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Per- and poly-fluoroalkyl substances (PFAS) Exposure and risk of bladder and prostate cancers: A systematic review and meta-analysis

Monireh Sadat Seyyedsalehi[(1)], *Sirui Zhang*[(2)], *Elizabeth Maria Kappil*[(2)], *Tongzhang Zheng*[(2)], *Paolo Boffetta*[(1,3,4)]

(1) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
(2) Brown University School of Public Health, Providence, RI, USA
(3) Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA
(4) Department of Family, Population and Preventive Medicine, Renaissance School of Medicine, Stony Brook University, Stony Brook, NY, USA

CORRESPONDING AUTHOR: *Paolo Boffetta, Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, 11794, USA. e-mail: paolo.boffetta@stonybrookmedicine.edu*

ABSTRACT

Objectives: PFAS are synthetic chemicals that humans may be exposed to through workplace or the environment. Previous studies have suggested a carcinogenic effect. In our review, we investigated the association between PFAS exposure and risk of bladder and prostate cancer.
Methods: We searched through IARC Monographs, ATSDR documents, and PubMed (up to January 2024) to find studies that examined the relationship between PFAS exposure and bladder and prostate cancer. Four reviewers independently screened studies, extracted data, and evaluated quality using a modified version of the Newcastle-Ottawa Scale (NOS). We conducted meta-analyses using random-effects models, stratified analyses, dose-response assessments, and evaluated publication bias.
Results: We included 21 independent studies in our meta-analysis. The findings didn't reveal an association between PFOA, PFOS, and PFAS exposure and bladder cancer, as well PFOA, PFNA and prostate cancer. However, we found an association between prostate cancer and total PFAS (RR = 1.12, 95% CI =1.06–1.18), based on two studies, and an association of borderline statistical significance with PFOS (RR = 1.04, 95% CI =0.98–1.11). There was no difference between outcome, region, year of publication, study design, quality score, and gender, exposure source and different levels of PFAS for both cancer types. Publication bias was excluded for prostate cancer studies (P = 0.71) and bladder cancer (P = 0.79).
Conclusion: Our research did not find a link between different types of PFAS exposure and bladder cancer. However, it supports a potential association between PFOS exposure and prostate cancer. Bias and confounding cannot be excluded.

Keywords: bladder; malignant; occupational factors; prostate; Perfluorooctanoic Acid; PFAS; Perfluorooctane sulfonic acid.

INTRODUCTION

Per- and polyfluoroalkyl substances, or PFAS, are a large group of manufactured compounds and synthetic chemicals used in various industries since the 1940s.[1] Common types include perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorobutane sulfonate (PFBS), perfluorohexanesulfonic acid (PFHxS) [2]. They are used in products like water-resistant fabrics, paints, and cleaning products [3]. Exposure can occur through water, air, and soil. Some PFAS are classified either as carcinogenic to humans (group 1) like PFOA or as possibly carcinogenic to humans (group 2B)

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like PFOS, particularly due to their association with kidney and testicular cancers according to the International Agency for Research on Cancer (IARC) reports in 2017 and 2024 [4,5]. Limited evidence also suggests an association with other cancer types [6,7].

Urinary cancers, including bladder and other urinary tract cancers (without kidney), account for about 3% of cancers worldwide, with a higher incidence in high-income countries (age-standardized rate [ASR]: 5.6 per 100,000). Globally, urinary cancers occur more frequently in men than in women, with a ratio of 2.5:1. Additionally, prostate cancer is the third most diagnosed malignancy, with 1,414,259 cases, making up 7.3% of the total cases and significantly impacting the male population [8].

Many factors have been linked to the development of bladder cancer, including occupational, lifestyle, and genetic factors. These include smoking, being overweight, lack of physical activity, uncontrolled hypertension, alcohol consumption, diet, and Schistosoma infection. Occupational exposures also play a significant role, particularly for men in high-risk job titles such as painters, machinists, printers, firefighters, hairdressers, and truck drivers who are exposed to substances like pesticides, chromium, aromatic amines, coal tars and pitches, polyaromatic hydrocarbons, and diesel engine exhaust [9–11]. Conversely, knowledge on modifiable risk factors of prostate cancer remains limited. However, previous individual epidemiologic studies have not definitively established whether elevated levels of PFOA and other PFAS are associated with prostate and bladder cancer incidence or mortality [12].

In this report, we aim to conduct a systematic review and meta-analysis of occupational and environmental observational studies which evaluated the association between exposure to overall and individual type of PFAS and bladder, and prostate cancer incidence and mortality.

METHODS

Data Sources, Search Strategy, Selection Criteria, and Quality Assessment

Details of the overall project reported elsewhere [13,14]. Shortly, this report is a part of extended systematic review and meta-analysis (PROSPERO database's registration No. CRD62024560837) with focus on association between exposure to different types of PFAS, including PFOA, PFOS, PFDA, PFNA and total PFAS, and solid and non-solid cancers other than kidney, liver and testis, which were included in a previous review 6, according to the COSMOS-E and PRISMA-statements (supplementary table 1a,b) [15,16]. We conducted the literature search on January 23, 2024, for English language peer-reviewed publications in PubMed and Scopus with no limit according to year of publication to identify relevant studies and, we added the reference lists of the IARC Monograph on PFOA/PFOS [4] and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile of PFAS [17]. The search strategy utilized the following MeSH terms (("PFOA" OR "Perfluorooctanoic Acid" OR "PFOS" OR "Perfluorooctane Sulfonic Acid" OR "PFAS" OR "per and poly fluoroalkyl substances" AND ("cancer" OR "malignant" OR "carcinoma" OR "neoplasm" OR "tumor" OR "myeloid" OR "lymphoma" OR "Hematologic")) (the complete search string is reported in Supplementary Table 2).

We included cohort, case-control, cross sectional, and ecological human occupational and environmental studies. Studies involving animals or other non-human experimental systems were excluded. Also, we excluded studies for which we couldn't find the full text of the relevant articles. Four reviewers independently screened the titles, abstracts, and full text and extracted data.

