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Case–Cohort Study of the Association between PFAS and Selected Cancers among Participants in the American Cancer Society's Cancer Prevention Study II LifeLink Cohort

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Background: Previous epidemiological studies found associations between exposure to per- and polyfluoroalkyl substances (PFAS) and some cancer types. Many studies considered highly exposed populations, so relevance to less-exposed populations can be uncertain. Additionally, many studies considered only cancer site, not histology.

Objectives: We conducted a case–cohort study within the American Cancer Society's prospective Cancer Prevention Study II (CPS-II) LifeLink cohort to examine associations between PFAS exposure and risk of selected cancers, considering histologic subtypes.

Methods: Serum specimens were collected from cohort participants during the period 1998–2001. This study included a subcohort (500 men, 499 women) randomly selected from participants without prior cancer diagnoses at serum collection, and all participants with incident (after serum collection) first cancers of the breast (females only, $n = 786$), bladder ($n = 401$), kidney ($n = 158$), pancreas ($n = 172$), prostate (males only, $n = 1{,}610$) or hematologic system ($n = 635$). PFAS concentrations [perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA)] were measured in stored serum. We assessed associations between PFAS concentrations and incident cancers, by site and histologic subtype, using multivariable Cox proportional hazards models stratified by sex and controlling for age and year at blood draw, education, race/ethnicity, smoking, and alcohol use.

Results: Serum PFOA concentrations were positively associated with renal cell carcinoma of the kidney among women [hazard ratio (HR) and 95% confidence interval (CI) per PFOA doubling: 1.54 (95% CI: 1.05, 2.26)] but not men. Among men, we observed a positive association between PFHxS concentrations and chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL, HR and 95% CI per PFHxS doubling: 1.34 (95% CI: 1.02, 1.75)]. We observed some heterogeneity of associations by histologic subtype within sites.

Discussion: This study supports the previously observed association between PFOA and renal cell carcinoma among women and suggests an association between PFHxS and CLL/SLL among men. Consideration of histologic subtypes might be important in future studies of PFAS-cancer associations. https://doi.org/10.1289/EHP13174

Introduction

Per- and polyfluoroalkyl substances (PFAS) are man-made chemicals used since the 1940s in many consumer products such as oil-, water-, and stain-resistant coatings for fabrics, leather, carpets, and food packaging materials; ski waxes; floor polishes; denture cleaners; shampoos; insecticides; and paints.[1–4] PFAS have also been used in industrial products such as firefighting foam, electronics, hydraulic fluids, and lubricants; in some medical products; and in several manufacturing processes.[2,5] Because the carbon–fluorine bond in PFAS is strong, PFAS are resistant to degradation and environmentally persistent.[2]

The two most studied PFAS are perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), but there are thousands of PFAS.[2,6,7] Human PFAS exposure occurs through drinking water, food, food packaging, household dust, indoor air, personal care products, and contact with contaminated materials.[8–11] PFAS exposure can also occur for a developing fetus during gestation and for infants through breastfeeding.[12] Workers in industries that use PFAS (e.g., chemical plant workers, firefighters) can have high levels of occupational exposure,[13–18] but lower-level PFAS exposures are widespread in the U.S. population.[19–21] Among 11 PFAS measured in the 1999–2000 National Health and Nutrition Examination Survey (NHANES), PFOA, PFOS, perfluorohexane sulfonic acid (PFHxS), and perfluorooctane sulfonamide (FOSA) were detected in all serum samples tested, and three other PFAS were detected in >90% of samples, including perfluorononanoic acid (PFNA), 2(N-Methyl-perfluorooctane sulfonamido) acetic acid, and 2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid.[19] Serum concentrations of some PFAS, including PFOA and PFOS, decreased[21,22] after PFOA and PFOS production was phased out in the United States, beginning in 2000[23]; however, several PFAS were still detected in the majority of the U.S. population in the 2017–2018 NHANES cycle.[24] Once in the human body, many PFAS have long half-lives (e.g., PFOA: 2.1–8.5 y,[8,25,26] PFOS: 3.1–7.4 y,[8,25] and PFHxS: 4.7–15.5 y[8,25]).

Findings of epidemiological and toxicological studies of PFAS health effects have been summarized by several groups, such as the C8 Science Panel,[27] the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) in the "Toxicological Profile for Perfluoroalkyls,"[8] and the National Academies of Sciences, Engineering and Medicine.[4] There is evidence for an association between exposure to some PFAS and several noncancer health outcomes, including decreased antibody responses to vaccines, high cholesterol levels, small decreases in birth

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weight, changes in serum levels of liver-associated enzymes and bilirubin, pregnancy-induced hypertension, thyroid disease, and ulcerative colitis.[4,8,27]

PFAS exposure has also been associated with some types of cancer. The International Agency for Research on Cancer (IARC) determined that there is "limited evidence" in both humans and animals for the carcinogenicity of PFOA (first published in 2014).[9,28] In rodents, PFOA has been associated with testicular Leydig cell adenomas, pancreatic acinar cell adenomas, and hepatocellular adenomas or carcinomas; and PFOS has been associated with hepatocellular adenomas and thyroid follicular cell adenomas.[2,8,9,29] Epidemiological studies of PFAS and cancer have been of three general types: *a*) studies of workers occupationally exposed to PFAS, *b*) studies in highly exposed communities, and *c*) studies in the general population (without specific sources of higher exposure). These studies have identified associations between various PFAS and several types of cancer (summarized in a recent review by Steenland and Winquist[30]). The most consistent associations have been associations between PFOA exposure and cancers of the testis[9,30–34] and kidney.[9,30–38] However, positive associations in some populations have also been observed between exposure to some PFAS and cancers of the prostate,[33,39,40] thyroid,[31,41] breast,[42–52] bladder,[53] ovary,[50] and liver[54–56]; as well as mesothelioma[35] and lymphatic and hematopoietic malignancies.[32,54]

Studies in populations with high exposures are important for determining whether PFAS exposure is associated with various types of cancer, because such studies can have good exposure contrasts and can detect effects that might occur only at high exposures. However, studies in the general population are necessary to determine whether PFAS exposure at levels that occur in the general population is associated with cancer.[30] To have sufficient power for detection of effects that are potentially small in magnitude at lower exposure levels, such general-population studies need to include a large number of cases. To date, studies of PFAS and cancer in the general population have been primarily case-control studies (nested[37,47,55,57–60] or nonnested[40,44,45,49,51,56,61–63]) focusing on single cancer sites (most commonly breast cancer,[44,45,47,49,51,57–59,61,63] but also prostate,[40,60] kidney,[37] liver,[55,56] and thyroid[62] cancer). One general-population cross-sectional study considered breast, uterine, ovarian, and prostate cancer.[50] There have been fewer general-population cohort or case-cohort studies of PFAS and cancer, including two cohort studies considering only an all-cancer outcome,[64,65] one case–cohort study of liver, pancreatic, bladder, and prostate cancers,[66] and two case–cohort studies of breast cancer.[46,48] Additional evidence from studies with strong study designs, such as large prospective cohort, case–cohort or nested case–control studies, is needed to provide information that communities need about PFAS exposure and cancer risk.

We assessed the association between PFAS exposure and subsequent development of cancer, among members of the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) LifeLink Cohort who had no previous cancer diagnosis. This study provides additional information about the relationship between PFAS exposure at general-population levels and several types of cancer, including hematologic malignancies that have not been considered in prior general-population studies, using a prospective study design and a large cohort. Because associations may vary by histologic type[37,67] (e.g., because of different underlying biologic mechanisms), and such variation might underlie differences in findings between studies of PFAS and cancer, in addition to considering cancers by site, the study considered histologic subtypes, which has rarely been done in studies of PFAS and cancer,[37,55] except for hematologic malignancy subtypes, for which several studies considered selected subtypes.[32,35,36,38,39,41,54,68]

Methods

Study Participants and Cancer Case Ascertainment

Starting in 1982, ACS enrolled 1,185,106 participants from 50 U.S. states and the District of Columbia in CPS-II (see Figure S1).[69] Participants completed a questionnaire and were followed for mortality through National Death Index (NDI) linkage. During the period 1992–1993, 184,194 CPS-II participants 50–74 y of age who resided in 21 states were recruited for participation in the CPS-II Nutrition Cohort. CPS-II Nutrition Cohort participants were followed for cancer incidence through periodic follow-up questionnaires (biennially 1997–2017). Additional cancer cases not self-reported were ascertained from NDI linkage. Incident cancers detected through self-report or NDI linkage were verified through medical record review or cancer registry linkage. A previous study assessing the validity of self-reported cancers in the CPS-II Nutrition Cohort estimated a sensitivity (proportion of participants with registry-documented cancer who self-reported any cancer) of 93% and a specificity (proportion of self-reported cancers that were confirmed through cancer registry matching) of 75% (varying by cancer site).[70] During the period 1998–2001, 39,371 surviving CPS-II Nutrition Cohort participants residing in urban or suburban areas of 20 states were recruited for participation in the CPS-II LifeLink Cohort. CPS-II LifeLink participants completed a LifeLink cohort baseline questionnaire and provided a blood sample (median age: 70 y overall; 71 y for men, 69 y for women). Blood was collected in serum separator tubes, and serum samples were stored at $\sim -130^{\circ}C$ (liquid nitrogen vapor phase).[69] CPS-II LifeLink participants were followed for cancer incidence along with other CPS-II Nutrition Cohort participants. All cancers were classified by site, histology, grade, and stage using standard Surveillance, Epidemiology and End Results Program definitions current at the time of diagnosis.[71] At the time of serum sample collection, CPS-II LifeLink Cohort participants provided informed consent for blood sample collection and storage and for future testing of the sample (identified by study identification number only) for factors that may be related to cancer. All aspects of the CPS-II cohort study were approved by the Emory University institutional review board. Data used in this analysis did not include personal identifiers.

