation between the age at the diseases onset and time of exposure was found ($P>0.05$). The mean survival time in exposed group was 9.03 ± 12.73 month, in control 12.14 ± 21.94 month, but this difference was not significant ($P=0.473$). More than 5 years survived 3 (1.72%) men only. The results of lung cancer types analysis are present in **Table 2**. Squamose cell lung carcinoma type seems to be the predominant type in both, control and exposed groups (62.52% and 53.12% respectively). Small cell lung carcinoma (SCLC) forms 25.00 % of all cases in chromium exposed workers and 16.32% in non exposed individuals. No correlation was found between the age at the diseases onset and time of exposure ($P>0.05$).

DISCUSSION

Lung cancer is currently the most common cause of cancer mortality in males worldwide. This is largely due to the effect of cigarette smoking as well as to exposure to other carcinogens. Our previous studies (Halasova *et al.* 2001; Halasova *et al.* 2005; Halasova *et al.* 2008) as well as many other epidemiological studies (Mosavi-Jarrahi *et al.* 2009; Zaebst *et al.* 2009; Zhou *et al.* 2009 ; Kerger *et al.* 2009; Wild *et al.* 2009; Bruske-Hohlfeld, 2009)

Table 1. Number of cases, mean age of onset of lung cancer and survival in different groups

Group	Number of cases	Age at onset (in years)	Range (in years)	P- value*	Survival (in month)	Range (in month)	P- value
Exposed	64	62.20 ± 9.08	39 - 82		9.03 ± 12.73	0.25 - 60	
Control	104	65.71 ± 10.50	43 - 87	0.018*	12.14 ± 21.94	0.5 - 210	0.473

*comparison between exposed and control by t-test

Table 2. Number and percentage of cases according to lung cancer type in different groups

	Exposed group		Control	
	No. of cases	Percentage	No. of cases	Percentage
Lung carcinoma type				
Squamous cell-epidermoid	34	53.12 %	65	62.52 %
Adenocarcinoma	9	14.06 %	14	13.53 %
Small cell/undifferentiated	16	25.00 %	17	16.32 %
Undifferentiated Large cell	5	7.81 %	8	7.71 %

showed that workers in ferrochromium industry have an excess risk for chromosomal injury and lung cancer and decreases the age at diseases onset. However, related information of chromium exposure influence on age at diseases onset in the literature is missing. Our presented findings have confirmed our previous results (Halasova *et al.* 2005) based on data from years 1985-2000, that chromium exposure decreases the age at diseases onset by 3.15 years in comparison with lung cancer patients without chromium exposure. Many researchers dealing with the age at diseases onset pointed their studies on genetic predispositions and concluded that genetic constitution can play an important role (Yang *et al.* 1999; Etzel *et al.* 2003; Schwartz, 2004; Bailey-Wilson *et al.* 2004; Matakidou *et al.* 2005; Xu *et al.* 2005) and appearance of lung cancer in first-degree relatives can increase the risk of early onset lung cancer 5 times (Cassidy *et al.* 2009; Ahn & Kang, 2009).

Analysing the portion of different lung cancer types we found some differences in comparison to published data. Travis *et al.* (1999) and Brambilla *et al.* (2001) presented, that adenocarcinoma is the predominant histological subtype of lung carcinoma in many countries.

In our study, squamous cell lung carcinoma type seems to be the predominant type in both, control and exposed groups (62.52% and 53.12%, respectively). Small cell lung carcinoma forms 25.00% of all cases in chromium exposed workers and 16.32% in non exposed individuals. Similar founding was published by Kavcova *et al.* (2006), where the spinocellular type of lung cancer was predominant and 25.00% of patient had small cell lung cancer.

Etzel *et al.* (2006) analysed 230 early onset lung cancer (EOLC) and 426 later-onset cases (LOLC). In their study, adenocarcinoma was the most common histological type (55.2%) among the EOLC cases. Median

survival was 16.7 months among the EOLC cases (19.2 months for the LOLC cases) and the 24-month survival rate was 20.6% for the EOLC cases and 29.5% for the LOLC cases.

Our findings did not showed significant difference between observed groups in the median survival. This parameter was poor in control and exposed group as well (9.03 ± 12.73 and 12.14 ± 21.94 month, respectively). More than 5 years surviving was found in 3 (1.72%) men only.

These findings support the need for further study in the characterisation and identification of genetic factors that influence and modulate the lung cancer risk and outcome with respect to smoking aspect as well.

Acknowledgements

This work was supported by Ministry of Health of the Slovak Republic, Grant No. 2007/48-UK-13.

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