The data extraction file contained demographic characteristics of the original studies such as the author's name, year of publication, country, study design type (cohort, case-control, ecological, and cross sectional), patient characteristics (gender), cancer type, PFAS types, PFAS exposure source (occupational or environmental), duration and level of exposure. We also extracted the effect size measures, such as relative risks (RRs), odds ratios (ORs), risk ratios, rate ratio, standardized mortality ratio (SMR), or standardized incidence ratio (SIR) as well as their respective 95% confidence intervals (CI). If results were reported only for subgroups, we combined them using a fixed effect meta-analysis. When RRs or CIs were not reported, we calculated them from the raw data if possible.

The eligible studies were critically appraised by four independent reviewers using a modified version of the Newcastle-Ottawa Scale (NOS) (Supplementary Table 3) [18] for case-control, ecological, and cohort studies. The scores were broken down into 2 categories: low quality if the study scored less than 8 and high quality if the study scored 8 or higher (Supplementary Table 4).

Statistical Analysis

Totally we identified of 39 independent studies related to different solid and non-solid cancer types other than liver, kidney and testicular cancer (Figure 1). We restricted this analysis to 21 studies reporting incidence and mortality RR and the respective 95% CIs related to bladder (n=14 studies) or prostate cancer (n=19 studies) (Figure 1) and examined their association with total and different types of PFAS. Heterogeneity among studies was assessed using the Q test, which evaluated variation across studies rather than within them, and the I^2 statistic, which indicates the percentage of variance in a meta-analysis attributable to study heterogeneity [19]. To account for heterogeneity in the design characteristics of the included studies, random-effects models were used for the meta-analysis [20]. We then conducted

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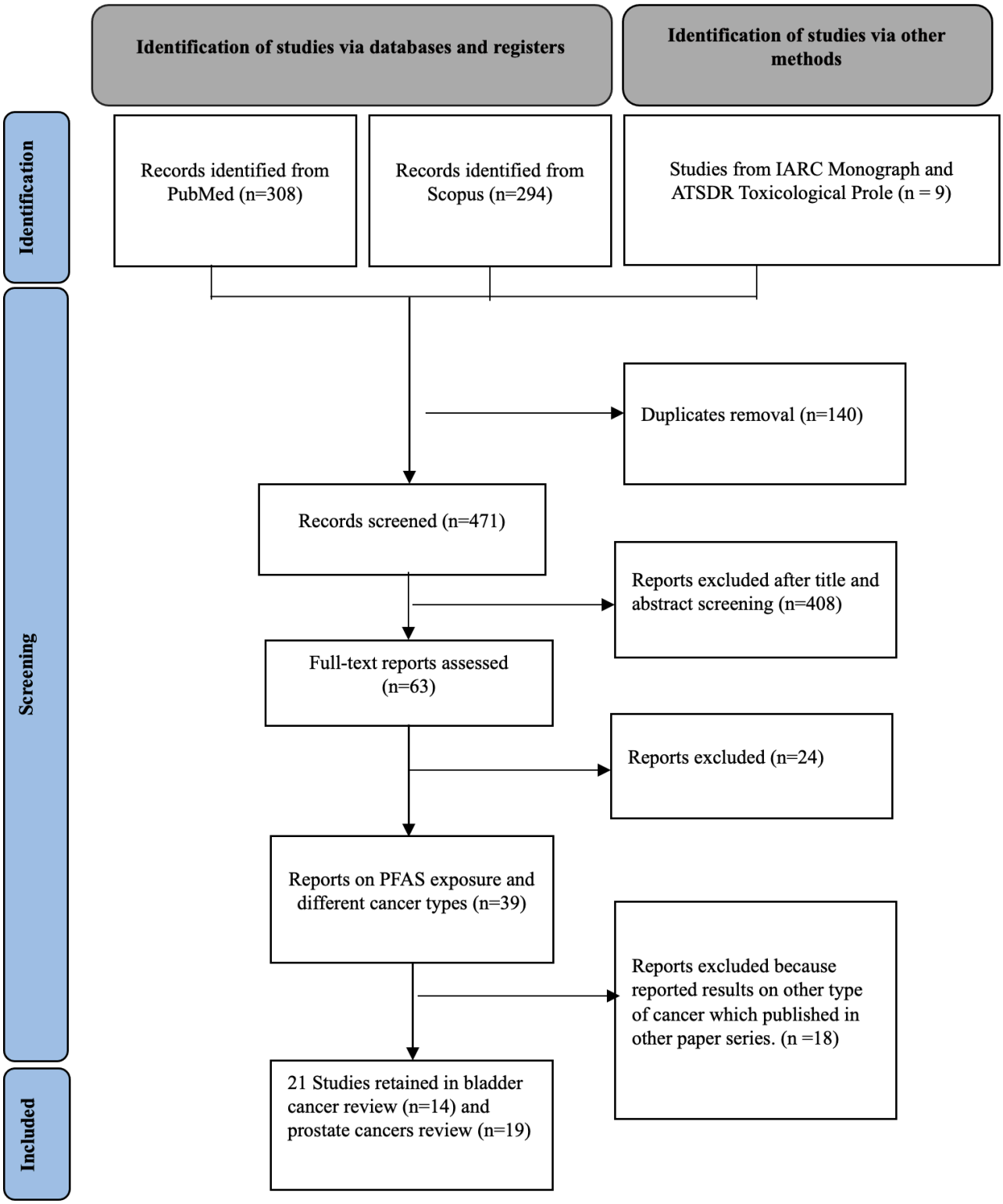
Figure 1. Selection of studies for inclusion in the review and meta-analysis



stratified analyses by region (North America, Europe, and other regions), study design (case-control, cohort, ecological), quality score (low quality or high quality), outcome (incidence or mortality), exposure source (environmental, occupational), gender (male, female, both), and year of publication (<2017 vs. ≥ 2017). We also extracted dose-response results, including analyses by level of low, medium, or high exposure (Supplementary table 5 and 6). We conducted a meta-analysis for each exposure category and performed a meta-regression of the linear trend for the respective exposure categories. Lastly, we assessed publication bias by creating a funnel plot and applying a regression asymmetry test [21]. All statistical analyses were completed using STATA version 17 (Stata, College Station, TX, USA).