Inclusion/Exclusion Criteria

We used a case–cohort study design, which includes all people from an eligible cohort who developed an outcome (or outcomes) of interest. This design also includes a subcohort of people randomly selected from the entire eligible cohort. The subcohort serves as a comparison group (and might include some who developed the outcome of interest). This design is efficient for studies that involve laboratory measurements because those measurements are only done for those who developed the outcome or outcomes of interest and for those in the subcohort.[72,73] The sampling frame (eligible cohort) for this study included all CPS-II LifeLink Cohort participants with no previous cancer diagnosis (other than nonmelanoma skin cancer) at the time of blood sample collection who had available stored serum samples (at least 500 μL). Women who did not report being postmenopausal at the time of the CPS-II Nutrition Cohort 1997 survey were excluded from the sampling frame. Because menstruation is a route of PFAS elimination,[74] premenopausal women would be expected to have lower serum PFAS levels. With few premenopausal women in the cohort (0.33%), it

would be difficult to control for this effect. From the sampling frame, the following participants were selected for the study:

1. Case groups: All participants with incident cancers for whom the first cancer diagnosis was kidney, bladder, breast (females only), prostate (males only), or pancreatic cancer, or lymphoma or leukemia; and
2. Subcohort: A simple random sample of 500 women and 500 men (~3% of the eligible cohort). Subcohort selection was stratified by sex to ensure an adequate number of subcohort participants in sex-specific analyses (for breast and prostate cancers).

PFAS Laboratory Testing Methods

Serum samples were tested by NMS labs for the linear isomers (only) of PFOA, PFOS, PFNA, PFHxS, FOSA, perfluorobutane sulfonic acid (PFBS), and perfluoroheptanoic acid (PFHpA) using high-performance liquid chromatography–tandem mass spectrometry. After addition of isotopically labeled internal standards, specimens were prepared for analysis by protein precipitation using acetonitrile and filtration through a phospholipid depletion phase. Analysis used high-performance liquid chromatography separation with negative-ion electrospray tandem mass spectrometry (LC-MS/MS) for detection and quantitation using a Sciex 4500 QTRAP with a Shimadzu Prominence Ultra-Fast LC system controlled by Sciex Analyst software. Reporting limits (ng/mL) were as follows: PFOA, 0.5; PFBS, 0.05; PFHxS, 0.05; PFOS, 0.5; PFHpA, 0.05; PFNA, 0.05; and FOSA, 0.1. However, the lower limit of quantitation varied by sample for samples needing dilution. Calibrators and quality control (QC) samples were included with each analytical run according to laboratory standard operating procedures (SOPs) with acceptance criteria of $\pm 20\%$ for all included QC samples, in addition to retention time, ion ratios, and calibration acceptance as specified in laboratory SOPs. The FOSA test was a new test for this laboratory, developed for this study.

Laboratory quality control. The NMS labs is CLIA-certified and routinely performs QC according to its SOPs for clinical and forensic testing. This process includes nonzero calibrators, blanks, and low- and high-QC samples. The lab also participates in the PFAS proficiency testing program conducted by Centre de Toxicologie du Quebec of Canada. For this study, QC duplicates were included with study samples for testing (for 5% of study samples). Laboratory personnel were blinded to the duplicates.

Methods for Data Analysis

Exposures. The primary exposures of interest were serum PFAS concentrations (PFOA, PFOS, PFNA, PFHxS, FOSA, PFBS, and PFHpA) measured in stored serum samples. The first five of these PFAS were selected because they were frequently detected (>90% detection) in samples from NHANES 1999–2000[19] and have been associated with some type of cancer in at least one study. The last two (PFBS and PFHpA) were automatically included in the laboratory's PFAS panel. PFAS analytes were considered separately. PFAS concentration values below the limit of detection (LOD) were replaced by the LOD divided by the square root of 2.[75] Analyses considered the PFAS concentrations using $\log_2$-transformed variables and quartile variables [defined among cases (primary analyses) or the subcohort (sensitivity analyses)].

Outcomes. The outcomes of interest were verified cancers of the kidney, bladder, breast (females only), prostate (males only), or pancreas; and lymphoma and leukemia. The selected cancer types included those found to be associated with PFAS exposure in previous studies and for which an adequate number of incident cases were observed in the CPS-II LifeLink Cohort. Although testicular, liver, and thyroid cancers are also of interest in relation to PFAS exposure, an insufficient number of cases were observed (all <65 cases) in the CPS-II LifeLink Cohort for examination of those cancer types.

In addition to the overall cancer groupings, we also considered subgroups by histologic type for selected cancer sites, defined based on *International Classification of Disease for Oncology* (ICD-O) histology codes (see Table S1). We defined our groups to be relatively homogeneous with respect to the cell type of origin.[76] For kidney cancer we considered a group referred to as "renal cell carcinoma/adenocarcinoma" (RCC), which included tumors coded as renal cell carcinoma, adenocarcinoma, or carcinoma not otherwise specified (excluding those coded as transitional cell carcinomas, carcinoid tumors or sarcomas, because they arise from other cell types[77]). For bladder cancer we considered transitional cell carcinoma (TCC-B), which is the most common type of bladder cancer.[77] This group excluded a small number of bladder cancers that were coded as squamous cell carcinoma, small cell carcinoma, signet ring carcinoma, papillary carcinoma not otherwise specified, carcinoma not otherwise specified, or adenocarcinoma not otherwise specified. We also defined a group comprising transitional cell carcinomas of the kidney or bladder (TCC-BK) to capture the common histologic type that can occur in the two sites.[77] For pancreatic malignancies we considered a subset that excluded islet cell tumors and neuroendocrine tumors, which originate from different cell types than the more common adenocarcinoma of the pancreas.[78] For hematologic malignancies, we used the proposed hierarchical classification for epidemiological research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium[79] to define several subgroups (see Figure S2).

Covariates. Covariates in our analytical models were selected *a priori*, using causal diagrams to identify potential confounders of the association between PFAS serum measurements and incident cancers. The selected confounders included well-established risk factors for each cancer type,[80–84] which might also be expected to be associated with PFAS exposure. We did not include body mass index (BMI) as a potential confounder in our primary analyses, because it might be on the causal pathway between PFAS exposure and the outcomes.[85] We did not include family history of cancer as a potential confounder, because it was unlikely to be associated with PFAS serum concentrations. Variables considered as potential confounders for all cancer types included sex; year of serum sample collection; age at serum collection; race and education from the 1982 baseline survey; and smoking status and alcohol consumption from the 1997 survey (or earlier surveys if missing on the 1997 survey). Information about race and ethnicity was self-reported using the following categories: White, Black, Hispanic, Asian, Other (specify). Because there were few non-White participants, the analyses collapsed race and ethnicity into categories of Non-Hispanic White and Hispanic or non-White race. In light of differences in incidence rates for several cancers by race/ethnicity,[86] race/ethnicity was included in models to control for the complex social factors that underlie these differences and that could act as confounders of the association between PFAS exposure and the cancers considered. We considered additional potential confounders in sensitivity analyses for specific cancers, including occupational exposure variables (yes/no) for exposure to coal dust, coal tar, diesel, dyes, and gasoline for bladder cancer; variables for occupational exposure to chemicals, coal dust, diesel, and gasoline for hematologic malignancies; low physical activity [<10 metabolic equivalent of task (MET) hours per week, based on information from 1997 survey, using information from 1992 if missing], oral contraceptive use (ever/never), menopausal hormone therapy use (ever/never), number of live births (0, 1, 2, 3, 4, ≥5), age at first live birth (<25, ≥25 y), age at menarche (<12, 12, 13, >13 y), and age at menopause (<45, 45 to <50, 50 to <53, ≥53 y) for breast cancer; and

BMI (<18.5 kg/m^2, 18.5 to <25.0 kg/m^2, 25.0 to <30.0 kg/m^2, ≥30.0 kg/m^2) for kidney cancer.

