Research article

The association between per- and polyfluoroalkyl substances (PFASs) and brain, esophageal, melanomatous skin, prostate, and lung cancer using the 2003–2018 US National Health and Nutrition Examination Survey (NHANES) datasets

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ABSTRACT

Introduction: The purpose of this study was to use the US National Health and Nutrition Examination Survey (NHANES) datasets to examine potential relationships between four per- and polyfluoroalkyl substance (PFAS) exposures and each type of cancer, specifically perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).
Methods: A logistic regression analysis was performed. A directed acyclic graph was plotted to adjust for the potential confounders.
Results: The odds ratio (OR) of brain cancer for a one-unit increase in ln (PFHxS) was 8.16 (95 % confidence interval [CI] 2.98–68.89). The OR of esophageal cancer for one unit increase of ln (PFOA) and ln (PFOS) was 5.10 (95 % CI 1.18–17.34) and 3.97 (95 % CI 1.24–11.42), respectively. The OR of melanoma for one unit increase of ln (PFOA) and ln (PFHxS) was 1.65 (95 % CI 1.07–2.58) and 1.55 (95 % CI 1.07–2.25), respectively. The OR of prostate cancer for one unit increase of ln (PFOS) and ln (PFNA) was 1.21 (95 % CI 1.00–1.48) and 1.27 (95 % CI 1.00–1.62), respectively. The OR of lung cancer for one unit increase of ln (PFOS) and ln (PFNA) was 2.62 (95 % CI 1.24–5.83) and 2.38 (95 % CI 1.00–5.52), respectively.
Discussion: Considering that brain, esophageal, and melanomatous skin cancers have not been targets of epidemiologic studies regarding PFAS exposure, future studies could target these cancers as outcomes of interest.

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1. Introduction

Emerging environmental contaminants known as per- and polyfluoroalkyl substances (PFASs) have a number of detrimental consequences on human health [1,2]. Several of these adverse health effects have been well documented and verified using data from epidemiologic studies. However, carcinogenic effect studies are at their initial step and require further investigation [3].

The US National Health and Nutrition Examination Survey (NHANES) datasets can be utilized to explore the possible link between exposure to several PFASs and cancer in different organ systems, despite the fact that the data is cross-sectional in nature.

The purpose of this study was to look into potential links between cancer in different organ systems and exposure to four PFAS (perfluorooctanoic acid [PFOA], perfluorooctane sulfonic acid [PFOS], perfluorohexane sulfonic acid [PFHxS], and perfluorononanoic acid [PFNA]). This information can be used to design future prospective epidemiological studies on PFAS exposure and the resultant increased risk of cancer.

2. Methods

2.1. Datasets

The US National Health and Nutrition Examination Survey (NHANES) is a program designed to assess the nutritional status and general health of adult and pediatric Americans. The NHANES is one of the main projects of the National Center for Health Statistics (CDC), a division of the Centers for Disease Control and Prevention. The website of NHANES is https://www.cdc.gov/nchs/nhanes/index.htm.

The NHANES program was extended to be a continuous assessment of many nutritional and health statuses in 1999. Every year, the study looks at about 5000 people, a nationally representative sample. The NHANES interview consists of questions about health, nutrition, socioeconomic status, and demographics. Medical, dental, and physiological measurements are included in the examination component, along with laboratory testing performed by highly qualified medical specialists.

2.2. Exposure and outcome variables

The exposure variables were the serum concentrations of PFOA, PFOS, PFHxS, and PFNA (all in ng/mL). For PFOA and PFOS, the linear and branched isomers were reported separately for the 2013–2014, 2015–2016, and 2017–2018 datasets. Only linear isomers were included in the datasets. Linear isomers of PFASs are usually eliminated more slowly than their corresponding branched isomers [4]. As high retention is an essential aspect of the adverse health effects of PFASs, the authors selectively included linear isomers if the data permitted this segregation.

The National Center for Environmental Health, Division of Laboratory Sciences, Centers for Disease Control and Prevention, Atlanta, GA, receives serum samples once they have been prepared, preserved, and delivered there for analysis. The NHANES Laboratory Procedures Manual contains comprehensive guidelines for gathering and processing specimens (https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/2011-12_laboratory_procedures_manual.pdf).

The outcome variable was the type of cancer that the patient was diagnosed with until the time of the survey (in their entire lifetime until the survey time). The question 'ever told you had cancer or malignancy?' was used to identify participants with no history of cancer diagnosis. This was because the answers to the former questions (the type of cancer the patient had been diagnosed with until the survey time) did not contain accurate information on the participants with no history of cancer (mixed with the 'not available (NA)' response). To exclude possible reverse causation, the authors restricted the time of cancer diagnosis to 10 years from the time of the survey.

2.3. Directed acyclic graph (DAG) and selection of confounders

The authors plotted a DAG to identify potential confounders. Confounders must simultaneously affect both the exposure (serum concentration of the four PFASs) and the outcome (the incidence of each cancer) [5]. We screened as many potential confounders as possible through an extensive literature review. A separate analysis was conducted for two additional potential confounders (educational level and parity).

2.4. Examination of reverse causation

The NHANES is a cross-sectional study. Therefore, the possibility of reverse causation exists [6]. Specifically, an increased serum concentration of PFASs could be the result of a history of cancer. To exclude the possibility of reverse causation, first, the authors examined several previous studies on the absorption and distribution of PFASs (exclusion based on domain knowledge). Second, the time of cancer diagnosis was restricted to 10 years prior to the survey. The questions on cancer history included a history of cancer diagnosed 40 or 50 years before the survey. This can cause reverse causation. The estimated elimination half-lives of PFASs in humans are 2.1–10.1 years for PFOA, 3.3–27 years for PFOS, 4.7–35 years for PFHxS, and 2.5–4.3 years for PFNA (www.atsdr.cdc.gov/toxguides/toxghttps://www.atsdr.cdc.gov/toxguides/toxguide-200.pdf). Based on these half-lives, the authors concluded that restricting the diagnosis time to 10 years before the survey was appropriate.

2.5. Descriptive analysis

For each type of cancer, the characteristics of patients with or without a history of cancer were summarized. For each subgroup, the minimum, first quartile, median, third quartile, maximum, and mean values of the four PFASs and confounders were summarized. The entire distribution of the two categorical confounders (educational level and parity) for patients with and without a history of cancer was provided.

2.6. Main statistical analysis

A logistic regression analysis using whether or not the patients had a history of each cancer as the dependent variable and the natural logarithm of each PFAS serum concentration as the primary independent variable was performed (ln PFOA, ln PFOS, ln PFHxS, and ln PFNA). Selected confounders were adjusted for inclusion as covariates in the logistic regression. The outcomes are reported as odds ratios (ORs) with 95 % confidence intervals (CIs). In the first analysis, the diagnostic time was restricted to 10 years prior to the survey. In the second analysis, two additional confounders (educational level of adults and parity) were adjusted for. Crude analysis results without any restriction on the diagnosis time are also provided in the supplementary materials. To check the linearity assumption of the logistic regression, the authors applied a generalized additive model to plot the association between the exposure variables and logit values.

2.7. Statistical software

R software version 4.2.3 was used for all statistical analyses. For the construction of the analysis dataset, the package 'dplyr' and 'tidyverse' were used. For logistic regression, the function 'glm' in the package 'stats' was used. For drawing a DAG, we used the DAGitty website version 3.1 (http://www.dagitty.net/). For linearity check, the function 'gam' in the 'mgcv' package was applied.

2.8. All corresponding R codes

All R codes will be provided in another methodology article.

3. Results

3.1. DAG and selection of confounders

Fig. 1 shows the DAG for this topic. The exposure and outcomes of interest were PFAS exposure (serum concentration of PFASs) and the incidence of each cancer, respectively. According to the DAG plotted and an extensive literature review, the authors concluded that body mass index (kg/m^2) [7], age in years at the time of screening [8], sex [8], estimated glomerular filtration rate (eGFR) [9], and smoking (serum cotinine) [10], can be possible confounders. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation [11]. The MDRD equation is as follows:

Estimated GFR (mL/min/1.73 m^2) = 175 × (Serum Creatinine [mg/dL])$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Based on a study that indicated that smoking could affect the serum concentration of PFASs [12], the serum cotinine level was included as a confounder. Because serum cotinine could be a better measure of cigarette smoking than self-reporting, based on
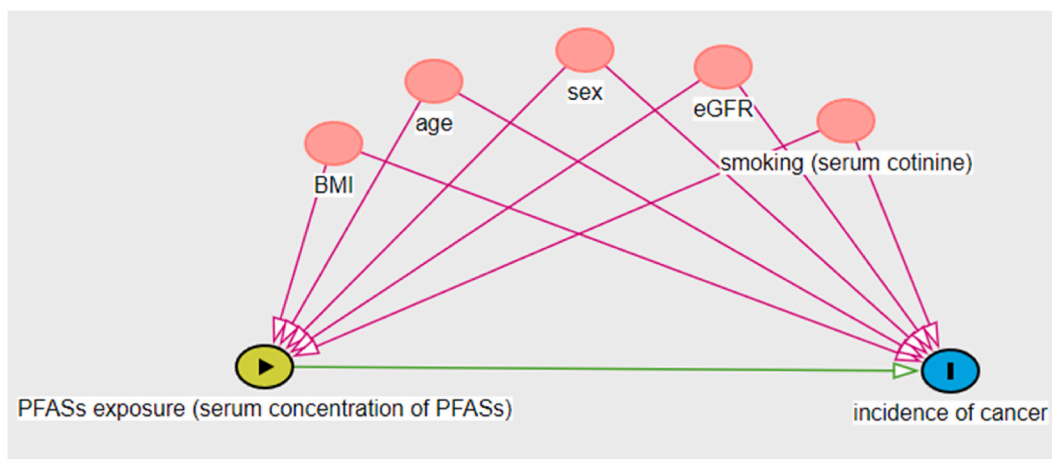

Fig. 1. Directed acyclic graph (DAG) on this topic.

Table 1

Descriptive analyses of the exposure, outcome, and confounder variables when diagnosis time is confined to 10 years before the survey time.

cancer type	cancer	statistical values	age (years)	gender	PFOA (ng/mL)	PFOS (ng/mL)	PFHxS (ng/mL)	PFNA (ng/mL)	eGFR (mL/min/1.73 m²)	cotinine (ng/mL)	BMI (kg/m²)
Brain cancer (NA: 5321)	no: 12913	minimum	20.00	male: 6203	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.42	3.70	0.80	0.50	74.53	0.02	24.20
		median	47.00	female: 6710	2.50	8.20	1.44	0.90	89.08	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.60	32.40
		maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		mean	48.25		3.19	12.96	2.15	1.16	90.96	57.02	29.08
	yes: 2	minimum	68.00	male: 2	4.30	13.80	3.10	1.07	38.19	0.01	28.68
		1st quartile	71.00	female: 0	4.90	14.83	5.55	1.13	43.70	0.01	29.19
		median	74.00		5.50	15.85	8.00	1.19	49.20	0.02	29.71
		3rd quartile	77.00		6.10	16.88	10.45	1.25	54.71	0.02	30.22
		maximum	80.00		6.70	17.90	12.90	1.31	60.21	0.02	30.73
		mean	74.00		5.50	15.85	8.00	1.19	49.20	0.02	29.71
Esophageal cancer (NA: 5319)	no: 12914	minimum	20.00	male: 6204	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.42	3.70	0.80	0.50	74.52	0.02	24.20
		Median	47.00	female: 6710	2.50	8.20	1.44	0.90	89.07	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.60	32.40
		Maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		Mean	48.25		3.19	12.96	2.15	1.16	90.96	57.02	29.08
	yes: 3	minimum	44.00	male: 2	5.40	28.90	0.80	0.90	63.65	0.02	23.98
		1st quartile	52.50	female: 1	5.85	31.05	0.95	1.35	69.21	0.09	26.42
		median	61.00		6.30	33.20	1.10	1.80	74.76	0.16	28.86
		3rd quartile	63.50		7.75	37.95	1.20	3.65	83.21	148.58	31.87
		maximum	66.00		9.20	42.70	1.30	5.50	91.67	297.00	34.87
		mean	57.00		6.97	34.93	1.07	2.73	76.69	99.06	29.24
Lung cancer (NA: 5298)	no: 12911	minimum	20.00	male: 6202	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.42	3.70	0.80	0.50	74.54	0.02	24.20
		Median	47.00	female: 6709	2.50	8.20	1.44	0.90	89.08	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.63	32.40
		Maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		Mean	48.24		3.19	12.96	2.15	1.16	90.96	57.03	29.08
	yes: 27	minimum	31.00	male: 15	0.10	2.10	0.20	0.30	36.25	0.01	15.98
		1st quartile	65.00	female: 12	2.00	8.00	1.20	0.90	60.76	0.02	21.73
		median	69.00		3.60	15.50	2.20	1.10	67.08	0.35	26.93
		3rd quartile	80.00		5.28	22.60	3.00	1.70	74.31	175.00	30.86
		maximum	84.00		7.80	108.00	18.80	6.15	128.57	556.00	49.40
		mean	68.33		3.60	20.02	3.17	1.53	69.58	87.63	27.11
Melanoma (NA: 5283)	no: 12909	minimum	20.00	male: 6202	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.41	3.70	0.80	0.50	74.53	0.02	24.20
		median	47.00	female: 6707	2.50	8.20	1.44	0.90	89.09	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.60	32.40
		maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		mean	48.24		3.19	12.95	2.15	1.16	90.96	57.02	29.08
	yes: 44	minimum	36.00	male: 30	1.00	0.68	0.80	0.06	21.70	0.01	18.60
		1st quartile	62.50	female: 14	2.52	7.08	1.60	0.90	61.76	0.01	24.00
		median	71.00		3.80	14.45	2.30	1.31	73.87	0.03	27.70
		3rd quartile	79.00		5.65	26.63	3.30	1.60	81.86	0.13	32.53
		maximum	82.00		15.40	58.20	11.40	5.50	111.97	455.00	41.30
		mean	69.30		4.43	19.27	3.25	1.49	72.11	50.50	28.68
Prostate cancer (NA: 5189)	no: 12909	minimum	20.00	male: 6199	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.42	3.70	0.80	0.50	74.54	0.02	24.20
		median	47.00	female: 6710	2.50	8.20	1.44	0.90	89.08	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.60	32.40
		maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		mean	48.24		3.19	12.95	2.15	1.16	90.97	57.02	29.08

Table 1 (*continued*)

cancer type	cancer	statistical values	age (years)	gender	PFOA (ng/mL)	PFOS (ng/mL)	PFHxS (ng/mL)	PFNA (ng/mL)	eGFR (mL/min/1.73 m^2)	cotinine (ng/mL)	BMI (kg/m^2)
	yes: 138	minimum	47.00	male: 138	0.40	0.90	0.20	0.10	8.90	0.01	17.70
		1st quartile	66.00		2.05	9.43	1.30	0.75	60.76	0.01	24.52
		median	72.00	female: 0	3.20	17.15	2.07	1.24	72.65	0.04	27.50
		3rd quartile	79.00		4.50	26.50	3.17	1.66	83.50	0.29	31.53
		maximum	85.00		21.60	192.00	10.80	8.10	134.74	664.00	51.10
		mean	71.58		3.81	22.57	2.74	1.46	72.63	31.37	28.51
Non-melanomatous skin cancer (NA: 5185)	no: 12909	minimum	20.00	male: 6201	0.07	0.07	0.07	0.06	2.05	0.01	14.10
		1st quartile	33.00		1.41	3.70	0.80	0.50	74.54	0.02	24.20
		median	47.00	female: 6708	2.50	8.20	1.44	0.90	89.10	0.05	28.00
		3rd quartile	62.00		4.10	16.70	2.51	1.40	105.16	11.70	32.40
		maximum	85.00		104.00	1270.00	81.60	80.77	298.26	1700.00	86.20
		mean	48.24		3.19	12.95	2.15	1.16	90.97	57.04	29.08
	yes: 142	minimum	20.00	male: 80	0.10	0.07	0.20	0.07	25.00	0.01	16.90
		1st quartile	58.00	female: 62	2.10	6.96	1.20	0.70	61.88	0.01	24.24
		median	71.00		3.15	12.20	2.00	0.98	72.45	0.02	27.40
		3rd quartile	79.75		4.68	18.48	3.20	1.44	84.32	0.27	31.27
		maximum	85.00		40.00	161.00	13.60	12.40	145.37	667.00	47.70
		mean	67.01		3.99	17.22	2.67	1.29	73.78	42.48	28.12

PFOA: perfluorooctanoic acid. PFOS: perfluorooctanesulfonic acid. PFHxS: perfluorohexanesulfonic acid. PFNA: perfluorononanoic acid. eGFR: estimated glomerular filtration rate. BMI: body mass index.
NA: not available.

previous studies, the authors selected serum cotinine as a confounding variable [13].

3.2. