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Association between arsenic levels in toenails and urine and prostate cancer risk: Findings from the MCC-Spain study

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ABSTRACT

Background: Arsenic (As) is a toxic metalloid widely distributed in the environment. Chronic exposure to As has been associated with the development of several types of cancer. However, its role in prostate cancer (PC) remains unclear.

Objective: To evaluate the relationship between As exposure and the risk of PC, considering different clinical tumour classifications and genetic susceptibility, and to compare biomarkers that may reflect distinct exposure windows.

Methods: We included 345 incident cases and 468 controls with available data on both urinary and toenail As concentrations within the MCC-Spain project. Toenail and urinary As levels were measured using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES), respectively. Genetic susceptibility was assessed using a polygenic risk score (PRS) based on Single-Nucleotide Polymorphisms. Associations between As exposure and PC were examined using mixed-effects and multinomial logistic regression models.

Results: Higher toenail As concentrations were associated with increased risk of PC [odds ratio (OR) comparing the fourth to first quartile: 1.94; 95 % confidence interval (CI):1.23–3.06]. Stratified analyses by tumor classification showed consistent risk increases for advanced and aggressive tumors [ISUP3-5 Relative risk ratio (RRR) quartile 4vs.1: 2.86 (1.16–7.06); AJCC IIB-IV RRR: 2.58 (1.48–4.50); cT2-cT4 RRR: 3.05 (1.55–5.99)]. No clear association was found with urinary As concentrations. Interaction analyses showed no evidence of effect modification by PRS.

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Conclusion: Elevated toenail As levels were associated with an increased risk of PC, especially in advanced disease, suggesting that toenails represent a more reliable biomarker for assessing long-term As exposure.

1. Introduction

Prostate cancer (PC) is the second most commonly diagnosed cancer and the fifth leading cause of mortality among men worldwide (Sung et al., 2021). While the aetiology of PC is not completely understood, well-established risk factors include age, race, genetic susceptibility, and family history (Grönberg, 2003). In contrast, evidence supporting environmental risk factors remains limited (IARC, 2012).

Arsenic (As) is a well-established human carcinogen, associated with cancers of the skin, lung, bladder, kidney, and possibly liver, with limited evidence for other sites (IARC, 2012). However, its link with PC is still inconclusive and largely based on studies using As concentrations in drinking water as a proxy for exposure (Bulka et al., 2016; Roh et al., 2017). Given that exposure to As can occur through multiple pathways beyond drinking water, assessing internal dose using biological markers is essential.

At the European level, the European Food Safety Authority (EFSA) has reported that the major contributors to dietary exposure to toxic inorganic arsenic (iAs) are rice, rice-based products, cereals, and drinking water. In Spain, where average seafood intake is among the highest in Europe, only surpassed by Iceland, Portugal, and Norway (FAO, 2022), seafood consumption represents the main source of As exposure, with most species present as organic (Navarro Serrano et al., 2016), which are considered less toxic. Yet, even if the contribution of seafood to iAs exposure is, on average, below levels of concern set by international organizations (Benchmark Dose Lower Confidence Limit for a 1 % response (BMDL01): 0.3–8 μg/kg body weight/day) (Domingo, 2024; Arcella et al., 2021), population averages may mask relevant variability.

Urinary As is the most commonly used biomarker, as it reflects recent exposure from various sources. Nevertheless, its short half-life limits its ability to capture long-term exposure. In contrast, toenail As serves as a biomarker of cumulative exposure over time, owing to the slow growth rate of nails, and is therefore considered a promising marker of chronic exposure (Signes-Pastor et al., 2021; Yaemsiri et al., 2010). Importantly, As^{3+} —one of the most toxic and health-relevant inorganic forms of As — binds strongly to keratin, and approximately 80 % of the As measured in toenail clippings consists of iAs, making toenails a reliable indicator of the biologically and toxicologically relevant fraction of exposure (Button et al., 2009; Hood et al., 2023). Despite their usefulness, few studies have examined urinary or toenail As in relation to PC risk, and existing evidence remains inconclusive. While some studies have reported positive associations with increased PC risk or mortality (Bulka et al., 2016; García-Esquinas et al., 2013; Hsueh et al., 2017; Roh et al., 2017), others have shown null or inconsistent results (Baastrup et al., 2008; Parada et al., 2020).

The present study assesses the association between As exposure and PC risk in the Spanish population, using data from the MCC-Spain incident case-control study. It also compares results for urinary and toenail As, while considering tumor aggressiveness, disease extent, and genetic susceptibility to PC.

2. Materials and methods

2.1. Study population

The Multicase-Control (MCC-Spain) study was a population-based study that included incident cases of several tumor types (breast, prostate, colorectal, gastric, and chronic lymphocytic leukaemia) along with matched population-based controls. The main objective of the study was to investigate the role of environmental and genetic factors in the aetiology of these cancers (www.mcc-spain.org). The study was approved by the ethics committee of the Instituto de Salud Carlos III and all participating centers (Castaño-Vinyals et al., 2015).

