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Blood cadmium levels as a marker for early lung cancer detection

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ABSTRACT

Background: We assessed whether blood cadmium levels were associated with incident lung cancer and could be used in the context of a screening program for early-stage lung cancer.
Material and methods: We measured blood cadmium levels among 205 lung cancer patients and 205 matched controls. Cases and controls were matched for sex, age and smoking history (total pack-years, years since cessation for former smokers).
Results: The odds ratio for those in the highest quartile of cadmium level (versus lowest) was four-fold (OR = 4.41, 95 % CI:2.01–9.67, $p < 0.01$). The association was present in former smokers (OR = 16.8, 95 % CI:3.96−71.2, $p < 0.01$), but not in current smokers (OR = 1.23, 95 % CI: 0.34–4.38) or in never smokers (OR not defined). Among former smokers, the association was present in both early- and late-stage lung cancer.
Conclusion: Blood cadmium levels may be a marker to help with the early detection of lung cancer among former smokers.

1. Introduction

The major factor responsible for lung cancer in Poland and around the world is cigarette smoking, but not all lung cancer patients have a history of smoking. The risk of lung cancer persists after smoking cessation. As the prevalence of smoking declines in many countries, the proportion of lung cancer cases that occur among non-smokers and ex-smokers is increasing [1,2].

Cadmium is classified as a group I carcinogen by IARC (International Agency for Research on Cancer) and has been associated with lung cancer [3,4]. Several environmental and occupational lung carcinogens have been identified, such as radon and heavy metals, including cadmium [5]. Epidemiological data have consistently pointed to cadmium as a risk factor for lung cancer [6–8]. An association between

Abbreviations: IARC, International Agency for Research on Cancer; ICP-MS, - Inductively Coupled Plasma Mass Spectrometry; CI, confidence interval; OR, odds ratio; CT, computed tomography; cfDNA, cell-free tumor DNA; hTERT, human telomerase reverse transcription gene; cfRNA, cell-free tumor RNA; TEP, tumor-educated platelets; CTCs, circulating tumor cells; MS-PCR, methylation-specific PCR.

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occupational exposure to cadmium and lung cancer has been reported among non-smokers [8]. Cadmium is used in many industrial processes, including the manufacturing of nickel cadmium batteries, solar cells, electroplating and silver soldering [9].

Cadmium is also present in water and food [10]. Sources of dietary cadmium include cereals, leafy vegetables and potatoes [11,12]. Spinach, offal and tofu contain high levels of cadmium [13]. Smoking is the major source of cadmium exposure among smokers [14].

Cadmium can directly damage DNA [15] and inhibit its repair [16] and may affect methylation [17,18]. Cadmium induces cancer through several mechanisms, including aberrant gene expression, inhibition of DNA damage repair, induction of oxidative stress and inhibition of apoptosis [19].

Our goal was to assess whether blood cadmium levels were associated with lung cancer occurrence in smokers and in non-smokers. If so, then blood cadmium could be a potential biomarker to select candidates for the early detection of lung cancer. Individuals with high cadmium levels might be good candidates for lung cancer screening.

2. Materials and methods

2.1. Study subjects

We conducted a case-control study of 205 patients with lung cancer and 205 controls. Cases were approached to participate in the research study during an outpatient visit to the Department of Thoracic Surgery in the Szczecin-Zdunowo Hospital between 2012 and 2017. In all cases, lung cancer was confirmed by histopathological examination.

For each lung cancer patient, we selected one unaffected individual who had agreed to participate in a research study at the International Hereditary Cancer Center, Pomeranian Medical University of Szczecin. Controls had no history of lung cancer or any other cancer. Control subjects were part of a population-based study of the 1.3 million inhabitants of Poland designed to identify familial aggregations of cancer. Cases and controls were matched for year of birth (± 4 years), sex, smoking status (pack-years ± 20 %) and (for non-smokers) years since smoking cessation (±4 years). The majority of cases and controls were residents of the west Pomeranian region in Poland. Blood samples for measuring cadmium level among the control group were taken from 2002 to 2016.