Descriptive analyses. All data analyses were done using SAS statistical software (version 9.4; SAS Institute Inc.). Initial descriptive analyses described the baseline subcohort and case groups in terms of demographics, categories of potential confounders, and serum PFAS concentrations.

Cox proportional hazard analyses. To examine the association between baseline PFAS serum concentrations and incident cancers, we used Cox proportional hazards models that accounted for the case–cohort design using Prentice weighting.[72,73] This approach includes all persons in the subcohort who had not yet developed the cancer of interest in the denominator of the pseudo-likelihood function for all risk sets for which they qualify with a weight of 1 (for those with events, up until the time they develop the cancer of interest; for those who are censored, for the duration of their follow up). Persons in the subcohort who developed the cancer of interest are included in the numerator of the pseudo-likelihood function at their time of failure with a weight of 1. Case-patients who are not in the subcohort are included in the numerator and denominator of the pseudo-likelihood function with a weight of 1 only at the time of their event and have a weight of 0 at all other times.[72,73,87] Variance estimation for parameters in the proportional hazards models used robust variance estimation.[88–90]

The outcome in each model was a verified cancer diagnosis (as described above). The time scale was time from serum sample collection. Follow-up time for each participant was calculated as the number of months from serum sample collection to the earliest of *a*) date of first diagnosis of any cancer other than nonmelanoma skin cancer, *b*) date of last survey return (unless the person died in the interval between the last survey and the time when the next survey was sent out), *c*) date of death or *d*) 30 June 2015 (end of follow-up). If a person's first cancer diagnosis was for the cancer of interest, the person's time ended as a case. If a person's first cancer diagnosis was for a cancer other than the cancer of interest, the person's time was censored at the time of that diagnosis.

To account for the fact that subcohort selection was stratified by sex, all models had separate baseline hazards by sex or were restricted to one sex. The primary models controlled for year of serum sample collection (single-year categories) and age at serum collection (<60, 60–64, 65–69, 70–74, 75–79, ≥80 y). The primary models also controlled for race (non-Hispanic White, other), education (high school graduate or less, vocational/trade school or some college, college graduate, graduate school), smoking status (current smoker, former smoker, ever smoked but unknown if current or former, never smoked), and alcohol consumption (nondrinker, <1 drink/wk, 1–6 drinks/wk, 1 drink/d, ≥2 drinks/d).

In sensitivity analyses, we considered models that used quartiles defined among the subcohort and models using collapsed categories for some variables (year of serum sample collection: 1998–1999, 2000–2001; age at serum collection: <64, 65–69, 70–74, ≥75 y; smoking status at the time of the 1997 follow-up survey: ever smoker, never smoker; alcohol consumption: nondrinker, <1 drink/wk, 1–6 drinks/wk, ≥1 drink/d). For bladder cancer, hematologic malignancies, breast cancer, and kidney cancer, we considered models that, in addition to the variables in the primary models, controlled for cancer-specific potential confounders, as specified above.

The proportional hazards assumption was assessed for each variable–outcome combination through examination of the correlation between weighted Schoenfeld residuals and follow-up time using the ZPH option in SAS PROC PHREG. The proportional hazards assumption for the $\log_2$-transformed continuous exposure variables was also evaluated through assessment of an interaction term between the exposure variable and follow-up time. There was no clear evidence of major violations of the proportional hazards assumption for the PFAS variables. The proportional hazards assumption also generally appeared to hold for other variables in the models. Exceptions included postmenopausal hormone therapy, and in some cases, age at serum collection. Therefore, we also considered models for all cancers that stratified the baseline hazard by age category (as specified above) and models for breast cancer that stratified the baseline hazard by postmenopausal hormone therapy use.

Quality control for data analysis. All SAS code for data preparation and analysis was reviewed by a second U.S. CDC National Center for Environmental Health (NCEH) statistician and an analyst from the ACS. All analytic results were reviewed by epidemiologists at both the U.S. CDC and the ACS.

Results

Study Population

Of 39,371 CPS-II LifeLink participants, 29,985 met the study inclusion criteria. From this group, 500 men and 500 women were randomly selected for the subcohort, but it was later determined that the available serum sample volume was insufficient for one woman; therefore, 500 men and 499 women in the subcohort were included in the study. Those in the subcohort were similar to those in the CPS-II LifeLink Cohort meeting the study inclusion criteria in terms of race/ethnicity, education, smoking status, and age at blood collection (Table S2). Characteristics of the subcohort are shown in Table 1 and Table S3 (includes breast cancer sensitivity analysis variables). Subcohort participants were predominantly of non-Hispanic White race/ethnicity (98% overall). At the time of the blood draw, 79% were ≥65 y of age. Forty-five percent had a college education or higher, 46% had never smoked, and 38% did not drink alcohol in 1997.

The number of CPS-II LifeLink Cohort participants meeting the study criteria who had verified first incident cancers after blood draw that were of interest in the study were as follows: 786 female breast cancer; 401 bladder cancer; 158 kidney cancer; 172 pancreatic cancer; 1,610 prostate cancer; and 635 hematologic malignancies (total number of cases across all included cancer sites = 3,762; Table 2). Characteristics of participants with verified incident cancers are shown in Table S3. Some participants with incident cancers were also in the subcohort, as shown in Table 2. Of the verified cancers, 91.5% were identified through self-report with subsequent verification, and 8.5% were identified through linkage with NDI and subsequently verified. The median follow-up time for members of the subcohort was 14.3 y (median 13.1 y for males and 14.7 y for females; minimum 1 month, maximum 17 y).

PFAS Exposures

Results for QC samples tested with the study samples showed intraclass correlation coefficients (ICCs) of >0.95 except for FOSA, for which the ICC was 0.32 for all samples and 0.57 after excluding one outlier (Table S4). Because of the poorer performance of the FOSA test, analyses using the FOSA serum concentrations were considered less reliable and are not presented.

All PFAS measured in the study were detected in >80% of subcohort participants except PFBS, which was detected in only 6% of subcohort participants and was not considered further in analyses (Table S5). Information on the distribution of PFAS serum concentrations among subcohort participants and persons with incident cancers is shown in Table 3, Table S6, and Figure S3. In the subcohort, PFOS had the highest concentrations (median 18.0 ng/mL), followed by PFOA (median 5.2 ng/mL) and PFHxS (median 3.1 ng/mL). PFHpA concentrations (median 0.10 ng/mL) were substantially lower than concentrations of other PFAS and had

Table 1. Subcohort characteristics ($n = 499$ women and 500 men).

	Total	Women	Men
	n (%)	*n* (%)	*n* (%)
Total	999 (100)	499 (100)	500 (100)
Year of serum collection			
1998	80 (8.0)	37 (7.4)	43 (8.6)
1999	308 (30.8)	156 (31.3)	152 (30.4)
2000	558 (55.9)	278 (55.7)	280 (56.0)
2001	53 (5.3)	28 (5.6)	25 (5.0)
Age category at serum collection (y)			
<60	33 (3.3)	28 (5.6)	5 (1.0)
60–64	174 (17.4)	96 (19.2)	78 (15.6)
65–69	321 (32.1)	165 (33.1)	156 (31.2)
70–74	303 (30.3)	145 (29.1)	158 (31.6)
75–79	134 (13.4)	51 (10.2)	83 (16.6)
≥80	34 (3.4)	14 (2.8)	20 (4.0)
Race/ethnicity[a]			
Non-Hispanic White	981 (98.2)	494 (99.0)	487 (97.4)
Hispanic or non-White race	14 (1.4)	5 (1.0)	9 (1.8)
Missing	4 (0.4)	0 (0.0)	4 (0.8)
Highest level of education			
8th grade or less	15 (1.5)	4 (0.8)	11 (2.2)
Some high school	24 (2.4)	7 (1.4)	17 (3.4)
High school graduate	205 (20.5)	132 (26.5)	73 (14.6)
Vocational/trade school	58 (5.8)	34 (6.8)	24 (4.8)
Some college	244 (24.4)	136 (27.3)	108 (21.6)
College graduate	252 (25.2)	128 (25.7)	124 (24.8)
Graduate school	196 (19.6)	57 (11.4)	139 (27.8)
Missing	5 (0.5)	1 (0.2)	4 (0.8)
Smoking status in 1997			
Nonsmoker	457 (45.7)	275 (55.1)	182 (36.4)
Current smoker	39 (3.9)	21 (4.2)	18 (3.6)
Former smoker	488 (48.8)	200 (40.1)	288 (57.6)
Ever smoker (unknown if current)	15 (1.5)	3 (0.6)	12 (2.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol consumption in 1997			
Nondrinker	378 (37.8)	218 (43.7)	160 (32.0)
<1 drink/wk	135 (13.5)	79 (15.8)	56 (11.2)
1–6 drinks/wk	326 (32.6)	149 (29.9)	177 (35.4)
1 drink/d	110 (11.0)	37 (7.4)	73 (14.6)
≥2 drinks/d	48 (4.8)	15 (3.0)	33 (6.6)
Missing	2 (0.2)	1 (0.2)	1 (0.2)
Body mass index (kg/m^2)			
<18.5	14 (1.4)	12 (2.4)	2 (0.4)
18.5 to <25	426 (42.6)	245 (49.1)	181 (36.2)
25 to <30	405 (40.5)	168 (33.7)	237 (47.4)
≥30	144 (14.4)	72 (14.4)	72 (14.4)
Missing	10 (1.0)	2 (0.4)	8 (1.6)

