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HEAVY METAL BURDEN IN PROSTATE CANCER PATIENTS: A COMPARATIVE ANALYSIS OF SELENIUM, CADMIUM, ALUMINUM, LEAD, IRON, AND MERCURY ACROSS TREATMENT STAGES USING ICP TECHNIQUE

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ABSTRACT

Background: We examined the levels of essential elements and other toxic elements in the blood of patients with prostate cancer (PCa), and found differences between the treatment group and the clinical group, with samples taken from each group separately; however, these differences are not clear.

Objective: To compare serum Se, Cd, Al, Pb, Fe, and Hg concentrations in healthy controls, untreated PCa, chemotherapy-treated PCa, and hormone-treated PCa.

Methods: The study included 120 men distributed equally across four independent clinical groups (n = 30 per group) in a cross-sectional design. The described serum digestion used 2.5 mL of sample and a 12.5-mL final volume (dilution factor 5), followed by ICP-OES. Statistical analyses included one-way ANOVA, Welch ANOVA, pairwise Welch comparisons, Holm adjustment, exploratory Pearson correlation analyses, and Fisher's z tests for comparing correlation coefficients.

Results: Mean Se was 99.88 ± 14.62 , 82.00 ± 15.36 , 86.08 ± 14.85 , and 92.81 ± 14.61 µg/L across control, untreated, chemotherapy, and hormone-therapy groups, respectively. All six elements differed overall among groups (all classical ANOVA $P < 0.0001$; Welch sensitivity tests $P < 0.001$). After Holm adjustment of 18 control contrasts, the hormone-therapy Al and Hg differences did not remain significant. In untreated PCa, Cd–Al and Al–Pb correlations passed within-group FDR adjustment; eight of 45 between-category correlation comparisons passed FDR correction using Fisher's z.

Conclusions: Serum element summaries varied across clinical categories, although the cross-sectional design precludes causal and treatment-effect inferences. Based on quantitative analyses of toxic metals at low concentrations, the validity of the method has been verified and the data are currently being analysed from the original records using the instruments

Keywords: False discovery rate, Selenium, Cadmium, Prostate cancer, Serum trace elements, Emission spectrometry, Cross-sectional, Plasmon optical

1 INTRODUCTION

Prostate cancer is one of the most common types of cancer amongst men worldwide, and this is a major cause of morbidity and mortality associated with this type of cancer[1]. Its symptoms and clinical progression are influenced by a combination of age and genetic predisposition to the disease, as well as androgen levels, hormonal status, lifestyle factors and environmental exposures. These biomarkers influence the availability of data supporting epidemiological hypotheses; however, a causal relationship between them and the disease cannot be established. Each of these elements may provide a biologically relevant link through which these associations can be studied; selenium contributes to the formation of antioxidants as well as selenium-containing proteins associated with the thyroid gland, whilst iron is essential for the transport of oxygen and the transport of, as well as cellular metabolism.[4,5]. The elements cadmium, lead and mercury are considered toxic and affect both oxidation-reduction signalling and enzymes and cellular functions. As for aluminium [2,3], it is an element found in large quantities in the environment; although it plays a significant role in prostate development, this remains unconfirmed, as the exact mechanism depends on... biological significance of the concentration depends very heavily on the sample matrix, the method of analysis and the time of sample collection[6,7,16]. Epidemiological studies have indicated an association between selenium and prostate cancer; however, the strength and consistency of these associations vary from one study to another, which does not confirm that the findings based on the observations that taking dietary supplements prevents prostate cancer[8]. It should be noted that the preventive evidence derived from uncontrolled studies cannot support the routine intake of selenium supplements for this purpose. Changes in serum iron levels may result from dietary patterns, inflammation, underlying diseases and transient physiological phenomena during treatment are not solely linked to tumour-related processes. Experimental biological models of carcinogenic pathways associated with cadmium may be used as a basis; however, this does not imply that laboratory mechanisms are equivalent to serum concentrations found in human populations[9,10]. It has been confirmed that a meta-analysis was conducted in 2025. dealing with toxic exposure and its unconfirmed association with the presence of cadmium, lead and mercury in serum; however, several positive point estimates have been confirmed across multiple studies involving different cohorts relating to mercury in blood and markers of oxidative stress[11]. These findings confirm that serum, whole blood and urine and prostate tissue are not biologically interchangeable matrices, as evidenced by comparisons of circulating metals in the blood between prostate cancer patients and those in control groups; although fewer reports describe untreated disease, as well as deprivation therapy and androgen-deprivation therapy, and their application to separate clinical categories within a common panel comprising six serum elements[12,13,15]. This study examines the levels of selenium, cadmium, lead, aluminium, mercury and iron across four groups, assessing the differences between the groups and the magnitude of the effects, whilst also investigating the correlations between the elements within each category of cancer patients, whilst taking into account the causes observed at a specific point in time. The primary objective can be summarised as a comparative description rather than a measurement of changes resulting from treatment.