Participants were recruited between 2008 and 2013. Inclusion criteria were: age between 20 and 85 years, ability to complete the questionnaires, signed informed consent, and residence in the hospital catchment area for at least 6 months before recruitment. Incident PC cases were histologically confirmed (International Classification of Diseases 10th Revision: C61, D07.5) and identified through oncology department records. Clinical registries were reviewed to obtain tumor characteristics, including the International Society of Urological Pathology (ISUP) grade (Epstein et al., 2016), the American Joint Committee on Cancer (AJCC) 8th edition stage (Buyyounouski et al., 2017), tumor clinical extension, Gleason score, and PSA at diagnosis. Population-based controls were randomly selected from Primary Care beneficiary lists within each hospital's reference area and were frequency-matched to cases by age, sex, and geographical area. The participation rate was 67.4 % among cases and 52.2 % among controls (Castaño-Vinyals et al., 2015; Castelló et al., 2018).

Participants were invited by phone and provided written informed consent. Those who agreed to participate completed an epidemiological questionnaire, administered face-to-face by trained interviewers, and a 140-item food frequency questionnaire (FFQ), which was completed at home and returned by email. The FFQ assessed dietary intake over the previous year, including seafood consumption (white fish, blue fish, mollusks, and crustaceans). The epidemiological questionnaire gathered information on sociodemographic characteristics, anthropometry, lifestyles, family and personal medical history, residential and occupational exposures, smoking, and physical activity. Diet and alcohol intake were assessed with a semi-quantitative FFQ previously validated in Spain (Marsit et al., 2006).

Of the initial 1112 incident PC cases and 1493 controls recruited across seven Spanish provinces, only 417 cases and 583 controls had both urine and toenail As measurements available, and were therefore considered for inclusion to enable comparisons across matrices. From this subgroup, exclusions were applied as follows: 21 cases and 53 controls were excluded due to missing creatinine values; 1 case and 3 controls due to extreme creatinine concentrations (<30 or >300 mg/dL); 18 controls with a history of prostate adenoma surgery; and 50 cases and 41 controls due to missing information on key cofounders, including BMI, family history of PC, or seafood intake. Thus, the final analytical sample included 345 cases and 468 controls from three provinces: Madrid, Asturias, and Cantabria (see Supplementary Fig. S1).

2.2. Polygenic risk score

At recruitment, peripheral blood samples were collected from participants, and the cellular fraction was used for DNA extraction and stored at −80 °C. Participants with available DNA (409 controls and 287 cases) (see Supplementary Fig. S1) were genotyped at the Centro Nacional de Genotipado (CEGEN-ISCIII) using the Infinium Human Exome BeadChip (Illumina, San Diego, USA).

To evaluate genetic susceptibility to PC, we constructed a polygenic risk score (PRS) as previously described (Gómez-Acebo et al., 2017). Briefly, single nucleotide polymorphisms (SNPs) associated with PC were selected from genome-wide association study (GWAS) results in European populations using Genome Browser, applying a significance threshold of $p < 5 \times 10^{-8}$ and restricting to studies that reported PC as the primary trait. The PRS was calculated using 56 SNPs located in our

dataset, as the sum of the allelic dosage for each SNP, weighted by its effect size derived from logistic regression models.

2.3. Arsenic exposure assessment in urine

Urine samples were collected on the day of the interview or the following day in pre-treated, acid-washed polypropylene containers. Aliquots were prepared (2 x 0.5 mL for creatinine and 8 x 3 mL for metals), labelled and stored at −90° until analyses. Urinary metals were quantified at the Laboratory of Environmental Analysis and Bioanalysis (University of Huelva) using Inductively Coupled Plasma-Mass Spectrometry equipped with an Octopole Reaction System (ICP-ORS-MS). Samples were diluted 5 times with 5 % solution of ultrapure nitric acid in ultrapure water before analysis. Total urine As levels were measured following previously validated protocols (García-Sevillano et al., 2014), with analysts blinded to case-control status. Quality control of the analysis was carried out with the following measures: (a) Two quality control materials per batch—Clincheck Urine Control for Trace Elements, Level I (commercially available QC material), and Standard Reference Material (SRM 2670a) -Toxic Elements in Freezed dried urine (high level)-(mean accuracy: 90 % ± 5 % over time); (b) Calibration every 20 samples; (c) Use of rhodium as internal standard, with reanalysis if deviation over 10 %; (d) Reagent blanks every 5 samples; (e) Duplicates analysed every 2.5 h of the sequence; and (f) Spike recovery analysis on reference materials. Measurements were performed in helium collision mode to reduce interference from molybdenum, tin, and chloride. The run-to-run precision for urine analyses showed a coefficient of variation of 5.2 %, and accuracy against the urine reference material (Clean-Chek CRM) demonstrated good agreement, with a measured As concentration of 42.7 μg/L compared to the expected value of 44.6 μg/L.

Creatinine concentration was determined by the Jaffé method (Peake and Whiting, 2006; Weber and van Zanten, 1991), using a photometric assay at 37 °C with Biosystems reagents (Barcelona, Spain). Total urine As concentrations were normalized by urinary creatinine to control for interindividual differences in urine dilution and expressed as μg/g creatinine.