Note: CPS-II, Cancer Prevention Study II; PFAS, per- and polyfluoroalkyl substances.
[a]Information about race and ethnicity was collected on the 1982 CPS-II baseline survey (self-reported) using check boxes for the following categories: White, Black, Hispanic, Asian, Other (specify). Because there were few non-White participants, the analyses considered race and ethnicity in categories of Non-Hispanic White and Hispanic or non-White race. In light of differences in incidence rates for several cancers by race/ethnicity,[86] race/ethnicity was included in models to control for the complex social factors that underlie these differences and that could act as confounders of the association between PFAS exposure and the cancers considered.

limited variability (interquartile range: 0.14 ng/mL). Because of the low concentrations and limited contrasts, results of models for PFHpA are not presented. Overall, the PFAS measurements in the subcohort are generally comparable to values from NHANES 1999–2000,[91] after accounting for the fact that our measurements were only for the linear isomers of PFOS and PFOA (Table S6). PFAS serum concentrations were moderately correlated with each other, with the highest correlations being between PFOS and PFOA concentrations (Table S7).

PFOA concentrations generally increased and PFHpA levels decreased with later years of serum collection. Trends for other PFAS were less clear. PFOS levels generally decreased with increasing age at serum collection. PFHxS and PFOA levels were higher in men than in women. PFAS concentrations were higher among those of Hispanic or nonwhite race/ethnicity than among non-Hispanic whites for all PFAS. PFNA concentrations generally increased with increasing education, whereas PFOA levels generally decreased with increasing education. PFHpA and PFHxS levels were generally higher among smokers than among nonsmokers. Concentrations of PFHpA, PFHxS, PFNA, and PFOA generally increased with increasing alcohol consumption (except for the highest alcohol consumption group, for all but PFHpA). PFOA and PFOS levels generally increased with increasing BMI (Table S8).

Statistical Analysis

Cancer sites. Results of primary models investigating associations between $\log_2$-transformed PFAS measures and incident cancer for the included cancer sites are shown in Figure 1 and Table S9; results for models considering quartiles among cases are shown in Table S9 and Figure S4. Overall, for the sexes combined, there were no clear associations between PFHxS, PFNA, PFOA, or PFOS and any of the cancer sites considered. In sex-specific analyses, the hazard ratio (HR) for PFOA in relation to kidney cancer was elevated among women [HR and 95% confidence interval (CI) per PFOA doubling: 1.33 (95% CI: 0.97, 1.83), $p = 0.076$]. When considered by PFOA quartiles among cases, kidney cancer HRs among women for PFOA quartiles 2–4 vs. quartile 1 were 0.80 (95% CI: 0.34, 1.87), 1.04 (95% CI: 0.45, 2.44) and 1.94 (95% CI: 0.87, 4.35). The HR for kidney cancer in relation to PFNA was somewhat elevated among men [HR per PFNA doubling: 1.20 (95% CI: 0.95, 1.52), $p = 0.124$; HRs for PFNA quartiles 2–4 vs. quartile 1: 1.16 (95% CI: 0.57, 2.36), 1.04 (95% CI: 0.51, 2.12) and 1.60 (95% CI: 0.78, 3.28)]. There was an apparent negative association between PFOA and pancreatic cancer among men [HR per PFOA doubling: 0.71 (95% CI: 0.52, 0.96), $p = 0.025$], although the pattern of HRs across quartiles was not monotonic [HRs for PFOA quartiles 2–4 vs. quartile 1: 0.82 (95% CI: 0.39, 1.72), 1.05 (95% CI: 0.51, 2.17) and 0.52 (95% CI: 0.25, 1.08)]. There was also an apparent negative association between PFOS and hematologic malignancies among women [HR per PFOS doubling: 0.79 (95% CI: 0.66, 0.95), $p = 0.013$], with a monotonic decrease in HRs across quartiles [HRs for PFOS quartiles 2–4 vs. quartile 1: 0.73 (95% CI: 0.45, 1.18), 0.71 (95% CI: 0.44, 1.16) and 0.56 (95% CI: 0.34, 0.91)].

Results did not substantially change when PFAS concentrations were considered in quartiles among the subcohort rather than quartiles among cases. Results were also similar for models with collapsed categories for some control variables, although the inverse association between the $\log_2$-transformed PFOA measure and pancreatic cancer among males was somewhat attenuated [HR per PFOA doubling: 0.76 (95% CI: 0.56, 1.02), $p = 0.067$]. Models for bladder cancer and hematologic malignancies that included additional covariates for occupational exposures produced HRs with wider CIs, but results were generally similar, and conclusions were unchanged. Models for breast cancer that controlled for additional covariates relevant to breast cancer, including models in which the baseline hazard was stratified by postmenopausal hormone use, showed results that were similar to the primary models. Results did not change using models for kidney cancer that also controlled for BMI. Results from models in which the baseline hazard was stratified by age category were very similar to primary model results.

Histologic subtypes. In models for histologic subtypes, RCC of the kidney was associated with PFOA exposure among women [HR per PFOA doubling: 1.54 (95% CI: 1.05, 2.26), $p = 0.027$; HRs for PFOA quartiles 2–4 vs. quartile 1: 1.33 (95% CI: 0.42, 4.19), 1.66 (95% CI: 0.54, 5.12) and 3.14 (95% CI: 1.04, 9.54)] but not men (Figure 2; Figure S5; Table S10). Among men, the HR for RCC in relation to PFNA concentration was similar to that observed for kidney cancer overall, but the pattern of hazard

Table 2. Number of cases of verified incident cancers among CPS-II LifeLink Cohort meeting study inclusion criteria.[a]

Cancer site and histologic subtypes	Verified cases among CPS-II LifeLink Cohort meeting study inclusion criteria[a] (total number of cases across all included cancer sites = 3,762)			Verified cases among participants who were also in the subcohort		
	All	Women	Men	All	Women	Men
Kidney-all	158	66	92	4	3	1
Renal cell carcinoma/adenocarcinoma (RCC)	109	43	66	3	3	0
Bladder-all	401	82	319	9	5	4
Transitional cell carcinoma of the bladder (TCC-B)	390	80	310	9	5	4
Transitional cell carcinoma of the bladder or kidney (TCC-BK)	437	102	335	10	6	4
Breast (female only)	NA[b]	786	NA[b]	NA[b]	11	NA[b]
Prostate (male only)	NA[b]	NA[b]	1,610	NA[b]	NA[b]	58
Pancreas- all	172	81	91	7	2	5
Non-islet cell carcinoma/neuroendocrine tumors	167	78	89	1	1	0
Hematopoietic (lymphoma, leukemia or myeloma)-(Heme)	635	284	351	16	3	13
Myeloid malignancies (MYELO)	80	32	48	0	0	0
Lymphoid malignancies (LYMPH)	549	248	301	16	3	13
Non-Hodgkin Leukemia/Lymphoma (NHL)[c]	537	241	296	16	3	13
NHL without Multiple Myeloma (NHL without MM)	436	197	239	13	2	11
B-cell NHL (B-NHL)	489	219	270	14	3	11
B-cell NHL without Multiple Myeloma (B-NHL without MM)	388	175	213	11	2	9
Diffuse Large B-cell Lymphoma (DLBCL)	125	56	69	4	0	4
Chronic lymphocytic leukemia/Small lymphocytic lymphoma/Mantle cell lymphoma (CLL/SLL)	141	66	75	3	0	3
Multiple myeloma (MM)	101	44	57	3	1	2

