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Prostate-Specific Antigen and Perfluoroalkyl Acids in the C8 Health Study Population

Alan Ducatman, MD, MS, Jianjun Zhang, MS, and Hongmin Fan, MD

Purpose: To inform questions raised by inconsistent findings regarding an association between perfluoroalkyl acids (PFAAs) and prostate cancer by assessing the relationship of PFAAs in human serum to prostate-specific antigen (PSA). **Materials and Methods:** Using 2005 to 2006 survey data from a large survey population, we compared serum PFAA concentrations in adult males with PSA concentrations adjusted for risk factors including age, body mass index, smoking status, and socioeconomic status. **Results:** Perfluoroalkyl acids are not consistently associated with PSA concentration in general, or with PSA more than 4.0. **Discussion:** These findings do not provide evidence that PFAA exposure is associated with PSA.

Perfluoroalkyl acids (PFAAs) are synthetic chemicals with a wide range of uses in industrial processes, household products, and building materials. Most are nearly indestructible in the environment, and can be detected in locations and species remote from points of manufacture. Perfluoroalkyl acids are present in household and office dust, or contaminating food or water. They are readily absorbed via inhalation, ingestion, or even transdermal absorption.[1] Once absorbed, longer chain PFAAs including those studied in this investigation tend to have human serum half-lives of 2 to 5 years, or more. Implementation of an agreement between the US Environmental Protection Agency and major manufacturers has begun to decrease human serum concentrations of many of these ubiquitous compounds in the United States,[2] with potential consequences for increased contamination in developing industrial nations,[3] and potential increases in related contaminant replacements.

Perfluoroalkyl acids are potential carcinogens. PFAA interactions with human physiology, pertinent to cancer development, include alterations in immune status,[4] in lipid concentrations,[5,6] and in the potential for endocrine disruption.[7,8] Perfluoroalkyl acids have also been associated with poorer semen quality in some,[9,10] but not all human studies.[11] Several urogenital cancer outcomes have been proposed as associated with PFAA exposure on the basis of epidemiologic research, including cancers of the kidney,[12–14] testicle,[12] and bladder.[15]

From the Department of Occupational and Environmental Health (Dr Ducatman), School of Public Health, and Department of Medicine, School of Medicine, and Clinical Translational Science Institute; Cancer Center (Drs Ducatman and Fan); Department of Biostatistics (Mr Zhang), School of Public Health, West Virginia University, Morgantown; and Department of Epidemiology and Statistics (Dr Fan), School of Public Health, Hebei United University, Tangshan, China.

This effort was supported, in part, by internal West Virginia University Health Science Center funds provided to Dr Ducatman and colleagues for biostatistical support and database maintenance.

Dr Ducatman held a previous contract with Brookmar, Inc, for web-hosted health communications with the survey population.

The authors declare no conflicts of interest.

Address correspondence to: Alan Ducatman, MD, MS, School of Public Health, West Virginia University, Morgantown, WV 26506 (aducatman@hsc.wvu.edu).

DOI: 10.1097/JOM.0000000000000319

Excess prostate cancer has been associated with perfluorooctanoic acid (PFOA) exposure in some studies,[16–19] and perfluorooctane sulfonate (PFOS) was additionally implicated in one of these; a case-control study of a European registry also suggested that the association may be specific to those with preexisting familial risk.[19] Results have not been consistent; however, PFOA and PFOS were not associated with prostate cancer in the Danish general population.[20] In worker studies, PFOS has also been inconsistently associated with prostate cancer.[16,21] Excess prostate cancer is a persistent, unresolved question for firefighters,[22–26] who also have workplace exposures to PFAAs.[27–29] Studies pertaining to the large C8 health population in the mid-Ohio Valley, which is also the source of this study, have yielded inconsistent prostate cancer results.[12,17] In one C8 population cancer study, historically estimated PFOA serum concentrations were used to create a cumulative exposure model, and retrospectively compared with cancer incidence in 14,894 male participants (including worker participants) who were alive at the time of a follow-up survey.[12] This study showed no association of modeled exposure with prostate cancer. A different study design considered geographically modeled PFOA exposures for cancer patients in cancer registry data from 13 counties that included the affected water districts of the C8 health study, and geocoded 3678 prostate cancer patients in the registry to exposure categories, comparing outcomes on the basis of exposure categories and also to other nonurogenital cancer outcomes as geocoded controls. Statistically significant excess adjusted odds ratios for prostate cancer were noted in the highest exposure category in some but not all of the modeled comparisons.[17]