2 MATERIALS AND METHODS

2.1 Study design and participants

A cross-sectional observational study included 120 men divided equally into four independent groups (n = 30 per group): apparently healthy controls, patients with newly diagnosed prostate cancer before systemic treatment, patients receiving chemotherapy, and patients undergoing hormone (androgen-deprivation) therapy. The grouping variable reflected the clinical status at serum collection; participants were not randomized to treatments and the variable categories were not paired with baseline specimens. The available cohort summaries did not include standardized disease stage, PSA, Gleason grade/Grade Group, treatment duration, or recruitment dates, limiting the ability to evaluate treatment-selection effects and clinical confounding.

2.2 Participant characteristics

Age and body mass index (BMI) were summarized as means $\pm$ SD within each group (Table 1). BMI was defined as mass in kilograms divided by height in meters squared. The analyses used the four clinical categories as exposure groups and the six serum element measurements as the outcomes of interest. Age, BMI, disease severity, renal function, smoking, dietary supplementation, and occupational exposure were considered potential confounding factors. Age and BMI were reported in Table 1, whereas the remaining factors could not be evaluated in the present analysis.

2.3 Serum collection and processing

Approximately 10 mL of fasting venous blood was collected according to the study description. Serum was separated by centrifugation at 3,000 rpm for 10 min, divided into aliquots, and stored at -80°C pending elemental determination.

Since exogenous contamination can materially affect low-abundance metal measurements, specimen containers, contact materials, reagents, and processing conditions must be trace-element compatible; the study record does not provide batch-specific process-blank or contamination-control values.

2.4 ICP-OES determination and concentration calculation

Serum elemental determination was performed using inductively coupled plasma optical emission spectrometry (ICP-OES; PerkinElmer Optima 8300 series) after microwave-assisted acid digestion. The described preparation combined 2.5 mL of serum, 5.0 mL of concentrated HNO₃, and 1.0 mL of 30% H₂O₂. The digestion programme consisted of 120 °C for 10 min followed by 180 °C for 20 min. After cooling, each digest was brought to a final volume of 12.5 mL with ultrapure water, yielding a nominal volumetric dilution factor of 5. Additional instrumental dilutions, if any, must be included in the concentration calculation.

For a blank-corrected digest concentration (C_{digest}), the serum-equivalent concentration (C_{serum}) is $C_{\text{serum}} = C_{\text{digest}} \times (V_{\text{final}}/V_{\text{serum}}) = 5 \times C_{\text{digest}}$. Concentrations of Se, Cd, Al, Pb, and Hg are given in µg/L of serum and Fe in mg/L. This calculation accounts for the stated volumetric dilution and does not itself establish analytical accuracy, recovery, sensitivity, or freedom from spectral and matrix interference.

The stated analytical approach included calibration standards and reference materials. At low trace-element concentrations, measurement validity requires element-specific wavelengths, representative calibration ranges, analytical and process blanks, method detection limits (LOD), limits of quantification (LOQ), quality-control recoveries, and assessment of interferences. Because batch-specific instrumental response, LOQ, and recovery information were not included in the available summaries, numerical concentrations and statistical group differences should not be regarded as independent proof of analytical quantifiability.

2.5 Analytical sensitivity and quality assurance

With the fivefold dilution, expected digest-equivalent group-mean concentrations were calculated as $C_{\text{digest}} = C_{\text{serum}}/5$. Across the four categories, these were 16.400–19.976 µg/L for Se, 0.104–0.250 µg/L for Cd, 0.488–0.808 µg/L for Al, 0.204–0.420 µg/L for Pb, 166.0–234.0 µg/L for Fe, and 0.110–0.220 µg/L for Hg (Table 3). These solution-level concentrations are arithmetic equivalents of the serum means rather than instrument-generated observations; validated method LOD and LOQ remain separate analytical quantities. In particular, mean Cd concentrations correspond to only 0.104–0.250 µg/L in the digest and call for documented calibration and blank control [18].

Quantitative elemental determination depends on demonstrating fit-for-purpose calibration linearity, analyte-specific emission wavelengths and background correction, process and reagent blanks, method detection and quantification limits, accuracy, precision, recovery, and evaluation of spectral and matrix interferences. Where a specimen response falls below the validated quantification limit, the value cannot be treated as an ordinary quantified concentration. No analytical validation parameter was inferred from the serum concentration results.

2.6 Statistical analysis

One-way ANOVA was evaluated ($df = 3,116$), and $\eta^2 = SS_{\text{between}}/(SS_{\text{between}} + SS_{\text{within}})$ quantified omnibus effect size. Because variances differed among clinical categories, Welch one-way ANOVA was computed as a heteroscedasticity-robust sensitivity analysis (Table 5). Six omnibus hypotheses were evaluated using Benjamini–Hochberg false-discovery-rate adjustment. The 18 control-versus-PCa contrasts were evaluated by two-sided Welch *t* tests with Satterthwaite degrees of freedom, 95% confidence intervals, and Holm family-wise adjustment. Normality, outliers, missingness, and covariate-adjusted models cannot be evaluated from grouped summary statistics. Benjamini–Hochberg FDR adjustment was applied separately across the 15 within-category correlations. All 15 element pairs were compared across each of the three pairs of PCa categories, generating 45 two-sided tests with one Benjamini–Hochberg correction across the whole family (Table 12). These approximate tests rely on group independence, rounded coefficients, and standard Pearson correlation assumptions.

