scientific reports

Check for updates

OPEN

A U-shaped association between blood selenium levels and prostate cancer: findings of a case-control study among Nigerian men

Onyinyechi Bede-Ojimadu[1,2]✉, Nwakasi Nnamah[2], Jude A. Onuegbu[2], Fiorella Barraza[3], Iain Grant-Weaver[3], Jideofor Orakwe[4], Joseph Abiahu[4], Nkiru Ezeama[5], Ejeatuluchukwu Obi[6], Orish Ebere Orisakwe[7] & Jerome Nriagu[8]

The ability of selenium to both prevent and induce cancer at varying biological concentrations has been reported in previous studies. We studied the associations between selenium exposure and prostate diseases such as prostate cancer (PCa) and benign prostatic hyperplasia (BPH), and estimated the optimal range of selenium concentrations that may be needed to prevent these diseases among Nigerian men. Blood and urine samples from men with histologically diagnosed PCa (*n* = 90), BPH (*n* = 97), and controls (*n* = 98) were analyzed for trace elements, including selenium. The associations between selenium concentrations and prostate diseases were estimated using logistic regression and restricted cubic splines. Men in the lowest and highest blood selenium tertiles had increased odds of PCa {AOR (95% CI): 2.90 (1.13, 7.46) and 4.42 (1.68, 11.59), respectively}. Compared with the first tertile of blood selenium, men in the highest tertile had significantly higher odds of BPH (AOR: 3.92; 95% CI: 1.68, 9.11). We found that a putative range of blood selenium concentration associated with minimum odds of PCa may lie between 125.55 and 134.86 µg/L. No significant association was observed between urinary selenium levels and PCa. The narrow-ranged U-type relationship between blood selenium concentration and PCa needs to be confirmed in larger longitudinal cohort studies.

Keywords Benign prostatic hyperplasia, Environmental exposure, Prostate cancer, Nigeria, Selenium

Selenium is an essential trace element that plays a vital role in several biological processes[1,2]. Of the many health benefits attributed to selenium, its role in cancer prevention has received the most significant research attention[3]. Data from mechanistic studies are highly suggestive of selenium's protective effect against cancers: it is an integral component of seleno-proteins such as glutathione peroxidases, which participate principally in the antioxidant defense system[4]. Selenium may also inhibit cellular proliferation,[5] induce apoptosis, facilitate DNA repair[5,6] and disrupt androgen receptor signaling[7].

Data from several studies support the protective role of selenium against cancers in prostate tissues[8,9]. The preferential accumulation of selenium in prostate tissues[8] as well as the enhanced local activity of seleno-proteins in these tissues[9] have been hypothesized as possible mechanisms through which selenium may protect prostate tissues against carcinogenesis[9]. Despite the plausibility of an association between selenium exposure and PCa, evidence from epidemiological studies has remained conflicting. The strongest evidence from human studies for a protective effect of selenium against PCa comes from the Nutritional Prevention of Cancer (NPC) trial[10] which reported an overall 52% reduction in PCa incidence among men supplemented with 200 µg selenium per day, during a mean follow-up of 7.9 years. However, further analysis of the data revealed that only participants in the lowest two tertiles of baseline plasma selenium concentrations (< 121.6 ng/mL) had significant reductions in PCa

[1]Department of Medical Laboratory Science, Kampala International University, Kampala, Uganda. [2]Department of Chemical Pathology, Nnamdi Azikiwe University, Awka, Nigeria. [3]Department of Renewable Resources, University of Alberta, 348B South Academic Building, Edmonton, Canada. [4]Division of Urology, Department of Surgery, Nnamdi Azikiwe University, Awka, Nigeria. [5]Department of Community Medicine and Primary Health Care, Nnamdi Azikiwe University, Awka, Nigeria. [6]Department of Pharmacology and Therapeutics, Nnamdi Azikiwe University, Awka, Nigeria. [7]Advanced Research Centre, European University of Lekfe, Lekfe, Turkey. [8]Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, USA. ✉email: onyinyechi.bede@kiu.ac.ug; giftbede@gmail.com

incidence, and there was no evidence of benefit in the highest tertile[11]. Subsequent trials in other populations, including the large Selenium and Vitamin E Cancer Trial, (SELECT), did not confirm the beneficial effect of selenium supplementation[12–14]. Instead, a higher risk of high-grade PCa was observed among men with higher baseline toenail selenium status (> 0.90 μg/g) in the SELECT study[15], suggesting that the association between selenium and PCa may vary among different populations and may be largely dependent on the selenium status of the population.

Despite its beneficial roles, selenium is toxic at excessive exposure levels, and there is a very narrow range between adequate and toxic selenium levels[16]. At higher concentrations, selenium may induce oxidative stress and therefore may play a role in the etiology and progression of cancers[17,18]. This underscores the need for adequate intake and careful monitoring to prevent both toxicity and deficiency.

Selenium is widely distributed in nature[19], and diet is the main source of selenium exposure to humans. Human exposure to selenium is dependent on its amount in food, which in turn depends on the selenium content of the soil where they are grown[20]. Reports on the selenium content of Nigerian food crops and soil indicate widespread variations across different locations[21,22]. A review of published studies found a very large variation in the selenium status of the Nigerian population[23]. The role of this variation in selenium exposure in the prevalence of prostate diseases in this population has not been investigated. Therefore, the current paper was designed to fill these gaps in knowledge as well as estimate possible optimal blood selenium level for low odds of these diseases in this population.

Methods

Study population

This case-control study was designed to investigate the mediating effects of environmental and lifestyle factors on PCa and BPH in men living in South-Eastern Nigeria. Description of the study population, questionnaire survey, collection and analysis of trace elements in urine and blood samples are described in detail in our earlier publication[24]. Briefly, the study recruited male participants attending urology and other clinics at Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. Cases consisted of newly (incident) histologically confirmed, treatment-naive PCa and BPH patients attending urology clinics. Control participants were patients enrolled in the urology clinics, general outpatient department and other clinics of the same hospital for minor health conditions, who had no prior diagnosis nor history of prostate or malignant disease of any site at the time of recruitment. These individuals were screened for possible clinical BPH using the International Prostate Symptoms Score (IPSS). Those who had a total IPSS score of less than 2 were further screened for PCa using serum total prostate-specific antigen (PSA) test. Serum PSA levels were quantitatively measured, and only individuals with total PSA values < 4 ng/mL were recruited as controls. We minimized potential selection bias by clearly defining and using the same inclusion and exclusion criteria for both cases and controls. Individuals with physician-diagnosed renal diseases, those with physical or mental inability, as well as those who reported recent intake (within the last 3 months before recruitment) of antioxidants or any supplement or medication that may interfere with their trace element status were excluded from the study. The controls were matched by age (+ 2 years) with the PCa and the BPH groups. A total of 285 participants: PCa ($n = 90$), BPH patients ($n = 97$) and Control participants ($n = 98$) were included in the study.

The study was approved by the Ethics Committee of NAUTH (NAUTH/CS/66/VOL.11/116/2018/056) and the University of Alberta, Edmonton, Canada (Pro00097779) and was carried out in accordance with the Declaration of Helsinki. Each participant gave written informed consent before recruitment.

Sample size determination, sample collection and handling

The minimum sample size for the study was determined using the Schlesselman[25] formula for matched case-control studies:

$$N = \left[\frac{(Z_{\alpha/2} + Z_{\beta})\sigma}{\Delta}\right]^2 \left(\frac{m+1}{m}\right)$$

This was based on the quantitative variable (difference in means of selenium concentrations). $Z_{\alpha/2}$ = standard normal deviate corresponding to the two-sided significance level of 5% ($P < 0.05$) = 1.96, Z_{β} = standard normal deviate corresponding to 80% power = 0.84, Δ = expected mean difference between cases and controls, m = ratio of controls to cases (1 for an equal number of cases and controls); σ = Population standard deviation calculated from the pooled standard deviation of a previous study. There was no previous Nigerian study that measured selenium in whole blood or urine of patients with prostate disorders. The sample size calculation was therefore based on the information (mean and standard deviations) of the study groups in a German study[26], which measured selenium in whole blood obtained from German patients with prostate disorders and healthy controls. Inputting all values into the equation, a minimum total sample size of 96 participants (32 PCa cases, 32 BPH cases and 32 controls) was obtained. However, more participants were recruited to improve the power of the study.

