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Article

Cadmium and Lead Levels and 8-Year Survival of Patients After Kidney Cancer Diagnosis

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Abstract

Background/Objectives: The objective of the present study was to determine the association between blood cadmium (Cd) and lead (Pb) levels and survival of the patients with kidney cancer. In this prospective study, we analyzed 272 consecutive, unselected kidney cancer patients and assessed their 8-year survival in relation to Cd and Pb levels. **Methods:** Cd and Pb concentrations were measured using inductively coupled plasma mass spectrometry (ICP-MS). Patients were categorized into four groups according to the quartile distribution of Cd and Pb levels, ranked in ascending order. Multivariable models were adjusted for covariates including age at diagnosis, sex, smoking status, type of surgery, histopathological classification and blood levels of selenium, zinc, copper, iodine, cadmium and lead. **Results:** We observed no association between blood Cd and Pb levels and all-cause mortality in patients with kidney cancer. **Conclusions:** To our knowledge, this study is the first to investigate the relationship between blood levels of cadmium and lead and kidney cancer survival.

Keywords: kidney cancer; survival; cadmium; lead

1. Introduction

The association between occupational and environmental exposure to heavy metals and cancer has been investigated, however the exact biological mechanisms underlying this relationship remain poorly understood [1]. Heavy metals are naturally present in the air, water and the Earth's crust. Due to their persistence in the environment, they are significant environmental pollutants associated with toxicity and an increased risk of human disease due to bioaccumulation, including cancer [2].

Certain heavy metals, particularly Cd and Pb, have been suggested to be potential risk factors for renal cell carcinoma [3–5]. Epidemiological studies suggest that prolonged occupational exposure especially in industries such as chemical manufacturing, rubber production and printing may increase the likelihood of developing renal cell carcinoma [3,4]. Despite these associations a definitive causal relationship has yet to be established [6].

Some studies have shown that heavy metals can promote oxidative damage to biomolecules [7,8]. By competing with essential ions of biological processes, toxic metals disrupt biomolecular structures and metal homeostasis and have been shown to facilitate cancer cell migration and invasion [9]. Exposure to heavy metals leads to the generation of free radicals such as reactive oxygen and nitrogen

species causing oxidative stress and cellular redox imbalance processes closely linked to carcinogenesis [10–12]. Substantial evidence suggests that heavy metal exposure disrupts epigenetic regulation, gene expression, protein function and metabolism [13].

Cohort studies have demonstrated that elevated blood Cd and Pb levels are associated with significantly increased all-cause or cancer-specific mortality [Tables 3,4].

Based on a review of the literature there are no reports examining the impact of Cd and Pb on the survival of patients with kidney cancer. By addressing this knowledge gap our research may provide novel insights into the prognostic significance of heavy metal exposure for survival of patients with renal cell carcinoma.

2. Materials and Methods

A total of 272 consecutive kidney cancer cases diagnosed at the Clinics of Urology and Oncological Urology, University Hospital in Szczecin, between 2014 and 2017 were included in the study. All patients provided written informed consent for the collection of blood samples. Samples were obtained at diagnosis, prior to initiation of treatment, between 08:00 and 11:00 a.m. following a minimum six-hours fasting period and were stored at -80°C in a dedicated research biobank until analysis. Under these storage conditions, the reliability of elemental analysis measurements is preserved. The study cohort was unselected with respect to age, sex, smoking status, surgical approach, histological subtype and cause of death. Data on environmental or social factors were not collected. Baseline characteristics of study subjects are presented in Table 1. Information on vital status and mortality was retrieved from the Polish Ministry of Internal Affairs and Administration in November 2023. The study protocol was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin (approval number KB-006/07/22).

2.1. Study Group

Table 1. Characteristics of the survivors of kidney cancer in the study.

Variables	Overall N =272	Living individuals N= 195	Deceased individuals N= 77
Age of diagnosis (mean)			
≤ 60 (50.12)	115 (42%)	92 (48%)	23 (29%)
>61 (67.66)	157 (58%)	103 (52%)	54 (71%)
Sex			
Female	115 (42%)	87 (45%)	28 (36%)
Male	157 (58%)	108 (55%)	49 (64%)
Smoking status			
No	90 (33%)	74 (38%)	16 (21%)
Current/Former smoker	182 (67%)	121 (62%)	61 (79%)
Kind of operation			
Nephrectomy	120 (44%)	83 (43%)	37 (48%)
Tumorectomy	152 (56%)	112 (57%)	40 (52%)
Fuhrman Grade			
*GI	72 (26%)	62 (31%)	10 (14%)
GII	120 (44%)	93 (47%)	27 (36%)
GIII	61 (22%)	37 (19%)	24 (30%)

GIV	20 (7.4%)	4 (2.5%)	16 (20%)
Clear cell carcinoma	237 (86%)	163 (83%)	74 (96%)
Papillary/Chromophobe	35 (14%)	32 (17%)	3 (4.0%)
Death due to cancer	-	-	18 (29%)
No	-	-	45 (71%)
Yes	-	-	14
Unknown			

*GI-GIV – Fuhrman Grade.