2.7 Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the Ethics Committee, College of Science, University of Kirkuk, Kirkuk, Iraq (Approval No. UOK-CoS-EC/2026-048). The study was conducted from March 2026 to September 2026. Written informed consent was obtained from all participants prior to blood sample collection and laboratory analysis. The confidentiality and anonymity of all participants were strictly maintained, and all biological samples were coded before laboratory measurements and statistical analysis. All sample collection, handling, and analytical procedures were performed in accordance with institutional ethical and laboratory safety requirements.

3 RESULTS

3.1 Demographic profile of the clinical groups

Each category comprised 30 participants (Table 1). The mean age ranged from 47.64 ± 6.63 years for controls to 51.80 ± 6.24 years for the hormone-therapy group. One-way ANOVA indicated a difference in mean age ($F(3,116) = 3.40$, $P = 0.020$), while BMI did not differ significantly ($F(3,116) = 2.25$, $P = 0.086$). Therefore, the study groups were not fully age matched, and all element comparisons below should be interpreted as unadjusted estimates.

Table 1: Age and body mass index of study participants by clinical group (mean $\pm$ SD; n = 30 per group).

Parameter	Control (n=30)	Untreated PCa (n=30)	Chemotherapy (n=30)	Hormone Therapy (n=30)
Age (years)	47.64 ± 6.63	48.12 ± 6.79	51.42 ± 6.08	51.80 ± 6.24
BMI (kg/m^2)	22.38 ± 1.86	23.19 ± 1.94	23.07 ± 2.16	23.72 ± 2.07

Age: omnibus $P = 0.020$; BMI: omnibus $P = 0.086$, One-way ANOVA; n = 30 per group.

3.2 Serum elemental concentrations

Serum concentrations of the six elements by group are summarized in Table 2. Mean Se concentrations were 99.88 ± 14.62 $\mu\text{g}/\text{L}$ in controls, 82.00 ± 15.36 $\mu\text{g}/\text{L}$ in untreated PCa, 86.08 ± 14.85 $\mu\text{g}/\text{L}$ in chemotherapy, and 92.81 ± 14.61 $\mu\text{g}/\text{L}$ in hormone therapy. Relative to controls, the reductions in mean Se were 17.9%, 13.8%, and 7.1%, respectively. The differences reflect measurements in different people rather than serial treatment responses.

Table 2: Serum Se, Cd, Al, Pb, Fe, and Hg concentrations across clinical groups (mean $\pm$ SD; n = 30 per group).

Element	Control	Untreated PCa	Chemotherapy	Hormone therapy
Se ($\mu\text{g}/\text{L}$)	99.88 ± 14.62	82.00 ± 15.36	86.08 ± 14.85	92.81 ± 14.61
Cd ($\mu\text{g}/\text{L}$)	0.52 ± 0.18	1.08 ± 0.42	1.25 ± 0.48	0.78 ± 0.30
Al ($\mu\text{g}/\text{L}$)	2.44 ± 0.92	3.99 ± 1.54	4.04 ± 1.37	3.12 ± 1.27
Pb ($\mu\text{g}/\text{L}$)	1.02 ± 0.38	1.83 ± 0.64	2.10 ± 0.91	1.41 ± 0.53
Fe (mg/L)	1.17 ± 0.19	0.99 ± 0.17	0.83 ± 0.27	1.01 ± 0.22
Hg ($\mu\text{g}/\text{L}$)	0.55 ± 0.28	0.92 ± 0.36	1.10 ± 0.36	0.70 ± 0.29