Sociodemographic, lifestyle and health information, including age, educational attainment, major occupation, marital status, smoking history, alcohol habits, history of diabetes, and family history of prostate disease, were collected via a questionnaire. Weight and height were measured using standard techniques and body mass index (BMI) was calculated by dividing weight by height squared. Whole blood and spot urine samples were collected from each participant using standard procedures. The samples were stored frozen at −20 °C until shipped to SWAMP Laboratory at the University of Alberta, Canada, for trace element analysis. On reaching their destination, the samples were stored at − 20 °C until analysis.

Measurement of trace element concentrations in whole blood and urine

Selenium concentrations in whole blood and urine samples were measured using an ICP-MS (iCAP-RQ, Thermo-Fisher Scientific). Briefly, about 6 mL of twice sub-boiled HNO3 (65%, trace grade) and 1 mL of hydrogen peroxide were added to about 0.5 mL of homogeneously mixed blood sample in an acid-cleaned PolyTetraFluoroEthylene (PTFE) vessel. The samples were digested overnight in a high-pressure microwave digestion system (Ultraclave, MLS, Leutkirch, Germany) as described by Shotyk et al.[27]. Samples were removed from the microwave, cooled at room temperature and made up to 20 mL with high-purity deionized water (Milli-Q water type 1, 18.2 MΩ cm at 25 °C; Millipore, Bedford, MA, USA) in acid-washed polypropylene centrifuge tubes (Eppendorf).

About 0.5 mL of each homogeneously mixed urine sample was dispensed into an acid-cleaned 15 mL polypropylene centrifuge tubes. This was diluted (1:20) with 9.5 mL of the diluent solution (containing 1.0% (v/v) nitric acid (HNO3, 65%), 0.02% (w/v) Triton X-100 in Milli-Q Water Type 1). The diluted urine samples were kept refrigerated until analysis. Certified Reference Materials (CRMs): ClinChek (levels I and II), NIST1643f and SPS-SW2 for urine and ClinChek (whole blood levels III) and NIST 1577 (Bovine liver) for whole blood were used for quality assurance. The CRMs were also prepared alongside the samples. To compensate for matrix effects and instrument drift, internal standard solutions of scandium and indium (^{45}Sc and ^{115}In) were introduced through a separate line along with the samples. All measurements were made in triplicate, and the average of the three readings was used as the concentration of each trace element in the samples. The limits of detection (LOD) and quantification (LOQ), method detection limit (MDL) and the recovery rates of the CRMs are presented in Supplementary Table S1.

Measurement of urinary creatinine concentration

Urinary creatinine was determined by spectrophotometric method using creatinine assay kits (Randox Laboratories Ltd, Crumlin, UK), following the manufacturer's instructions. Creatinine adjustments were performed by dividing urinary selenium concentrations (µg/L) by creatinine concentrations (g/L).

Statistical analysis

All measured urine and blood samples had values above the limits of detection for the five trace elements (selenium, zinc, iron, copper and manganese) used in this study. Given the skewed nature of the data, the few missing values were replaced by median values of the individual trace elements. Blood and urine selenium concentrations were summarized by median (interquartile range). Kruskal-Wallis H tests with Bonferroni adjustments were used to compare the distributions of selenium concentrations among groups. Categorical variables were reported as counts and percentages, and comparisons among the groups were performed using the Chi-square ($\chi 2$) test. Two case-control comparisons were made (PCa *versus* controls and BPH *versus* controls). The associations of selenium with PCa and BPH were determined using logistic regression. Linear associations of selenium concentrations with PCa and BPH were explored by entering blood and urinary selenium concentrations as ln-transformed continuous variables in the logistic regression models. Selenium concentrations were further categorized into tertiles based on the distribution among controls, with the lowest tertiles serving as the reference group. In a subsequent analysis, the middle tertile was compared with the lowest and highest tertiles. Corrections for multiple comparisons were made using the Bonferroni correction. Based on previous knowledge of their associations with prostate diseases, we included age, BMI, family history of PCa (yes/no), smoking history (never/ever), and major occupation (civil servants, priests and related jobs/ farmers, industrialists and related jobs/ automobile repairers, metal workers, commercial drivers) as covariates in the regression models. Possible effect of other trace elements associated with oxidative stress (copper, zinc, manganese and iron) was evaluated by including these elements as ln-transformed variables in Model B of the logistic regression. Before their inclusion in the model, multicollinearity was assessed among these elements using variance inflation factors (VIF). The calculated VIF values ranged from 1.35 to 1.84 for the blood trace elements and 1.65 to 2.81 for the creatinine-adjusted urine trace elements, and were within the acceptable VIF threshold of < 5[28], indicating low correlation among these variables. These variables were therefore included jointly in regression model B. Further adjustment was made for diabetes status, given its significance at the bivariate level (Model C). Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) model[29] selection was used to select the best-fitted model among the linear model and a set of spline models with knots at different locations. The model with the lowest AIC/BIC value was considered the best-fitted model.

Restricted cubic splines in fully adjusted logistic regression models were used to evaluate the non-linear association between blood selenium concentrations and PCa, as well as determine the optimal cut-point for blood selenium concentrations for the lowest odds of PCa[30]. Given the small sample size, a three-knot model was used to provide an adequate balance of flexibility and parsimony. Knot locations were placed at the 10th, 50th and 90th percentiles of the blood and urine distributions among the study population.

Sensitivity analyses were conducted to evaluate the robustness of the estimated relationship between selenium and prostate disorders. Given that acute kidney impairment is a common finding among patients with prostate disorders, which may alter their creatinine excretion and make creatinine normalization less reliable, separate analyses were conducted using absolute urine selenium concentrations. Based on previous knowledge of their associations with prostate diseases, subgroup analyses were conducted by age (≤ 70; >70), smoking history (never; ever) and family history of prostate diseases (yes/no). Because the shape of the dose-response curve may be affected by the location of the knots, we also considered placements of knots in alternative locations at 5th, 50th and 95th percentiles. Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 27 (SPSS Inc., Chicago, IL, USA) and R (version 4.5.1; https://www.R-project.org/). The significance level of 0.05 was used in all analyses.

Results

The general characteristics of the study participants are presented in Table 1. There were no significant differences in median age (interquartile ranges) among the study groups. Compared with the control group, participants with PCa had lower BMI {median (IQR): 23.7 kg/m^2 (21.7, 25.5) vs. 24.8 kg/m^2 (22.6, 27.7); $p = 0.003$}, were more likely to be smokers and less likely to have diabetes. Socio-demographic, lifestyle and clinical characteristics, including age, education level, marital status, smoking history, family history of prostate diseases and BMI, did not differ between the BPH and control groups. However, compared with the control group, participants with BPH and PCa were less likely to have diabetes (Table 1). Differences in the distribution of blood selenium concentrations between the PCa and control groups were not statistically significant. Compared with the control group, the BPH group had significantly higher concentration of blood selenium (Median (interquartile range): 125.00 µg/L (110.75–145.00) *versus* 155.50 µg/L (128.75–203.75), respectively). There were no statistically significant differences in creatinine-adjusted urine selenium concentrations between the control and the two case groups (Table 1).

Table 2 presents the results of the regression analysis for the association between blood and urine selenium concentrations and PCa. There was no significant linear association between blood selenium concentrations (as an ln-transformed continuous variable) and PCa (Adjusted odds ratio (AOR): 1.52; 95% CI: 0.42, 5.52). However, there was evidence of non-linear association between blood selenium concentrations and PCa: compared with men in the first tertile of blood selenium, men in the second tertile had lower odds of PCa (AOR: 0.35; 95% CI: 0.13, 0.89). Using the middle tertile as the reference group (Table 3), an increased odds of PCa was observed among men in the lowest tertile (AOR: 2.90; 95% CI: 1.13, 7.46), as well as those in the highest tertile of blood selenium (AOR: 4.42; 95% CI: 1.68, 11.59). With further adjustment for diabetes status, a slight reduction in the effect size in the lowest tertile (AOR: 2.33; 95% CI: 0.89, 6.07) and a slight increase in effect size in the highest tertile of blood selenium (AOR: 4.69; 95% CI: 1.75, 12.52) were observed (Table 3, Model C).