2.4. Arsenic exposure assessment in toenails

Toenail clippings (from big toes) were collected in paper envelopes at room temperature. Samples were cleaned twice using Triton solution, acetone, and Milli-Q® water (Millipore, Watford, UK) in an ultrasonic bath, then digested using a 4:1 solution of nitric acid and hydrogen peroxide in a microwave digestion system and diluted to 5 mL with Mili-Q water. As (and 15 other metals) were measured by ICP-MS (XSeries 2, Thermo Scientific) at the Environmental Bioanalytical Chemistry Unit (University of Huelva, Spain). Concentrations were calculated using the following equation: [Real](ng/g) = [Equipment] (ng/g) (dilution factor (g))/(sample weight(g)). Quality control procedures included: (a) Analysis of hair certified reference material CRM GBW 07601 (mean accuracy of 90 %); (b) Calibration checks every 20 samples; (c) Rhodium as internal standard, with reanalysis if deviation over 10 %; (d) Reagent blanks every 5 samples; (e) Duplicate samples every 2.5 h; and (f) Spiking of reference materials. A validation test was performed using toenail samples analysed in two different laboratories (Environmental Bioanalytical Chemistry Unit of the University of Huelva and Mass Spectrometry Unit of the University of Oviedo, Spain). The run-to-run precision for toenail analyses showed a coefficient of variation of 5.7 %, and accuracy against the reference material (CRM GBW 07601) demonstrated good agreement, with a measured As concentration of 0.28 μg/g compared to the expected value of 0.27 μg/g.

As toenail levels were corrected using the COMET approach (Pastor-Barriuso et al., 2025), which adjusts for bias related to toenail mass and batch effects. This model standardized values as if all samples had been analysed in the average batch and with the geometric mean mass, accounting for sex, age (in 5-year groups), and province. This correction follows previous findings on the relevance of sample mass in metal biomonitoring (Gutiérrez-González et al., 2019; Signes-Pastor et al., 2021).

2.5. Statistical analyses

First, a descriptive analysis was conducted to characterize the study population. The association between As and PC risk was evaluated using mixed-effects logistic regression models, with As concentrations categorized into quartiles based on their distribution among controls, and province of residence included as a random effects term.

Two models were fitted: (a) a basic model including design-derived variables (age and education) as fixed effects; and (b) an adjusted model, which additionally included BMI one year before recruitment, family history of PC, and seafood intake. Seafood intake was considered due to its influence on urinary As levels, mainly through the ingestion of arsenobetaine, a non-toxic organic As species (Navarro Serrano et al., 2016; Navas-Acien et al., 2011) that may confound associations with toxic species. However, the extent to which arsenobetaine accumulates in toenails remains unclear and is likely negligible (Anwar, 2005; Cottingham et al., 2013; Slotnick et al., 2007; Tabata et al., 2006). Given the high affinity of iAs for keratin-rich tissues (Button et al., 2009; Hood et al., 2023), toenails may preferentially accumulate inorganic forms, making them a more suitable matrix than urine for assessing long-term exposure to toxic As species in populations with high seafood intake.

To explore potential heterogeneity by clinical tumor characteristics, additional multinomial logistic regression models were fitted using the same covariates. For this purpose, cases were stratified according to clinical extension at diagnosis (localized: cT1–cT2 vs. advanced: cT2b–cT4), tumor grade (ISUP 1–2 vs. 3–5; AJCC 8th ed. I–IIA vs. IIB–IV), and tumor aggressiveness (low grade: Gleason = 6 vs. high grade: Gleason >6). Prostate-specific antigen (PSA) levels at diagnosis were also considered (<10 ng/mL vs. ≥10 ng/mL) (see Supplementary Tables S1 and S2).

Finally, the role of the genetic susceptibility was analysed by including an interaction term between As levels and the PRS for PC, categorized into tertiles.

All statistical analyses were performed using Stata version 17, with two-sided p-values <0.05 considered statistically significant.

3. Results

The main characteristics of study participants, stratified by urinary and toenail As biomarkers, are shown in Table 1. Median total urinary As levels were slightly higher in PC cases (67.2–85.8 μg/g creatinine) compared to controls (62.6–77.6 μg/g creatinine). In toenails, As levels were significantly higher among cases (0.23–0.25 μg/g) than controls (0.20–0.22 μg/g). No notable differences were observed between cases and controls in terms of age, BMI, and seafood. However, PC cases had lower educational attainment and a greater proportion with a family history of the disease. Based on the AJCC 8th edition staging system, 53.3 % of PC cases were classified as stage IIB–IV. According to the ISUP grading system, 19.4 % of cases were assigned grades 3, 4, or 5. Regarding clinical T stage, 71.9 % of tumors were cT1a–cT2a, while 26.1 % were cT2b–T4. Additionally, 52.2 % of cases had a Gleason score >6, and 26.7 % had PSA levels ≥10 ng/mL at diagnosis.

Table 2 presents the main results for the association between As levels measured in urine and toenails and the risk of PC. No association was observed between urinary As levels and PC risk. In contrast, men in the highest quartile of toenail As had a significantly increased risk of PC (Odds ratio [OR]: 2.11; 95 % confidence interval [95 %CI]: 1.38–3.22; *p*-trend across quartiles <0.001), and this association remained robust after adjusting for potential confounders, including seafood intake (adjusted OR for Q4 vs. Q1: 1.94; 95 %CI: 1.23–3.06; *p*-trend across quartiles: 0.001).