Blood samples were taken from patients at the time of diagnosis but before treatment and stored at −80 °C. All subjects were requested to fast for six hours before blood sample collection.

The study was conducted in accordance with the Helsinki Declaration and with the consent of the Ethics Committee of Pomeranian Medical University in Szczecin under the number KB-0012/73/10.

The characteristics of the individuals included in the study are shown in the Table 1.

Table 1
Characteristics of individuals for lung cancer study.

Characteristics	Cases (n = 205)	Controls (n = 205)
Birth year range	1930–1966	1931–1968
Age at sample, mean (range, years)	63.5 (47–81)	62.2 (42–82)
Sex		
Male	151	151
Female	54	54
Packyears, mean (range)	33.6 (3–135)	30.8 (2.5–100)
Years after cessation of smoking, mean (range) (former smokers)	8.28 (1–31)	8.55 (1–30)
Smoking status		
Current smokers	106	106
Former smokers	86	86
Never smokers	13	13
Stage		
I	69	–
IA	36	–
IA1	4	–
IA2	17	–
IA3	15	–
IB	33	–
II	36	–
IIA	16	–
IIB	20	–
III	79	–
IIIA	43	–
IIIB	31	–
IIIC	5	–
IV	14	–
IVA	10	–
IVB	4	–
Missing	7	–
Histology		
Adenocarcinoma	86	–
Squamous cell carcinoma	75	–
Large cell carcinoma	10	–
Combined large cell – small cell carcinoma	2	–
Small cell carcinoma	12	–
Other	20	–

2.2. Measurement of cadmium level

Total Cadmium (Cd) concentration in blood samples was measured by inductively coupled plasma mass spectroscopy (ICP-MS) technique using Elan DRC-e (PerkinElmer, USA) instrument. To achieve the maximum sensitivity for blood cadmium concentrations in blood of non-occupationally exposed population the isotope ^{114}Cd was selected for quantification. ^{114}Cd in low concentration suffers for spectral interference of $^{98}Mo^{16}O^{+}$, $^{96}Mo^{18}O^{+}$ or $^{97}Mo^{16}OH^{+}$ and isobaric overlap of ^{118}Sn. To remove the $^{98}Mo^{16}O^{+}$, $^{96}Mo^{18}O^{+}$ and $^{97}Mo^{16}OH$ from ^{114}Cd signal, analysis was performed in DRC (Dynamic Reaction Cell) mode with oxygen (O_2, purity >0,9999) as a reaction gas. Under these conditions, non-interfering molybdenum dioxides are formed. To avoid overlap of tin isotope (^{118}Sn) a standard mathematical correction was set (^{114}Cd – 0,027250 * ^{118}Sn). To compensate instrument drift and matrix effects rhodium was set as internal standard.

Blank reagent consisted of high purity water (>18 MΩ), TMAH (AlfaAesar), Triton X-100 (PerkinElemer), n-butanol (Merck) and disodium EDTA (Sigma Aldrich).

Calibration curve standards (0,1; 0,2; 0,5 μg/L) were prepared by diluting stock solution (50 μg/L) of 10 mg/L Multi-element Calibration Standard 3 (PerkinElmer Pure Plus, USA) with Blank Reagent. External calibration method was used. Correlation coefficient for Cd calibration curve was always greater than 0,999.

Accuracy and precision of method were validated using three different certified reference material – NIST 955c (NIST, USA), BCR 634 (Sigma Aldrich) and Plasmonorm Whole Blood Level 1 (Clincheck, Germany).

2.3. Statistical analysis

Study participants were assigned to one of three categories according to smoking status: current, former and never. We established the range of cadmium levels in the controls and based on these, we established cut-off levels for quartiles. The quartiles were determined using controls only and included both non-smokers and smokers. We considered the bottom quartile of cadmium levels to be the reference group and used this category in all analyses.