As shown in Table 4, all the spline models outperformed the linear model for the association between blood selenium and PCa. Spline model B (adjusted for the parameters in model B; with knots at 10th, 50th and 90th percentile of blood selenium; AIC = 232.82; BIC = 268.42) and Spline model C (adjusted for the parameters in model B + diabetes status; with knots at 10th, 50th and 90th percentile of blood selenium; AIC = 226.71 BIC = 265.55) were the best-fitted models and were reported here. In the sensitivity analyses, using alternative knot locations in spline model D (adjusted for the parameters in model B; with knots at 5th, 50th and 95th percentiles of blood selenium) gave higher AIC and BIC values. The results of the restricted cubic splines revealed a non-linear relationship between blood selenium concentrations and PCa ($p_{non-linear} = 0.003$; Fig. 1A). Lowest

Variables[a]	Study groups			*p*-values[b]	
	PCa (n = 90)	BPH (n = 99)	Controls (n = 98)	PCa vs. Controls	BPH vs. Controls
Age	71.00 (65.00, 76.25)	70.00 (62.50, 75.50)	68.50 (62.00, 75.00)	0.071	0.659
Marital status				0.072	0.613
Single	0 (0)	1 (1)	2 (2)		
Married	77 (85.6)	87 (89.7	90 (91.8)		
Divorced	13 (14.4)	9 (9.3)	6 (6.1)		
Education attainment				0.990	0.332
No formal education	7 (7.8)	3 (3.1)	8 (8.2)		
Primary education	47 (52.2)	55 (56.7)	49 (50)		
Secondary education	24 (26.7)	23 (23.7)	28 (28.6)		
Tertiary education	12 (13.3)	16 (16.5)	13 (13.3)		
BMI (Kg/M^2)	23.52 (21.30–25.35)	25.10 (23.23–27.32)	24.86 (22.64–27.65)	0.006	1.000
Smoking history				0.012	0.113
Non-smoker	35 (38.9)	45 (46.4)	56 (57.1)		
Smoker	55 (61.1)	52 (53.6)	42 (42.9)		
Family history of PCa				0.777	0.764
No	74 (82.2)	80 (82.3)	79 (80.6)		
Yes	16 (17.8)	17 (17.7)	19 (19.4)		
Diabetes				0.005	0.001
No	80 (88.9)	89 (91.8)	71 (72.4)		
Yes	10 (11.1)	8 (8.2)	27 (27.6)		
Blood selenium concentrations (µg/L)	124.50 (102.50–159.75)	155.50 (128.75–203.75)	125.00 (110.75–145.00)	1.000	<0.001
Urine selenium concentrations (µg/L)	18.40 (9.85–26.88)	14.10 (9.50–25.25)	20.10 (12.48–33.78)	1.000	0.138
Creatinine-adjusted urine selenium concentrations (µg/gCr)	22.44 (13.70–31.38)	16.93 (9.77–26.33)	16.66 (12.58–26.44)	0.249	0.745

Table 1. Characteristics of the study participants. BMI = Body mass index; BPH = Benign prostatic hyperplasia; PCa = Prostate cancer; a = categorical variables are presented as number of counts (percentages); b = P-values are based on Kruskal Walis H test (median) with Bonferroni adjustments for continuous variables and Pearson's Chi –square tests for categorical variables.

Variables	Unadjusted model	Model A	Model B	Model C
Blood selenium (μg/L)				
Ln-transformed blood selenium	1.29 (0.47, 3.53)	1.72 (0.59, 5.02)	1.52 (0.42, 5.52)	2.22 (0.57, 8.56)
Tertile 1 (< 116)	Reference	Reference	Reference	Reference
Tertile 2 (117–134)	0.31 (0.14, 0.70)*	0.33 (0.14, 0.79)*	0.35 (0.13, 0.89)	0.43 (0.17, 1.12)
Tertile 3 (> 135)	1.15 (0.60, 2.21)	1.45 (0.78, 1.67)	1.52 (0.67, 3.44)	2.01 (0.88, 4.77)
Urine selenium (μg/L)				
Ln-transformed urine selenium	0.79 (0.55, 1.13)	0.80 (0.55, 1.17)	0.55 (0.30, 1.00)	0.58 (0.31, 1.06)
Tertile 1 (< 14.70)	Reference	Reference	Reference	Reference
Tertile 2 (14.71–28.30)	1.13 (0.57, 2.21)	1.05 (0.51, 2.16)	0.88 (0.36, 2.14)	0.78 (0.32, 1.93)
Tertile 3 (> 28.31)	0.63 (0.30, 1.30)	0.60 (0.28, 1.32)	0.40 (0.13, 1.22)	0.42 (0.14, 1.33)
Creatinine-adjusted urine selenium (μg/g creatinine)				
Ln-transformed urine selenium	1.25 (0.88, 1.79)	1.14 (0.78, 1.67)	0.62 (0.32, 1.18)	0.63 (0.33, 1.22)
Tertile 1 (< 14.71)	Reference	Reference	Reference	Reference
Tertile 2 (14.72–23.22)	0.61 (0.28, 1.31)	0.52 (0.23, 1.19)	0.36 (0.14, 0.95)	0.38 (0.14, 1.01)
Tertile 3 (> 23.23)	1.52 (0.77, 2.97)	1.31 (0.64, 2.66)	0.78 (0.30, 2.05)	0.80 (0.30, 2.12)

Table 2. Odds ratios (95% confidence intervals) for associations between whole blood and urinary selenium concentrations and prostate cancer among Nigerian men. ORs = Odds ratios; *= significant association at $p < 0.0163$ (Bonferroni adjustment); Model A was adjusted for ln-transformed age, ln-transformed body mass index, major occupation, smoking frequency and family history of prostate cancer. Model B was further adjusted for ln-transformed blood and urine zinc, copper, manganese and iron concentrations, respectively.

Blood Selenium tertiles (μg/L)	Unadjusted ORs	Model A	Model B	Model C
Tertile 1 (< 116)	3.25 (1.42, 7.43	3.05(1.26, 7.38)*	2.90 (1.13, 7.46)	2.33 (0.89, 6.07)
Tertile 2 (117–134)	Reference	Reference	Reference	Reference
Tertile 3 (> 135)	3.73 (1.63, 8.52)*	4.44 (1.82, 10.80)*	4.42 (1.68, 11.59)*	4.69 (1.75, 12.52)*

Table 3. Odds ratios (95% confidence intervals) for associations between whole blood selenium concentrations and prostate cancer among Nigerian men, using middle tertile as the reference category. ORs = Odds ratios; *= significant association at $p < 0.0163$ (Bonferroni adjustment); Model A was adjusted for ln-transformed age, ln-transformed body mass index, major occupation, smoking history and family history of prostate cancer. Model B was further adjusted for ln-transformed blood zinc, copper, manganese and iron concentrations. Model C was further adjusted for diabetes status.

Model	Location of knots	AIC	BIC	Log-Likelihood	Number of parameters (df)
Linear model	–	256.41	292.01	-117.2052	11
Spline model B	3 knots at 10th, 50th and 90th percentiles	232.82	268.42	-105.4099	11
Spline model C	3 knots at 10th, 50th and 90th percentiles	226.71	265.55	-101.3550	12
Spline model D (sensitivity analysis)	3 knots at 5th, 50th and 95th percentiles	239.15	274.75	-108.5737	11

Table 4. Comparison between Log-Likelihood, AIC and BIC of the linear and spline models.

odds of PCa were observed at blood selenium concentrations between 125.55 and 134.86 μg/L. With further adjustment for diabetes status, the non-linear relationship was consistent ($p_{non-linear} = 0.004$). However, the range between the two blood selenium values for the lowest odds of PCa became narrower (125.21–129.02 μg/L; Fig. 1B). No statistically significant association was observed between urine selenium concentrations and PCa (Table 2; Fig. 1C).