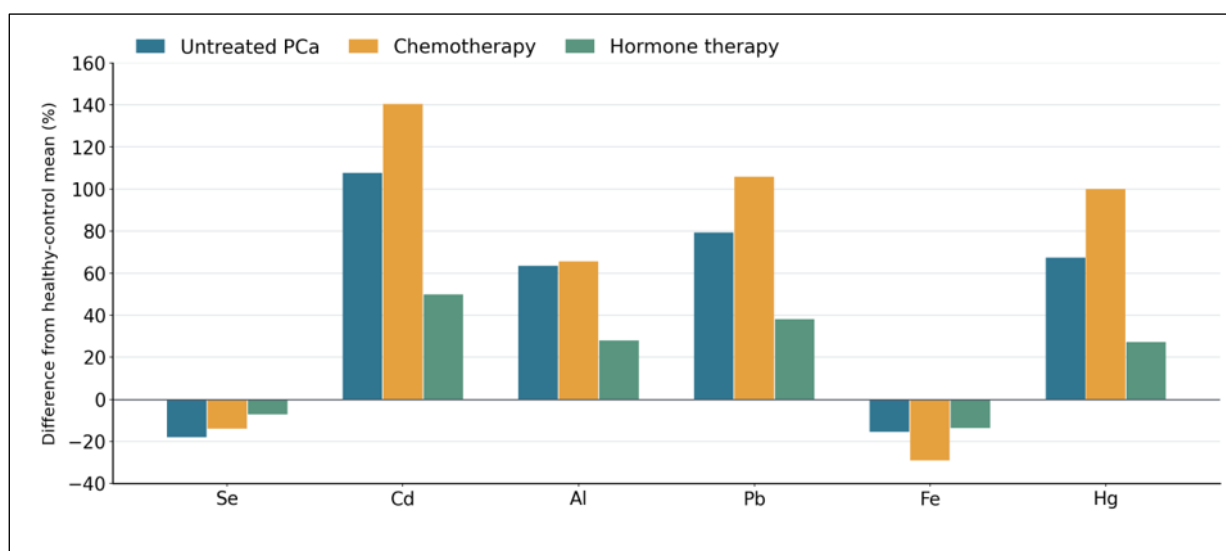


Figure 1: Relative differences in group-mean serum element concentrations compared with controls. Percentages were calculated from Table 2 means; each group comprises different participants (n = 30).

Mean Cd, Al, Pb, and Hg concentrations were higher in all three PCa categories than in controls, with their highest values in the chemotherapy category: Cd $1.25 \pm 0.48 \mu\text{g/L}$, Al $4.04 \pm 1.37 \mu\text{g/L}$, Pb $2.10 \pm 0.91 \mu\text{g/L}$, and Hg $1.10 \pm 0.36 \mu\text{g/L}$. Mean Fe showed the opposite pattern, with $0.83 \pm 0.27 \text{ mg/L}$ in chemotherapy compared with $1.17 \pm 0.19 \text{ mg/L}$ in controls. Figure 1 displays percent changes in these group means relative to the control means without implying subject-level trajectories or causal treatment effects.

The corresponding group-mean concentrations expected in the fivefold-diluted digest are summarized in Table 3. They represent volumetric equivalents of the reported serum means.

Table 3: Calculated group-mean analyte concentrations in the final digest after fivefold dilution ($\mu\text{g/L}$).

Analyte	Control	Untreated PCa	Chemotherapy	Hormone therapy
Se	19.976	16.400	17.216	18.562
Cd	0.104	0.216	0.250	0.156
Al	0.488	0.798	0.808	0.624
Pb	0.204	0.366	0.420	0.282
Fe	234.000	198.000	166.000	202.000
Hg	0.110	0.184	0.220	0.140

3.3 Omnibus tests and effect sizes

One-way ANOVA identified statistically significant between-group variation for all six elements (all $P < 0.0001$; Table 4). Effect sizes ranged from $\eta^2 = 0.178$ for Se to $\eta^2 = 0.380$ for Cd. Welch ANOVA, which does not assume equal group variances, yielded the same omnibus significance decisions for every element (Table 5). The omnibus tests indicate that not all group means are equal; the individual control-group contrasts are reported in Table 6.

Table 4: One-way ANOVA of serum elements across four groups (df between = 3, df within = 116).

Element	SS between	SS within	F(3,116)	P	FDR q	η^2
Se	5541.860	25625.809	8.36	<0.0001	<0.0001	0.178
Cd	9.404	15.347	23.69	<0.0001	<0.0001	0.380
Al	52.730	194.526	10.48	<0.0001	<0.0001	0.213
Pb	20.250	48.227	16.24	<0.0001	<0.0001	0.296
Fe	1.740	5.403	12.45	<0.0001	<0.0001	0.244
Hg	5.270	12.229	16.66	<0.0001	<0.0001	0.301

ANOVA calculations were based on group-level data ($n = 30$ per group); Benjamini–Hochberg FDR adjustment covers the six omnibus tests.

Table 5: Welch one-way ANOVA sensitivity analysis allowing unequal group variances.

Element	Welch F	df1	df2	P	FDR q
Se	8.145	3	64.43	0.0001	0.0001
Cd	31.327	3	59.99	<0.0001	<0.0001
Al	12.882	3	63.18	<0.0001	<0.0001
Pb	19.664	3	61.95	<0.0001	<0.0001
Fe	11.271	3	63.71	<0.0001	<0.0001
Hg	16.549	3	64.06	<0.0001	<0.0001

All six element-level omnibus tests retained $P < 0.001$ after adjustment across the six tests.