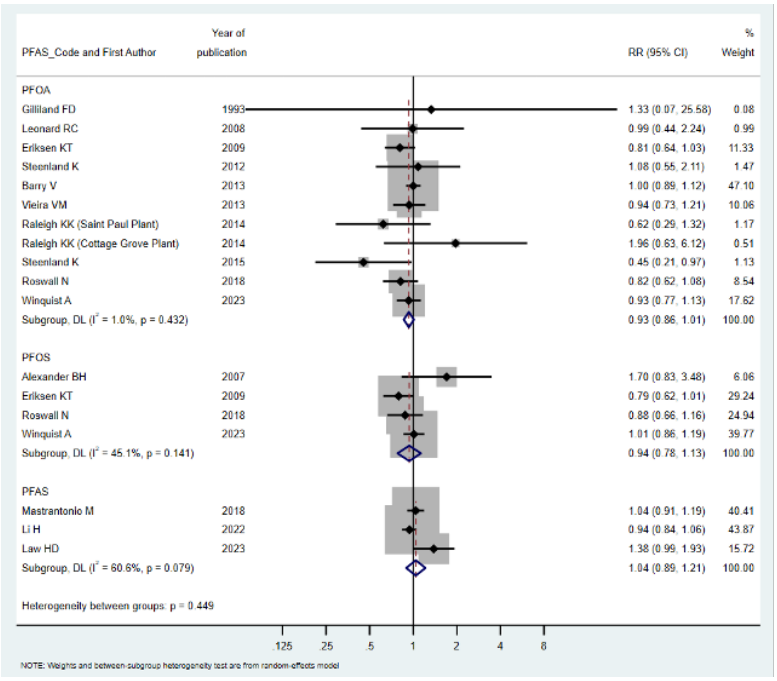
RESULTS

Among the 21 studies retained in the review, [22–42] 15 cohort, studies 5 case-control, studies and 1 ecological study reported 209 different risk estimates for bladder and prostate cancer considering different types of PFAS, genders and outcomes. Details of these studies are provided in Supplementary Table 4.

The findings revealed a lack of association between PFOA, PFOS, and PFAS exposure and bladder cancer (Figure 2a, Table 1) as well PFOA, PFNA and prostate

Figure 2. Forest plot (random-effects model) of results on the association between PFAS exposure and a) bladder cancer, b) prostate cancer

a) Bladder



b) Prostate

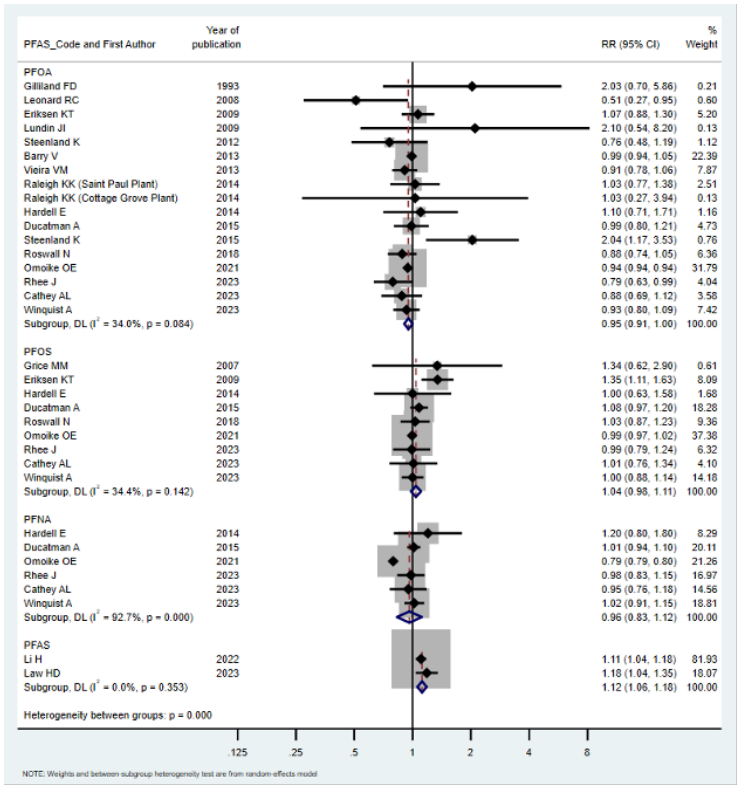


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Table 1. Results of the meta-analyses of bladder and prostate cancer stratified by region, study design, quality score, outcome, gender, year of publication

Cancer type	Characteristic	N risk estimates	RR (95% CI)	p heterogeneity
Bladder	**Overall**			
	Region			
	North America	11	0.98(0.91-1.06)	0.05
	Europe	6	0.91(0.83-1.00)	
	Other regions	1	1.38(0.99- 1.93)	
	Study design			
	Case control	1	0.94(0.73-1.21)	0.44
	Cohort	17	0.94(0.87-1.02)	
	Ecological	1	1.04(0.91-1.19)	
	Quality score			
	Low quality (< 8)	10	0.98(0.87-1.09)	0.58
	High quality (>= 8)	8	0.93(0.86-1.02)	
	Years of puplication			
	<2017	11	0.91(0.80-1.04)	0.35
	>=2017	7	0.98(0.90-1.06)	
	Outcome			
	Incidence	12	0.97(0.89- 1.05)	0.21
	Mortality	6	0.85(0.71-1.02)	
	Gender			
	Men	4	0.99(0.90-1.09)	0.27
	Women	3	0.84(0.69-1.00)	
	Both	17	0.95(0.89-1.02)	
	Exposure			
	Occupational	7	0.96(0.64-1.45)	0.96
	Environmental	11	0.96(0.89-1.02)	
	Type of PFAS			
	PFOA	11	0.93(0.86- 1.01)	0.45
	PFOS	4	0.94(0.78- 1.13)	
	PFAS	3	1.04(0.89-1.21)	
	PFOA			
	Region			
	North America	9	0.96(0.88- 1.05)	0.09
	Europe	2	0.81(0.68-0.97)	
	Other regions	0	-	
	Study design			
	Case control	1	0.94(0.73-1.21)	0.86
	Cohort	10	0.92(0.83- 1.01)	
	Quality score			
	Low quality (< 8)	5	0.87(0.73-1.03)	0.40
	High quality (>= 8)	6	0.95(0.85-1.04)	
	Years of puplication			
	<2017	9	0.93(0.82-1.05)	0.71
	>=2017	2	0.89(0.76-1.04)	
	Outcome			
	Incidence	6	0.92(0.81-1.05)	0.47
	Mortality	5	0.84(0.66-1.06)	
	Gender			
	Men	2	0.93(0.74-1.17)	0.99
	Women	1	0.91(0.63-1.31)	
	Both	10	0.92(0.84-1.01)	
	Exposure			
	Occupational	6	0.84(0.56-1.25)	0.59
	Environmental	5	0.94(0.86-1.02)	