Odds ratios for the association between selenium exposure markers and BPH are presented in Table 5. There was a positive association between blood selenium concentrations and BPH among the study participants: Compared to men in the lowest tertile of blood selenium, those in the highest tertile were at higher odds of BPH (AOR: 3.92; 95% CI: 1.68, 9.11). As shown in Fig. 1D, there was no evidence of a non-linear association between blood selenium concentrations and BPH ($p_{non-linear} = 0.238$). Urine selenium concentrations, as ln-transformed continuous variable, were associated with a reduction in odds of BPH (AOR: 0.44; 95% CI: 0.24, 0.81). Compared to men in the lowest tertile of urine selenium, those in the second tertile were at lower odds of BPH (AOR: 0.35; 95% CI: 0.15, 0.84). The inverse association between urine selenium and BPH, although suggestive, was not significant, comparing the highest with the lowest tertile of urine selenium (AOR: 0.48;

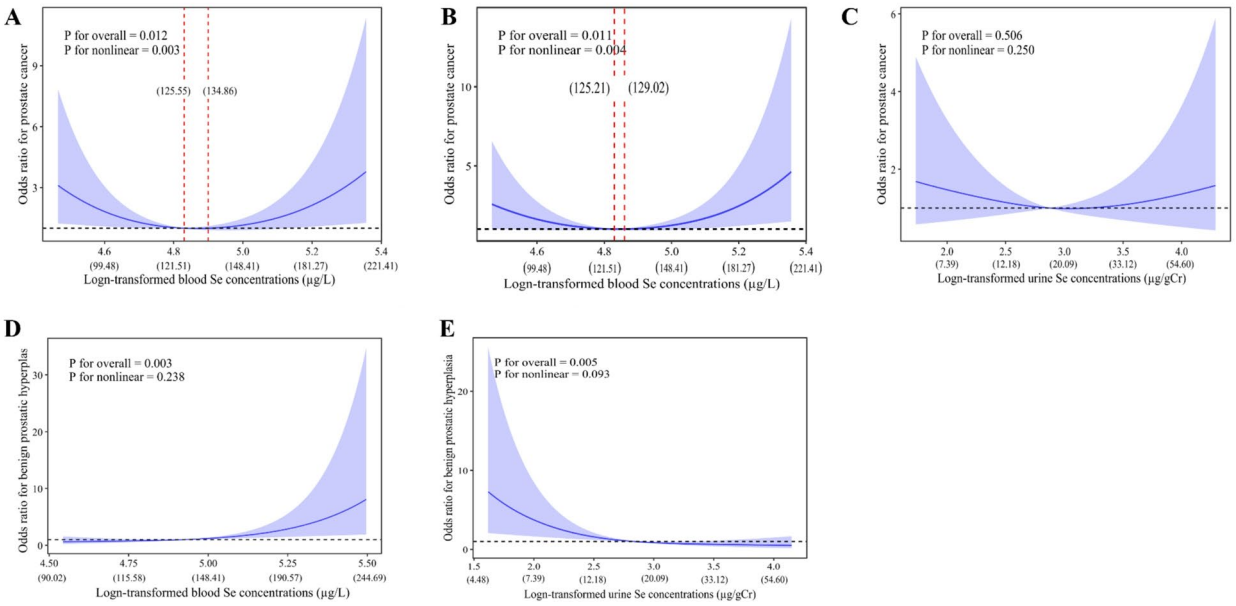

Fig. 1. Restricted cubic splines for association between selenium status and prostate diseases.

Variables	Unadjusted model	Model A	Model B	Model C
Blood selenium (μg/L)				
Log-transformed blood selenium	13.21 (4.70, 37.16)*	15.46 (5.23, 45.70)*	7.62 (2.15, 27.10)*	11.42 (2.99, 43.59)*
Tertile 1 (< 116)	Reference	Reference	Reference	Reference
Tertile 2 (117–134)	0.71 (0.28, 1.80)	0.74 (0.28, 1.96)	0.68 (0.25, 1.85)	0.85 (0.31, 2.36)
Tertile 3 (> 135)	5.10 (2.44, 10.65)*	5.85 (2.72, 12.55)*	3.92 (1.68, 9.11)*	5.50 (2.44, 13.49)*
Urine selenium (μg/L)				
Ln-transformed urine selenium	0.63 (0.44, 0.90)*	0.62 (0.43, 0.89)*	0.40 (0.23, 0.70)	0.42 (0.24, 0.75)
Tertile 1 (< 14.70)	Reference	Reference	Reference	Reference
Tertile 2 (14.71–28.30)	0.52 (0.26, 1.03)	0.51 (0.26, 1.03)	0.45 (0.20, 1.05)	0.41 (0.17, 0.96)
Tertile 3 (> 28.31)	0.44 (0.22, 0.88)	0.40 (0.20, 0.83)	0.25 (0.09, 0.67)*	0.26 (0.09, 0.75)*
Creatinine-adjusted urine selenium (μg/g Creatinine)				
Ln-transformed urine SeCr	0.85 (0.59, 1.22)	0.82 (0.56, 1.20)	0.44 (0.24, 0.81)*	0.45 (0.28, 0.84)*
Tertile 1 (< 14.71)	Reference	Reference	Reference	Reference
Tertile 2 (14.72–23.22)	0.55 (0.27, 1.13)	0.50 (0.24, 1.04)	0.35 (0.15, 0.84)	0.33 (0.14, 0.82)
Tertile 3 (> 23.23)	0.97 (0.43, 2.18)	0.80 (0.41, 1.58)	0.48 (0.19, 1.20)	0.45 (0.18, 1.14)

Table 5. Odds ratios (95% confidence intervals) for associations between whole blood and urinary selenium concentrations and benign prostatic hyperplasia among Nigerian men. ORs = Odds ratios; *= significant association at $p < 0.0163$ (Bonferroni adjustment); Model A was adjusted for ln-transformed age, ln-transformed body mass index, major occupation, smoking frequency and family history of prostate cancer. Model B was further adjusted for ln-transformed blood and urine zinc, copper, manganese and iron concentrations, respectively.

95% CI: 0.19, 1.20). However, as shown in the restricted cubic spline, the non-linear relationship between urine selenium concentrations and BPH was not statistically significant ($p_{non-linear} = 0.093$; Fig. 1E).

We used several sensitivity analyses to evaluate the robustness of the observed relationship between selenium concentrations and prostate disorders. Use of absolute urine selenium values did not change the significance of the differences in mean urine selenium concentrations between cases and control participants (Table 1) nor the direction of associations with PCa and BPH (Tables 2 and 5, respectively). Subgroup analyses by age, smoking history and family history of prostate disease with restricted cubic spline showed that the U-shaped association between blood selenium and PCa was consistent in all subgroups (Supplementary figure S1; Table 6). Significant interaction was observed between blood selenium concentration and smoking history (p-interaction = 0.006). Compared with the middle tertile, the odds of PCa for the lowest and highest tertiles of blood selenium were strongly significant among never-smokers but not significant among ever-smokers (Table 6). In the RCS models,

Groups	Prostate cancer				Benign prostatic hyperplasia			
	Tertiles of blood selenium concentrations (μg/L)				Tertiles of blood selenium concentrations (μg/L)			
	Tertile 1 (< 116)	Tertile 2 (117–134)	Tertile 3 (> 135)	*p*- for interaction	Tertile 1 (< 116)	Tertile 2 (117–134)	Tertile 3 (> 135)	*p*-for interaction
Age				0.802				0.197
≤ 70 years	[P/C = 21/19] 3.82 (0.81, 18.04)	[P/C = 3/17] 1	[P/C = 20/19] 4.84 (1.08, 21.73)		[B/C = 38/19] 1.61 (0.32, 8.03	[B/C = 5/17] 1	[B/C = 7/19] 4.55 (1.11, 18.69	
> 70 years	[P/C = 20/13] 2.97 (0.77, 11.40)	[P/C = 8/15] 1	[P/C = 18/15] 3.23 (1.25, 21.95)		[B/C = 34/13] 1.58 (0.34, 7.35)	[B/C = 5/15] 1	[B/C = 8/15] 7.50 (1.69, 33.31)	
Smoking History				0.006*				0.544
Never-smokers	[P/C = 20/17] 23.41 (2.55, 214.96)	[P/C = 1/23] 1	[P/C = 14/16] 41.85 (4.39, 398.81)		[B/C = 36/17] 1.03 (0.20, 5.42)	[B/C = 5/23] 1	[B/C = 4/16] 9.73 (2.45, 38.69)	
Ever-smokers	[P/C = 21/15] 0.98 (0.24, 3.97	[P/C = 10/9] 1	[P/C = 24/18] 1.00 (0.24, 4.18)		[B/C = 36/15] 1.67 (0.36, 7.81)	[B/C = 5/9] 1	[B/C = 11/18] 3.08 (0.70, 13.55)	
Family history of prostate disease				0.173				0.671
No	[P/C = 30/26] 3.38 (1.11, 10.23)	[P/C = 9/24] 1	[P/C = 35/29] 4.57 (1.43, 14.61)		[B/C = 58/26] 1.49 (0.46, 4.79)	[B/C = 8/24] 1	[B/C = 14/29] 5.13 (1.71, 15.41)	
Yes	[P/C = 11/6] 2.05 (0.19, 22.15)	[P/C = 2/8] 1	[P/C = 3/5] 6.50 (0.90, 47.04)		[B/C = 14/6] 0.93 (0.05,18.97)	[B/C = 2/8] 1	[B/C = 1/5] 7.86 (0.88, 70.07)	

