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U-Shaped Association between Whole Blood Selenium and Cancer Mortality in U.S. Adults with Chronic Kidney Disease: A NHANES-Based Cohort Study

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Abstract: Background: Chronic kidney disease (CKD) is accompanied by a substantial burden of cancer-related death, but the prognostic role of selenium in this setting is not well defined. Previous CKD studies have focused mainly on serum selenium and composite outcomes. Whether whole-blood selenium has a nonlinear relation with cancer mortality has not been established. We therefore examined this association in U.S. adults with non-dialysis-dependent CKD. Methods: We conducted a retrospective cohort study using NHANES 2013–2018 data. The analysis included 1,941 adults with non-dialysis-dependent CKD (928 men and 1,013 women). Baseline whole-blood selenium was measured by inductively coupled plasma mass spectrometry. Cancer mortality was the primary endpoint; all-cause and cardiovascular mortality were secondary endpoints, identified by National Death Index linkage through December 31, 2019. Weighted Cox models and restricted cubic splines were used, with recursive procedures applied to locate a possible change point. Results: Over a median follow-up of 33.0 months, 40 participants died from cancer, 218 died from any cause, and 79 died from cardiovascular disease. The spline model supported a U-shaped cancer-mortality curve (P for non-linearity = 0.026), with the lowest estimated risk at 236.4 μg/L. Below that value, each 1 μg/L increment corresponded to a 1.6% lower cancer-mortality hazard (HR 0.984, 95% CI 0.969–0.998); above it, the hazard rose by 1.6% per increment (HR 1.016, 95% CI 1.008–1.028). Selenium deficiency (<173.2 μg/L) was associated with higher all-cause mortality (HR 1.627, 95% CI 1.212–2.183). Conclusions: In this NHANES CKD cohort, whole-blood selenium was related to cancer mortality in a U-shaped pattern rather than a simple linear gradient. The estimated turning point was 236.4 μg/L. Because the study is observational and cancer deaths were few, these values should be treated as hypothesis-generating and tested in prospective studies before being used to guide supplementation.

Keywords: Chronic Kidney Disease; Whole Blood Selenium; NHANES; Cancer; Mortality.

1. Introduction

CKD affects more than 850 million people worldwide and its age-standardized mortality increased by 41.5% between 1990 and 2017 [1]. Cancer is an important component of this excess risk. In a 2025 individual-participant meta-analysis of 54 cohorts (1,319,308 participants), an eightfold higher urinary albumin-to-creatinine ratio was associated with an 8% increase in incident cancer (HR 1.08, 95% CI 1.06–1.10) [2]. Persistent inflammation, oxidative stress, defective DNA repair, and retention of uremic solutes provide plausible links between impaired kidney function and tumor progression [3]. Nutritional factors that can be modified without worsening renal disease therefore deserve closer study.

Selenium is obtained chiefly from grains, meat, fish, eggs, and dairy products [4]. Its biological effects are mediated through selenoproteins, including glutathione peroxidases, thioredoxin reductases, and selenoprotein P, which participate in redox control, inflammatory signaling, and immune regulation [5,6]. Epidemiologic data generally associate adequate selenium status with lower cancer incidence or mortality. For example, a 2025 meta-analysis of 20 prospective studies reported a 15% lower cancer-mortality risk per standard-deviation increase in selenium (RR 0.85, 95% CI 0.78–0.94) [7], while another pooled analysis linked higher dietary selenium intake with lower cancer risk [8]. The relationship may not remain protective at high concentrations: excess supplementation has been associated with type 2 diabetes and prostate-cancer risk [9,10].

Low selenium status is common in CKD. Concentrations in serum and whole blood tend to fall as eGFR declines and are often below those observed in healthy controls [11]. Reported whole-blood values range from roughly 67 to 350 μg/L across populations, with CKD cohorts usually near the lower end [12]. Several processes may contribute: reduced protein intake limits dietary selenium [13]; indoxyl sulfate can suppress hepatic selenoprotein-P synthesis and disturb liver-kidney transport [14]; chronic inflammation increases selenium utilization; and impaired excretion alters homeostasis [11,14]. These changes may intensify oxidative and immune dysfunction, creating a biologically credible pathway to poorer cancer outcomes.