2.2. Sample Collection and Storage

From each patient, one venous blood sample (10 mL each) was collected. The sample was transferred into an EDTA (ethylenediaminetetraacetic acid) tube and stored at -80°C until analysis. On the day of analysis, whole blood samples were thawed, mixed by vortexing and centrifuged at $5000\times g$ for 5 min prior to further processing.

2.3. Measurement Methodology

Levels of Cd and Pb in blood were determined using inductively coupled plasma mass spectrometry (ICP-MS) (ELAN DRC-e and NexION 350D systems, Perkin Elmer, Canada/USA). Prior to each analytical run, the instrument was tuned and calibrated with freshly prepared external calibration standards at concentrations of 1, 2, 3, 4, 5, 10, 50, 75, 100, 120, 150, and 170 $\mu\text{g/L}$, obtained by diluting a 10 $\mu\text{g/mL}$ Multi-Element Calibration Standard 3 (PerkinElmer Pure Plus, Shelton, CT, USA) in blank reagent. Oxygen was used as the reaction gas, and correlation coefficients for calibration curves consistently exceeded 0.999. Technical details are available upon request.

2.4. Quality Control

The accuracy and precision of all measurements were verified using certified reference materials (CRM): Clincheck Plasmonorm Blood Trace Elements Level 1 (Recipe, Munich, Germany). In addition, the testing laboratory participates in the independent external quality assessment scheme QMEQAS (Quebec Multielement External Quality Assessment Scheme) organized by the Institut National de Santé Publique du Québec. Detailed plasma operating settings and mass spectrometer acquisition parameters are available upon request.

2.5. Statistical Analysis

To assess the relationship between blood Cd and Pb levels and kidney cancer survival, univariable and multivariable Cox proportional hazards regression models were calculated. Each element levels were categorized by quartiles. The quarter associated with the lowest number of deaths was selected as the reference category. A standardized follow-up period of 8 years was applied in all analyses.

Multivariable COX regression models include following variables: age at diagnosis (≤ 60 vs. >60 years), sex (female vs. male), smoking status (non-smoker vs. current/former smoker), type of surgery (nephrectomy vs. tumorectomy), Fuhrman nuclear grade (G I–IV) and histopathological classification (clear cell vs. papillary–chromophobe) and blood levels of Se, Zn, Cu, I, Cd and Pb.

Since this cohort had already been examined for associations between survival in kidney cancer patients and blood levels of Se, Cu, I and Zn, it raised the question of whether including Pb and Cd concentrations as additional predictors might overload the constructed regression models. Accordingly, a variable selection procedure was applied using bidirectional stepwise regression, to select predictors that produced the most appropriate model fit as evaluated using the Akaike Information Criterion (AIC). As a another and more restrictive procedure – the Boruta algorithm was also applied to validate the selected variables.

In order to visualize survival across quartiles of blood Cd and Pb levels, Kaplan–Meier survival curves were generated. Statistical significance was defined as $p \leq 0.05$. All analyses, data management and graphics were prepared using the R statistical environment (R version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria, 2025).

The functionality of the base statistical environment was extended by the additional packages, including: gtsummary (version 2.2.0), dplyr (version 1.1.4), survival (version 3.8.3), ggplot2 (version 3.5.2), WriteXLS (version 6.7.0), and readxl (version 1.4.5).

3. Results

The summary of univariable and multivariable COX proportional hazard regression models are presented in Table 2 and in supplementary (Supplementary Material Table S1).

Table 2. Correlation between Cd and Pb levels in blood and all-cause mortality in kidney cancer patients.