The association of cadmium level and lung cancer occurrence was estimated with odds ratios (OR) and 95 % confidence intervals using univariable conditional logistic regression for matched pairs. We estimated odds ratios for lung cancer and cadmium, according to three quartiles, using the lowest quartile as the reference. We generated odds ratios for all subjects and then separately for smokers, former smokers and never smokers. We also generated odds ratios according to lung

cancer stage.

3. Results

Among the 205 controls, the mean blood cadmium level was 1.17 μg/L (range 0.14 μg/L to 6.96 μg/L). The mean level was 1.66 μg/L for current smokers (range 0.32 μg/L to 6.96 μg/L) and 0.68 μg/L for former smokers (range 0.17 μg/L to 3.61 μg/L) and 0.51 μg/L for never smokers (range 0.14 μg/L to 1.49 μg/L).

Among all cases, the mean blood cadmium level was 1.47 μg/L (range 0.17 μg/L to 9.33 μg/L). The mean level was 1.93 μg/L for current smokers (range 0.27 μg/L to 9.33 μg/L) and 1.06 μg/L for former smokers (range 0.24 μg/L to 4.61 μg/L) and 0.52 μg/L for never smokers (range 0.17 μg/L to 1.15 μg/L).

In the overall analysis (including all 205 lung cancer cases and paired controls) there was a positive significant association with blood cadmium levels and lung cancer (Table 2). The odds ratio for those within the highest cadmium quartile, compared to the baseline quartile was 4.41 (95 % CI 2.01−9.67); the odds ratio was 2.83 (95 % CI 1.30−6.16) for the third quartile compared to the baseline quartile and the odds ratio was 2.13 (95 % CI 1.09−4.19) for the second quartile compared to the baseline quartile.

We further analyzed the data according to smoking status (current, former and never smoker). We did not see an association with blood cadmium among current smokers (Table 3). In contrast, the association was very strong among former smokers (Table 4). Among former smokers, the odds ratios for those with the highest cadmium levels, compared to the baseline level was 16.8 (95 % CI 3.96−71.2) for quartile IV, 6.55 (95 % CI 1.86−23.0) for quartile III and 3.94 (95 % CI 1.45−10.7) for quartile II.

Among those cases who had quit smoking more than five years ago (and the matched controls), the odds ratio for those with a cadmium level in the highest quartile, compared to the baseline quartile was 6.75 (95 % CI 0.59–362, $p = 0.14$). Among those cases who had quit smoking in the past five years (and the matched controls), the odds ratios for those with the highest cadmium levels, compared to the baseline level was 13.6 (95 % CI 2.29–115, $p < 0.01$).

No association between blood cadmium level and lung cancer was observed in the subgroup of never smokers (Table 5), but the numbers were very small.

For those with patients with stage I-II lung cancer, the association between blood cadmium levels and lung cancer in former smokers the OR was 50.8 (95 % CI 3.60–718) for quartile IV and was 9.06 (95 % CI 1.15–71.6) for quartile III (Table 6).

For patients with stage III-IV lung cancer the OR was 7.43 (95 % CI 1.21–45.4) for quartile IV and was 5.58 (95 % CI 1.08–28.9) for quartile III (Table 7).

The association between blood cadmium and lung cancer occurrence among former smokers could not be accounted for by a difference in the cumulative exposure to cigarettes; among former smokers with and without lung cancer, the number of pack years was similar (Table 8).

4. Discussion and conclusion

We found a strong and significant association between blood cadmium level and a recent diagnosis of lung cancer. The blood samples in the cases were taken shortly after diagnosis but before chemotherapy. Our study suggests that blood cadmium level may be a marker of lung cancer occurrence and may be informative in selecting individuals who might benefit from surveillance for early detection of lung cancer.