Table 1
Sociodemographic, Lifestyle, Dietary, and Clinical Characteristics of Prostate Cancer Cases and Controls in the case- MCC-Spain study.

	All			Individuals with PRS information		
	Controls	Cases		Controls	Cases	
	n =468	**n = 345**	p-val	**n = 409**	**n = 287**	p-val
As levels (μg/g)						
Urine, GM (95 %CI)	69.7 (62.6–77.6)	75.9 (67.2–85.8)	0.31	73.4 (65.4–82.3)	77.0 (67.2–88.2)	0.60
Toenails, GM (95 %CI)	0.21 (0.20–0.22)	0.24 (0.23–0.25)	<0.001	0.21 (0.20–0.22)	0.24 (0.23–0.25)	<0.001
Sociodemographic variables						
Age, $\bar{x}$ (SD)	66.4 (8.4)	65.86 (7.5)	0.39	66.10 (8.48)	65.72 (7.60)	0.54
Education, n (%)			0.06			0.10
≤Primary School	212 (45.3)	185 (53.6)		179 (43.8)	149 (51.9)	
Secondary School	142 (30.4)	88 (25.5)		125 (30.6)	76 (26.5)	
University or more	114 (24.4)	72 (20.9)		105 (25.7)	62 (21.6)	
Lifestyle-related variables						
Smoking, n (%)			0.67			0.92
Never	138 (29.5)	92 (26.7)		119 (29.1)	80 (27.9)	
Former >1 yr	225 (48.1)	174 (50.4)		195 (47.7)	141 (49.1)	
Smoker/former ≤1 yr	104 (22.2)	78 (22.6)		94 (22.9)	65 (22.7)	
Unknown	1 (0.21)	1 (0.3)		1 (0.2)	1 (0.4)	
BMI, $\bar{x}$ (SD)	27.07 (3.5)	27.45 (3.7)	0.14	27.2 (3.4)	27.4 (3.80)	0.35
Dietary intake, $\overline{X}$ (SD)						
Selenium (mg/d)	98.6 (32.0)	97.4 (29.0)	0.60	98.8 (32.3)	96.9 (28.9)	0.46
Energy (Kcal/d)	2014.7 (674)	2016.8 (589)	0.96	2010.6 (665)	2023.9 (605)	0.79
Grains (g/d)	213.5 (92.1)	215.0 (81.3)	0.80	213.3 (91.5)	213.1 (80.4)	0.98
Legumes (g/d)	56.3 (34.5)	56.6 (39.0)	0.91	55.5 (34.2)	54.9 (37.5)	0.83
Rice (g/d)	25.2 (18.7)	26.4 (20.3)	0.38	25.0 (18.7)	24.6 (16.6)	0.79
Seafood (g/d)	66.46 (34.5)	65.39 (32.6)	0.65	66.7 (34.2)	64.3 (31.9)	0.34
Province, n (%)						
Madrid	247 (52.8)	203 (58.8)	<0.001	237 (57.9)	167 (58.2)	<0.001
Asturias	86 (18.4)	10 (2.9)		51 (12.5)	0 (0.0)	
Cantabria	135 (28.8)	132 (38.3)		121 (29.6)	120 (41.8)	
Family history of PC, n (%)						
No	429 (91.7)	274 (79.4)	<0.001	372 (91.0)	226 (78.8)	<0.001
2nd degree	5 (1.1)	11 (3.19)		5 (1.2)	11 (3.8)	
One of 1st degree	33 (7.1)	51 (14.8)		31 (7.6)	43 (15.0)	
Unknown	1 (0.2)	3 (0.9)		1 (0.2)	2 (0.7)	
Clinical classification at diagnosis						
AJCC, n (%)						
I-IIA		157 (45.5)			130 (45.3)	
IIB-IV		184 (53.3)			155 (54.0)	
Unknown		4 (1.2)			2 (0.7)	
ISUP, n (%)						
1 + 2		270 (78.3)			224 (78.1)	
3 + 4+5		67 (19.4)			57 (19.9)	
Unknown		8 (2.3)			6 (2.1)	
Stage, n (%)						
cT1-cT2a		248 (71.9)			207 (72.1)	
cT2b-T4		90 (26.1)			73 (25.4)	
Unknown		7 (2.0)			7 (2.4)	
Gleason, n (%)						
= 6		156 (45.2)			128 (44.6)	
>6		180 (52.2)			153 (53.3)	
Unknown		9 (2.6)			6 (2.1)	
PSA, n (%)						
<10		252 (73.0)			211 (73.5)	
≥10		92 (26.7)			76 (26.5)	
Unknown		1 (0.3)			0 (0.0)	

AJCC: American Joint Committee on Cancer; BMI: Body mass index; CI: Confidence Interval; GM: Geometric Mean; ISUP: International Society of Urological Pathology; PC: Prostate Cancer; PSA: Prostate-specific antigen; $\bar{x}$: arithmetic mean; yr: Year.

Table 2
Odds Ratios (OR) and 95 % confidence intervals (95 %CI) for the Association Between As levels and Prostate Cancer Risk in MCC-Spain Case Control Study.