The prostate-specific antigen (PSA) test measures a protease produced primarily by prostate gland cells. The limitations and controversies concerning the use of serum PSA testing for prostate cancer screening are well-known and complex. Among professional societies, which continue to recommend screening, the recommendation is generally directed at men aged 50 to 69 years.[30,31] Concepts of shared clinician–patient decision making may extend recommendations to younger and older ages in the presence of specific risk factors, including race, family history, and symptoms.[31,32] Detected elevations in PSA are not exclusively due to cancer, and are also attributed to benign prostate hyperplasia,[33] prostate inflammation,[34] urinary retention,[35] local trauma,[36] and PSA increases with age.[37]

Because different study designs led to different inferences concerning prostate cancer in the C8 health population, we investigated the relationship of the PSA clinical biomarker to the PFAA exposure biomarker within the same population. This study question was whether serum biomarkers of PFAA exposure associated with temporally concurrent PSA screening test concentrations in adult males.

METHODS

Data Sources and Study Participants

The C8 health study enrolled 69,030 participants in 2005 to 2006; initial eligibility was based on a court settlement for those who lived, worked, or went to school in one of the six water districts variably contaminated with PFOA from a chemical facility located in the mid-Ohio Valley, along the Ohio-West Virginia border. The survey design methods have been published; the survey participation was an estimated 81% of the eligible resident population.[38] Among

participants, PFOA was substantially higher in five of the six water C8 population districts than recorded in the US NHANES populations for the same period, and PFOS concentrations were similar to US norms.[38,39] Adult males older than 20 years, who had measured PSA values and PFAA concentrations, were eligible for this study.

Biomarkers

Blood processing, serum assay, and quality assurance methods have been described in other publications.[6,38] Briefly, blood was collected from participants and serum was separated for PFAA analysis and shipped on dry ice to the analysis laboratory. PFAA assays deployed a protein precipitation extraction method with reverse-phase high-performance liquid chromatography/tandem mass spectrometry. Detection relied on a triple-quadrupole mass spectrometer in a preselected reaction monitoring mode, monitoring for the M/Z transitions of 10 PFAA species, with an internal[13] C-PFAA standard corresponding to the specific target compound. Assay results were transferred to the C8 Health Project's Windows-based information system. Of the 10 PFAA compounds tested in survey serums, four were detected in virtually all participants and can be assessed using standard statistical techniques for relations to PSA serum concentrations and for PSA serum concentrations. These were PFOA, PFOS (the two most common PFAA contaminants to date in our society), perfluorohexane sulfonate, and perfluorononanoic acid.

Prostate-specific antigen was one of a large suite of clinical laboratory results collected during the 2005 to 2006 C8 Health Survey. PSA testing was performed by a single commercial laboratory using the Beckman Coulter Access automated chemiluminescent immunoassay system. Proficiency testing results with within- and between-run measures of imprecision have been published.[40] For simplicity, PSA 4.0 or more was used to investigate associations of potential clinical significance, because it is sometimes used as a screening cutoff.