In this study the association was limited to former smokers. It is unclear why cadmium levels do not predict lung cancer risk in those who

Table 2
Blood cadmium levels and the occurrence of lung cancer (all patients).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	27	48	1.00	–
II	0.46−0.92	53	54	**2.13 (1.09−4.19)**	**0.03**
III	0.93−1.36	49	51	**2.83 (1.30−6.16)**	**<0.01**
IV	1.37−9.33	76	52	**4.41 (2.01−9.67)**	**<0.01**

Table 3
Blood cadmium levels and the occurrence of lung cancer (current smokers).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	5	5	1.00	–
II	0.46−0.92	12	16	0.69 (0.17−2.87)	0.62
III	0.93−1.36	31	39	0.78 (0.21−2.93)	0.71
IV	1.37−9.33	58	46	1.23 (0.34−4.38)	0.75

Table 4
Blood cadmium levels and the occurrence of lung cancer (former smokers).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	16	36	1.00	–
II	0.46−0.92	35	33	**3.94 (1.45−10.7)**	**<0.01**
III	0.93−1.36	17	12	**6.55 (1.86−23.0)**	**<0.01**
IV	1.37−9.33	18	5	**16.8 (3.96−71.2)**	**<0.01**

Table 5
Blood cadmium levels and the occurrence of lung cancer (never smokers).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	5	6	1.00	–
II	0.46−0.92	6	5	2.00 (0.37−10.9)	0.42
III	0.93−1.36	1	0	nd.[a]	ns.[b]
IV	1.37−9.33	0	1	nd.[a]	ns.[b]

[a] nd. - not defined.
[b] ns. - not specified.

Table 6
Blood cadmium levels and the occurrence of stage I-II of lung cancer (former smokers).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	12	20	1.00	–
II	0.46−0.92	12	16	3.21 (0.65−15.8)	0.15
III	0.93−1.36	9	7	**9.06 (1.15−71.6)**	**0.04**
IV	1.37−9.33	12	2	**50.8 (3.60−719)**	**<0.01**

Table 7
Blood cadmium levels and the occurrence of stage III-IV of lung cancer (former smokers).

Range No	Cd level [μg/L]	Cases	Controls	OR (95 % CI)	p-value
I	0.14−0.45	4	16	1.00	–
II	0.46−0.92	22	16	**4.57 (1.26−16.6)**	**0.02**
III	0.93−1.36	8	5	**5.58 (1.08−28.9)**	**0.04**
IV	1.37−9.33	6	3	**7.43 (1.21−45.4)**	**0.03**

Table 8
Pack-years of cigarette consumption among cases and controls.

	Cases		Controls	
	n	Pack-years	n	Pack years
Current smokers	106	37.0	106	32.5
Former smokers	86	29.4	86	28.7

are currently smoking. Our data shows that current smoking increases the average blood cadmium level. It is possible that the data on current smokers is unreliable because the smoking habits of patients may change shortly after a diagnosis of lung cancer and among these patients, current cadmium levels are not a reliable indicator of past exposure. In contrast, the smoking habits of controls may be more representative of lifetime consumption

Current approaches for the early diagnosis of lung cancers include diagnostic imaging and liquid biopsy. Studies on the use of low-dose computed tomography (CT) for early diagnosis of lung cancer have provided inconsistent results. A study performed in US on a 53,454 persons with high risk for lung cancer reported a 20 % reduction in mortality from lung cancer with low-dose computed tomography compared to standard chest radiography [20]. Smaller research studies from Europe cancer show inconsistent results [21,22].

A liquid biopsy uses a few milliliters of blood for diagnosis, prognosis and prediction of a therapeutic response [23]. Among the potentially useful markers in the detection of lung cancer are circulating cell-free tumor DNA (cfDNA), human telomerase reverse transcription gene (hTERT), TP53 mutations in the plasma cfDNA; cell-free tumor RNA (cfRNA); exosomes; tumor-educated platelets (TEP); circulating tumor cells (CTCs); plasma microRNAs [23,24], and tumour-related antigens (p53, NY-ESO-1, CAGE, GBU4−5, Annexin 1 and SOX2) [25].