Evidence specific to CKD remains incomplete. Many prior studies excluded people with kidney disease or treated them only as a small subgroup, and the shape of the selenium-cancer curve is still debated. A Vietnamese study reported a U-shaped association with turning points near 70–90 μg/L [15], but those values may not transfer to populations with higher selenium exposure or to patients with altered renal handling. General-population reference ranges may consequently lead to either insufficient or excessive supplementation in CKD. A study using NHANES data found lower all-cause and cardiovascular mortality with higher serum selenium [16], but serum reflects a shorter exposure window than whole blood and cancer-specific outcomes were not examined.

We used NHANES 2013–2018 to address three questions: whether whole-blood selenium is associated with cancer

mortality in U.S. adults with non-dialysis-dependent CKD; whether that association is nonlinear; and whether a concentration range associated with the lowest observed risk can be estimated. The analyses also examined all-cause and cardiovascular mortality as secondary outcomes.

2. Materials and Methods

2.1. Study Population and Inclusion/Exclusion Criteria

We assembled participants from the 2013–2014, 2015–2016, and 2017–2018 NHANES cycles (29,400 individuals in total). Eligible participants were adults aged 18 years or older who met the CKD definition described below and had a valid whole-blood selenium result. We excluded individuals receiving dialysis and those without mortality follow-up information. After these exclusions, 1,941 participants remained for analysis (Figure 1).