(*continued*)

Table 1. Results of the meta-analyses of bladder and prostate cancer stratified by region, study design, quality score, outcome, gender, year of publication (continued)

	Characteristic	N risk estimates	RR (95% CI)	p heterogeneity
Prostate	**Overall**			
	Region			
	North America	25	0.96(0.90-1.03)	0.01
	Europe	8	1.08(0.99-1.18)	
	Other regions	1	1.18(1.04-1.35)	
	Study design			
	Case control	17	1.05(0.98-1.12)	0.09
	Cohort	21	1.04(0.99-1.10)	
	Quality score			
	Low quality (< 8)	19	1.01(0.96-1.06)	0.75
	High quality (>= 8)	11	1.02(0.95-1.10)	
	Years of puplication			
	<2017	18	1.04(0.97-1.12)	0.13
	>=2017	16	0.97(0.90- 1.04)	
	Outcome			
	Incidence	26	1.00(0.95-1.06)	0.52
	Mortality	8	0.95(0.81-1.12)	
	Exposure			
	Occupational	8	1.11(0.78- 1.56)	0.61
	Environmental	22	1.01(0.97- 1.05)	
	Type of PFAS			
	PFOA	17	0.95(0.91-1.00)	<0.001
	PFOS	9	1.04(0.98-1.11)	
	PFNA	6	0.96(0.83-1.12)	
	PFAS	2	1.12(1.06-1.18)	
	PFOA			
	Region			
	North America	6	1.00(0.97-1.02)	0.2
	Europe	3	1.14(0.93- 1.41)	
	Other regions	0	-	
	Study design			
	Case control	5	0.94(0.94- 0.94)	0.73
	Cohort	12	0.98(0.88- 1.09)	
	Quality score			
	Low quality (< 8)	9	0.92(0.84-1.01)	0.19
	High quality (>= 8)	8	0.99(0.94-1.04)	
	Years of puplication			
	<2017	12	1.00(0.90-1.10)	0.28
	>=2017	5	0.94(0.94-0.94)	
	Outcome			
	Incidence	11	0.96(0.91- 1.00)	0.59
	Mortality	6	0.90(0.71- 1.13)	
	Exposure			
	Occupational	7	1.08(0.74-1.60)	0.48
	Environmental	10	0.94(0.94-0.94)	

cancer (Figure 2b, Table 1). Conversely, we found an association between prostate cancer and total PFAS (RR = 1.12, 95% CI =1.06–1.18, 2 risk estimates), and an association of borderline statistical significance with PFOS (RR = 1.04, 95% CI =0.98–1.11, 9 risk estimates) (Figure 2b, Table 1).

Publication bias was excluded through the Egger test for prostate cancer studies (P = 0.71) and bladder cancer (P = 0.80); funnel plots are shown in Figure 3.

Results of stratified analyses according to selected characteristics are reported in Table 1. There was no difference according to outcome, region, year of publication, study design, quality score, and gender, exposure source for both cancer types. A similar stratified analysis limited to PFOA exposure showed no effect modification.

Results on different levels of PFAS exposure didn't reveal any dose trend for bladder and prostate cancer (Table 2). The relative risks of different levels of PFAS exposure from each study included in our analysis are reported in Supplementary Table 5 (for bladder cancer) and Supplementary Table 6 (for prostate cancer).

Figure 3. Funnel plot of results on the association between PFAS exposure and a) bladder cancer, b) prostate cancer