The promoter hypermethylation of a seven-gene panel: P16, PAX5β, MGMT, DAPK, GATA5, GATA4, RASSF1A in sputum can identify smokers at high-risk for lung cancer up to three years before clinical diagnosis [26]. Another study assessed the methylation profiles of non-small cell lung cancer using methylation-specific PCR (MS-PCR) in tissues and plasma samples. Nine genes (APC, CDH13, KLK10, DLEC1, RASSF1A, EFEMP1, SFRP1, RAR-β and P16INK4A) exhibited a significantly higher methylation frequency in lung cancer cells compared to normal tissue [27].

The results of our study may be helpful in refining the patient population who may benefit from screening CT of the lung. Previous studies have shown that among former smokers, cadmium levels may be predictive of the presence of lung cancer [8,28]. By screening for cadmium levels it may be possible to identify high-risk individuals among former smokers who merit surveillance. The correlation was present for early stage lung cancers that may be amenable to treatment. Among former smokers 58 % had a cadmium levels (above 0.45 μg/L) that is associated with an odds ratio of 3.94 and above for lung cancer.

In our study, among never-smokers the range of blood cadmium was wide (range 0.17 μg/L to 1.15 μg/L) and this implicates sources of cadmium other than smoking. We cannot exclude that some study subjects have had occupational exposure to cadmium. We did not see an association between cadmium level and lung cancer risk among non-smokers but further studies focused on occupational exposure to cadmium and lung cancer risk are warranted.

There are several possible mechanistic reasons for the observed association. Cadmium may be a carcinogen that persists in the blood after smoking cessation and the lung cancer is a direct effect of cadmium exposure. It is also possible that cadmium is a surrogate for other carcinogens, such as other heavy metals that are also in cigarettes and is a proxy for cumulative exposure to cigarettes. It is also possible that lung cancer itself influences the level of cadmium in the blood. Prospective studies and close analysis of dietary and occupational sources of cadmium may help distinguish between these possibilities.

In summary, blood cadmium level may be valuable marker for early detection of lung cancers particularly in former smokers. Prospective studies of cadmium and lung cancer and studies which incorporate cadmium level in lung cancer screening studies may extend these results.

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CRediT authorship contribution statement

Marcin R. Lener: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Edyta Reszka:** Methodology, Data curation, Writing - review & editing. **Wojciech Marciniak:** Methodology, Formal analysis, Investigation, Data curation. **Monika Lesicka:** Methodology, Investigation, Project administration. **Piotr Baszuk:** Methodology, Formal analysis, Data curation. **Ewa Jabłońska:** Methodology, Investigation, Data curation, Writing - review & editing. **Katarzyna Białkowska:** Methodology, Investigation. **Magdalena Muszyńska:** Investigation, Resources. **Sandra Pietrzak:** Investigation, Data curation. **Róża Derkacz:** Resources. **Tomasz Grodzki:** Resources, Project administration. **Janusz Wójcik:** Resources, Data curation. **Małgorzata Wojtyś:** Resources, Data curation. **Tadeusz Dębniak:** Resources, Data curation. **Cezary Cybulski:** Resources, Data curation. **Jacek Gronwald:** Resources, Data curation. **Bartosz Kubisa:** Resources. **Jarosław Pieróg:** Resources. **Piotr Waloszczyk:** Investigation, Resources, Data curation. **Rodney J. Scott:** Writing - review & editing. **Anna Jakubowska:** Conceptualization, Data curation, Writing - review & editing, Project administration. **Steven A. Narod:** Methodology, Writing - original draft, Writing - review & editing. **Jan Lubiński:** Conceptualization, Investigation, Data curation, Writing - original draft, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

Jan Lubiński is CEO of Read-Gene SA which offers measurement of micro- and macroelements level and DNA testing. These authors are part-time employees of Read-Gene: WM, RD, JG, CC. The other authors declare that they have no conflicts of interest.

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