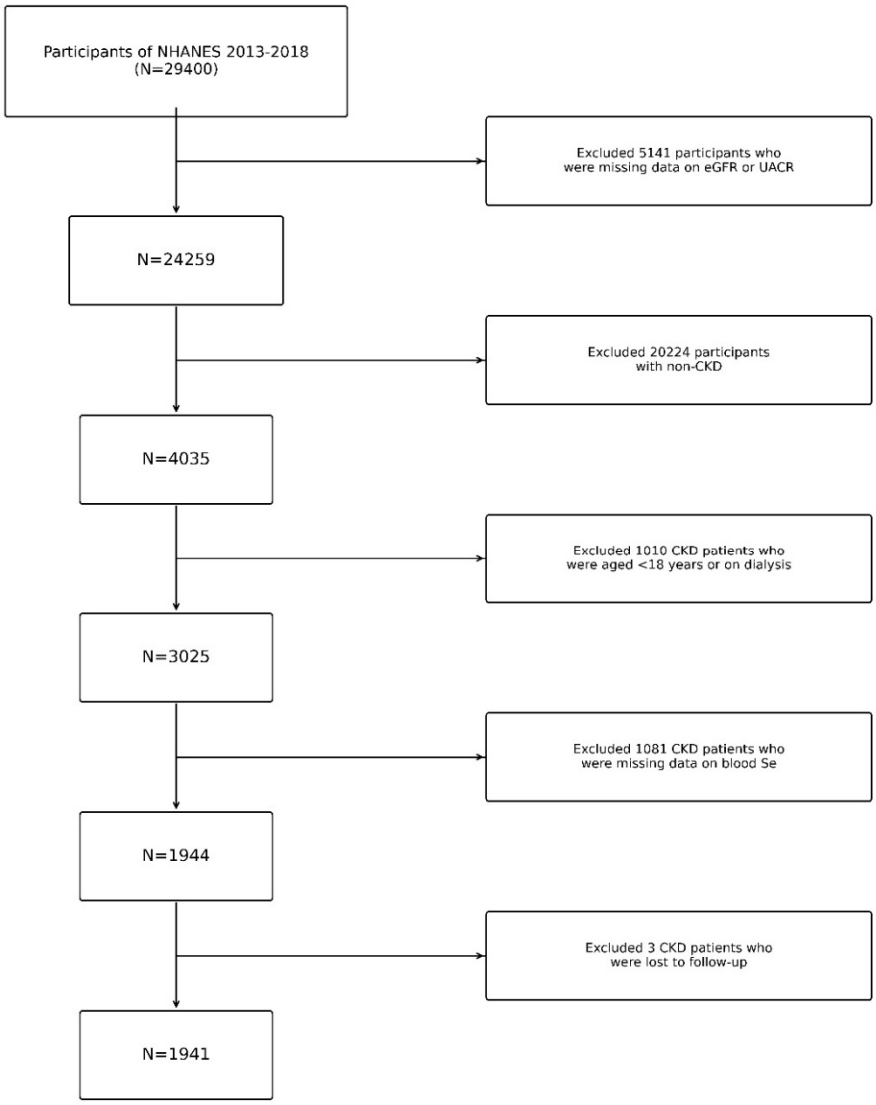


Figure 1. Sample selection flowchart from the National Health and Nutrition Examination Survey (NHANES 2013–2018)

2.2. CKD Diagnosis and Staging Criteria

CKD was defined according to the 2024 KDIGO framework [17]. A participant qualified if eGFR was below 60 mL/min/1.73 m², calculated with the race-free CKD-EPI equation, or if the urinary albumin-to-creatinine ratio (UACR) was at least 30 mg/g. For covariate adjustment, eGFR categories were grouped as G3 (30–59), G4 (15–29), or G5 (<15 mL/min/1.73 m²). UACR values came from NHANES laboratory measurements.

2.3. Exposure Variable: Whole Blood Selenium Measurement and Deficiency Definition

NHANES laboratories measured whole-blood selenium by inductively coupled plasma mass spectrometry; the assay detection limit was 24.48 μg/L. We classified selenium deficiency as <173.2 μg/L, using the U.S. reference range reported by Jain and Choi [18].

2.4. Outcome Variables: Ascertainment of Mortality

Vital status and cause of death were obtained by linking NHANES records to the public National Death Index file, with follow-up ending on December 31, 2019. We used the ICD-10 underlying-cause codes supplied in the linkage file to define cancer and cardiovascular deaths.

2.5. Covariate Extraction

Questionnaires provided age, sex, race/ethnicity, household income, education, smoking, alcohol use, and histories of hypertension, diabetes, coronary heart disease, heart failure, and stroke. Race/ethnicity was grouped as Mexican American, non-Hispanic Asian, non-Hispanic Black, non-Hispanic White, other Hispanic, or other race. Anthropometric measurements were taken at mobile examination centers. BMI was calculated from measured weight and height and grouped as normal, overweight, or obese. Physical activity was categorized from the Global Physical Activity Questionnaire. eGFR and UACR were retained as laboratory-derived kidney measures.

2.6. Statistical Analysis

All analyses incorporated NHANES sampling weights, strata, and primary sampling units. Participants were divided into selenium quartiles. Continuous variables are reported as mean (SD) or median (IQR), as appropriate, and categorical variables as counts and percentages. Weighted chi-square and Kruskal-Wallis tests compared baseline groups. Cox proportional-hazards models were fitted separately for cancer, all-cause, and cardiovascular mortality. Model 1 was unadjusted, Model 2 included age, sex, and race/ethnicity, and Model 3 additionally included socioeconomic, kidney-function, lifestyle, and comorbidity variables. Hazard ratios (HRs) are presented with 95% CIs. Restricted cubic splines were used to inspect departures from linearity [19]; when indicated, recursive searches identified a candidate knot and two-piecewise Cox models estimated slopes on either side. A likelihood-ratio test compared the linear and piecewise specifications. Sensitivity analyses excluded deaths within 12 or 24 months and observations with extreme selenium values.

3. Results

3.1. Baseline Characteristics of the Study Population

The analytic sample contained 1,941 adults with non-dialysis-dependent CKD: 928 men and 1,013 women. Median follow-up was 33.0 months (IQR 21.0–54.0). During follow-up, 40 cancer deaths, 218 deaths from any cause, and 79 cardiovascular deaths occurred. Median age was 64.0 years (IQR 50.0–75.0), and median whole-blood selenium was 191.7 μg/L (IQR 176.4–207.8).