Table 6. Subgroup analysis of the association between blood selenium concentrations and prostate diseases. ORs = Odds ratios; *= significant association at $p < 0.0163$ (Bonferroni adjustment); all analyses were adjusted for ln-transformed age, ln-transformed body mass index, major occupation, smoking history, family history of prostate cancer, ln-transformed blood zinc, copper, manganese and iron concentrations, except for the covariate defining the subgroup, P/C = number of PCa/controls per teritile of blood selenium; B/C = number of BPH/controls per teritile of blood selenium.

a change in the location of the knots affected the shape of the dose-response curve (Supplementary figure S2), and did not reveal the non-linear association between blood selenium concentrations and prostate cancer.

Discussion

The results of this study show that men in both extremes of blood selenium status had higher odds of PCa. Higher levels of blood selenium were associated with BPH. These associations were consistent even after adjustments for several confounding variables, including other antioxidant trace elements, as well as in subgroup analyses. The U-shaped association between blood selenium and PCa was significantly stronger among never-smokers than in ever-smokers. In contrast, there was a suggestive inverse association between urinary selenium levels and BPH.

As in this study, U-shaped associations with selenium exposure have been reported for several health outcomes, including cardiovascular diseases[31], all-cause cancer and cardiovascular mortality[32,33], metabolic syndrome[34]. Waters et al.[35] in a canine model, demonstrated a U-shaped dose-response relationship between toenail selenium status and the extent of DNA damage within prostatic tissues. A more recent hospital-based case-control study in Vietnam has also reported a U-shaped association between selenium intake and several cancers including stomach, colon, rectum, and lung cancers[36]. However, the study was based on a food frequency questionnaire on dietary selenium intake and did not report for PCa[36]. Previous reports on the association between selenium biomarkers and PCa have generally been inconsistent. While two meta-analyses comprising of 17[37] and 25 studies[38] reported inverse associations between serum/plasma selenium and PCa, another meta-analysis comprising a total of 4527 PCa patients and 6021 control subjects from 15 prospective studies of mostly European men did not observe significant association between blood/plasma selenium levels and PCa[39], but noted inverse associations between toenail selenium levels and PCa overall and between blood/plasma selenium and risk of aggressive disease[39].

Previous studies have generally alluded to the fact that there is a small separation between the two arms of the U-curve; that is, between over-exposure and under-exposure doses of selenium that are associated with adverse health outcomes[40–42]. Reports from the large NPC trial[11] revealed that participants in the lowest two tertiles of baseline plasma selenium concentrations (< 121.6 ng/mL; equivalent to about 152 μg/L of whole blood Se[40]) had significant reductions in PCa incidence following selenium supplementation, with no evidence of benefit among individuals in the highest tertile. The SELECT study on the other hand, reported higher risk of high-grade PCa among men with higher baseline toenail selenium status (> 0.90 μg/g)[15]. The finding of the present study corroborates these previous findings in the US population, providing evidence of a U-shaped association between selenium and PCa in a distinct African population. These findings suggest there is a narrow range of blood selenium levels that may be protective against PCa, and that the effect of selenium exposure on PCa risk may be largely dependent on baseline selenium status of a population. The observed inconsistency in reported

findings from studies on the association between selenium and PCa may be attributed to differences in the ranges of baseline selenium exposure in the different population groups studied.

This paper represents the first attempt to determine the specific thresholds in blood selenium concentration below and above which an individual may likely be at risk of prostate cancer. The estimated cut-points for blood selenium for the lowest odds of PCa, as determined by the RCS plot in this study, may lie between 125.55 and 134.86 µg/L (Fig. 1A). Given the case-control study design, the preliminary nature and the relatively small sample size of this study, this range of blood selenium concentrations should be considered a putative threshold, which requires validation in larger prospective cohort studies. However, the estimate is within the broad plasma selenium concentrations of 39.5–197.4 ng/mL (equivalent to 49.4–246.8 µg/L of whole blood selenium) proposed by Rocourt and Cheng[42] as the optimum range. Based on data from the selenium-replete US population, it was demonstrated that selenoprotein P (which is the main supplier of selenium to body tissues) reaches its optimal activity at serum selenium concentrations of about 125 ng/mL[43], equivalent to about 156.25 µg/L of whole blood Se[40], which is not far removed from our value.

Several mechanistic studies support the protective effect of selenium against PCa. Earlier studies reported that selenium accumulates preferentially in the normal human prostate gland[8,44,45]. The localization of seleno-proteins such as glutathione peroxidase 1 (GPx1) in the nucleus and selenoprotein-15 (SELENOF) in the plasma membrane of normal prostate epithelial cells have been reported[46,47]. In addition, healthy prostate tissues express high levels of selenium binding protein-1[48], which has been shown to negatively regulate oxidative phosphorylation in healthy prostate cells[48]. These reports indicate that seleno-proteins may play important protective roles in healthy prostate tissues, preventing prostate carcinogenesis through their antioxidant properties[6]. Other mechanisms by which selenium may mediate against carcinogenesis include induction of apoptosis[49,50], inhibition of DNA damage, enhancement of oxidative DNA repair capacity[6] and disruption of androgen receptor signaling[7]. Corcoran et al.[51] have reported that inorganic selenium (sodium selenate) significantly retarded the growth of primary prostatic tumors and the development of retroperitoneal lymph node metastases, which was associated with a decrease in angiogenesis. Also, the ability of selenium nanoparticles (alone and in combination with other drugs) to effectively inhibit growth, migration and invasion of metastatic PCa cells in a concentration-dependent manner was demonstrated[49]. These mechanistic studies suggest that suboptimal Se levels may contribute to DNA damage, which could help explain the associations observed in this study.

On the other hand, prostate tissues can accumulate selenium and hence, are susceptible to its toxicity, as there is a very narrow range between selenium adequacy and toxicity[16]. Selenium, at higher concentrations, may induce oxidative stress, thereby promoting cancer[17,18]. There is a tight regulation of seleno-protein synthesis following selenium exposure. At sub-optimal selenium levels, selenium is utilized in the biosynthesis of seleno-proteins, leading to increased activity of these proteins[52]. However, when seleno-proteins reach their optimal activity (at optimum selenium concentration), additional selenium exposure results in increased selenium metabolism, but not further increase in seleno-protein synthesis/activity. Many of the resulting intermediate selenium metabolites (including selenite, selenocystine, methylseleninic acid, Se-methylselenocysteine) are highly redox-active[52,53], oxidizing thiol groups of proteins and generating reactive oxygen species, which may lead to cellular damage and carcinogenesis[52,54,55]. Although this study measured other antioxidant trace elements, other antioxidants (for example, GPx, SELENOP) and oxidative stress markers (for example, F2-isoprostanes) not measured in our study may limit the full establishment of the underlying biological mechanisms of selenium's effect on prostate diseases. Future mechanistic studies with simultaneous measurement of these markers with blood selenium levels would provide direct evidence linking the observed U-shaped association to molecular actions of selenium.