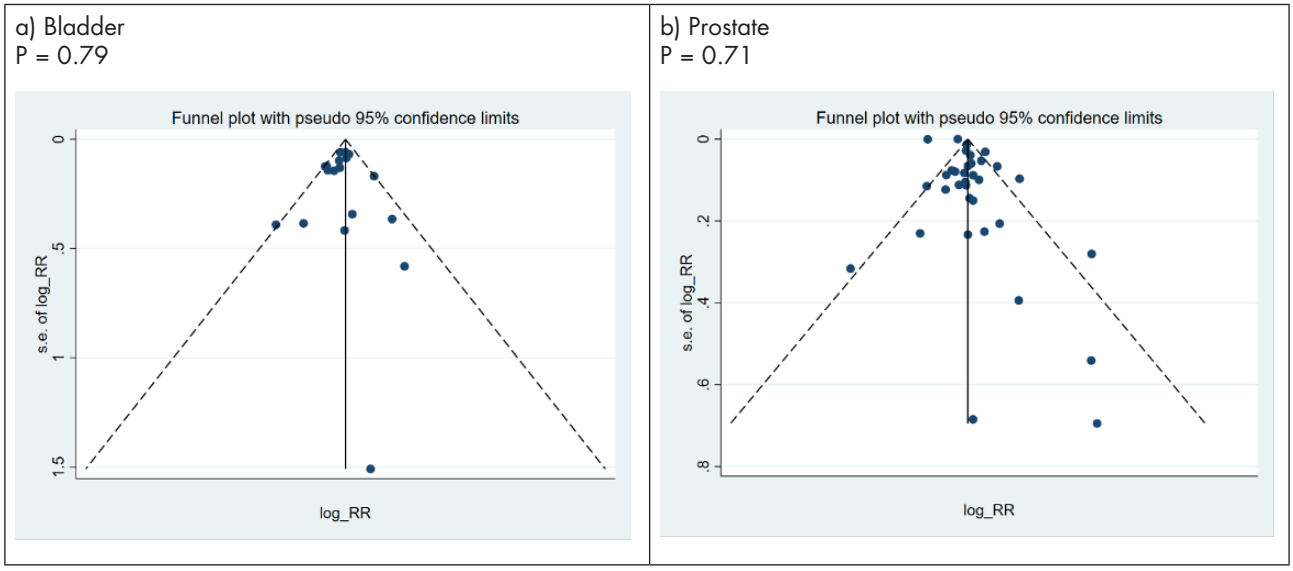

Table 2. Meta-analysis of results on level of PFAS exposure

Characteristic	PFAS type	Dose category	RR (95% CI)	p trend
Prostate	**PFOA**	Low (9 studies)	0.88(0.73-1.06)	0.85
		Medium (9 studies)	0.91(0.79-1.04)	
		High (9 studies)	0.85(0.70-1.03)	
	PFOS	Low (5 studies)	1.11(0.94-1.29)	0.82
		Medium (4 studies)	1.10(0.93-1.30)	
		High (5 studies)	1.08(0.91-1.27)	
	PFNA	Low (2 studies)	0.83(0.65-1.06)	0.27
		Medium (2 studies)	0.99(0.76-1.28)	
		High (2 studies)	1.02(0.78-1.33)	
Bladder	**PFOA**	Low (7 studies)	0.83(0.67-1.03)	0.92
		Medium (7 studies)	0.94(0.77-1.15)	
		High (7 studies)	0.84(0.63-1.10)	
	PFOS	Low (4 studies)	1.01(0.70-1.47)	0.36
		Medium (3 studies)	0.98(0.77-1.26)	
		High (4 studies)	0.82(0.58-1.16)	
* The p-value of test for linear trend.				

DISCUSSION

Our systematic review and meta-analysis found no association between PFAS exposure and risk of bladder cancer, but we found a borderline association in studies which focused particularly on prostate cancer and PFOS exposure. In addition, there was an association between total PFAS exposure and prostate cancer, which however was based on two studies only.

Previous individual reports, included in our review, have shown that there is a correlation between exposure to certain types of PFAS and the development of prostate [27,32,43] and bladder [44] cancers in specific populations. While the precise way in which PFAS contributes to cancer is not completely understood, some studies have suggested various possible mechanisms. Initially, their potential impact on the normal human prostate stem-progenitor cells (SPCs) may lead to altered transcriptomes and metabolomes, potentially promoting a preneoplastic state and increasing the risk of prostate cancer with prolonged exposure [45]. Additionally, a hormone-dependent effect of PFAS has been suggested. Apart from disrupting hormones and damaging DNA, PFAS can also cause inflammation and raise levels of related markers in the body, which may ultimately contribute to the development of cancer [54]. These findings offer valuable insights into the potential mechanisms by which PFAS could influence the development of prostate and bladder cancer [46,47]. However, if present, the carcinogenic effect is not supported by strong mechanistic evidence and needs more future studies.

Since certain PFAS are primarily eliminated from the body through urine, this can result in prolonged exposure of the kidneys and other urinary organs to these chemicals. Also, previous research has specifically documented their possible impact on the incidence of kidney cancer, which is attributed to oxidative stress and epigenetic mechanisms associated with tubular reabsorption [48,49]. However, we did not encounter the same evidence of a possible association with bladder cancer. This might be because the concentration of PFAS in the urine collected in the bladder is lower, and the urine is expelled from the body after a short period of time [50]. Another reason for this is that most cohort studies, which primarily focused on mortality, did not have direct measurements of PFAS. These studies typically only examined a few major PFAS and had a limited number of specific cancer cases. Additionally, many of these studies lacked proper control groups and did not consider the potential influence of positive or negative confounding factors. There is a lack of published evidence from ongoing large-cohort studies.

Our systematic review and meta-analysis had certain limitations. The primary concern was the scarcity of studies available, especially those focusing on the impact of exposure to specific PFAS compounds other than PFOA or PFOS, the limited information on dose-response, and the lack of details on clinical aspects such as muscle invasiveness for bladder and tumor grade for prostate cancer, and the low power of stratified analyses. Additionally, it is crucial to consider various confounding factors that can impact the outcomes of studies on bladder and prostate cancer. These factors should be carefully considered when interpreting the results. For bladder cancer, factors such as tobacco smoking, being overweight, having diabetes, and a lack of physical activity should be taken into consideration [51]. When it comes to prostate cancer, age, race, family history, and genetics (such as the BRCA1 or BRCA2 gene variant) can also play a role [52]. However, it is worth noting that many of the studies included in our review, especially cohort studies, did not adjust for potential non-occupational and occupational confounders. This is especially important for bladder cancer, as 17 out of 19 relative risks were extracted from cohort studies. It is important to acknowledge that case-control studies may introduce other types of bias [53]. The stratification analysis we conducted did not reveal any heterogeneity in the results based on the characteristics we considered. The lack of studies from regions like Latin America, East Asia, and sub-Saharan Africa was another limitation. As a last note, along with reporting the dose of exposure, working on duration particular to evaluate long-term and chronic effects of PFAS can be helpful, which are not addressed in most studies.

In spite of these limitations, to the best of our knowledge, this systematic review and meta-analysis represents the first comprehensive examination of the potential link between environmental and occupational exposure to PFAS and bladder and prostate cancer. Thus, it may be useful to summarize the limitations of different reports and to suggest improvements for future research.

In conclusion, our research did not find a link between different types of PFAS exposure and bladder cancer. However, it supports a possible association between PFOS exposure and prostate cancer, not supported by limited dose-response results. Bias and potential confounding cannot be excluded.

ABBREVIATIONS

Agency for Toxic Substances and Disease Registry, ATSDR; Endocrine-disrupting chemicals, EDCs; International Agency for Research on Cancer, IARC; Nitrogen dioxide, NO_2; Odds ratio, OR; Risk ratio, rate ratio, RR; Standardized mortality ratio, SMR; Standardized incidence ratio, SIR; Stem-progenitor cells, SPCs; Perfluorooctanoic Acid PFOA; Per- and polyfluoroalkyl substances, PFAS; Perfluorooctane sulfonic acid, PFOS; Perfluorononanoic acid, PFNA; Perfluorobutane sulfonate, PFBS; Perohexanesulfonic acid, PFHxSrfluo

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The study was conducted with internal resources of the participating institutions.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

PB and TZ and MSS conceived and designed the study, MSS, EK, and SZ selected the studies and extracted the data, MSS conducted the statistical analysis; MSS and EK drafted the manuscript; SZ, TZ, and PB provided substantial comments to the results and manuscript.