Note: CPS-II, Cancer Prevention Study II; NA, not applicable; PFAS, per- and polyfluoroalkyl substances.
[a]Study inclusion criteria for case-patients included the following: *a*) no previous cancer diagnosis (other than nonmelanoma skin cancer) at the time of blood sample collection (1998–2001), *b*) at least 500 μL of stored serum available for the study, *c*) for women, postmenopausal as of the time of the 1997 survey, and *d*) no previous diagnosis during follow up of another type of cancer (other than non-melanoma skin cancer). All cases that met the study inclusion criteria had PFAS measurements.
[b]Breast cancer was considered for females only, and prostate cancer was considered for males only.
[c]Model results for NHL and B-NHL were very similar, so only B-NHL results are presented in tables and graphs.

ratios across PFNA quartiles was not monotonic. No clear associations were observed for TCC-B or TCC-BK for the sexes combined or considered separately. Models with collapsed categories of some control variables, models with additional control for occupational exposures (for transitional cell carcinoma), and models with baseline hazard stratification by age category at baseline all gave similar results for RCC, TCC-B, and TCC-BK, although in models with collapsed control variables, the association between RCC and PFOA among women was slightly attenuated [HR per PFOA doubling: 1.40 (95% CI: 0.99, 1.98), $p = 0.055$; HRs for PFOA quartiles 2–4 vs. quartile 1: 1.32 (95% CI: 0.43, 4.04), 1.42 (95% CI: 0.47, 4.29) and 2.85 (95% CI: 0.98, 8.31)]. Results for pancreatic cancer excluding islet cell and neuroendocrine tumors were similar to results for pancreatic cancer overall.

In models for hematologic subtypes (Figure 3; Table S10; and Figure S6), there was a positive association between chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and PFHxS among men [HR per PFHxS doubling: 1.34 (95% CI: 1.02, 1.75), $p = 0.033$], and the trend across quartiles was nearly monotonic [HRs for PFHxS quartiles 2–4 vs. quartile 1: 2.10 (95% CI: 0.83, 5.36), 1.85 (95% CI: 0.75, 4.56), and 3.01 (95% CI: 1.21, 7.48)]. There was some evidence of negative associations between myeloid malignancies and PFNA and PFOA among women [HR per concentration doubling 0.62 (95% CI: 0.39, 0.98), $p = 0.043$ for PFNA; and 0.60 (95% CI: 0.39, 0.90), $p = 0.013$ for PFOA], although the trends across quartiles among cases were not monotonic. For lymphoid malignancies overall and for the subgroups of B-cell non-Hodgkin leukemia/lymphoma (B-NHL) and multiple myeloma (MM), there was evidence of a negative association with PFOS among women, with monotonic or nearly monotonic trends across quartiles [e.g., for MM, HR per PFOS doubling: 0.69 (95% CI: 0.49, 0.98), $p = 0.036$; HRs for PFOS quartiles 2–4 vs. quartile 1: 0.71 (95% CI: 0.27, 1.90), 0.59 (95% CI: 0.18, 1.96) and 0.42 (95% CI: 0.16, 1.14)]. For MM, negative associations were also observed for PFNA, PFOA, and PFOS for both sexes combined and for PFOA and PFOS among men; however, trends across quartiles among cases were not monotonic. Collapsing categories of some control variables, including control for additional occupational variables, and stratification of the baseline hazard by age category at baseline and did not change conclusions for models of hematologic subtypes.

Discussion

In this case–cohort study we observed a positive association between baseline PFOA serum concentrations and incident kidney cancer among women, with the observed association being stronger in analyses restricted to RCC. No associations between baseline PFOA serum concentrations and incident kidney cancer or RCC were observed among men. Among men there was a suggestion of a positive association between baseline PFHxS concentrations and CLL/SLL. We also observed some apparent negative associations between baseline PFAS serum concentrations and pancreatic cancer among men (for PFOA) and hematologic malignancies among women (for myeloid malignancies in relation to PFOA and PFNA and for MM in relation to PFOS) and possibly men (for MM in relation to PFOA and PFOS).

Several previous studies have found positive associations between PFOA exposure and kidney cancer[31,32,35–37,41] or between exposure to drinking water contaminated with a mixture of different PFAS, including PFOA, and kidney cancer.[38,68] In an assessment published in 2017, the IARC concluded there was "limited evidence in humans for the carcinogenicity of PFOA," based on positive associations that had been observed for kidney and testicular cancers, and classified PFOA as "possibly carcinogenic to humans."[9] Since that time, additional studies have provided more evidence for a

Table 3. PFAS serum concentrations (ng/mL) among subcohort participants ($n = 999$; 499 women and 500 men) and participants of the LifeLink Cohort with incident cancers.[a,b]

		Both sexes			Women			Men		
Type of PFAS	Group	P25	Median	P75	P25	Median	P75	P25	Median	P75
PFHpA	Subcohort	0.06	0.10	0.20	0.06	0.10	0.18	0.07	0.11	0.22
PFHpA	Bladder cancer cases	0.06	0.10	0.20	0.07	0.09	0.16	0.06	0.10	0.20
PFHpA	Breast cancer cases	NA[c]	NA[c]	NA[c]	0.06	0.10	0.19	NA[c]	NA[c]	NA[c]
PFHpA	Kidney cancer cases	0.07	0.11	0.19	0.07	0.10	0.16	0.07	0.11	0.21
PFHpA	Pancreas cancer cases	0.06	0.10	0.19	0.06	0.10	0.18	0.07	0.10	0.19
PFHpA	Prostate cancer cases	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	0.06	0.10	0.18
PFHpA	Hematologic malignancy cases	0.07	0.11	0.20	0.07	0.10	0.18	0.06	0.11	0.21
PFHxS	Subcohort	2.00	3.10	5.10	1.80	2.80	5.00	2.10	3.30	5.30
PFHxS	Bladder cancer cases	2.10	3.00	4.90	1.60	2.65	3.70	2.20	3.20	5.00
PFHxS	Breast cancer cases	NA[c]	NA[c]	NA[c]	1.70	2.80	5.20	NA[c]	NA[c]	NA[c]
PFHxS	Kidney cancer cases	2.10	3.30	4.90	2.20	3.05	4.90	2.05	3.35	4.65
PFHxS	Pancreas cancer cases	1.80	2.95	4.85	1.50	2.70	5.20	1.90	3.20	4.80
PFHxS	Prostate cancer cases	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	2.20	3.30	5.10
PFHxS	Hematologic malignancy cases	2.00	3.00	5.20	1.80	2.80	4.90	2.20	3.30	5.30
PFNA	Subcohort	0.49	0.67	0.98	0.49	0.67	0.96	0.49	0.67	0.99
PFNA	Bladder cancer cases	0.47	0.68	1.00	0.43	0.62	1.00	0.47	0.69	1.00
PFNA	Breast cancer cases	NA[c]	NA[c]	NA[c]	0.46	0.67	1.00	NA[c]	NA[c]	NA[c]
PFNA	Kidney cancer cases	0.51	0.68	1.00	0.51	0.66	0.98	0.52	0.72	1.00
PFNA	Pancreas cancer cases	0.45	0.63	1.00	0.43	0.62	0.97	0.47	0.63	1.00
PFNA	Prostate cancer cases	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	0.49	0.70	1.00
PFNA	Hematologic malignancy cases	0.45	0.65	1.00	0.45	0.63	0.99	0.45	0.68	1.00
PFOA	Subcohort	3.90	5.20	6.90	3.70	5.00	6.90	4.00	5.20	6.95
PFOA	Bladder cancer cases	3.80	5.10	6.70	3.60	4.30	6.60	3.90	5.20	6.80
PFOA	Breast cancer cases	NA[c]	NA[c]	NA[c]	3.70	5.00	6.90	NA[c]	NA[c]	NA[c]
PFOA	Kidney cancer cases	3.90	5.20	7.30	3.80	5.35	7.60	3.90	5.05	7.20
PFOA	Pancreas cancer cases	3.85	5.10	6.30	3.80	5.00	7.00	3.90	5.10	6.20
PFOA	Prostate cancer cases	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	4.00	5.30	6.90
PFOA	Hematologic malignancy cases	3.80	5.00	6.70	3.70	4.90	6.55	3.80	5.10	6.80
PFOS	Subcohort	13.00	18.00	25.00	13.00	18.00	25.00	13.50	18.00	25.50
PFOS	Bladder cancer cases	13.00	18.00	25.00	11.00	16.00	22.00	13.00	19.00	25.00
PFOS	Breast cancer cases	NA[c]	NA[c]	NA[c]	12.00	17.00	24.00	NA[c]	NA[c]	NA[c]
PFOS	Kidney cancer cases	13.00	18.00	26.00	11.00	19.50	27.00	14.00	18.00	24.00
PFOS	Pancreas cancer cases	12.00	18.00	25.00	11.00	18.00	25.00	12.00	19.00	25.00
PFOS	Prostate cancer cases	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	14.00	19.00	26.00
PFOS	Hematologic malignancy cases	12.00	17.00	24.00	12.00	16.00	23.00	13.00	18.00	25.00

Note: NA, not applicable; P25, 25th percentile; P75, 75th percentile; PFAS, per- and polyfluoroalkyl substances; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

[a]Values below the limit of detection were imputed as the limit of detection divided by the square root of 2.