In line with the observed interaction between selenium and smoking history in this study, Le et al.[32] have reported a stronger association with never smokers than among smokers. Another cross-sectional study on the effect of dietary selenium on PSA levels reported higher odds of having high PSA levels, among nonsmokers than smokers[56]. Although the exact mechanism is not yet identified, these studies suggest that smoking status may modify the effect of selenium on PCa risk. Lower plasma selenium concentration and erythrocyte glutathione peroxidase activities have been reported in tobacco smokers than in nonsmokers[57]. Tobacco smoking may affect selenium metabolism through its numerous oxidants which increase oxidative stress and the body's demand for antioxidant defenses, including selenium-dependent enzymes[58]. The observed interaction between selenium exposure and smoking status remained significant even after adjustment for multiplicity. This suggests that the effect of tobacco smoking may override the dose-dependent effect of selenium in non-smokers. More research is indicated to elucidate the interaction between selenium exposure, smoking, and PCa. The consistent U-shaped relationship observed in the different subgroups may suggest a genuine effect less likely due to random chance. To ensure that the overall risk of a Type I error remains controlled at 5%, we corrected for multiple comparisons using the Bonferroni correction. However, given the smaller sample sizes in the subgroups and the attendant wide confidence intervals, which indicate limited statistical power and precision, there is a high tendency of overfitting, and the generalizability of these results is limited. Larger studies are needed to further investigate these relationships, confirm the findings and obtain more reliable effect size estimates.

Our bivariate analysis suggested that individuals with prostate diseases were less likely to have diabetes mellitus compared with the control group. Higher levels of testosterone (as seen in PCa patients) have been associated with a lower risk of developing type 2 diabetes, as this hormone plays a major role in the regulation of insulin sensitivity[59]. On the other hand, lower testosterone levels increase insulin resistance and have been reported among diabetic patients[60]. The insulin-like growth factor (IGF) system has been identified as a possible bridge linking the inverse association between PCa and diabetes. IGF-I is known for its role in promoting cancer cell growth, survival, angiogenesis and migration. Higher IGF-I levels have been consistently reported in PCa risk[61], while low levels are reported in diabetic patients[62]. To test for the possible effect of diabetes status on the observed relationship between blood selenium and PCa, further adjustment for diabetes status was made in our

regression models. This further adjustment resulted in significant attenuation of the reported effect size, but did not alter the direction of the effect nor the observed U-shaped relationship. This observation suggests that diabetes status may be a significant confounding factor of the relationship between selenium status and PCa and should be considered in studies investigating this relationship. Findings across several studies also suggest a U-shaped relationship between selenium and diabetes[63]. The SELECT study found no effect of selenium supplementation on cancer prevention, but reported a non-significant higher incidence of type 2 diabetes among long-term selenium supplemented individuals compared to those on placebo[13]. Together with our findings, these reports warrant more targeted research on the complex relationship between selenium, PCa and diabetes.

The observed lower BMI among treatment-naive PCa participants compared with the controls in our bivariate analyses may be explained by the fact that a significant number of PCa patients present to the clinics with advanced diseases, when their weights may have been affected by the disease. Higher BMI has been associated with increased risk of PCa in several longitudinal studies[64]. The nature of association observed in this study may reflect effect of cancer on BMI and not vise -versa.

There is limited evidence for the influence of selenium exposure on BPH. Eichholzer et al.[65] reported an inverse association between serum selenium levels and BPH in a sample of European men. The observed difference in the association of whole blood and urinary selenium status with prostate disorders in this study may reflect the fact that these two selenium markers assessed different windows of selenium exposure. Urinary (as well as plasma) selenium reflects recent selenium intake while whole blood (or erythrocytes) selenium concentrations reflect long-term selenium intake[66,67]. However, as BPH and PCa are age-related, their associations with biomarkers such as urinary selenium, with relatively short half-life, should be interpreted cautiously. Blood selenium has longer life span of blood cells[66,67] and therefore, may be a better indicator of cumulative exposure than plasma or urinary selenium for assessment of association with chronic diseases such as BPH and PCa. This is evidenced by the lack of significant correlation between the two markers (Supplementary Figure S3). Both biomarkers were however, analyzed in this study to provides a more robust set of data for a better understanding of the relationship between selenium and prostate health across these windows of exposure, as well as give insight into possible reasons for inconsistencies seen in results from previous studies. The observed inverse association between urinary selenium and BPH warrants further investigation in larger studies.

The observed U-shaped relationship in this study emphasizes the need to maintain a balance in selenium status for prostate cancer prevention. However, the generalizability of the estimated optimal range of 125.55–134.86 µg/L to other populations requires great caution due to significant variation in selenium levels across diverse population groups[19]. Dietary selenium levels, the main source of selenium exposure to humans, are highly dependent on local soil content, which in turn varies significantly across different locations[20], ranging from low selenium regions in Europe and China to high selenium areas in North America[68]. Individuals' dietary patterns also play a significant role in their selenium exposure, with consumers of seafood and nuts maintaining adequate levels, while those who depend mostly on plant-based diets may suffer deficiency. Given these variations, the threshold for risk may differ among populations depending on their background exposure levels. This emphasizes the need for region-specific dietary recommendations for selenium. Furthermore, an individual genetic polymorphism may likely modulate the response to varying levels of selenium exposure[69]. For example, a study among the German population reported that carriers of one or two T alleles of the selenoprotein gene, *GPx1* Pro198Leu (rs1050450; C > T) may have significantly reduced odds of prostate cancer compared with the homozygous C individuals[70]. These underscore the need to integrate genetic testing with selenium status, which may aid in optimizing selenium intake across diverse populations.

Important strengths of this study include the use of whole blood selenium, which is considered a biomarker of long-term exposure to selenium, and the use of a highly sensitive ICP-MS instrument, with adequate quality control measures that ensured accuracy of the data. Measurement and adjustment for the most relevant confounding factors, including demographic variables and other antioxidant trace elements (zinc, copper, iron and manganese), also constitute a strength of the study. Certain limitations of the study should however, be considered in interpreting the current results. First, the case-control nature does not allow us to infer any causality between selenium exposure and prostate diseases. Second, selection of an adequate (prostate disease-free) control group was difficult. Although the control participants were screened with IPSS and PSA test, men with subclinical prostate diseases may have been included in this group. Third, the possible effect of other factors, such as socioeconomic and dietary factors, which were not measured in this study, may not be ruled out. For example, intake of dietary antioxidant micronutrients such as lycopene, β-carotene, and α-tocopherol is known to influence an individual's selenium levels. Also, socioeconomic factors such as income levels could influence selenium levels by affecting individual's food choices as well as access to healthy diets and overall nutritional intake. Although we controlled for several PCa risk factors and excluded individuals on antioxidant/micronutrient supplements and those who had used these supplements in the last 3 months before recruitment, the effects of diet and income level were not considered, which could affect the strength of the reported associations. These limitations underscore the need for larger prospective studies to fully elucidate the role of selenium exposure in prostate diseases in this population, as well as increase the generalizability of the results to a wider population.

Conclusion

This study found that both very low and very high blood selenium levels are independently associated with PCa. We found a narrow range between the two limbs of the U-type response curve, and hypothesize for the first time, that a putative optimum range of blood selenium concentration associated with minimum odds of PCa may lie between approximately 125.55 and 134.86 µg/L. Thus, the present paper highlights the need for a tightly controlled selenium intake in this population. Given the wide variation in soil selenium content, the resultant variation in selenium exposure, as well as the lack of dietary guidelines for selenium among the

Nigerian population, a nationwide survey is warranted to establish a baseline selenium level and identify good dietary sources of selenium in this environment. Such data would be useful in the development of region-specific dietary guidelines for selenium aimed at minimizing selenium deficiency and preventing its toxicity among this population. In addition, the government may play a role by providing advanced diagnostic equipment for selenium biomarker analysis, which is mostly unavailable or expensive in this resource-poor setting. This is critically needed for quantitative assessment of an individual's baseline selenium status, as well as genetic screening tests, allowing for personalized interventions. Targeted nutritional education on the benefits as well as toxicity of selenium should incorporate promotions on the use of locally available selenium-rich foods while guiding against the use of selenium-based supplements, which may expose an individual to a toxic dose of selenium. These may help reduce the likelihood of exposure to toxic selenium levels, which have been linked to prostate diseases in this and other studies.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 13 September 2025; Accepted: 9 December 2025
Published online: 12 December 2025