CONFLICTS OF INTEREST

PB acted as an expert in litigation involving PFAS exposure, unrelated to the present work. Other authors declare no conflict of interest.

ETHICS APPROVAL STATEMENT

No Ethics Approval

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LIST OF SUPPLEMENTARY TABLES

Number	Title
Supplementary Table 1a	PRISMA Checklist
Supplementary Table 1b	PRISMA Abstract Checklist
Supplementary Table 2	Detailed search strategy used on the different databases.
Supplementary Table 3	NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
Supplementary Table 4	Selected characteristics of the studies included in the review and meta-analysis.
Supplementary Table 5	Relative risk of bladder cancer by level of PFAS exposure
Supplementary Table 6	Relative risk of prostate cancer by level of PFAS exposure

APPENDIX

Supplementary Table 1a. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			p1, line2
Title	1	Identify the report as a systematic review.	P1, line 3
ABSTRACT			P2, line 43
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			P3, line 86
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3, line 88–112
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3, line 113–115
METHODS			P4, line 122
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P4, lines 139–143
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p 4, lines 129–133
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p, line 134–138, and supplementary table2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p4 and figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P4, line 144–152
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P4, line 144–152
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P4, line 144–152
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P 4, lines 153–156
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A

(*continued*)

Supplementary Table 1a. PRISMA Checklist (continued)

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p 4, lines 150–152
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P5, lines 161–177
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P5, lines 166–175
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P 5, lines 175
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			P 6
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p6, lines 193–197
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p6, lines 193. and supplementary table 4
Study characteristics	17	Cite each included study and present its characteristics.	supplementary table 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p6, lines 201, and figure 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	supplementary table 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P6, lines 198–202Figure 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p6, lines 203–209, and table 1
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p6, lines 200–202, and figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A

(*continued*)

Supplementary Table 1a. PRISMA Checklist (continued)

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			P7
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P7, lines 210–236
	23b	Discuss any limitations of the evidence included in the review.	P7–8, lines 249–236
	23c	Discuss any limitations of the review processes used.	P7–8, lines 249–236
	23d	Discuss implications of the results for practice, policy, and future research.	p8, lines 168–272
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p4, line 124–127
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p4, line 124–127
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p1, line 22
Competing interests	26	Declare any competing interests of review authors.	P1, line30
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P1, line 32

Supplementary Table 1b. PRISMA Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes

(*continued*)

Supplementary Table 1b. PRISMA Abstract Checklist (continued)

Section and Topic	Item #	Checklist item	Reported (Yes/No)
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	N/A
Registration	12	Provide the register name and registration number.	No

Supplementary Table 2. Detailed search strategy used on the different databases.

Database	Search string
PubMed	(("PFOA"[Text Word] OR "Perfluorooctanoic Acid"[Text Word] OR "PFOS"[Text Word] OR "Perfluorooctane Sulfonic Acid"[Text Word] OR "PFAS"[Text Word] OR "per and poly fluoroalkyl substances"[Text Word]) AND ("cancer"[Text Word] OR "malignant"[Text Word] OR "carcinoma"[Text Word] OR "neoplasm"[Text Word] OR "tumor"[Text Word] OR "myeloid"[Text Word] OR "lymphoma"[Text Word] OR "Hematologic"[Text Word])) AND (humans[Filter])
Scopus	(TITLE-ABS-KEY ("PFOA") OR TITLE-ABS-KEY ("Perfluorooctanoic Acid") OR TITLE-ABS-KEY ("pfosa") OR TITLE-ABS-KEY ("Perfluorooctane Sulfonic Acid") OR TITLE-ABS-KEY ("pufas") OR TITLE-ABS-KEY ("per and poly fluoroacyl substances")) AND (TITLE-ABS-KEY("cancer") OR TITLE-ABS-KEY("malignant") OR TITLE-ABS-KEY("carcinoma") OR TITLE-ABS-KEY("neoplasm") OR TITLE-ABS-KEY("tumor") OR TITLE-ABS-KEY("myeloid") OR TITLE-ABS-KEY("lymphoma") OR TITLE-ABS-KEY("Hematologic")) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (EXACTKEYWORD,"Human") OR LIMIT-TO (EXACTKEYWORD,"Humans") OR LIMIT-TO (EXACTKEYWORD,"Male") OR LIMIT-TO (EXACTKEYWORD,"Female")) AND (EXCLUDE (SUBJAREA,"ARTS") OR EXCLUDE (SUBJAREA,"EART") OR EXCLUDE (SUBJAREA,"SOCI") OR EXCLUDE (SUBJAREA,"VETE") OR EXCLUDE (SUBJAREA,"MATE") OR EXCLUDE (SUBJAREA,"ENGI") OR EXCLUDE (SUBJAREA,"COMP") OR EXCLUDE (SUBJAREA,"CENG") OR EXCLUDE (SUBJAREA,"MULT") OR EXCLUDE (SUBJAREA,"BIOC") OR EXCLUDE (SUBJAREA,"PHAR") OR EXCLUDE (SUBJAREA,"NURS") OR EXCLUDE (SUBJAREA,"AGRI") OR EXCLUDE (SUBJAREA,"IMMU") OR EXCLUDE (SUBJAREA,"CHEM") OR EXCLUDE (SUBJAREA,"NEUR") OR EXCLUDE (SUBJAREA,"PSYC") OR EXCLUDE (SUBJAREA,"DENT") OR EXCLUDE (SUBJAREA,"PHYS"))

Supplementary Table 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES (maximum score: 9)
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation **(1)**
b) yes, eg record linkage **(1)** or based on self-reports **(0.5)**
c) no description **(0)**

2) Representativeness of the cases
a) consecutive or obviously representative series of cases **(1)**
b) potential for selection biases or not stated **(0)**

3) Selection of Controls
a) community controls **(1)**
b) hospital controls **(0.5)**
c) no description **(0)**

4) Definition of Controls
a) no history of disease (endpoint) **(1)**
b) no description of source **(0)**

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for age, gender, province **(0)**
b) study controls for age, gender, province +smoking **(1)**
c) study controls for age, gender, province +smoking + other additional factors **(2)**