			Basic Model	Adjusted Model
	Controls	Cases	OR[a] (95 %CI)	OR[b] (95 %CI)
Urine As levels (μg/g)				
Q1 <31.54	119	86	1.00	1.00
Q2 [31.54–76.25)	118	87	1.01 (0.69–1.49)	0.97 (0.64–1.48)
Q3 [76.25–150.65)	116	71	0.81 (0.54–1.21)	0.83 (0.54–1.28)
Q4 ≥150.65	115	101	1.09 (0.75–1.59)	1.10 (0.73–1.66)
***p*-trend**			0.890	0.799
Toenail As levels (μg/g)				
Q1 <0.18	144	85	1.00	1.00
Q2 [0.18–0.23)	132	91	1.10 (0.76–1.59)	1.13 (0.76–1.69)
Q3 [0.23–0.31)	112	98	1.62 (1.10–2.37)	1.73 (1.15–2.60)
Q4 ≥0.31	80	71	2.11 (1.38–3.22)	1.94 (1.23–3.06)
***p*-trend**			0.000	0.001

Q: quartile; *p*-trend: p value of a trend test. [a]Models adjusted for sex, educational levels (as a fixed effect), and province of residence (as a random effect). [b]Models further adjusted by BMI, seafood consumption, and family history of PC.

These findings were further supported in dose-response curves (Fig. 1). While urinary As showed no clear association with PC risk (Fig. 1a), toenail As exhibited a marked increase in risk up to approximately 0.3 μg/g, beyond which the curve plateaued (Fig. 1b).

When examining the association between As exposure and PC clinical characteristics, a non-linear trend toward increased risk was observed for urinary As and more aggressive and advanced tumors; however, these associations did not reach statistical significance. Similarly, analyses using toenail As showed no significant heterogeneity across clinical subgroups (Tables 3 and 4), Gleason scores, or PSA levels at diagnosis, but the magnitude of association was stronger in advanced and aggressive disease, suggesting a possible association between toenail As and PC risk depending on tumor characteristics (see Supplementary Tables S1 and S2). Furthermore, there were no significant differences in the possible modifying effect by tertiles of PRS (p-heterogeneity >0.05); nevertheless, with toenail as a biomarker, we observed a major impact in the first and third tertiles of PRS (Table 5).

4. Discussion

In this case-control study conducted in a population with moderate exposure, toenail As concentrations were associated with an increased risk of PC. In contrast, urinary As concentrations were not significantly associated with overall PC risk, underscoring the importance of the biological matrix used for exposure assessment.

Toenail As concentrations (geometric mean [GM]: 0.21 μg/g in controls and 0.24 μg/g in cases) were similar to, although sometimes slightly higher than, those reported for non-occupationally and non-environmentally exposed populations from Europe and North America (Signes-Pastor et al., 2021). By contrast, total urinary As concentrations (69.7 μg/g creatinine in controls and 75.9 μg/g creatinine in cases) were an order of magnitude higher than levels typically observed in the general U.S. population (NHANES, 2017–2018, GM: 6.94 μg/g creatinine; 95 % CI: 6.08–7.93) (CDC, 2024). These concentrations, however, were within the range reported in the Canadian general population (average: 89.5 μg/g for iAs + arsenobetaine) (Health Canada, 2021). Differences between populations are likely explained, at least in part, by dietary habits, since arsenobetaine from fish and seafood contributes substantially to total urinary As, especially in countries with higher fish consumption, such as Canada and Spain, compared with the U.S. In fact, U.S. populations with frequent seafood intake have been shown to exhibit substantially higher total urinary As concentrations, largely driven by organic As species (Jones et al., 2016).

Toenails incorporate As from the bloodstream during their growth, reflecting exposures that occurred roughly 5–18 months before collection (Signes-Pastor et al., 2021). Studies have shown high reproducibility of toenail As measurements over time, both in highly exposed populations in Bangladesh (Huyck et al., 2007) and in the US (Signes-Pastor et al., 2019), suggesting they reliably represent longer-term exposure. In fact, some evidence indicates that toenail As may reflect exposure over periods of 3–6 years in adults (Garland et al., 1993; Karagas et al., 2001). Compared with urine, toenail measurements may better capture the chronic exposure relevant to PC cancer development, although studies with repeated measures over time would strengthen this evidence. Moreover, our results suggest that in populations with high seafood intake, when As is not speciated, toenail levels may better reflect iAs exposure than urine.

As previously described in the introduction, previous studies have frequently used drinking water As concentrations as markers of exposure. In fact, the earliest evidence linking As exposure to PC risk came from an ecological study in Southwestern Taiwan, which reported increased PC mortality in populations chronically exposed to drinking water As levels >150 μg/L compared to national rates (Chen et al., 1988). At lower concentrations, the evidence is less consistent. In Iowa, a population-based study reported higher PC incidence among individuals in both the middle (2.07–2.98 μg/L) and highest (2.99–18.6 μg/L) tertiles of drinking water As compared with the lowest (<2.07 μg/L) (Roh et al., 2017). Similarly, in Illinois, county-level analyses showed increased PC incidence in areas with drinking water As concentrations in the highest tertile (1.61–16.23 μg/L) relative to the lowest (<0.70 μg/L) (Bulka et al., 2016). In contrast, a prospective cohort study in Denmark, where mean drinking water As exposure was 1.2 μg/L (range: 0.05–25.3 μg/L), found no significant association with PC risk