Variables	Vital status			Univariable COX Regression			Multivariable COX Regression*		
	Overall n=272 ¹	Alive n=195 ¹	Deceased n=77 ¹	HR ²	95% CI	p- value	HR ²	95% CI	p- value
Pb									
II (reference): 12.17-16.27	68 (25%)	52 (27%)	16 (21%)	—	—	—	—	—	—
I: 4.12-12.12	68 (25%)	47 (24%)	21 (27%)	1.53	0.80 - 2.93	0.2	2.12	0.98 - 4.60	0.056
III: 16.35-21.77	68 (25%)	47 (24%)	21 (27%)	1.38	0.72 - 2.64	0.3	1.05	0.50 - 2.20	0.9
IV: 21.82-445,068.42	68 (25%)	49 (25%)	19 (25%)	1.23	0.63 - 2.39	0.5	1.03	0.47 - 2.22	>0.9
Cd									
II (reference): 0.23 - 0.44	68 (25%)	52 (27%)	16 (21%)	—	—	—	—	—	—
I: 0.2 - 0.23	68 (25%)	51 (26%)	17 (22%)	1.13	0.57 - 2.24	0.7	1.04	0.49 - 2.17	>0.9
III: 0.44 - 0.91	68 (25%)	48 (25%)	20 (26%)	1.40	0.73 - 2.70	0.3	1.09	0.55 - 2.16	0.8
IV: 0.92 - 59,795.57	68 (25%)	44 (23%)	24 (31%)	1.79	0.95 - 3.38	0.071	1.58	0.79 - 3.16	0.2

¹n (%), ²HR = Hazard Ratio, CI = Confidence Interval, *multivariable model included: age, sex, smoking status, type of surgery, histopathological classification and blood levels of Se, Cu, I, Zn, Cd and Pb.

3.1. Cadmium

There is a non-statistically significant association (HR = 1.79; $p = 0.071$) between all-cause mortality and blood cadmium levels in 4th quartile compared with 2nd quarter, although the result suggests a potential trend toward an effect. Nevertheless, in the multivariable approach, we did not observe a significant association between blood Cd levels and all-cause mortality in the entire group of patients with kidney cancer and blood Cd levels in 4th quartile vs 2nd quartile (HR = 1.58; $p = 0.2$).

3.2. Lead

There is no statistically significant association between blood Pb levels and all-cause mortality in kidney cancer patients using the univariable approach, however there is a borderline association between survival in kidney cancer patients and blood Pb levels in 1st quarter compared to 2nd quarter (HR = 2.12; $p = 0.056$).

3.3. Verification of Selected Variables

In order to assess the validity of including blood Cd and Pb levels as additional variables in the analysis, a sequence of bidirectional stepwise regression analyses was performed on the entire study group ($n = 272$), which resulted in a suggestion to eliminate them from the multivariate model as those that do not improve the fit of the final model. Similar suggestion was applied according to surgical variables.

Analysis based on the Boruta classification algorithm also suggested that these variables should not be included in the final multivariable model, as they increased model complexity without improving its performance.

The performed analyses do not support a detectable association between blood levels of Cd and Pb and survival in patients with kidney cancer. Consequently, additional subgroup analyses were not performed.

4. Discussion

In this prospective study we did not find that blood Cd and Pb levels were associated with changes of all-cause mortality in kidney cancer patients.

Several epidemiological studies have prospectively investigated the relationship between Cd exposure and mortality as summarized in Table 3.

Table 3. Levels of Cd and their impact on all-cause mortality and cancer mortality.

Study	Group (n)	Follow-Up (Years)	Sample	Results
Nakagaw H. et al. 2006 [16]	3,119 populations in the Cd-contaminated Kakehashi River Basin (Japan) (1403)	15	urine	Among subjects with high urinary Cd levels ($\geq 10 \mu\text{g/g Cr}$) no significant increase in the mortality risk ratio for malignant neoplasms (esophagus n-5, stomach n-45, colon and rectum n-29, liver n-11, pancreas n-23, lung n-42, breast n-4, uterus n-1) was observed.