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) **(1)**
b) structured interview where blind to case/control status **(1)**
c) interview not blinded to case/control status **(0.5)**
d) written self-report or medical record only **(0.5)**
e) no description **(0)**

2) Same method of ascertainment for cases and controls
a) yes **(1)**
b) no **(0)**

3) Non-Response rate
a) one or both groups over 90% **(1)**
b) one or both groups between 60- 90% **(0.5)**
c) one or both groups under 60% **(0)**
d) no statemen **(0)**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES (maximum score: 10)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community **(2)**
b) somewhat representative of the average _____ in the community **(1)**
c) selected group of users eg nurses, volunteers **(0.5)**
d) no description of the derivation of the cohort **(0)**

(*continued*)

Supplementary Table 3 (continued)

2) Selection of the non-exposed cohort
a) drawn from the same community as the exposed cohort **(1)**
b) drawn from a different source **(0.5)**
c) no description of the derivation of the non-exposed cohort **(0)**

3) Ascertainment of exposure
a) secure record (eg surgical records) **(1)**
b) structured interview **(1)**
c) written self-report **(0.5)**
d) no description **(0)**

4) Demonstration that outcome of interest was not present at start of study
a) yes **(1)**
b) no **(0)**

Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for age, gender, province **(0)**
b) study controls for age, gender, province +smoking **(1)**
c) study controls for age, gender, province +smoking + other additional factors **(2)**

Outcome
1) Assessment of outcome
a) independent blind assessment **(1)**
b) record linkage **(1)**
c) self-report **(0.5)**
d) no description **(0)**

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) **(1) (average 15 years)**
b) no **(0)**

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for over 90% **(1)**
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) between 60- 90% **(0.5)**
c) follow up rate < ____% (select an adequate %) and no description of those lost under 60% **(0)**
d) no statemen **(0)**

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Supplementary Table 4. Selected characteristics of the studies included in the review and meta-analysis

Ref.	First author, Year of publication	Country	Study type	Measurement source	Gender	Exposure source	PFAS type	Cancer type	Outcome	Adjusted list other than gender and age, calendar period	Quality score
22	Gilliland FD, 1993	US - Minnesota	Cohort	Job History	Male	Occupational	PFOA	Prostate, Bladder	Mortality	Race	8
23	Grice MM, 2007	US - Alabama	Cohort	Questionnaire	Male	Occupational	PFOS	Prostate	Mortality	–	4.5
24	Alexander BH, 2007	US - Minnesota	Cohort	Work History	Both	Occupational	PFOS	Bladder	Incidence	–	5.5
25	Leonard RC, 2008	US - West Virginia	Cohort	Serum Sample	Male, Both	Occupational	PFOA	Prostate, Bladder	Mortality	–	6.5
26	Eriksen KT,2009	Denmark	Cohort	Questionnaire	Male	Environmental	PFOA, PFOS	Prostate, Bladder	Incidence	Education, BMI, dietary fat intake, fruit and vegetable intake	9
27	Lundin JI,2009	US - Minnesota	Cohort	Work History	Male	Occupational	PFOA	Prostate	Mortality	–	8
28	Steenland K,2012	US - West Virginia	Cohort	Serum Sample	Male, Both	Occupational	PFOA	Prostate, Bladder	Mortality	–	7
29	Barry V,2013	US - West Virginia	Cohort	Serum Sample	Male, Both	Environmental	PFOA	Prostate, Bladder	Incidence	Smoking, alcohol consumption, education	8.5
30	Vieira VM,2013	US - Ohio & West Virginia	Case-Control	Serum Sample	Male, Both	Environmental	PFOA	Prostate, Bladder	Incidence	Smoking status, insurance provider	7
31	Raleigh KK ,2014	US - Minnesota	Cohort	Work History	Male	Occupational	PFOA	Prostate, Bladder	Mortality, Incidence	–	8
32	Hardell E,2014	Sweden	Case-Control	Serum Sample	Male	Environmental	PFOA, PFOS, PFAS, PFNA	Prostate	Incidence	BMI and year of blood sampling.	6.5
33	Ducatman A,2015	US - Ohio & West Virginia	cohort	Serum Sample	Male	Environmental	PFOA, PFOS, PFNA	Prostate	Incidence	–	6.5
34	Steenland K,2015	US	Cohort	Serum Sample	Male, Both	Occupational	PFOA	Prostate, Bladder	Incidence	Race, education, BMI, and time-varying smoking, alcohol consumption	7.5
35	Mastrantonio M,2018	Italy	Ecological	Drinking Water	Both	Environmental	PFAS	Bladder	Incidence	-	6.5

(*continued*)

Supplementary Table 4. Selected characteristics of the studies included in the review and meta-analysis (continued)

Ref.	First author, Year of publication	Country	Study type	Measurement source	Gender	Exposure source	PFAS type	Cancer type	Outcome	Adjusted list other than gender and age, calendar period	Quality score
36	Roswall N,2018	Denmark	Cohort	Serum Sample	Male, Both	Environmental	PFOA, PFOS	Prostate, Bladder	Mortality	Smoking status, alcohol consumption, abstainer, waist circumference, leisure-time sports, education, area-level socioeconomic status	6.5
37	Omoike OE,2021	USA	Case Control	Serum Sample	Male, Both, Female	Environmental	PFOA, PFOS, PFNA	Prostate	Incidence	Education, race/ethnicity, PIR, BMI, serum cotinine.	6.5
38	Li H,2022	Sweden	Cohort	Drinking Water	Male	Environmental	PFAS	Prostate, Bladder	Incidence	–	7.5
39	Rhee J,2023	USA	Nested Case Control	Serum Sample	Male	Environmental	PFOA, PFOS, PFNA	Prostate	Incidence	BMI, smoking status, family history of prostate cancer, history of diabetes	7
40	Cathey AL,2023	USA	Case Control	Serum Sample	Male	Environmental	PFOA, PFOS, PFNA	Prostate	Incidence	poverty-income ratio, race, education, BMI	9
41	Law HD,2023	Australia	Cohort		Male, Both	Environmental	PFAS	Prostate, Bladder	Incidence	–	6.5
42	Winquist A,2023	USA	Cohort	Serum Sample	Male, Female, Both	Environmental	PFOA, PFOS, PFNA	Prostate, Bladder	Incidence	age at serum collection, race, education, smoking status, alcohol consumption	9