Table 1. Baseline Characteristics of CKD Patients Stratified by Whole Blood Selenium Quartiles

Characteristics	Q1 (n=485)	Q2 (n=485)	Q3 (n=485)	Q4 (n=486)	P value
Age (years)	67.0 (53.0, 79.0)	66.0 (51.0, 75.0)	63.0 (48.0, 74.0)	61.0 (48.0, 72.0)	0.076
Sex, n (%)					0.003*
Male	202 (32.9)	222 (37.9)	241 (45.4)	263 (47.6)	
Female	283 (67.1)	263 (62.1)	244 (54.6)	223 (52.4)	
Race/Ethnicity, n (%)					0.013*
Non-Hispanic Asian	29 (3.6)	40 (4.3)	43 (3.9)	76 (7.4)	
Non-Hispanic Black	131 (14.7)	99 (10.7)	111 (12.8)	84 (9.1)	
Non-Hispanic White	221 (68.6)	199 (66.4)	209 (68.7)	203 (66.0)	
Other	104 (13.2)	147 (18.6)	122 (14.5)	123 (17.4)	
College or above, n (%)	200 (44.9)	240 (56.1)	237 (56.1)	248 (59.4)	0.017*
Poverty-income ratio	2.1 (1.2, 3.2)	2.3 (1.3, 4.3)	2.4 (1.3, 5.0)	2.5 (1.4, 5.0)	0.030*
Hypertension, n (%)	357 (69.6)	353 (66.1)	342 (67.5)	350 (71.6)	0.626
Diabetes, n (%)	185 (35.4)	207 (35.5)	195 (32.5)	219 (37.3)	0.712
Coronary heart disease, n (%)	64 (16.3)	51 (8.2)	39 (6.3)	47 (7.3)	<0.001*
Stroke, n (%)	50 (10.8)	52 (7.9)	47 (6.9)	46 (8.5)	0.345
Smoking, n (%)	243 (50.7)	234 (47.3)	226 (49.4)	227 (46.5)	0.785
Alcohol use, n (%)	255 (54.1)	253 (56.3)	261 (61.6)	239 (54.1)	0.248
eGFR (mL/min/1.73m²)	57.1 (45.0, 92.3)	66.8 (52.6, 99.1)	65.5 (52.4, 94.3)	80.5 (55.7, 103.5)	<0.001*
UACR (mg/g)	40.2 (13.4, 81.5)	45.0 (12.9, 90.3)	42.4 (11.0, 108.4)	46.5 (18.3, 112.7)	0.425
BMI (kg/m²)	28.6 (24.9, 33.9)	29.6 (24.8, 34.5)	29.7 (25.5, 35.3)	30.2 (25.6, 35.2)	0.582
Physical activity (MET)	1200.0 (480.0, 3600.0)	1640.0 (600.0, 4800.0)	1680.0 (600.0, 5840.0)	1440.0 (720.0, 3600.0)	0.043*

*Notes: Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; BMI: body mass index; MET: metabolic equivalent of task. * $P < 0.05$.*

Selenium quartiles differed in several baseline characteristics (Table 1). Median selenium increased from 162.3 μg/L in Q1 to 219.0 μg/L in Q4. The proportion of men rose from 32.9% to 47.6% (P = 0.003), as did the proportion with college education or above (44.9% to 59.4%, P = 0.017). eGFR was higher in Q4 than Q1 (80.5 vs. 57.1 mL/min/1.73 m², P < 0.001), while physical activity also varied across groups (P = 0.043). Coronary heart disease was more frequent in Q1 than Q4 (16.3% vs. 7.3%, P < 0.001).

3.2. Association between Whole Blood Selenium and Cancer Mortality

3.2.1. Cox Proportional Hazards Regression Analysis

Forty cancer deaths were observed. With Q1 as the reference, the fully adjusted model showed a lower hazard in Q4 (HR 0.301, 95% CI 0.097–0.935, P = 0.038). Estimates for Q2 and Q3 were not statistically significant (HR 0.535 and 0.997, respectively).