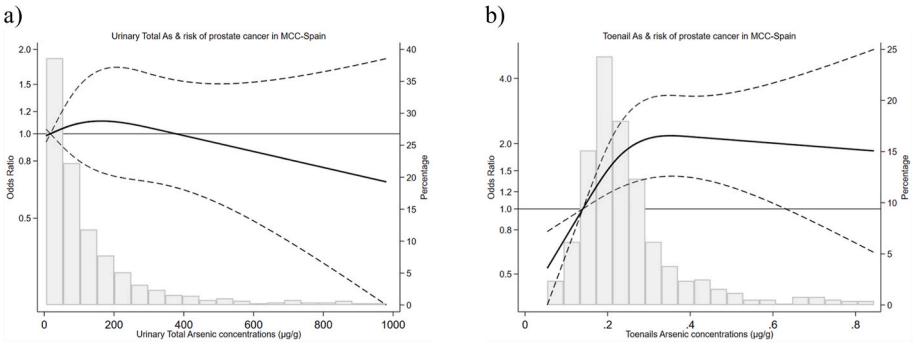

Fig. 1. Odds ratios (ORs) for prostate cancer in relation to arsenic exposure, measured by a) urinary arsenic and b) toenail arsenic concentrations. ORs (solid lines) and 95 % confidence intervals (dashed lines) were estimated using restricted cubic spline models with knots placed at the 10th, 50th, and 90th percentiles of the arsenic distribution. The reference value corresponds to the 10th percentile: 17.6 μg/g for urinary arsenic and 0.1 μg/g for toenail arsenic. Models were adjusted for age, education, body mass index (BMI), family history of prostate cancer, and seafood intake (as a fixed effect), with province of residence included as a random effect.

Table 3
Relative Risk Ratios (RRR) and 95 % Confidence Intervals (95 %CI) for the association between As levels and Prostate Cancer Risk in MCC-Spain Case Control Study, according to ISUP grading and AJCC 8th edition stage.

	Co	ISUP grading					AJCC stage (8th ed)				
		1 + 2 (n = 270)		3 + 4+5 (n = 67)			I-IIA (n = 157)		IIB-IV (n = 184)		
		Ca	RRR (95 %CI)	Ca	RRR (95 %CI)	*p*-het	Ca	RRR (95 %CI)	Ca	RRR (95 %CI)	*p*-het
Urine As (μg/g)						0.073					0.103
Q1 <31.54	119	73	1.00	13	1.00		47	1.00	39	1.00	
Q2 [31.54–76.25)	118	61	0.80 (0.51–1.25)	24	1.79 (0.85–3.78)		38	0.72 (0.43–1.22)	48	1.29 (0.76–2.17)	
Q3 [76.25–150.65)	116	59	0.83 (0.53–1.31)	9	0.69 (0.28–1.72)		33	0.67 (0.39–1.14)	36	1.02 (0.58–1.77)	
Q4 ≥150.65	115	77	1.00 (0.65–1.55)	21	1.44 (0.67–3.10)		39	0.74 (0.44–1.24)	61	1.56 (0.93–2.60)	
***p*-trend**			0.936		0.882			0.238		0.164	
Toenail As (μg/g)						0.097					0.114
Q1 <0.18	144	70	1.00	11	1.00		43	1.00	41	1.00	
Q2 [0.18–0.23)	132	69	1.01 (0.66–1.56)	21	2.41 (1.08–5.37)		35	0.77(0.45–1.30)	54	1.59 (0.96–2.62)	
Q3 [0.23–0.31)	112	72	1.52 (0.98–2.35)	23	3.87 (1.74–8.63)		50	1.52 (0.92–2.50)	47	1.98(1.18–3.34)	
Q4 ≥0.31	80	59	1.97 (1.22–3.17)	12	2.86 (1.16–7.06)		29	1.52 (0.85–2.69)	42	2.58 (1.48–4.50)	
***p*-trend**			0.002		0.005			0.032		0.000	

AJCC: American Joint Committee on Cancer. Co: controls; Ca: cases; CI: Confidence Interval; ISUP: International Society of Urological Pathology; *p*-het: heterogeneity p value; *p*-trend: p value of a trend test; RRR: relative risk ratio. Models were adjusted by age, educational level, BMI, family history of PC, seafood intake (as a fixed effect), and province of residence (as a random effect). 8 cases with complete information on all the covariates did not have information on ISUP grading. 4 cases with complete information on all the covariates did not have information on AJCC stage (8th edition).

Table 4
Relative Risk Ratios (RRR) and 95 % Confidence Intervals (95 %CI) for the association between As levels and Prostate Cancer Risk in MCC-Spain Case Control Study, according to Tumor Extension.

			cT1-cT2a (n = 248)		cT2b-T4 (n = 90)	*p*-het
	Co	Ca	RRR (95 %CI)	Ca	RRR (95 %CI)	
Urine As (μg/g)						0.634
Q1 <31.5	119	61	1.00	23	1.00	
Q2 [31.54–76.245)	118	68	1.04 (0.66–1.63)	18	0.81 (0.40–1.64)	
Q3 [76.248–150.65)	116	51	0.82 (0.51–1.32)	18	0.88 (0.44–1.80)	
Q4≥150.65	115	68	1.03 (0.65–1.62)	31	1.27 (0.67–2.41)	
***p*-trend**			0.868		0.400	
Toenail As (μg/g)						0.171
Q1 <0.18	144	61	1.00	23	1.00	
Q2 [0.18–0.23)	132	67	1.09 (0.70–1.70)	23	1.30 (0.67–2.52)	
Q3 [0.23–0.31)	112	76	1.74 (1.12–2.71)	18	1.48 (0.73–2.98)	
Q4≥0.31	80	44	1.64 (0.99–2.74)	26	3.05 (1.55–5.99)	
***p*-trend**			0.009		0.002	