	men 1716 women)			Malignant neoplasms for men (HR-0.92; 95%CI, 0.53-1.61); for women (HR-0.99; 95%CI, 0.61-1.59).
Arisawa K. et al. 2007 [17]	275 adults living in a Cd-polluted area, Nagasaki (114 men and 161 women)	23	urine	mortality from all cancers (neoplasms n-37, stomach n-5, colorectal n-1, lung n-9, prostatic n-1) were significantly higher among subjects with urinary beta2-microglobulin (U-beta2M) ≥ 1000 microg/g creatinine than among the remainder of the cohort (HR-2.58; 95 % CI,1.25-5.36).
Nawrot T.S. et al. 2008 [18]	476 subjects randomly recruited from low- exposure areas on Cd and 480 randomly recruited from high-exposure areas on Cd, Belgium	22	urine	The results showed that a doubling of uCd was associated with an increased risk of total mortality, HR were 1.20 (95% CI, 1.03–1.39; $p = 0.018$) with all cancers mortality (n-60) HR-1.45 (95% CI, 1.17–1.79; $p = 0.0007$) with lung cancer mortality (n-21) HR-1.60 (95% CI, 0.99–2.56; $p = 0.051$) with gastrointestinal cancer mortality (n-16) HR-1.25 (95% CI, 0.72–2.15; $p = 0.43$) and with urogenital cancer mortality (n-6) HR-1.09 (95% CI, 0.42–2.83; $p = 0.87$).
Menke A. et al. 2009 [19]	13,958 participants in the Third National Health and Nutrition Examination Survey (NHANES III)	12	urine	A 2-fold increase in creatinine-corrected urinary cadmium were associated with all-cause mortality HR-1.28 (95% CI, 1.15-1.43) and with cancer mortality (n-439; 140–208 (ICD-9), C00–C97 (ICD-10) HR-1.55 (95% CI, 1.21-1.98).
Adams SV. et al. 2012 [20]	20,024 (9,388 men and 10,636 women) participants in Third National Health and Nutrition Examination	6	urinary	A 2-fold increase in uCd was associated with a 26% higher adjusted hazard of cancer (lung n-131, pancreatic n-23 and non-Hodgkin lymphoma n-11) mortality among men (95% CI, 7–48%) and a 21% higher hazard of cancers (lung n-76, leukemia n-13, ovarian n-13 and uterine n-7) among women (95% CI, 4–42%). Individuals in the highest quartile of uCd had a 70% higher risk of death from all

	Survey (NHANES III)			cancers among men (95% CI, 20–140%) and a 34% higher hazard among women (95% CI, –3–85%) compared with those in the lower three quartiles.
Adams S.V. et al. 2012 [21]	20,024 (9,388 men and 10,636 women) participants in the Third National Health and Nutrition Examination Survey (NHANES III)	18	urine	<p>A 2-fold increase Cd was associated with a 26% (95%CI, 7–48) and 21% (95%CI, 4–42) higher HR of cancer death among men and women. HR from all cancers was 70% (95%CI, 20–140) higher for men and 34% (95% CI, 3–85) for women, for individuals in the uppermost quartile uCd than for those in the lower quartiles.</p> <p>For individuals in the uppermost quartile of uCd (>0.580 µg/g) there was an association with increased all-cancer mortality (n=420); for lung cancer mortality (n=131) (HR-1.70; 95% CI, 1.20–2.40); for pancreas cancer mortality (n=23) (HR-7.25; 95% CI, 1.77–29.80); for Non-Hodgkin’s Lymphoma (n=11) (HR-25.83; 95% CI, 3.93–169.6).</p>
Tellez-Plaza M. et al. 2012 [22]	8,989 individuals in the National Health and Nutrition Examination	5	blood urine	Increasing Cd exposure was associated with HR for all-cause mortality (n=524): 1.50 (95% CI, 1.07–2.10) for blood and 1.52 (95% CI, 1.00–2.29) for urinary.
Lin Y.S.et al. 2013 [23]	5,204 (2,474 men and 2,730 women) participants in Third National Health and Nutrition Examination Survey (NHANES III)	12	urine	Compared with the lower quartiles, the HR for all-cause mortality (n=569) in tertile 3 (>1.05 µg/g) was 1.65 (95% CI, 1.13–2.41; $p = 0.01$) for women and 3.13 (95% CI, 1.88–5.20; $p < 0.001$) for men.
García-Esquinas E. et al. 2014 [24]	cohort of 3,792 American	2	urine	Comparing the 80th versus the 20th percentiles of U-Cd HR were 1.30 (95% CI, 1.09–1.55; $p < 0.001$) for total cancer