3.4 Differences from healthy controls

The control-group contrasts in Table 6 indicated lower mean Se during untreated PCa (difference $-17.88 \mu\text{g/L}$; 95% CI -25.63 to -10.13) and chemotherapy ($-13.80 \mu\text{g/L}$; 95% CI -21.42 to -6.18). The hormone-therapy Se difference did not meet nominal significance ($P = 0.0660$). Cd, Al, Pb, and Hg means were higher, and Fe means were lower, across the PCa categories. After Holm adjustment of all 18 comparisons, the Al and Hg differences for hormone therapy compared with healthy controls had adjusted $P = 0.0636$ and 0.0922 , respectively, and did not remain significant. Hedges g standardized contrasts are summarized in Table 7.

Table 6: Control-group differences with 95% Welch confidence intervals and unadjusted / Holm-adjusted P values.

Element	Untreated PCa	Chemotherapy	Hormone therapy
Se	-17.880 [-25.630, -10.130] <0.0001 / 0.0002	-13.800 [-21.416, -6.184] 0.0006 / 0.0036	-7.070 [-14.624, +0.484] 0.0660 / 0.0922
Cd	+0.560 [+0.391, +0.729] <0.0001 / <0.0001	+0.730 [+0.540, +0.920] <0.0001 / <0.0001	+0.260 [+0.132, +0.388] 0.0002 / 0.0014
Al	+1.550 [+0.891, +2.209] <0.0001 / 0.0002	+1.600 [+0.995, +2.205] <0.0001 / <0.0001	+0.680 [+0.106, +1.254] 0.0212 / 0.0636
Pb	+0.810 [+0.537, +1.083] <0.0001 / <0.0001	+1.080 [+0.716, +1.444] <0.0001 / <0.0001	+0.390 [+0.151, +0.629] 0.0019 / 0.0094
Fe	-0.180 [-0.273, -0.087] 0.0003 / 0.0020	-0.340 [-0.461, -0.219] <0.0001 / <0.0001	-0.160 [-0.266, -0.054] 0.0038 / 0.0154
Hg	+0.370 [+0.203, +0.537] <0.0001 / 0.0004	+0.550 [+0.383, +0.717] <0.0001 / <0.0001	+0.150 [+0.003, +0.297] 0.0461 / 0.0922

Each cell reports mean difference [95% CI] on the first line, and raw P / Holm-adjusted P on the second line. Differences are group minus control; Se, Cd, Al, Pb, and Hg are in $\mu\text{g/L}$; Fe is in mg/L . The family of 18 comparisons was adjusted using Holm's procedure.

Standardized contrasts with healthy controls are additionally expressed as Hedges g (Table 7).

Table 7: Hedges g for each independent PCa group versus healthy controls.

Element	Untreated PCa	Chemotherapy	Hormone therapy
Se	-1.177	-0.924	-0.477
Cd	+1.711	+1.988	+1.037
Al	+1.206	+1.353	+0.605
Pb	+1.519	+1.529	+0.835
Fe	-0.985	-1.437	-0.768
Hg	+1.132	+1.683	+0.519

Positive g indicates a higher group mean than controls; negative g indicates a lower group mean. Standardization uses pooled SD and the Hedges small-sample correction with $df = 58$.

3.5 Within-group correlations in untreated PCa

Among untreated PCa participants, Cd–Al ($r = 0.488$, $P = 0.0062$, $q = 0.0465$) and Al–Pb ($r = 0.505$, $P = 0.0045$, $q = 0.0465$) were the only inter-element correlations passing the 15-test FDR threshold (Table 8). Cd–Pb ($r = 0.454$, $q = 0.0588$) and Al–Hg ($r = 0.362$, $q = 0.1849$) were not retained after adjustment. These positive associations do not establish a common exposure source, biological mediation, or direction of action.

Table 8: Pearson correlations among serum elements in untreated PCa (n = 30), with P and FDR-adjusted q values.

Element pair	Pearson r	P	FDR q
Se–Cd	-0.149	0.4305	0.7175
Se–Al	-0.162	0.3926	0.7175
Se–Pb	-0.039	0.8358	0.9205
Se–Fe	0.193	0.3059	0.7175
Se–Hg	0.062	0.7465	0.9205
Cd–Al	0.488	0.0062	0.0465
Cd–Pb	0.454	0.0118	0.0588
Cd–Fe	0.130	0.4926	0.7389
Cd–Hg	0.296	0.1127	0.3380
Al–Pb	0.505	0.0045	0.0465
Al–Fe	0.021	0.9108	0.9205
Al–Hg	0.362	0.0493	0.1849
Pb–Fe	0.019	0.9205	0.9205
Pb–Hg	0.164	0.3854	0.7175
Fe–Hg	-0.030	0.8731	0.9205

Benjamini–Hochberg q values were calculated for the 15 element-pair correlations; q < 0.05 denotes FDR significance.

3.6 Within-group correlations during hormone therapy

In the hormone-therapy category, Se correlated negatively with Al ($r = -0.568$), Pb ($r = -0.744$), and Hg ($r = -0.477$), and positively with Fe ($r = 0.457$) (Table 9). These four element-pair associations remained significant after Benjamini–Hochberg FDR adjustment across 15 correlation tests. Nominal associations for other elements did not survive the same adjustment. The pattern is exploratory and cannot be attributed to hormonal therapy without a longitudinal comparison or appropriate confounder control.