Co: controls; Ca: cases; CI: Confidence Interval; *p*-het: heterogeneity p value; *p*-trend: p value of a trend test; RRR: relative risk ratio. Models were adjusted by age, educational level, BMI, family history of PC,seafood intake (as a fixed effect), and province of residence (as a random effect). 7 cases with complete information on all the covariates did not have information on cT.

Table 5
Relative Risk Ratios (RRR) and 95 % Confidence Intervals (95 %CI) for the association between As levels and Prostate Cancer Risk in MCC-Spain Case Control Study, according to Genetic Susceptibility to Prostate Cancer.

		ALL (n = 287)			PRS2 T1 (n = 47)			PRS2 T2 (n = 84)			PRS2 T3 (n = 156)		
	Co	Ca	OR[a] (95 %CI)	Co	Ca	OR[b] (95 %CI)	Co	Ca	OR[b] (95 %CI)	Co	Ca	OR[b] (95 %CI)	*p*-het
Urine As (μg/g)													0.30
Q1 <31.54	103	70	1.00	27	7	1.00	39	24	1.00	37	39	1.00	
Q2 [31.54–76.25)	95	74	1.10 (0.70–1.75)	29	15	1.98 (0.66–5.94)	36	23	1.00 (0.45–2.21)	30	36	1.06 (0.53–2.15)	
Q3 [76.82–150.65)	105	58	0.82 (0.51–1.31)	36	14	1.90 (0.64–5.64)	35	19	0.74 (0.34–1.63)	34	25	0.72 (0.34–1.51)	
Q4 ≥150.65	106	85	1.08 (0.69–1.68)	38	11	1.15 (0.38–3.54)	34	18	0.65 (0.29–1.46)	34	56	1.49 (0.77–2.91)	
***p*-trend**			0.97			0.86			0.24			0.47	
Toenail As (μg/g)													0.58
Q1 <0.18	124	71	1.00	47	10	1.00	38	21	1.00	39	40	1.00	
Q2 [0.18–0.23)	123	73	1.12 (0.73–1.73)	43	16	1.80 (0.71–4.58)	46	22	0.92 (0.43–1.98)	34	35	1.17 (0.59–2.30)	
Q3 [0.23–0.31)	94	81	1.84 (1.18–2.88)	22	12	3.44 (1.22–9.72)	32	25	1.69 (0.77–3.71)	40	44	1.32 (0.69–2.53)	
Q4 ≥0.31	68	62	2.20 (1.34–3.61)	18	9	3.15 (0.99–9.96)	28	16	1.30 (0.54–3.11)	22	37	2.47 (1.15–5.32)	
***p*-trend**			0.00			0.03			0.25			0.05	

Co: controls; Ca: cases; CI: Confidence Interval; *p*-het: heterogeneity p value; *p*-trend: p value of a trend test; PRS: Polygenic Risk Score; RRR: relative risk ratio; T: Tertiles. [a] Models were adjusted by age, educational level, BMI, family history of PC, seafood intake (as a fixed effect), and province of residence (as a random effect). [b] Models were adjusted by age, province of residence, educational level, BMI, family history of PC, and seafood intake, including an interaction with PRS (tertiles).

across exposure categories (Baastrup et al., 2008). Using internal biomarkers, a study in Native Americans aged 45–74

found that participants in the 80th percentile of urinary inorganic + methylated As (versus the 20th percentile) had a 3.30-fold higher risk of prostate cancer mortality (HR 3.30; 95 % CI: 1.28–8.48) (García-Esquinas et al., 2013). More recently, a case-control study in Taiwan (318 cases, 318 controls) found that high urinary iAs concentrations (>29.28 μg/g) were associated with increased PC risk (Hsueh et al., 2017). Finally, in a study conducted in North Carolina among European-American men with newly diagnosed prostate cancer, those in the highest tertile of urinary As (≥6.03 μg/L vs lowest) had a significantly increased odds of aggressive tumors (OR = 1.77; 95 % CI: 1.05–2.98) (Parada et al., 2020).

An interesting aspect of this study was its evaluation of whether the effect of As exposure varies according to men's genetic predisposition to PC and tumor aggressiveness. Although these results should be interpreted cautiously due to limited statistical power, they suggest that the PRS did not significantly modify the association between As and PC. To better capture the clinical and biological heterogeneity of PC, we incorporated multiple classification systems, including ISUP grade (Epstein et al., 2016), AJCC 8th edition stage, and tumor clinical extension (Buyyounouski et al., 2017). Overall, we observed a significant association between total As levels in toenails and increased PC risk, with notably stronger effects for tumors exhibiting aggressive features or advanced stage. In contrast, although total urinary As was not significantly associated with overall PC risk, there was a non-linear trend toward higher risk for more aggressive and advanced tumors. These findings underscore the importance of focusing on clinically significant cases, as early-stage diagnoses may include indolent tumors unlikely to progress, potentially diluting true associations.