[b]The total number of cases of each type of cancer were as follows: bladder cancer, 401; breast cancer, 786; kidney cancer, 158; pancreas cancer, 172; prostate cancer, 1,610; hematologic malignancies, 635.

[c]Breast cancer was considered for females only, and prostate cancer was considered for males only.

positive association between PFOA and kidney cancer,[34,37,38,68] including one study by Shearer et al. that found an association specifically with RCC.[37] That study was the only previous study of PFAS and kidney cancer in a population with general-population exposure levels. It found an association between PFOA and RCC among both women and men that was slightly stronger than the association found in our study (overall adjusted odds ratio = 1.68; 95% CI: 1.07, 2.63), but that study population was somewhat younger than the CPS-II LifeLink population, and they considered linear and branched isomers of PFOA combined (as opposed to only linear isomers in this study).[37] Associations have been examined separately by sex in only three previous studies of PFOA and kidney cancer,[37,38,68] and all found stronger associations among women than among men. In the study by Shearer et al., associations were somewhat stronger among women than among men.[37] A study that compared kidney cancer incidence in a county exposed to PFAS-contaminated drinking water (primarily PFHxS and PFOS and to a lesser extent PFOA) and an unexposed county found higher standardized incidence ratios for kidney cancer in more highly exposed groups among women but not among men; internal comparisons within the exposed county, however, found positive associations with kidney cancer that were not significantly different for women and men.[68] An ecological study that compared cancer incidence between an area with PFAS-contaminated drinking water and unexposed areas found higher kidney cancer risk in exposed areas that was more pronounced among women.[38]

In contrast to our finding that PFOA might be inversely associated with pancreatic cancer among men, previous studies that have reported on an association between PFOA and pancreatic cancer have found associations that were either null[31,41] or positive but not statistically significant.[35,36,39,66,92,93] The only previous study in a population with general-population-level PFAS exposures found a slightly positive, nonmonotonic association with PFOA.[66] The negative association with pancreatic cancer observed in our study should be interpreted with caution. The negative association observed using the $\log_2$-transformed measure was not supported by the quartile analysis (which showed a nonmonotonic trend). In addition, these analyses might have been impacted by left truncation as discussed below.

In this study, PFHxS, PFNA, PFOA, and PFOS were not associated with hematologic malignancies considered as a group for the sexes combined, but there was an apparent negative association between PFOS and hematologic malignancies as a group among women. Previous studies of PFAS and hematologic malignancies considered as a group have all been occupational studies among highly exposed, primarily male populations. Those studies yielded mixed findings. Two studies (one primarily PFOS exposure and one primarily PFOA exposure) found negative associations[39,53]

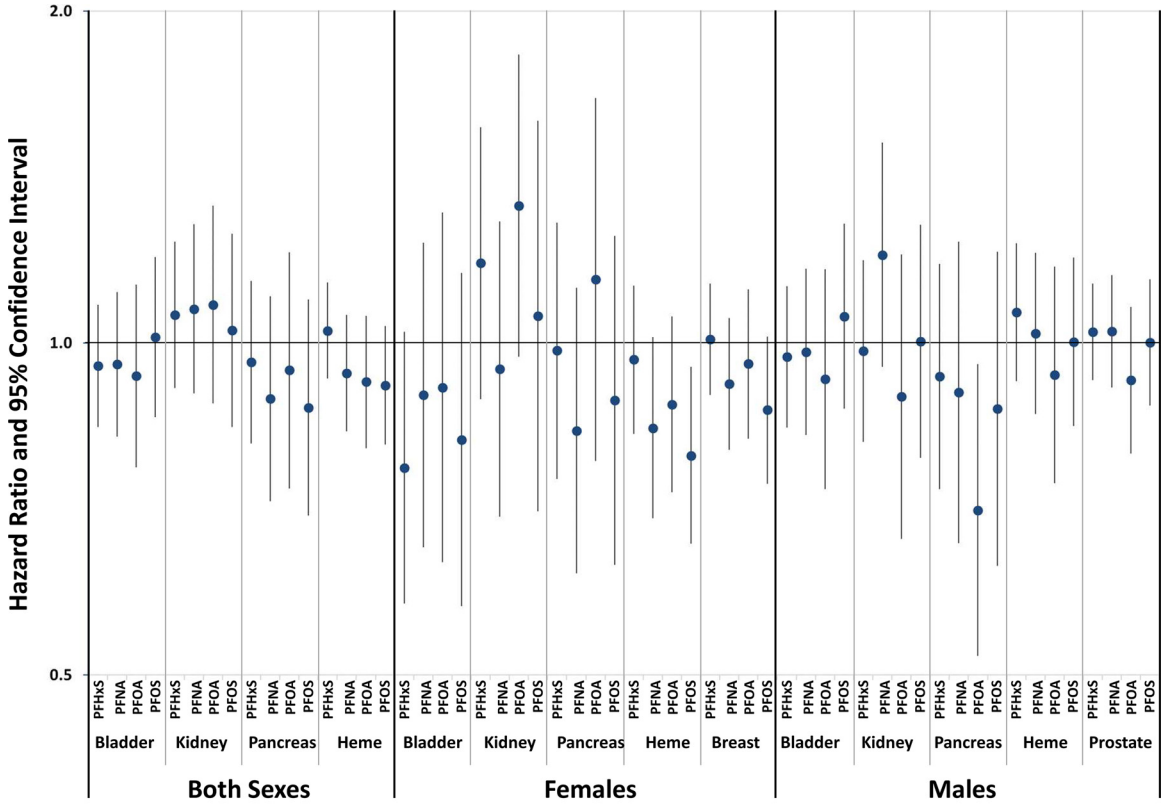

Figure 1. Hazard ratios and 95% confidence intervals for overall cancer sites per doubling of PFAS concentrations (using $\log_2$-transformed measures) by sex and type of PFAS, case–cohort study of association between PFAS and selected cancers among participants in the Cancer Prevention II LifeLink cohort, 1998–2015. All models had separate baseline hazards by sex or were restricted to one sex. The primary models controlled for year of serum sample collection (single-year categories), age at serum collection (<60, 60–64, 65–69, 70–74, 75–79, ≥80 y), race (non-Hispanic White, other), education (high school graduate or less, vocational/trade school or some college, college graduate, graduate school), smoking status (current smoker, former smoker, ever smoked but unknown if current or former, never smoked), and alcohol consumption (nondrinker, <1 drink/wk, 1–6 drinks/wk, 1 drink/d, ≥2 drinks/d). The overall number of cancers (both sexes) included in the models were as follows: bladder, 396; kidney, 156; pancreas, 171; hematologic malignancies (Heme), 626. See Table S9 for numerical data. Note: PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

and four (all primarily PFOA exposure) found positive associations,[36,41,54,92] with only one positive association being statistically significant.[54] Some of the heterogeneity might be due to lack of consideration of histologic subtypes.

In our study, we observed some heterogeneity in PFAS associations between hematologic malignancy histologic subtypes and between sexes, with a positive association observed for PFHxS and CLL/SLL among men, possible negative associations between PFNA and PFOA and myeloid malignancies among women, negative associations between PFOS and B-NHL and MM among women, and negative associations between PFOA and PFOS and MM among men. Relatively few previous studies (all conducted among occupational or community populations with high PFAS exposure) have considered associations between PFAS and hematologic malignancy histologic subtypes, and the subtypes considered have varied between studies. Several studies considered groups of leukemia or lymphoma, which did not align with ours.[31,32,35,36,38,39,41] However, some considered groups that generally aligned with ours. Only one previous study (in a community with high exposures, predominantly to PFOS and PFHxS) considered CLL as a subgroup and found a negative association among women and a positive association among men in the highest exposure group, neither of which was statistically significant.[68] This finding is in general agreement with our finding of a positive association between PFHxS and CLL/SLL only among men. Several studies considered the broader subgroup of non-Hodgkin lymphoma (NHL), for which we observed negative associations with PFOS among women. Four studies considered NHL in highly exposed, predominantly male, occupational cohorts with primarily PFOA exposure, of which three found positive associations with NHL,[35,41,54] and one found a negative association.[36] Four studies considered NHL in highly exposed communities. One study that compared a community with exposure primarily to PFOS and PFHxS with an unexposed community found negative associations with NHL for the highest exposure group in males and females.[68] A study in a community with high PFOA exposure found a positive association with NHL in the most highly exposed group for the sexes combined.[32] A study in a community with PFAS exposures of unspecified composition found a positive association for NHL, in comparison with unexposed areas, among men and a negative association among women.[38] Three studies considered MM as a subgroup, for which we observed negative associations with PFNA, PFOA, and PFOS among both men and women; all were conducted in highly exposed occupational or community populations and found negative associations,[32,36,68] with one (in a community with high PFOS and PFHxS exposures) finding the negative association in both men and women.[68] Therefore, there is some agreement between previous studies and our findings for hematological histologic subgroups, especially for the more specific subgroups of CLL and MM, although no previous studies considered populations with general-population-level PFAS exposure.