Statistical Analysis

Data were analyzed using SAS version 9.3. Descriptive statistics (means ± standard deviation, percentages) were calculated overall and by the PSA level (<4.0 and ≥4.0) for adult men with no missing variables. Separate linear models were fit to compare mean levels of each PFAA concentration between the two PSA level groups, adjusting for the unquestioned positive influence of age on population PSA concentration, as well as hypothesized negative influences on PSA status of smoking,[41–43] alcohol intake,[44] and body mass index.[42,45] All PFAA concentrations were natural log-transformed to achieve approximate normality. These models were stratified by age (<50 and ≥50 years). Model-adjusted geometric means of each of the concentrations, by PSA group and age strata, were estimated on their raw scale. Comparisons of these geometric means by the PSA group were made by computing the ratio and 95% confidence interval, with statistical significance ($\alpha = 0.05$) indicated when the interval did not include 1. Further examination of scatter plots and linear regression of raw PSA levels (log-transformed) and each of the log-transformed concentrations was performed to examine any possible full relationships.

RESULTS

Table 1 provides demographic information for all adult male participants. In this unadjusted examination, both PFOA and PFOS seem to be associated with the condition of PSA more than 4.0. This apparent relationship is misleading. As expected, the condition of PSA 4.0 ng/mL or more is strongly and positively influenced by age, as is the PFAA concentration.

Table 2 presents the age-stratified and fully adjusted model for those 49 years old or less ($n = 9619$), and 50 years old or more ($n = 3819$), including only those who have all variables used in adjustments. PFOS findings are nearly significant in men aged 50 years or more, but the differences between groups in PFAA serum concentrations are very small. Further omitting those men who reported a history of prostate cancer ($n = 428$) decreased the mean population PSA values, but otherwise did not change these findings. Thus, no PFAA evaluated in this study provided consistent evidence of an association with clinically significant increases in PSA across age groups. Graphical examination via scatterplots, as well as linear regression of the actual PSA levels by each of the PFAA concentrations (Table 3), was performed to evaluate unsuspected relationships, and also indicated no discernible relationships. Table 3 indicates there is no clear directional trend in the entire population, and associations are not significant.

DISCUSSION

These results do not support the hypothesis that PFAAs are associated with clinically higher PSA. By inference, they may also fail to provide additional support for the hypothesis that PFAAs are associated with prostate cancer. Conversely, the absence of an association with PSA could be interpreted to argue against bias attributable to early detection and overdiagnosis,[46] known to be associated with using the PSA test, as a potential contributing explanation for the PFAA studies that did find additional incident or matched prostate cancer cases.

Perfluorocarbon compounds including PFAAs have been found to have complex interactions with inflammatory systems in vivo and in vitro, and directly suppress some types of cytokine secretion by immune cells,[47] while enhancing other types of immune response, such as mast cell release of histamine.[48] The PSA test used for prostate cancer screening is considered to be affected by inflammation in the prostate gland,[34] but whether that inflammation relates

TABLE 1. Baseline Characteristics of PSA Population*

Characteristics	Whole Cohort ($n = 25,412$)	PSA < 4.0 ($n = 24,538$)	PSA ≥ 4.0 ($n = 686$)
Age, yrs, mean ± SD	46.28 ± 15.43	45.74 ± 15.12	66.71 ± 10.90
BMI, mean ± SD	28.80 ± 5.53	28.82 ± 5.55	27.93 ± 4.48
Smoking status (current smoker), %	47.54	47.77	38.92
Race (white), %	96.45	96.43	96.94
PFHxS (C6s), ng/mL, mean ± SD	3.58 ± 2.15	3.58 ± 2.14	3.48 ± 2.20
PFOA (C8), ng/mL, mean ± SD	40.22 ± 3.50	40.07 ± 3.49	46.03 ± 3.85
PFOS (C8s), ng/mL, mean ± SD	22.18 ± 1.97	22.11 ± 1.98	25.10 ± 1.83
PFNA (C9), ng/mL, mean ± SD	1.47 ± 1.63	1.47 ± 1.63	1.35 ± 1.61

*Male and 20 years old or more.