	Indians from Arizona			<p>mortality, 2.27 (95% CI, 1.58-3.27; $p < 0.001$) for lung cancer mortality (n=77) and 2.40 (95% CI, 1.39-4.17; $p = 0.002$) for pancreatic cancer mortality (n=12).</p> <p>Moreover, this study did not demonstrate a significant association between Cd concentration and mortality from liver n=42, esophageal n=48, stomach n=48, colon n=64, breast n=50, prostate n=32, kidney n=51, lymphatic n=74 cancers.</p>
Suwazono Y. et al. 2015 [25]	2,657 cohort (1067 men and 1590 women)	19	urine	<p>U-Cd was significantly associated with increased mortality. In men, the Q3 (1.96-3.22) and Q4 (≥ 3.23) of U-Cd showed a significant positive HR-1.35 (95% CI, 1.03-1.77) and HR -1.64 (95% CI, 1.26-2.14) respectively for all-cause mortality compared with the Q1 (< 1.14). In women, the Q4 of U-Cd (≥ 4.66) also showed a significant HR-1.49 (95% CI, 1.11-2.00) for all-cause mortality compared with the Q1 (< 1.46).</p>
Pietrzak S. et al. 2021 [26]	336 patients with lung cancer	2	blood	<p>The HR for all-cause mortality was 1.56 (95% CI, 1.02-2.36; $p = 0.04$) for patients in Q3 ($> 1.13-1.86$) compared with those in Q1 (0.23-0.67).</p>
Zhu K. et al. 2022 [27]	5113 participants in Third National Health and Nutrition Examination Survey (NHANES III)	15	blood	<p>Positive association between Cd and all-cause mortality risk was identified for Q4 vs Q1 HR-1.58 (95% CI, 1.22-2.03; $p < 0.001$). In the joint analysis participants in Q4 of blood Cd and Pb had a HR of 2.09 (95% CI, 1.35-3.24) for all-cause mortality compared with those in Q1.</p>
Laouali N. et al. 2023 [14]	14,311 participants in Third National Health and Nutrition Examination	6	urine	<p>UCd levels from the 5th to the 95th percentiles were associated with risk differences of 6.22% (95% CI, 4.51-12.00); HR-2.09 (95% CI, 1.75-5.42) for all-cause mortality and 0.64% (95% CI, -0.98- 2.80); HR-2.08 (95% CI, 0.42-40.73) for cancer mortality.</p>

	Survey (NHANES III)			
Zhang W. et al. 2024 [15]	8017 participants of the National Health and Nutrition Examination Survey (NHANES)	13	urinary	After adjusting for all covariates, high Cd levels significantly increased the risk of all-cause mortality, with the HR-1.67 (95% CI; 1.30-2.13; $p<0.001$). Moreover, they found that the combined effect of cadmium, lead, thallium and LE8 (Life's Essential 8) was positively associated with all-cause mortality.
Yifei Y. et al. 2025 [28]	3,453 individuals who self-reported a physician-diagnosed malignant tumor (1806 females and 1647 males)	19	blood	This study demonstrated a significant positive association between whole blood Cd concentration and all-cause mortality among cancer survivors, with a HR of 1.73 (95% CI, 1.39–2.16). Higher blood Cd levels were also significantly associated with increased cancer-specific mortality risk in patients with skin and soft tissue cancers 30.5% (HR-2.72; 95% CI, 1.73–4.26; $p<0,0001$).

We found 15 prospective studies examining the effect of Cd exposure on all-cause mortality or cancer mortality (Table 3). In these studies, all-cause mortality was significantly higher in individuals with increased Cd levels in urine or blood [14,15,18,19,22,23,25–28]. Eight studies reported a positive association between Cd concentrations in urine or blood and mortality from cancers of the stomach, colon, lung, prostate, gastrointestinal tract, genitourinary system, pancreas and non-Hodgkin's lymphoma [14,17–21,24,28]. However, two studies did not find a significant association between Cd levels and mortality from liver, esophageal, stomach, colorectal, pancreatic, breast, prostate or kidney cancers [16,24].

The results of the systematic review suggest inconsistent findings. However, our observation that increased Cd levels were not associated with renal cancer mortality is consistent with the findings reported by Garcia-Esquinas et al. [24]. In our study, we evaluated patients with renal cancer, whereas Garcia-Esquinas et al. examined a cohort of American Indians. Several limitations should be noted in the study by Garcia et al., including the small number of renal cancer deaths, the determination of the cause of death based on death certificates rather than cancer registry data and the use of a single urine sample to measure Cd levels. The strengths of this study include its prospective design and long-term follow-up.

Akin et al. examined the effects of Cd and Pb on the cadherin–catenin complex in the Renca mouse RCC cell line. The aim of the study was to investigate the potential role of these metals in tumor progression. [40]. Pb induced a concentration-dependent loss of E-cadherin, whereas Cd increased p120-catenin expression. Both metals significantly reduced the formation of Renca cell aggregates, indicating disruption of the cadherin–catenin complex. Furthermore, exposure to Cd and Pb resulted in pro-metastatic changes, including decreased cell–cell aggregation and increased cell migration and invasion in established RCC cell lines. These findings suggest that Cd and Pb may contribute to RCC progression.