Using <173.2 μg/L to define deficiency, the adjusted cancer-mortality estimate was higher among deficient participants (HR 1.855, 95% CI 0.938–3.671), although the confidence interval included the null value (P = 0.076).

Table 2. Cox Regression Analysis of the Association between Whole Blood Selenium and Cancer Mortality

	Q1 (Ref)	Q2	Q3	Q4	Se <173.2
Deaths, n (%)	14 (3.0)	8 (1.6)	14 (3.0)	4 (0.8)	14 (3.0)
Model 1	1.00	0.51 (0.21–1.20)	0.83 (0.40–1.74)	0.24 (0.08–0.72)*	2.05 (1.07–3.93)*
Model 2	1.00	0.53 (0.22–1.28)	0.94 (0.44–1.99)	0.28 (0.09–0.87)*	1.83 (0.95–3.54)
Model 3	1.00	0.54 (0.22–1.30)	1.00 (0.46–2.15)	0.30 (0.10–0.94)*	1.86 (0.94–3.67)

*Notes: Data are presented as HR (95% CI). Model 1: Unadjusted. Model 2: Adjusted for age, sex, and race/ethnicity. Model 3: Fully adjusted. * P < 0.05.*

3.3. Non-linear Association Analysis

We next modeled selenium as a continuous exposure with restricted cubic splines (Figure 2). After covariate adjustment, the curve for cancer mortality departed from linearity (P = 0.026) and formed a U-shaped pattern.

The recursive search placed the minimum of the curve at 236.4 μg/L (Table 3). Below this concentration, each additional μg/L was associated with a lower hazard (HR 0.984, 95% CI 0.969–0.998, P = 0.029); at or above it, the slope reversed (HR 1.016, 95% CI 1.008–1.028, P = 0.010). The likelihood-ratio comparison favored the two-piecewise model (P = 0.026).

3.4. Association between Whole Blood Selenium and Secondary Outcomes

All-cause and cardiovascular mortality were examined as secondary endpoints. The cohort experienced 218 all-cause deaths and 79 cardiovascular deaths. Kaplan-Meier curves differed across selenium quartiles (log-rank P < 0.001), with the lowest survival in Q1 (Figure 3).

In Model 3, all-cause mortality was lower in Q2 (HR 0.694, 95% CI 0.488–0.987, P = 0.042), Q3 (HR 0.670, 95% CI 0.463–0.969, P = 0.033), and Q4 (HR 0.491, 95% CI 0.325–0.742, P < 0.001) than in Q1. Deficiency was associated with higher all-cause mortality (HR 1.627, 95% CI 1.212–2.183, P = 0.001). The fully adjusted cardiovascular estimate was not statistically significant (HR 1.519, 95% CI 0.917–2.517, P = 0.104).

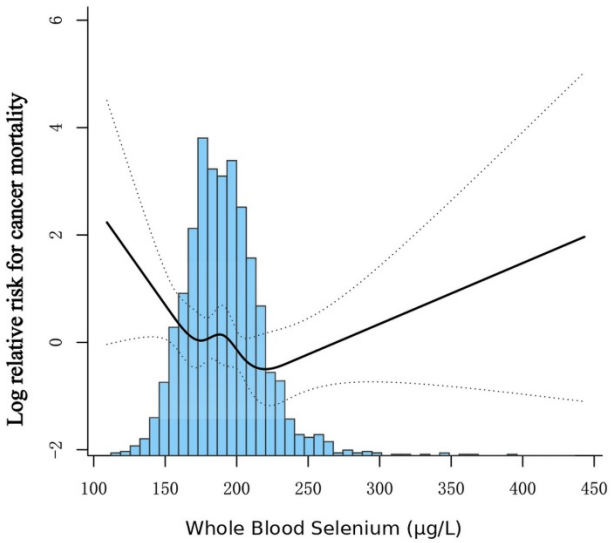


Figure 2. Curve fitting results of whole blood selenium and cancer mortality events