Table 9: Pearson correlation coefficients (r) in the hormone-therapy group (n = 30).

Variable	Se	Cd	Al	Pb	Fe	Hg
Age	-0.093	-0.015	0.016	-0.090	-0.161	0.108
BMI	-0.129	0.027	0.045	-0.032	-0.075	0.113
Cd	0.191	--	-0.044	-0.123	-0.121	0.178
Al	-0.568*	-0.044	--	0.370	-0.408	0.370
Pb	-0.744*	-0.123	0.370	--	-0.395	0.379
Fe	0.457*	-0.121	-0.408	-0.395	--	-0.275
Hg	-0.477*	0.178	0.370	0.379	-0.275	--

* FDR q < 0.05 among the 15 element–element correlations, assessed across 15 element-pair correlations; demographic correlations are presented descriptively.

3.7 Within-group correlations during chemotherapy

In the chemotherapy category, Se–Cd ($r = 0.656$), Se–Al ($r = 0.661$), Se–Pb ($r = 0.444$), Cd–Al ($r = 0.610$), and Cd–Pb ($r = 0.536$) correlations survived the 15-test FDR threshold (Table 10). By contrast, the nominal inverse Cd–Fe association ($r = -0.382$, P approximately 0.037) was not significant following FDR correction. Figure 2 presents the reported element–element correlation patterns in each of the three PCa categories; these patterns are descriptive and are not formal evidence that correlations differ statistically between categories.

Table 10: Pearson correlation coefficients (r) in the chemotherapy group (n = 30).

Variable	Se	Cd	Al	Pb	Fe	Hg
Age	-0.180	-0.381	-0.118	-0.226	0.269	-0.144
BMI	-0.073	-0.214	0.014	-0.240	0.371	-0.304
Cd	0.656*	--	0.610*	0.536*	-0.382	0.218
Al	0.661*	0.610*	--	0.297	-0.189	0.099
Pb	0.444*	0.536*	0.297	--	-0.300	0.144
Fe	-0.152	-0.382	-0.189	-0.300	--	-0.236
Hg	0.278	0.218	0.099	0.144	-0.236	--

* FDR $q < 0.05$ among 15 element–element correlations assessed across 15 element-pair correlations. Age- and BMI-related coefficients are descriptive and were not included in the 15-test FDR family.

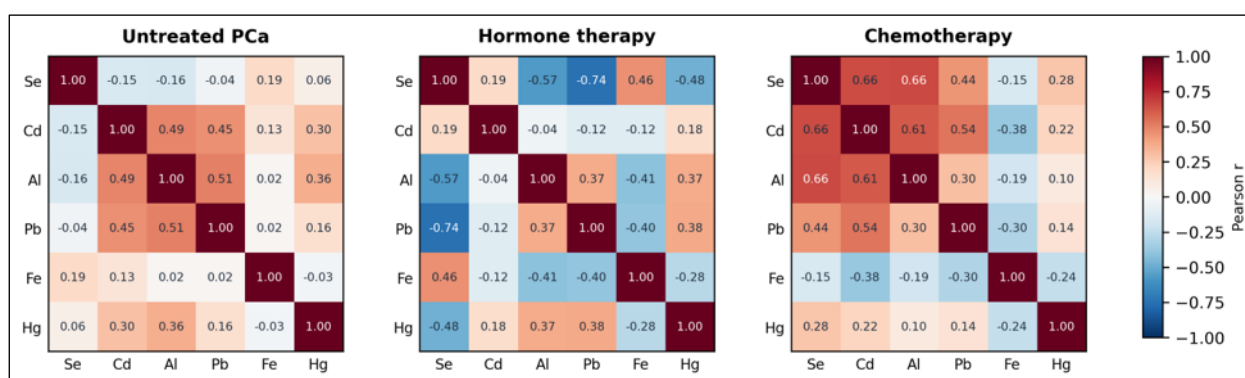


Figure 2: Within-group Pearson correlation patterns among six serum elements. The correlation matrices reproduce the coefficients in Tables 8–10; formal between-group comparisons are presented in Table 12.

4 DISCUSSION

4.1 Interpretation of serum element profiles

The analysis identified lower mean Se and Fe and higher mean Cd, Al, Pb, and Hg across the PCa clinical categories relative to healthy controls. The chemotherapy group generally displayed the largest unadjusted mean differences, while the hormone-therapy group was closer to control means for several elements. This ordering is descriptive: it may reflect underlying differences in disease severity, treatment indication, nutritional status, comorbidities, renal function, occupational history, age, or other unrecorded exposures. A cross-sectional comparison cannot establish whether a treatment lowered or raised any concentration.