BMI; Body mass index

Supplementary Table 5. Relative risk of bladder cancer by level of PFAS exposure

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
PFOA	Eriksen KT, 2009	low	Q2	0.71(0.46,1.07)
		medium	Q3	0.92(0.61,1.39)
		high	Q4	0.81(0.53,1.24)
	Steenland K, 2012	low	Q1	1.24(0.15,4.47)
		medium	Q2	2.49(0.97,5.78)
		high	Q3	0.39(0.01,2.17)
		very high	Q4	0.36(0.1,2.01)
	Vieira VM, 2013	Low		0.9(0.6,1.4)
		Medium		0.9(0.6,1.4)
		High		1.2(0.8,2)
		Very high		0.62(0.2,1.5)
	Raleigh KK, 2014	Low	Cottage Grove, Q1	0.4(0.01,2.25)
		Medium	Cottage Grove, Q2	0.93(0.11,3.38)
		High	Cottage Grove, Q3	1.61(0.44,4.13)
		Very high	Cottage Grove, Q4	0.53(0.01,2.97)
	Steenland K, 2015	low	Q2	0.32(0.08,1.33)
		medium	Q3	0.95(0.28,3.14)
		high	Q4	0.23(0.05,0.93)
	Roswall N, 2018	low	Q2	1.02(0.63,1.65)
		medium	Q3	0.87(0.55,1.4)
		high	Q4	0.61(0.37,0.99)
	Winquist A, 2023	low	3.850-<5.100	0.84(0.56,1.26)
		medium	5.100-<6.300	0.87(0.58,1.3)
		high	>=6.300	0.86(0.58,1.27)
PFOS	Alexander BH, 2007	low		2.26(0.91,4.67)
		high		1.74(0.64,3.79)
	Eriksen KT, 2009	low	Q2	0.76(0.5,1.16)
		medium	Q3	0.93(0.61,1.41)
		high	Q4	0.7(0.46,1.07)
	Roswall N, 2018	low	Q2	1.17(0.72,1.87)
		medium	Q3	0.93(0.57,1.52)
		high	Q4	0.59(0.36,0.98)
	Winquist A, 2023	low	13.000-<18.000	0.81(0.54,1.21)
		medium	18.000-<25.000	1.07(0.72,1.6)
		high	>=25.000	0.96(0.64,1.44)

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Supplementary Table 6. Relative risk of prostate cancer by level of PFAS exposure

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
PFOA	Eriksen KT, 2009	low	Q2	1.09(0.78,1.53)
		medium	Q3	0.94(0.67,1.32)
		high	Q4	1.18(0.84,1.65)
	Steenland K, 2012	low	Q1	1.07(0.39,2.34)
		medium	Q2	0.82(0.3,1.78)
		high	Q3	0.65(0.21,1.51)
		very high	Q4	0.57(0.16,1.46)
	Vieira VM, 2013	Low	Q1	1.1(0.8,1.5)
		Medium	Q2	0.8(0.6,1)
		High	Q3	0.8(0.5,1.1)
		Very high	Q4	1.5(0.9,2.5)
	Raleigh KK, 2014	Low	Q1	0.66(0.21,1.54)
		Medium	Q2	1.15(0.5,2.27)
		High	Q3	0.37(0.08,1.07)
		Very high	Q4	1.29(0.56,2.54)
		Low	Q1	0.34(0.25,1.6)
		Medium	Q2	1.12(0.53,2.37)
		High	Q3	0.36(0.11,1.17)
		Very high	Q4	1.32(0.61,2.84)
	Steenland K, 2015	Low	Q2	1.81(0.69,4.78)
		Medium	Q3	2.45(0.96,6.25)
		High	Q4	1.88(0.72,4.88)
	Roswall N, 2018	Low	PFOA, Q2	0.77(0.57,1.04)
		Medium	PFOA, Q3	1.02(0.76,1.38)
		High	PFOA, Q4	0.88(0.65,1.18)
	Rhee J, 2023	Low	≥2.90, <3.80	0.75(0.53,1.07)
		Medium	≥3.80, <4.67	0.72(0.49,1.07)
		High	≥4.67, <6.50	0.67(0.44,1.03)
		very high	≥6.50	0.54(0.32,0.91)
	Winquist A, 2023	Low	3.850-<5.100	0.82(0.6,1.11)
		Medium	5.100-<6.300	0.93(0.68,1.27)
		High	>=6.300	0.83(0.61,1.14)

(*continued*)

Supplementary Table 6. Relative risk of prostate cancer by level of PFAS exposure (continued)

PFAS type	First Author, year	Exposure level	Dose detail	RR (95% CI)
PFOS	Winquist A, 2023	Low	13.000-<18.000	0.94(0.7,1.26)
		Medium	18.000-<25.000	1.11(0.81,1.5)
		High	>=25.000	1.08(0.8,1.46)
	Grice MM, 2007	low	0.39-0.89 ppm	1.36(0.61,3.02)
		high	1.30-1.97 ppm	1.08(0.44,2.69)
	Eriksen KT, 2009	Low	Q2	1.35(0.97,1.87)
		Medium	Q3	1.31(0.94,1.82)
		High	Q4	1.38(0.99,1.93)
	Roswall N, 2018	Low	PFOS, Q2	1.2(0.89,1.62)
		Medium	PFOS, Q3	0.97(0.72,1.31)
		High	PFOS, Q4	0.94(0.69,1.27)
	Rhee J, 2023	Low	≥19.10, <25.50	0.93(0.64,1.37)
		Medium	≥25.50, <33.50	1.07(0.69,1.66)
		High	≥33.50, <47.12	0.88(0.53,1.46)
		very high	≥47.12	0.84(0.45,1.58)
PFNA	Rhee J, 2023	Low	≥0.3, <0.5	0.88(0.57,1.34)
		Medium	≥0.5, <0.7	0.88(0.55,1.4)
		High	≥0.7, <1.0	0.98(0.58,1.67)
		very high	≥1.0	1.05(0.58,1.91)
	Winquist A, 2023	Low	0.450-<0.630	0.81(0.6,1.09)
		Medium	0.630-<1.000	1.04(0.76,1.41)
		High	>=1.000	1.03(0.76,1.41)