Chronic Cd exposure induces oxidative stress through the generation of reactive oxygen species (ROS) and depletion of antioxidant defense systems leading to DNA damage and genomic instability

[29–33]. Cd has also been shown to inhibit programmed cell death and stimulate cellular proliferation thereby promoting the accumulation of damaged cells [34]. Furthermore, cadmium disrupts DNA repair pathways and may induce epigenetic alterations, including aberrant DNA methylation and dysregulated microRNA expression [35–37]. In addition, Cd exhibits estrogen-mimicking activity, interfering with hormone-regulated signaling pathways [38]. Moreover, Cd may impair tumor suppressor function by inhibiting p53 activity and altering cell-cycle regulation [35,36,39].

Pb can induce direct DNA damage, including double-strand breaks, interfere with DNA synthesis, repair mechanisms, disrupt cell-cycle control and apoptotic pathways [56,59]. By inactivating glutathione and antioxidant enzymes, Pb promotes the generation of reactive oxygen species (ROS) leading to oxidative stress and subsequent DNA damage [57,58]. In addition, Pb has been shown to affect epigenetic regulation including alterations in DNA methylation patterns and histone modifications which may result in aberrant gene expression [58]

Although epidemiological evidence for Pb is less consistent, its toxicity is well established. Several prospective studies have examined the association between Pb exposure and mortality as shown in Table 4.

Table 4. Levels of Pb and their impact on cancer and all-cause mortality.

Study	Group	Follow-Up (Years)	Sample	Results
Lustberg M. et al. 2002 [41]	4,292 participants of the Second National Health and Nutrition Examination Survey (NHANES II)	4	blood	Individuals with baseline blood Pb levels of 20 to 29 microg/dL (1.0-1.4 micromol/L) had 46% increased all-cause mortality (HR-1.46; 95% CI, 1.14-1.86) and 68% increased cancer mortality (25.8% of deaths; ICD-9 codes 140-240) (HR-1.68; 95% CI, 1.02-2.78) compared with those with blood Pb levels of less than 10 microg/dL (<0.5 micromol/L)
Menke A. et al. 2006 [42]	13,946 participants of the Third National Health and Nutrition Examination Survey (NHANES III)	12	blood	When participants in the highest tertile of blood Pb ($\geq 0.17 \mu\text{mol/L}$ [$\geq 3.62 \mu\text{g/dL}$]) were compared with those in the lowest tertile ($< 0.09 \mu\text{mol/L}$ [$< 1.94 \mu\text{g/dL}$]), the HR for all-cause mortality was 1.25 (95% CI, 1.04–1.51; $p=0.002$). There was no association between blood Pb and cancer mortality (ICD-9 codes 140 to 239; ICD-10 codes C00-C97 and D00-D48) and lung cancer (ICD-9 codes 162.2 to 162.9; ICD-10 code C34).

Schober S. et al. 2006 [43]	9,757 participants of the Third National Health and Nutrition Examination Survey (NHANES III)	6	blood	Using blood Pb levels <5 µg/dL as the reference, we found that the relative risk of all-cause mortality was 1.24 (95% CI, 1.05–1.48) for individuals with blood Pb levels of 5–9 µg/dL and 1.59 (95% CI, 1.28–1.98) for those with levels ≥10 µg/dL ($p < 0.001$) and the relative risk of cancer mortality was 1.44 (95% CI, 1.12–1.86) for individuals with blood Pb levels of 5–9 µg/dL and 1.69 (95% CI, 1.14–2.52) for those with levels ≥10 µg/dL ($p < 0.01$).
Weisskopf M.G. et al. 2009 [44]	868 subgroup of the VA NAS, a multidisciplinary longitudinal study of aging in men	8	bone	They found that patella bone Pb was associated with a significantly increased rate of all-cause mortality. For all-cause mortality the HR for participants in the highest tertile of patella Pb compared with those in the lowest tertile was 2.52 (95% CI, 1.17–5.41; $p=0.02$). Blood Pb was not associated with any mortality category.
Khalil N. et al. 2009 [45]	cohort study of 533 women	2	blood	Women with blood Pb concentrations > or = 8 microg/dL (0.384 µmol/L) had 59% increased risk of multivariate adjusted all cause mortality HR-1.59 (95% CI, 1.02-2.49; $p=0.041$) compared to women with blood Pb concentrations < 8 µg/dL (< 0.384 µmol/L).
Chowdhury R. et al. 2014 [46]	58,368 men	20	blood	The lung cancer mortality ratio n-382 in the highest BL category was 1.20 (95% CI, 1.03-1.39). Moreover, this study did not demonstrate a significant association between Pb concentration and mortality from brain n-30, kidney n-28, stomach n-23, esophagus n-37, larynx n-16 and bladder n-22 caner.