4.2 Selenium and iron

The untreated PCa group had a 17.9% lower mean Se concentration than controls; corresponding mean differences were 13.8% and 7.1% in the chemotherapy and hormone-therapy groups. The direction of the Se contrast is consistent with a 2025 synthesis of eight Se studies reporting lower serum Se in PCa overall [16], and with an independent clinical comparison by Saleh et al. [14]. Nonetheless, supplementation cannot be recommended as a preventive or therapeutic intervention on this basis, particularly given the absence of preventive benefit in a major randomized trial [8]. The higher cross-sectional Se mean in hormone therapy is not evidence of within-person restoration.

Mean Fe was lower in all three PCa categories relative to controls, most prominently in chemotherapy (0.83 vs. 1.17 mg/L). However, serum Fe alone does not establish iron deficiency, distinguish functional deficiency from inflammation, or quantify total iron stores. Importantly, Saleh et al. observed increased serum Fe in their PCa group [14], whereas a 2025 meta-analysis did not identify a statistically significant pooled difference in serum Fe [16]. Tissue-based findings have also linked lower prostatic Fe with subsequent biochemical recurrence [15]. These apparently divergent patterns emphasize the need to specify the biological matrix and clinical setting rather than portray serum Fe changes as universal.

4.3 Cadmium, aluminum, lead, and mercury

Cadmium, Al, Pb, and Hg mean values were higher in PCa categories than in controls. For example, the chemotherapy Cd mean (1.25 µg/L) was approximately twice the control mean (0.52 µg/L), and the Pb mean was 2.10 versus 1.02 µg/L. After the specified fivefold digestion dilution, however, Cd and other trace metals enter the low-µg/L or sub-µg/L solution range. Accordingly, the numerical precision of the group comparisons should be distinguished from the independently required analytical sensitivity and control of contamination, spectral interference, and matrix effects.

Experimental studies connect Cd exposure with oxidative stress and cell signaling [9,10], but causation in human PCa is not established by serum concentrations. The 2025 toxic-metal meta-analysis of seven studies (691 participants) found nonsignificant pooled differences for serum Cd, Pb, and Hg, despite positive point estimates for Cd and Pb [11]. The present positive mean contrasts therefore contribute an additional descriptive pattern, not proof of carcinogenic accumulation, disease progression, or chemotherapy-induced metal retention.

Pizent et al. evaluated 103 cases and 91 controls in Croatian and Serbian cohorts and found higher blood Hg in PCa cases, with concurrent associations involving oxidative-stress measures [12]. However, blood Hg from that study cannot be numerically equated with serum Hg in the present series. Similarly, prostate tissue concentrations and associations with recurrence reported by Sarafanov et al. [15] address a different compartment and outcome. Table 11 places representative published results alongside the present study to distinguish agreements in direction from differences in matrix, participant selection, and endpoint.

4.4 Comparison with published clinical and synthesis studies

Published results show both concordant and discordant patterns across matrices and study settings. Table 11 summarizes directly verifiable sample counts or synthesis coverage, element panels, and directional observations. Numerical values from tissue or whole-blood studies have deliberately not been converted into serum-equivalent concentrations.

Table 11: Contextual comparison of serum and other-matrix studies on trace and toxic elements in prostate cancer.

Study / year	Population / design	Matrix / method	Principal finding	Ref.
Present study	120 men; four categories (30 each)	Serum; ICP-OES	Lower Se and Fe; higher Cd, Al, Pb, Hg in PCa categories vs controls	—
Saleh et al., 2020	40 PCa; 22 BPH; 30 healthy	Serum; ICP-MS	Lower Se and higher Fe in PCa vs control groups	[14]
Pizent et al., 2022	103 PCa; 91 controls; two cohorts	Blood/serum; metal panel	Higher blood Hg in PCa and oxidative-stress associations	[12]
Devi et al., 2025	7 studies; 691 participants	Serum; systematic review	Pooled Cd, Pb, and Hg contrasts not statistically significant	[11]
Devi et al., 2025	12 studies; serum trace-element synthesis	Serum; meta-analysis	Lower pooled Se; no significant pooled Fe difference	[16]
Sarafanov et al., 2011	80 men; 40 recurrence pairs	Prostate tissue; ICP-MS	Lower tissue Fe associated with biochemical recurrence	[15]

4.5 Inter-element correlations and multiple testing

FDR-controlled untreated-PCa associations were restricted to Cd–Al and Al–Pb. Other nominal correlations did not withstand adjustment across the 15 element-pair hypotheses. Correlations may reflect shared exposure sources, dietary factors, biological transport, laboratory artefacts, or random variation. The coefficient matrices describe pairwise linear association within each clinical group rather than evidence of causation.

Correlations also differed statistically between some independent clinical groups under Fisher’s z comparisons. Of 45 between-group tests, eight survived FDR correction (Table 12). The largest contrasts involved Se–Al and Se–Pb between hormone therapy and chemotherapy; additional differences concerned Se–Cd and Se–Al between untreated and chemotherapy categories, Se–Pb between untreated and hormone-therapy categories, and Se–Hg, Cd–Al, and Cd–Pb between the two treatment categories. These tests establish statistical differences among the reported correlation coefficients under the stated assumptions, not treatment-caused biological change. Without paired observations or

comprehensive adjustment for disease stage, renal function, nutritional intake, and environmental exposure, such patterns should not be attributed to a specific mechanism.

Table 12: Between-group differences in Pearson correlations: Fisher z tests (45 two-sided contrasts).

Pair	Untreated vs hormone (z / P / q)	Untreated vs chemo (z / P / q)	Hormone vs chemo (z / P / q)
Se–Cd	-1.262 / 0.2069 / 0.4656	-3.439 / 0.0006 / 0.0065	-2.177 / 0.0295 / 0.1172
Se–Al	+1.768 / 0.0771 / 0.2168	-3.520 / 0.0004 / 0.0065	-5.288 / <0.0001 / <0.0001
Se–Pb	+3.382 / 0.0007 / 0.0065	-1.897 / 0.0579 / 0.1736	-5.278 / <0.0001 / <0.0001
Se–Fe	-1.095 / 0.2735 / 0.5469	+1.281 / 0.2002 / 0.4656	+2.376 / 0.0175 / 0.0875
Se–Hg	+2.135 / 0.0327 / 0.1172	-0.821 / 0.4117 / 0.5789	-2.956 / 0.0031 / 0.0234
Cd–Al	+2.122 / 0.0339 / 0.1172	-0.645 / 0.5191 / 0.6674	-2.767 / 0.0057 / 0.0364
Cd–Pb	+2.254 / 0.0242 / 0.1090	-0.400 / 0.6893 / 0.7973	-2.653 / 0.0080 / 0.0448
Cd–Fe	+0.927 / 0.3539 / 0.5567	+1.959 / 0.0501 / 0.1611	+1.032 / 0.3022 / 0.5469
Cd–Hg	+0.460 / 0.6455 / 0.7850	+0.307 / 0.7588 / 0.8370	-0.153 / 0.8784 / 0.9193
Al–Pb	+0.616 / 0.5381 / 0.6726	+0.918 / 0.3588 / 0.5567	+0.302 / 0.7626 / 0.8370
Al–Fe	+1.669 / 0.0951 / 0.2518	+0.780 / 0.4354 / 0.5813	-0.889 / 0.3741 / 0.5611
Al–Hg	-0.034 / 0.9729 / 0.9729	+1.028 / 0.3038 / 0.5469	+1.062 / 0.2881 / 0.5469
Pb–Fe	+1.605 / 0.1086 / 0.2715	+1.207 / 0.2274 / 0.4873	-0.398 / 0.6910 / 0.7973
Pb–Hg	-0.858 / 0.3911 / 0.5678	+0.075 / 0.9400 / 0.9614	+0.933 / 0.3509 / 0.5567
Fe–Hg	+0.927 / 0.3540 / 0.5567	+0.774 / 0.4392 / 0.5813	-0.153 / 0.8781 / 0.9193

Each cell shows Fisher z / unadjusted two-sided P / Benjamini–Hochberg q. FDR was controlled across all 45 independent between-group comparisons; eight contrasts had $q < 0.05$. Positive z indicates a stronger correlation in the first named category.

4.6 Study strengths and limitations

The use of a common six-element panel across four specified clinical categories provides a focused basis for exploring differences in serum elemental profiles. Important limitations remain. First, direct checks of the distributions, missing observations, outliers, and covariate-adjusted models were not performed. Second, while the sample preparation uses a fivefold volumetric factor, demonstrated analyte-specific LOD, LOQ, calibration, blank, matrix-recovery, and reference-material performance were not available for independent assessment. At sub- $\mu\text{g/L}$ digest concentrations, these data are central to quantitative confidence. Third, clinical treatment categories were neither randomly allocated nor longitudinally paired. Disease stage, PSA, grade group, treatment details, comorbidity, renal function, dietary supplements, smoking, and potential occupational exposures were not available for confounder adjustment. Group ages differed ($P = 0.020$). Fourth, the analyses include multiple comparisons, and multiplicity adjustment does not remove the possibility of chance findings. Prospective investigation with well-characterized populations, participant-level models, and independently demonstrated trace-level analytical performance is needed to establish clinical relevance.

5 CONCLUSIONS

In this four-category cross-sectional comparison of 120 men, lower Se and Fe and higher Cd, Al, Pb, and Hg were observed in PCa categories relative to controls. All six elements exhibited overall differences under both classical and Welch ANOVA. Eight cross-category differences in element-pair correlations survived correction of 45 Fisher tests. Nevertheless, age imbalance and unmeasured clinical and environmental confounding preclude causal interpretation or assessment of treatment-induced changes. Reliable quantitative inference for low-level metals depends on verified analytical calibration, method quantification limits, blank control, and recovery performance.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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