Table 3. Non-linear Association Analysis between Whole Blood Selenium and Cancer Mortality

Outcome	Model	Selenium (μg/L)	HR (95% CI)	P non-linear
Cancer mortality	I (Linear)	Per 1 μg/L	0.99 (0.98–1.01)	—
	II (Non-linear)	<236.4	0.98 (0.97–1.00)*	0.026*
		≥236.4	1.02 (1.01–1.03)*	

*Notes: Model I: Linear. Model II: Two-piecewise with inflection point at 236.4 μg/L. HR per 1 μg/L increase. * P < 0.05.*

Spline analyses suggested an L-shaped relation for both all-cause and cardiovascular mortality, with candidate thresholds at 164.9 and 166.8 μg/L, respectively. Below each threshold, higher selenium was associated with lower risk; above the threshold, the estimates were not statistically distinguishable from no association. Thus, the shape of the association differed by endpoint.

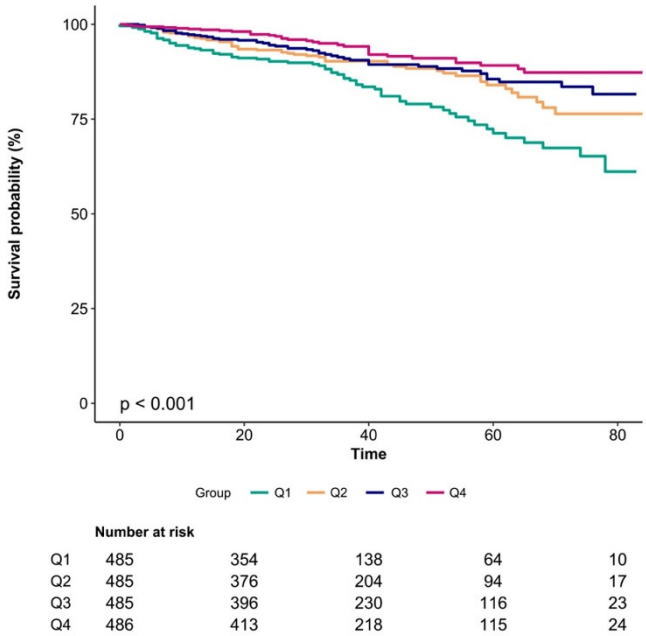


Figure 3. Kaplan-Meier survival curves of CKD patients after grouping by quartiles

3.5. Sensitivity Analyses

The direction of the main association was stable in sensitivity analyses. Excluding deaths during the first 12 months produced an HR of 0.989 (95% CI 0.974–1.005); excluding deaths during the first 24 months produced an HR of 0.979 (95% CI 0.956–1.001); and removing extreme selenium values produced an HR of 0.993 (95% CI 0.978–1.008).

4. Discussion

Using NHANES 2013–2018, we evaluated 1,941 adults with non-dialysis-dependent CKD over a median of 33 months. The central finding was a nonlinear association between whole-blood selenium and cancer mortality, with the estimated minimum at 236.4 μg/L. Earlier NHANES work considered serum selenium and all-cause or cardiovascular mortality [16]; our analysis used whole blood and focused on cancer death.

The inverse contrast between Q1 and Q4 is compatible with pooled observational evidence linking higher selenium status to lower cancer mortality [7,20,21]. At the same time, the curve did not continue downward across the full exposure range. The U-shaped form and the higher turning point than that reported in Vietnam [15] may reflect differences in background selenium intake, renal handling, and population composition. These explanations remain speculative because only 40 cancer deaths were available.

Cancer mortality and non-cancer outcomes did not share the same exposure-response shape. Cancer mortality was U-shaped, whereas all-cause and cardiovascular mortality were approximately L-shaped. This divergence argues against treating selenium as a uniformly beneficial exposure and suggests that biologic windows may differ across disease pathways [22]. Any clinical interpretation should therefore consider cancer and cardiovascular outcomes together.

A biphasic mechanism is biologically plausible. At adequate concentrations, selenoproteins support peroxide removal, redox balance, DNA repair, and immune function [5,23]. Once selenoprotein synthesis is near saturation, additional selenium may instead increase reactive metabolites, oxidative injury, or mitochondrial stress [24]. The present data cannot test these mechanisms, but they provide a rationale for evaluating both deficiency and excess in future CKD studies.

CKD may amplify variation in selenium exposure. Protein restriction can reduce intake, while indoxyl sulfate and inflammation may alter transport and utilization [13,14,25]. Lower eGFR has also been associated with lower selenium concentrations [11]. Conversely, reduced clearance may

increase the consequences of excessive supplementation, and prior trials have raised concerns about metabolic effects at higher exposure [26–28]. These competing processes help explain why reference values derived from healthy adults may not apply directly to CKD.

The estimated 236.4 μg/L turning point exceeds values reported in several other populations. The difference could reflect the relatively high baseline selenium concentration in this U.S. sample, CKD-related changes in oxidative stress, or random variation from the small number of cancer events. It should not be interpreted as a universal treatment target.

Intervention evidence is mixed. A Cochrane review of eight randomized trials found no overall reduction in cancer incidence with selenium supplementation [29]. Trials conducted in selenium-replete populations, including SELECT [30,31], may have had little room for benefit; an earlier skin-cancer trial also failed to establish a general preventive benefit [33]. In contrast, the Linxian trial in a selenium-deficient setting reported lower cancer mortality with combined micronutrient supplementation [32]. These contrasts support testing supplementation according to baseline status rather than assuming that more selenium is better.

The findings may help define hypotheses for clinical research, but they do not establish a supplementation regimen. Participants below 173.2 μg/L may warrant nutritional assessment, while those above 236.4 μg/L should not receive additional selenium solely on the basis of this observational analysis. Thresholds should be recalibrated in populations with different dietary exposure and verified in prospective trials.

5. Limitations

This study has limitations. Its retrospective observational design prevents causal inference. NHANES provided one selenium measurement, so within-person change could not be assessed. Only 40 cancer deaths occurred, limiting precision and precluding reliable analyses by cancer type. Functional markers such as selenoprotein P and GPx activity were unavailable [34]. Dietary quality, cancer family history, and genetic variation were not fully captured, leaving potential residual confounding. Finally, the U.S. exposure distribution may not represent selenium-deficient regions.

6. Conclusion

In U.S. adults with non-dialysis-dependent CKD, whole-blood selenium showed a U-shaped association with cancer mortality, with the lowest modeled risk near 236.4 μg/L. All-cause and cardiovascular mortality displayed different, approximately L-shaped patterns. These results support further study of exposure ranges rather than indiscriminate supplementation. Because the analysis is observational and event numbers are limited, the reported thresholds require confirmation in well-designed prospective and randomized studies.

Author Contributions

Conceptualization, Y.Y. and J.H.; Methodology, Y.Y. and J.H.; Software, Y.Y.; Validation, Y.Y. and J.H.; Formal Analysis, Y.Y.; Investigation, Y.Y. and J.H.; Resources, J.H.; Data Curation, Y.Y.; Writing – Original Draft Preparation, Y.Y.; Writing – Review & Editing, Y.Y. and J.H.; Visualization, Y.Y.; Supervision, J.H.; Project Administration, J.H. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

This study used publicly available data from the National Health and Nutrition Examination Survey (NHANES). The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and written informed consent was obtained from all participants at the time of data collection. As this study involved secondary analysis of de-identified public data, no additional ethical approval was required.

Informed Consent Statement

Written informed consent was obtained from all participants by the National Health and Nutrition Examination Survey (NHANES) at the time of data collection.

Data Availability Statement

The original data presented in this study are openly available from the National Health and Nutrition Examination Survey (NHANES) database at https://wwwn. cdc.gov/ nchs/ nhanes/.

Conflicts of Interest

The authors declare no conflicts of interest.

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