The mechanisms through which PFAS might lead to cancer are not entirely clear. PFOA and PFOS have not been found to be directly mutagenic, although PFOA might lead to DNA damage

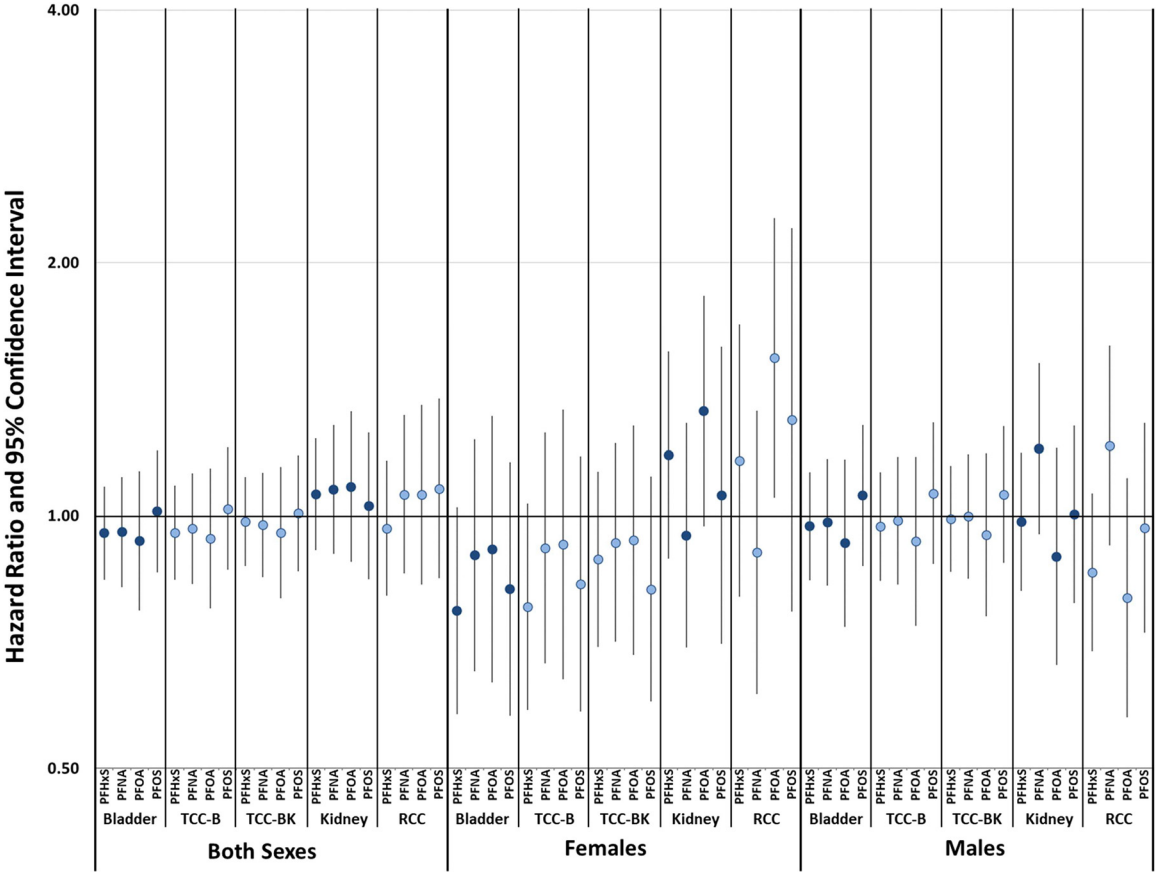

Figure 2. Hazard ratios and 95% confidence intervals for overall cancer sites (dark circles) and histologic subtypes (light circles) for bladder and kidney cancers per doubling of PFAS concentrations (using $\log_2$-transformed measures) by sex and type of PFAS, case–cohort study of association between PFAS and selected cancers among participants in the Cancer Prevention II LifeLink cohort, 1998–2015. All models had separate baseline hazards by sex or were restricted to one sex. The primary models controlled for year of serum sample collection (single-year categories), age at serum collection (<60, 60–64, 65–69, 70–74, 75–79, ≥80 y), race (non-Hispanic White, other), education (high school graduate or less, vocational/trade school or some college, college graduate, graduate school), smoking status (current smoker, former smoker, ever smoked but unknown if current or former, never smoked), and alcohol consumption (nondrinker, <1 drink/wk, 1–6 drinks/wk, 1 drink/d, ≥2 drinks/d). The overall number of cancers (both sexes) included in the models were as follows: bladder, 396; TCC-B, 385; TCC-BK, 432; kidney, 156; RCC, 107. See Tables S9 and S10 for numerical data. Note: PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; RCC, renal cell carcinoma; TCC-B, transitional cell carcinoma of the bladder; TCC-BK, transitional cell carcinoma of the bladder or kidney.

by leading to reactive oxygen species generation and oxidative stress.[8,9,94] Some mechanisms through which PFOA and PFOS led to tumors in rodents involved peroxisome proliferator-activated receptor α (PPARα) activation.[8] PPARα is a nuclear receptor that affects several cellular processes; including metabolism of lipids, glucose, glycogen, and amino acids; among many others.[95] There is some evidence that PPARα is expressed in human renal cell carcinomas; and that PPARα antagonists can reduce renal cell carcinoma cell viability, inhibit overactive glycolysis in renal cell carcinoma cells, and reduce renal cell carcinoma tumor growth.[96,97] If PPARα activation has relevance to kidney carcinogenesis, that might align with the finding that genes found to be associated with kidney cancer are related to metabolic processes, such as glycolysis.[98,99] However, the human relevance of carcinogenic mechanisms involving PPARα is uncertain.[8,9,95,99,100] There is evidence that carcinogenic effects of PFOA in experimental animals might also be mediated through PPARα-independent mechanisms, such as activation of other nuclear receptors, endocrine disruption, epigenetic changes, and effects on inflammatory pathways.[9,94,101]

Strengths of this study include its prospective nature and the large size of the underlying cohort, which gave rise to a relatively large number of cases for each of the cancer sites considered, in comparison with many previous studies. The underlying study also had good follow-up and accurate methods for identifying incident cancers. The fact that this study was conducted in a population with general-population-level PFAS exposures is also a strength, allowing us to evaluate evidence of associations with cancer for PFAS exposures occurring outside of occupational or otherwise highly exposed populations. Finally, the consideration of histologic subtypes, which has not commonly been done in previous studies is also a strength. Our findings suggest that consideration of histologic subtypes might be important to understanding the relationship between PFAS exposure and cancer, especially for hematologic malignancies.