References

1. Ibrahim, S. A. Z., Kerkadi, A. & Agouni, A. Selenium and health: an update on the situation in the middle East and North Africa. *Nutrients* **11** (7), 1457 (2019).
2. Rayman, M. P. Selenium intake, status, and health: a complex relationship. *Hormones (Athens)* **19** (1), 9–14 (2020).
3. Hatfield, D. L., Tsuji, P. A., Carlson, B. A. & Gladyshev, V. N. Selenium and selenocysteine: roles in cancer, health, and development. *Trends Biochem. Sci.* **39** (3), 112–120 (2014).
4. Hariharan, S. & Dharmaraj, S. Selenium and selenoproteins: it's role in regulation of inflammation. *Inflammopharmacology* **28** (3), 667–695 (2020).
5. Zeng, H. & Combs, G. F. Jr Selenium as an anticancer nutrient: roles in cell proliferation and tumor cell invasion. *J. Nutr. Biochem.* **19** (1), 1–7 (2008).
6. de Rosa, V. et al. Low doses of selenium specifically stimulate the repair of oxidative DNA damage in LNCaP prostate cancer cells. *Free Radic Res.* **46** (2), 105–116 (2012).
7. Chun, J. Y. et al. Mechanisms of selenium down-regulation of androgen receptor signaling in prostate cancer. *Mol. Cancer Ther.* **5** (4), 913–918 (2006).
8. Sabichi, A. L. et al. Selenium accumulation in prostate tissue during a randomized, controlled short-term trial of l-selenomethionine: a Southwest oncology group study. *Clin. Cancer Res.* **12** (7 Pt 1), 2178–2184 (2006).
9. Diwadkar-Navsariwala, V. et al. Selenoprotein deficiency accelerates prostate carcinogenesis in a Transgenic model. *Proc. Natl. Acad. Sci. U.S.A.* **103** (21), 8179–8184. https://doi.org/10.1073/pnas.0508218103 (2006).
10. Duffield-Lillico, A. J. et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the nutritional prevention of cancer trial. *BJU Int.* **91** (7), 608–612 (2003).
11. Duffield-Lillico, A. J. et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the nutritional prevention of cancer trial. *Cancer Epidemiol. Biomarkers Prev.* **11** (7), 630–639 (2002).
12. Allen, N. E. et al. European prospective investigation into cancer and nutrition. Plasma selenium concentration and prostate cancer risk: results from the European prospective investigation into cancer and nutrition (EPIC). *Am. J. Clin. Nutr.* **88** (6), 1567–1575 (2008).
13. Lippman, S. M. et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the selenium and vitamin E cancer prevention trial (SELECT). *JAMA* **301** (1), 39–51 (2009).
14. Marshall, J. R. et al. Phase III trial of selenium to prevent prostate cancer in men with high-grade prostatic intraepithelial neoplasia: SWOG S9917. *Cancer Prev. Res. (Phila).* **4** (11), 1761–1769 (2011).
15. Kristal, A. R. et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. *J. Natl. Cancer Inst.* **106** (3), djt456 (2014).
16. Zwolak, I. & Zaporowska, H. Selenium interactions and toxicity: a review. Selenium interactions and toxicity. *Cell. Biol. Toxicol.* **28** (1), 31–46 (2012).
17. Barchielli, G., Capperucci, A. & Tanini, D. The role of selenium in pathologies: an updated review. *Antioxidants (Basel)* **11** (2), 251 (2022).
18. Galan-Chilet, I. et al. Javier Chaves F. Plasma selenium levels and oxidative stress biomarkers: a gene-environment interaction population-based study. *Free Radic Biol. Med.* **74**, 229–236 (2014).
19. Nriagu, J. O. Global cycling of selenium. In *Occurrence and Distribution of Selenium* (ed Ihnat, M.), 327–340 (CRC, 1989).
20. Kieliszek, M. & Błażejak, S. Current knowledge on the importance of selenium in food for living organisms: A review. *Molecules* **21** (5), 609 (2016).
21. Gbadebo, A. M., Babalola, O. O. & Ajigbotesho, F. L. Selenium concentration in food and blood of residents of Abeokuta Metropolis, Southwestern Nigeria. *J. Geochem. Explor.* **107** (2), 175–179 (2010).
22. Zarmai, S., Eneji, I. S. & Sha'Ato, R. Analysis of selenium content in root and tuber plants in central Nigeria. *Am. J. Anal. Chem.* **4**, 739–743 (2013).
23. Adeniyi, M. J. & Agoreyo, F. O. Nigeria and the selenium micronutrient: A review. *Ann. Med. Health Sci. Res.* **8**, 5–11 (2018).
24. Bede-Ojimadu, O. et al. Cadmium exposure and the risk of prostate cancer among Nigerian men: effect modification by zinc status. *J. Trace Elem. Med. Biol.* **78**, 127168 (2023).
25. Schlesselman, J. J. *Case-Control Studies: Design, Conduct, Analysis* (Oxford University Press, 1982).
26. Muecke, R. et al. Whole blood selenium levels (WBSL) in patients with prostate cancer (PC), benign prostatic hyperplasia (BPH) and healthy male inhabitants (HMI) and prostatic tissue selenium levels (PTSL) in patients with PC and BPH. *Acta Oncol.* **48** (3), 452–456 (2009).
27. Shotyk, W. et al. Sphagnum mosses from 21 ombrotrophic bogs in the Athabasca bituminous sands region show no significant atmospheric contamination of heavy metals. *Environ. Sci. Technol.* **48** (21), 12603–12611 (2014).
28. James, G., Witten, D., Hastie, T. & Tibshirani, R. *An Introduction To Statistical Learning: With Applications in R*, 2nd edn (Springer, 2021).
29. Vrieze, S. I. Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the bayesian information criterion (BIC). *Psychol. Methods.* **17** (2), 228–243. https://doi.org/10.1037/a0027127 (2012).