Lanphear B.P. et al. 2018 [47]	14,289 nationally representative sample of adults	23	blood	An increase in blood Pb concentration from 1.0 µg/dL to 6.7 µg/dL (0.048 µmol/L to 0.324 µmol/L), representing the 10th to 90th percentiles, was associated with an increased risk of all-cause mortality HR-1.37, 95% CI, 1.17–1.60).
Pietrzak S. et al. 2021 [26]	336 patients with lung cancer	2	blood	The HR of death from all causes was 1.18 (95% CI, 0.76–1.82; $p=0.47$) for lead in patients from the lowest concentration quartile Q1(5.91–15.57) compared with those in the highest quartile Q3 (>30.32–149.44).
Leroyer A. et al 2022 [48]	2,177 male workers at a non-ferrous metal smelter	35	blood	Compared to the regional population they did not find an excess risk of all-cause mortality (n-913) (Standardized mortality ratio-SMR) 0.96, 95%CI:0.90-1.02), nor of cancer (n-338) mortality (SMR=0.97, 95% CI:0.87-1.08). Significant excess risk of cancer mortality was found for employees who worked in this non-ferrous metal smelter (n-139) for a period of between 15 and 29 years (SMR=1.23, 95% CI:1.04-1.45). Pb exposure was associated with the an excess mortality from colon-rectum-anus cancer (n-6) SMR-2.84, 95%CI, 1.04–6.18); lip-oral cavity-pharynx cancer HR-2.86 (95%CI, 0.69–11.96 and HR-0.79, 95% CI, 0.13–4.80 for the intermediate and high cumulative exposure categories of lead, respectively) and deaths from liver cancer (HR = 3.26, 95%CI: 0.25–41.72 and HR = 13.36, 95%CI,1.30–137.2 for intermediate and highly exposed workers, respectively).
Zhu K. et al. 2022 [27]	7,420 participants of the Third National Health and Nutrition	15	blood	When comparing the extreme quartiles (Q4 vsQ1) for all-cause mortality the HR was 1.51 (95%CI, 1.25-1.82) for blood Pb ($p<0.001$). In

	Examination Survey (NHANES III)			the combined analysis, compared with participants in the lowest tertiles of blood Pb and Cd participants in the highest tertiles had an HR-2.09 (95% CI, 1.35-3.24) for all-cause mortality.
Laouli N. Et al. 2023 [14]	14,311 participants of the Third National Health and Nutrition Examination Survey (NHANES III)	22	blood	Increases in blood Pb levels from the 5th to the 95th percentiles were associated with risk differences of 4.17% (95% CI, 1.54-8.77) and 6.22% (95%CI, 4.51-12.00); HR- 2.38 (95% CI, 1.14-2.96) for all-cause mortality and 1.32% (95% CI, -0.09-3.67) and 0.64% (95%CI, -0.98-2.80) HR- 3.87 (95% CI, 1.12-7.91) for cancer mortality, respectively.
Yifei Y. et al. 2025 [28]	3,453		blood	A positive association was found between blood lead and cancer-specific mortality (HR = 1.83, 95 % CI: 1.13-2.97). A high blood lead levels were significantly associated with greater mortality risk in patients with reproductive system cancers 29 %. HR-1.83 (95 % CI, 1.13-2.97; $p=0.05$).

We identified 11 prospective studies that examined the association between Pb exposure and all-cause or cancer-specific mortality (Table 4). Among these studies, elevated Pb levels in blood or bone were significantly associated with higher all-cause mortality [14,26,27,41–45,47,48]. Five studies reported a positive relationship between blood Pb concentrations and mortality from lung cancer, cancers of the lip-oral cavity, pharynx and reproductive system cancers [14,28,41,46,48]. In contrast, three studies did not find a significant association between Pb levels and mortality from lung, brain, esophageal, stomach, larynx, bladder or kidney cancers [42–44,46].

Similar observations were reported by Chowdhury et al., who also did not observe a significant association between elevated Pb levels and kidney cancer [46]. Their study included 58,368 men and had a prospective design with long-term follow-up.

The relationship between Pb levels and mortality in our study population appears to follow a U-shaped patterned a U- or J-shaped curve describing the association between Pb levels and cancer, all-cause and cause-specific mortality such as cardiovascular mortality. These studies have shown that at very low Pb levels, the risk of death was higher [28,41,43,44,47].

Approximately 75–95% of total body Pb is stored in the bones, where its biological half-life ranges from 5 to 19 years [49,50]. In contrast, the half-life of Pb in blood is about 1 month [51]. Therefore, blood Pb levels primarily reflect recent exposure rather than cumulative body burden. With aging, bone resorption releases Pb back into the bloodstream, contributing to higher blood Pb levels in older individuals [52,53]. Studies suggest that both cumulative and current exposure to lead are associated with a decline in kidney function [54,55].

In the present study, we did not observe an association between blood Cd and Pb levels and mortality among patients with renal cancer. The results presented in Tables 3 and 4 indicate that

elevated levels of Cd and Pb in blood, urine or bone were significantly associated with higher all-cause mortality or mortality from cancers of the lung, lip–oral cavity, pharynx, reproductive system, stomach, colon, prostate, gastrointestinal tract, genitourinary system, pancreas and non-Hodgkin lymphoma. In contrast, some studies did not find a significant association between Cd and Pb concentrations and mortality from lung, brain, esophageal, stomach, laryngeal, bladder, kidney, liver, colorectal, pancreatic, breast or prostate cancers. Study populations differ in terms of age, comorbidities, lifestyle, environmental exposure and genetics. In many studies Cd and Pb levels in the populations examined may be too low to significantly affect mortality. The toxic effect may be related to long-term accumulation which a single measurement cannot capture. Other mechanisms of cancer progression such as genetic mutations, tumor microenvironment and immune response may have a greater influence on mortality than the presence of Cd or Pb. It should be noted, however, that most of the available evidence comes from general population cohorts or experimental models rather than studies specifically evaluating post-diagnosis survival in kidney cancer patients. Differences in study populations may partially explain these discrepant findings. Moreover, our multivariable models were adjusted not only for age at diagnosis, sex, smoking status, type of surgery and histopathological classification but were also further extended to include blood concentrations of selenium, zinc, copper, iodine, cadmium and lead, which may attenuate associations.

In our previous studies, we examined the association between selenium (Se), zinc (Zn), copper (Cu) and iodine (I) concentrations in blood/serum and kidney cancer mortality [60–62]. Our findings showed that patients with the lowest Se and Zn levels and the highest Cu and I levels had significantly higher all-cause mortality from kidney cancer. Moreover, when all analyzed elements—selenium, zinc, copper, iodine, cadmium and lead—were included in the multivariable statistical models, these associations remained consistent (Table 2). Similar relationships between higher Se and Zn levels and reduced mortality have been reported in patients with breast, prostate, stomach, lung, laryngeal, pancreatic, melanoma, colon cancers and leukemia [63–77]. The elevated Cu levels have been associated with poorer survival in hepatocellular carcinoma as well as in gastric, breast, prostate, lung and laryngeal cancers [64,74,78–82]. In turn in patients with advanced gastric cancer, lower I intake has been linked to poorer progression-free survival [83–85].

Our study has limitations. The key limitation is that we conducted it at a single medical centre and the sample size was relatively small. Additionally, our study did not have detailed information on environmental or occupational factors or dietary intake. Blood lead and cadmium levels were measured only once. Despite these limitations, this is the first prospective study to investigate the impact of Cd and Pb levels on survival in kidney cancer patients, using blood samples collected at diagnosis prior to treatment. These results provide a valuable foundation for future research and highlight the potential for multi-center validation studies. Moreover, our findings offer an opportunity to initiate collaborations with other researchers worldwide to confirm the prognostic role of microelements and, if validated, explore their optimization through diet or supplementation as a means to improve survival in kidney cancer patients.

5. Conclusions

In conclusion, our findings did not demonstrate that Cd or Pb play a significant role in the clinical course or survival of patients with renal cell carcinoma. However, our results highlight the need for further studies to confirm these observations.

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Institutional Review Board Statement: This study was approved by Ethics Committee of the Pomeranian Medical University in Szczecin, Poland, under number KB-006/07/22 (22 January 2022).

Informed Consent Statement: All participants gave informed written consent prior to serum donating.

Data Availability Statement: Our data contain potentially sensitive information; therefore, we have not included them with our manuscript. The Pomeranian University of Medicine Ethics Committee will grant access to all researchers who meet the criteria for access to confidential data.

Conflicts of Interest: Jan Lubiński is the CEO of Read-Gene SA, which offers measurements on micro- and macro-elemental levels. These authors are part-time employees of Read-Gene: Wojciech Marciniak, Róża Derkacz and Piotr Baszuk. The other authors, Elżbieta Złowocka-Perłowska, Aleksandra Tołoczko-Grabarek, Katarzyna Gołębiowska, Marcin Słojewski, Artur Lemiński, Michał Soczawa, Helena Rudnicka, Marcin R Lener, Jacek Gronwald and Rodney J Scott, declare that they have no conflicts of interest.

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