This study also has several limitations that are important to consider when interpreting the results. Because 98% of those in the underlying cohort were of non-Hispanic White race/ethnicity, generalizability to other groups might be limited. Because the sampling frame (source of both cancer cases and the subcohort) excluded those with a prior diagnosis of cancer (other than nonmelanoma skin cancer), generalizability to those with prior cancers might also be limited. In addition, participants in the cohort that was the source for this study were initially enrolled in 1982, and this study draws from the subset of participants who survived until 1998–2001 without developing cancer other than nonmelanoma

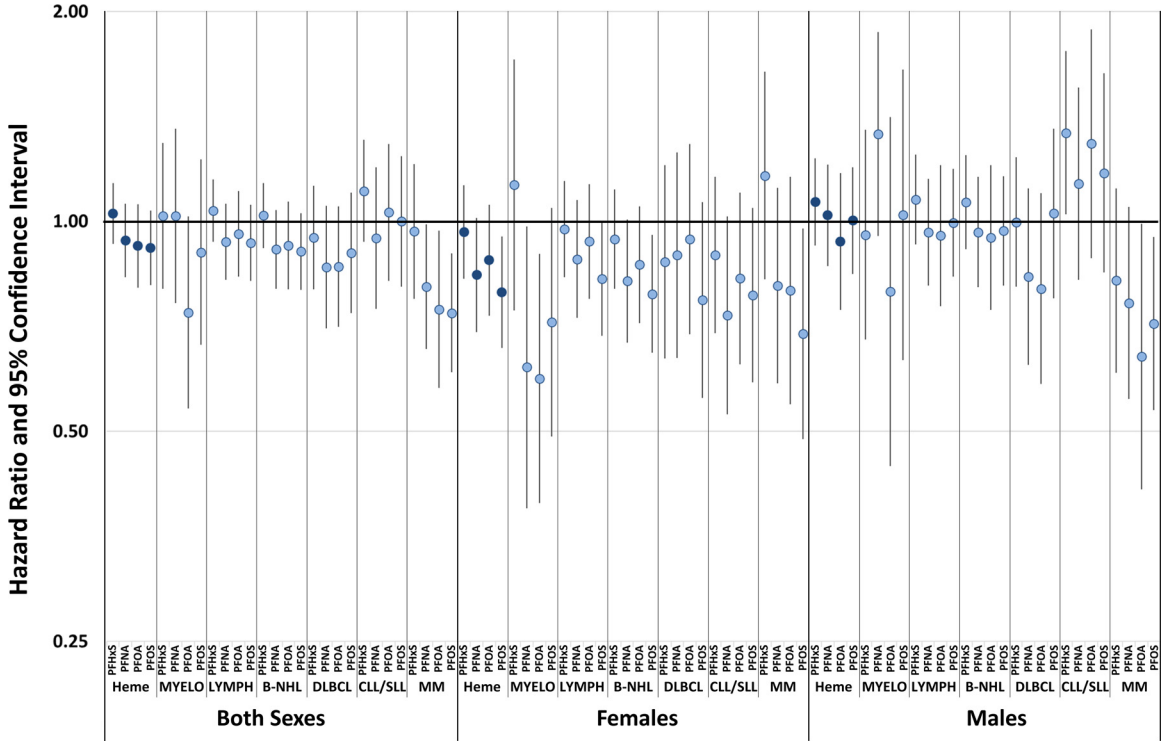

Figure 3. Hazard ratios and 95% confidence intervals for overall hematologic malignancies (dark circles) and histologic subtypes (light circles) for hematologic subtypes per doubling of PFAS concentrations (using $\log_2$-transformed measures) by sex and type of PFAS, case–cohort study of association between PFAS and selected cancers among participants in the Cancer Prevention II LifeLink cohort, 1998–2015. All models had separate baseline hazards by sex or were restricted to one sex. The primary models controlled for year of serum sample collection (single-year categories), age at serum collection (<60, 60–64, 65–69, 70–74, 75–79, ≥80 y), race (non-Hispanic White, other), education (high school graduate or less, vocational/trade school or some college, college graduate, graduate school), smoking status (current smoker, former smoker, ever smoked but unknown if current or former, never smoked), and alcohol consumption (nondrinker, <1 drink/wk, 1–6 drinks/wk, 1 drink/d, ≥2 drinks/d). The overall number of cancers (both sexes) included in the models were as follows: Heme, 626; MYELO, 80; LYMPH, 540; B-NHL, 483; DLBCL, 123; CLL/SLL, 140; MM, 99. See Tables S9 and S10 for numerical data. Note: B-NHL, B-cell non-Hodgkin leukemia/lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma/mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; Heme, hematologic malignancies; LYMPH, lymphoid malignancies; MM, multiple myeloma; MYELO, myeloid malignancies; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

skin cancer. At the time of the baseline serum collection in 1998–2001, 79% of those included in our subcohort were ≥65 y of age. PFAS exposure has been ongoing in the United States for many years. PFAS production started in the 1940s, and global emissions of perfluoroalkyl carboxylic acids (such as PFOA and PFNA) steadily increased until approximately 2000–2002.[23,102] PFAS concentrations in human serum in the U. S. NHANES survey were first measured during the 1999–2000 NHANES cycle, and PFOS, PFOA, PFHxS, and FOSA were detected in all samples.[19] Therefore, CPS-II LifeLink Cohort participants almost certainly were exposed to several PFAS for many years before serum collection in 1998–2001, and the study is left-truncated. In the presence of varying susceptibility to the effect of exposure on disease, left truncation can lead to bias in measures of the effect of an exposure on disease.[103–106] Bias resulting from left truncation can occur because those who are most susceptible to the effect of exposure on disease are lost over time from the population that remains at risk for the outcome, leaving a population that is less susceptible to the effects of the exposure on disease.[103,104] This is a type of selection bias,[106] the magnitude of which can increase with increasing time between the start of exposure and study enrollment[103]; it can lead to underestimation of positive associations and can result in an exposure that has a harmful effect appearing to have a protective effect.[105–107] Ongoing exposure prior to enrollment also complicates control for some variables, such as BMI, which might confound some PFAS associations but might also be caused by PFAS exposure and therefore potentially on the causal pathway between PFAS exposure and the outcome.[104] Some left-truncation is unavoidable in U.S. epidemiological studies of PFAS and cancer outside historical settings. However, for this study, the effect of left truncation might have been particularly pronounced, because observation for many participants started at an age that is older than the median age at diagnosis for some of the cancers considered, especially for kidney and breast cancers.[108] Left-truncation could have led to underestimation of some HRs and could explain some of our observed negative associations but is unlikely to have led to overestimation of HRs.

Another study limitation is that that PFAS serum concentrations are available for only one point in time, and the degree to which this measurement would adequately represent a person's PFAS exposure history is uncertain. However, there are several reasons to expect that the serum concentrations would adequately reflect a person's longer-term exposures. Our analysis can be considered as essentially addressing the question of whether people with higher PFAS serum concentrations have a higher cancer incidence than those with lower PFAS concentrations, with the assumption being that a person's PFAS exposure ranking in relation to others with similar covariates (e.g., age, sex) and with serum drawn around the same time remains relatively stable over time, even if absolute concentrations change. This assumption is likely reasonable, given *a*) the long half-lives of several PFAS,[8,25,26] and *b*) the facts that PFAS have been used for long

periods of time,[102] are persistent in the environment,[102] and have only relatively recently come to attention in drinking water.[10] One study that examined within-individual changes in serum PFAS concentrations over time in a population with PFAS exposure at general-population levels found that the ranking of individuals' serum concentrations remained relatively stable, even though absolute concentrations changed over time.[109] Our PFAS serum concentrations were also only for the linear isomers of the PFAS considered, which might limit comparability of our findings to those of other studies of PFAS and cancer.

It is also important to note that concentrations of the various PFAS were correlated, so HRs for one type of PFAS should be interpreted as possibly also representing the effects of other correlated PFAS. The number of cancer cases in our study did not allow for more complex models controlling for other PFAS. Nevertheless, there is no guarantee that models controlling for other PFAS would be less biased than single-PFAS models. If unmeasured exposures (e.g., diet) confound the association between the outcome and one type of PFAS, but not another type of PFAS, including both types of PFAS in the model could amplify, not decrease, bias.[110] In addition, associations could be confounded by other correlated but unmeasured PFAS. Nevertheless, the inability to control for other PFAS limits our ability to confidently conclude that associations observed for kidney cancer among women and CLL/SLL among men are solely attributable to specific PFAS. Consideration of PFAS mixtures is an important area for exploration in future studies of PFAS and cancer.

Although this study includes more cases of the cancers considered than many previous studies, the number of cases for some of the cancer subtypes considered might have been small relative to the number of variables in our models, with some variables involving multiple parameters. Some have suggested that having fewer than 10 cases per model parameter can lead to bias,[111,112] but others have suggested that bias is unlikely with case counts as low as five cases per parameter.[113] Models for bladder, breast, prostate, and the larger hematologic malignancy subgroups had an ample number of cases relative to the number of parameters, but models for kidney cancer, pancreatic cancer and smaller hematologic subtypes had a fewer cases per parameter (Table S11). Model results should be interpreted considering this limitation. The fact that models with collapsed categories of some control variables gave similar conclusions provides some reassurance that low case numbers might not have seriously biased the primary model results. Finally, our results should be interpreted with consideration of the fact that there are multiple comparisons, and some observed associations could be due to chance or unknown sources of bias.

In conclusion, this study provides important information supporting the previously observed association between PFOA and kidney cancer, particularly among women, at general population-level PFAS exposures. It also contributes to evidence relating to PFAS exposure and specific types of hematologic malignancies, which have been less commonly studied, and not previously studied in a population with general-population-level PFAS exposures. It suggests a possible association between PFAS exposure and CLL/SLL among men that could be followed-up in future studies. Study findings also indicate that consideration of histologic subtypes might be important in future studies of PFAS and cancer, especially for hematologic malignancies.

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