Experimental studies support multiple mechanisms by which iAs may contribute to PC development and progression. Chronic As exposure can increase oxidative stress through mechanisms such as glutathione depletion and enhanced lipid peroxidation (Pi et al., 2002). This is accompanied by the generation of reactive oxygen species (ROS) that damage DNA, induce chromosomal instability (Eckstein et al., 2016), and may contribute to mutagenesis and tumor initiation. Moreover, As can induce epigenetic alterations, including changes in DNA methylation, histone modifications, and deregulated microRNA expression (Marsit et al., 2006; Riedmann et al., 2015). These modifications may lead to dysregulated gene expression (either suppression or activation) depending on the cellular context, contributing to oncogenesis. As has also been shown to disrupt hormone signalling pathways. It can inhibit androgen receptor (AR) transcriptional activity by preventing AR-chromatin binding (Rosenblatt and Burnstein, 2009), or conversely, promote androgen independence in prostate cells via activation of the Ras/MAPK signalling pathway (Benbrahim-Tallaa and Waalkes, 2008; Weber and Gioeli, 2004). Chronic exposure may lower the androgen requirement of prostate cells to subphysiological levels, enabling tumor growth despite androgen deprivation (Benbrahim-Tallaa et al., 2007). In addition, As may alter tumor-stroma interactions, facilitating local invasion and tumor progression (Shearer et al., 2016). While short-term exposure may induce apoptosis or disrupt cell survival pathways, long-term exposure has been shown to promote malignant transformation (Li et al., 2018). Notably, in experimental models using prostate epithelial stem cells, chronic low-level exposure to arsenite induces rapid malignant transformation, characterized by PSA overexpression, increased matrix metalloproteinase-9 secretion, and tumor formation in vivo (Achanzar et al., 2002; Tokar et al., 2010). This transformation includes the acquisition of cancer stem cell-like traits, with loss of differentiation control and androgen independence, hallmarks associated with advanced and aggressive PC (Benbrahim-Tallaa et al., 2007).

One of the main strengths of this study is the use of a population sample drawn from the largest case-control study in Spain, which enabled us to perform multinomial analyses across different clinical classifications of PC. Additionally, the histopathological confirmation of cases ensures diagnostic accuracy and enhances the reliability of our findings. Another key advantage is the availability of genetic susceptibility data, which allowed us to evaluate As exposure effects across varying levels of genetic predisposition and to explore interactions between As and genetic risk. Furthermore, the application of correction methods for As measurement in toenails, particularly the COMET approach, strengthens the study's credibility by minimizing bias due to variable sample mass and laboratory batch differences. This correction improves statistical power and precision, making toenail As a robust biomarker for assessing exposure and its relation to cancer risk. However, the study has limitations. Potential selection bias cannot be entirely ruled out, though we mitigated this by adjusting for educational level, a factor likely to differ between cases and controls, in our multivariate models. Additionally, in populations with high arsenobetaine exposure, total urinary As may not accurately reflect toxic As exposure relevant to cancer risk, as it includes non-toxic organic As species. The lack of As speciation data may therefore have led to misclassification of iAs exposure, potentially biasing the results toward the null. Moreover, urinary As reflects primarily recent exposure and may be influenced by short-term factors such as changes in drinking water sources, travel-related variations in water consumption, and dietary patterns, which could further contribute to exposure misclassification. These limitations should be considered when interpreting the observed lack of association between total urinary As and prostate cancer risk. To address these limitations, we adjusted analyses for seafood intake and used toenail As as an alternative biomarker.

5. Conclusions

Our findings support that elevated levels of As in toenails are associated with an increased risk of PC, with notably stronger associations observed for aggressive disease. Our findings underscore the relevance of focusing on clinically significant cases, as early-stage diagnoses may include indolent tumors unlikely to progress, potentially diluting true associations. Also, the absence of a clear association between urinary As levels and PC in our study suggests that urine may be a less suitable biomarker for chronic As exposure related to PC in populations with high seafood intake. Future research should consider non-linear exposure-response models and aim to validate these findings in larger cohorts with As speciation data.

CRediT authorship contribution statement

Elena Varea-Jiménez: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roberto Pastor-Barriuso:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Ángeles Sierra:** Writing – review & editing. **Trinidad Dierssen-Sotos:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Guillermo Fernández Tardón:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Nuria Aragonés:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Inés Gómez-Acebo:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Gemma Castaño-Vinyals:** Writing – review & editing. **Jose Luis Gómez-Ariza:** Writing – review & editing, Resources, Project administration, Investigation. **Manolis Kogevinas:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **Víctor Moreno:** Investigation, Data curation. **Pablo Fernández-Navarro:** Investigation, Data curation. **Marina Pollán:** Writing – review & editing, Methodology, Investigation, Funding acquisition. **Beatriz Pérez-Gómez:** Writing – review & editing, Validation, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Esther García-Esquinas:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization.

Ethics

The Ethics Committee of all participating centers approved the study protocol.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2026.123767.

Data availability

Data will be made available on request.

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