BMI, body mass index; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PSA, prostate-specific antigen; SD, standard deviation.

TABLE 2. Model-Adjusted* Geometric Means and Ratios of Geometric Means, by Age Strata

	Age (20–49 yrs; $n = 9169$)			Age (50–69 yrs; $n = 3819$)		
	Geometric Mean (95% CI)			Geometric Mean (95% CI)		
Exposure	PSA < 4.0	PSA ≥ 4.0, $n = 19$	Ratio (95% CI)	PSA < 4.0	PSA ≥ 4.0, $n = 148$	Ratio (95% CI)
PFHxS (C6S), ng/mL	3.62 (3.37–3.90)	3.23 (2.24–4.64)	0.89 (0.62–1.27)	3.17 (2.87–3.50)	3.40 (2.92–3.97)	1.07 (0.95–1.22)
PFOA (C8), ng/mL	40.25 (36.01–44.99)	46.39 (26.65–80.76)	1.15 (0.67–1.98)	46.75 (39.15–55.82)	44.78 (33.93–59.09)	0.96 (0.77–1.20)
PFOS (C8S), ng/mL	19.48 (18.32–20.70)	18.54 (13.67–25.13)	0.95 (0.71–1.28)	19.82 (18.09–21.71)	21.82 (18.92–25.17)	1.10 (0.98–1.23)
PFNA (C9), ng/mL	1.47 (1.41–1.54)	1.26 (1.00–1.57)	0.85 (0.69–1.06)	1.31 (1.23–1.40)	1.36 (1.22–1.51)	1.04 (0.95–1.13)

*Adjusted for (values included for geometric mean) age (35 or 60 years), smoking status (never), average alcohol intake (one to three drinks per day), and body mass index (28 kg/m^2).

CI, confidence interval; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PSA, prostate-specific antigen.

TABLE 3. Linear Models of PSA With PFAA Exposures and Adjusted Factors* by Age Strata

	Age (20–49 yrs)		Age (50–69 yrs)	
Covariant	Estimate	*P*	Estimate	*P*
PFHxS (C6S), ng/mL	1.00	0.25	1.00	0.65
PFOA (C8), ng/mL	1.00	0.90	1.00	0.72
PFOS (C8S), ng/mL	1.00	0.71	1.00	0.99
PFNA (C9), ng/mL	1.00	0.67	1.02	0.30

*Adjusted for (values included for geometric mean estimates) age, smoking status, average alcohol intake, and body mass index.

PFAA, perfluoroalkyl acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PSA, prostate-specific antigen.

to predictive prostate cancer risk is less clear.[49] This study does not support an effect of PFAAs on PSA, by inflammatory pathways or otherwise.

A strength of our approach is that we could achieve age- and other risk factor-adjusted associations of a variety of PFAAs in a large group of men, looking at a number of PFAA species in serum individually. The further ability to evaluate a "normal" value cutoff in the relevant age group moves the consideration from statistical association in a large population to whether the exposure is associated with clinical screening triggers. It is not associated. This study also has important weaknesses. It relies on one-time measures. These are likely to be representative of a long period in the case of the PFAAs with their very long half-lives, but may be less representative of PSA concentrations over time. Even for PFAAs, adult serum concentrations may not represent earlier and potentially critical periods of human development leading to increased risk of cancer. Prevalence data also inadequately represent the relationship of imperfect clinical biomarkers with incident cancer outcomes, even for cancers such as prostate cancer with generally long survival times. Nevertheless, incidence and case-control studies of PFAA exposure and prostate cancer already exist; this study was performed to inform those results regarding PSA findings only.

In summary, we sought but did not find a relationship of the most commonly encountered human serum PFAA concentrations with PSA.

ACKNOWLEDGMENTS

The authors thank Linda Lilly (WVU School of Public Health) for manuscript support, and Jean Siebert (WVU Health Science Center Library and School of Public Health faculty) for advice about search strategies.

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