30. Gauthier, J., Wu, Q. V. & Gooley, T. A. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transplant.* **55** (4), 675–680. https://doi.org/10.1038/s41409-019-0679-x (2020).
31. Zhang, X., Li, X., Zhang, W. & Song, Y. Selenium and cardiovascular disease: epidemiological evidence of a possible U-Shaped relationship. In *Selenium Molecular and Integrative Toxicology* (ed Michalke, B.) (Springer, 2018).
32. Bleys, J., Navas-Acien, A. & Guallar, E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch. Intern. Med.* **168** (4), 404–410 (2008).
33. Tan, Q. H. et al. A U-Shaped relationship between selenium concentrations and All-Cause or cardiovascular mortality in patients with hypertension. *Front. Cardiovasc. Med.* **8**, 671618 (2021).
34. Zhou, L. et al. Diverse associations of plasma selenium concentrations and selenop gene polymorphism with metabolic syndrome and its components. *Oxid. Med. Cell Longev.* **2020**, 5343014 (2020).
35. Waters, D. J. et al. Prostate cancer risk and DNA damage: translational significance of selenium supplementation in a canine model. *Carcinogenesis* **26** (7), 1256–1262 (2005).
36. Le, N. T. et al. A U-shaped association between selenium intake and cancer risk. *Sci. Rep.* **14** (1), 21378. https://doi.org/10.1038/s41598-024-66553-5 (2024).
37. Cui, Z., Liu, D., Liu, C. & Liu, G. Serum selenium levels and prostate cancer risk: A MOOSE-compliant meta-analysis. *Medicine (Baltimore)* **96** (5), e5944 (2017).
38. Cai, X. et al. Selenium exposure and cancer risk: an updated meta-analysis and meta-regression. *Sci. Rep.* **20**, 19213 (2016).
39. Allen, N. E. et al. Endogenous Hormones, nutritional biomarkers and prostate cancer collaborative Group. Selenium and prostate cancer: analysis of individual participant data from fifteen prospective studies. *J. Natl. Cancer Inst.* **108** (11), djw153 (2016).
40. Muecke, R. et al. Whole blood selenium levels and selenium supplementation in patients treated in a family Doctor practice in Golßen (State of Brandenburg, Germany): A laboratory study. *Integr. Cancer Ther.* **17** (4), 1132–1136 (2018).
41. Penney, K. L. et al. A large prospective study of SEP15 genetic variation, interaction with plasma selenium levels, and prostate cancer risk and survival. *Cancer Prev. Res. (Phila).* **3** (5), 604–610 (2010).
42. Rocourt, C. R. & Cheng, W. H. Selenium supranutrition: are the potential benefits of chemoprevention outweighed by the promotion of diabetes and insulin resistance? *Nutrients* **5** (4), 1349–1365 (2013).
43. Burk, R. F., Norsworthy, B. K., Hill, K. E., Motley, A. K. & Byrne, D. W. Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial. *Cancer Epidemiol. Biomarkers Prev.* **15** (4), 804–810 (2006).
44. Arnold, W. N. & Thrasher, J. B. Selenium concentration in the prostate. *Biol. Trace Elem. Res.* **91** (3), 277–280 (2003).
45. Gianduzzo, T. R. et al. Prostatic and peripheral blood selenium levels after oral supplementation. *J. Urol.* **170** (3), 870–873 (2003).
46. Ekoue, D. N. et al. GPX1 localizes to the nucleus in prostate epithelium and its levels are not associated with prostate cancer recurrence. *Antioxid. (Basel).* **7** (11), 167 (2018).
47. Ekoue, D. N. et al. Correlations of SELENOF and SELENOP genotypes with serum selenium levels and prostate cancer. *Prostate* **78** (4), 279–288 (2018).
48. Elhodaky, M., Hong, L. K., Kadkol, S. & Diamond, A. M. Selenium-binding protein 1 alters energy metabolism in prostate cancer cells. *Prostate* **80** (12), 962–976 (2020).
49. An, Y. & Zhao, J. Functionalized selenium nanotherapeutics synergizes with Zoledronic acid to suppress prostate cancer cell growth through induction of Mitochondria-Mediated apoptosis and cell cycle S phase arrest. *Front. Oncol.* **11**, 685784 (2021).
50. Jiang, W. et al. In vivo molecular mediators of cancer growth suppression and apoptosis by selenium in mammary and prostate models: lack of involvement of Gadd genes. *Mol. Cancer Ther.* **8** (3), 682–691 (2009).
51. Corcoran, N. M., Najdovska, M. & Costello, A. J. Inorganic selenium retards progression of experimental hormone refractory prostate cancer. *J. Urol.* **171** (2 Pt 1), 907–910 (2004).
52. Misra, S., Boylan, M., Selvam, A., Spallholz, J. E. & Björnstedt, M. Redox-active selenium compounds–from toxicity and cell death to cancer treatment. *Nutrients* **13** (5), 3536–3556 (2015).
53. Spallholz, J. E. Free radical generation by selenium compounds and their prooxidant toxicity. *Biomed. Environ. Sci.* **10** (2–3), 260–270 (1997).
54. Lazard, M., Dauplais, M., Blanquet, S. & Plateau, P. Recent advances in the mechanism of Selenoamino acids toxicity in eukaryotic cells. *Biomol. Concepts.* **8** (2), 93–104 (2017).
55. Lee, K. H. & Jeong, D. Bimodal actions of selenium essential for antioxidant and toxic pro-oxidant activities: the selenium paradox (Review). *Mol. Med. Rep.* **5** (2), 299–304 (2012).
56. Wei, B., Tan, W., Wang, S., Guo, Z. & Gan, S. Interaction between smoking status and dietary selenium intake affects PSA: A cross-sectional study. *Urol. Oncol.* **41** (12), 483e1–483e9. https://doi.org/10.1016/j.urolonc.2023.07.009 (2023).
57. Kocyigit, A., Erel, O. & Gur, S. Effects of tobacco smoking on plasma selenium, zinc, copper and iron concentrations and related antioxidative enzyme activities. *Clin. Biochem.* **34** (8), 629–633. https://doi.org/10.1016/s0009-9120(01)00271-5 (2001).
58. Beane Freeman, L. E. et al. Is the inverse association between selenium and bladder cancer due to confounding by smoking? *Am. J. Epidemiol.* **181** (7), 488–495. https://doi.org/10.1093/aje/kwu324 (2015).
59. Milionis, C., Koukkou, E., Venaki, E. & Ilias, I. Testosterone and glucose homeostasis in adult males: current insights and future prospects. *Discov. Med.* **36** (184), 865–873. https://doi.org/10.24976/Discov.Med.202436184.81 (2024).
60. Khalil, S. H. A. et al. Diabetes surpasses obesity as a risk factor for low serum testosterone level. *Diabetol. Metab. Syndr.* **16** (1), 143. https://doi.org/10.1186/s13098-024-01373-1 (2024).
61. Liu, G., Zhu, M., Zhang, M. & Pan, F. Emerging role of IGF-1 in prostate cancer: A promising biomarker and therapeutic target. *Cancers (Basel).* **15** (4), 1287. https://doi.org/10.3390/cancers15041287 (2023).
62. Suda, K. et al. The influence of type 2 diabetes on serum GH and IGF-I levels in hospitalized Japanese patients. *Growth Horm. IGF Res.* **29**, 4–10 (2016).
63. Ge, S. et al. A cross-sectional analysis of dietary selenium intake and type 2 diabetes risk in adults: insights from NHANES 2011–2016. *Front. Nutr.* **12**, 1583590 (2025).
64. Di, H. et al. The impact of obesity and sexual behavior on prostate cancer risk is mediated by testosterone levels: a Mendelian randomization study and mediation analysis. *Prostate Int.* **12** (2), 96–103 (2024).
65. Eichholzer, M. et al. Effects of selenium status, dietary glucosinolate intake and serum glutathione S-transferase α activity on the risk of benign prostatic hyperplasia. *BJU Int.* **110** (11 Pt C), E879–E885 (2012).
66. Ayling, R. M. Clinical biochemistry of nutrition. In *Clinical Biochemistry: Metabolic and Clinical Aspects* (eds Marshall, W. J. & Bangert, S. K.), 3 edn, 180–199 (Churchill Livingstone, 2014).
67. Pfeiffer, C. M., Schleicher, R. L. & Caldwell, K. L. Biochemical indices. In *Encyclopedia of Human Nutrition* (ed Caballero, B.), 3 edn., 156–174 (Academic, 2013).
68. Zhao, X. et al. Selenium spatial distribution and bioavailability of soil-plant systems in China: a comprehensive review. *Environ. Geochem. Health* **46** (9), 341. https://doi.org/10.1007/s10653-024-02126-9 (2024).
69. Ferreira, R. R. et al. Current Understanding of human polymorphism in Selenoprotein genes: A review of its significance as a risk biomarker. *Int. J. Mol. Sci.* **25** (3), 1402. https://doi.org/10.3390/ijms25031402 (2024).
70. Steinbrecher, A. et al. Effects of selenium status and polymorphisms in Selenoprotein genes on prostate cancer risk in a prospective study of European men. *Cancer Epidemiol. Biomarkers Prev.* **19** (11), 2958–2968. https://doi.org/10.1158/1055-9965.EPI-10-0364 (2010).

Acknowledgements
The authors are most grateful to Professor William Shotyk, director of the SWAMP Laboratory, University of Alberta, for providing the ICP-MS facility and reagents for trace element analyses. We also thank the staff members of the SWAMP Lab, especially Tracy Gartner for the administrative support and Camilla Gutierrez, for digesting the blood samples. We gratefully acknowledge Professor Oranusi, C. K., Dr. Onuigbo, C. O. and other clinicians and nurses at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, for their assistance in recruitment of study participants.

Author contributions
Onyinyechi Bede-Ojimadu: Conceptualization, Methodology, Investigation, Formal analysis, Writing- Original draft preparation, editing. Nwakasi Nnamah and Jude A Onuegbu: supervision, review and editing. Fiorella Barraza and Iain Grant-Weave: Investigation. Jideofor Orakwe and Joseph Abiahu: Resources and supervision. Nkiru Ezeama: Data analysis; Ejeatuluchukwu Obi, Orish Ebere Orisakwe and Jerome Nriagu: Resources and supervision, review and editing. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
The study was approved by the Ethics Committee of NAUTH (NAUTH/CS/66/VOL.11/116/2018/056) and University of Alberta, Edmonton, Canada (Pro00097779) and was carried out in accordance with the Declaration of Helsinki. Each participant gave written informed consent before recruitment.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-32341-y.

Correspondence and requests for materials should be addressed to O.B.-O.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.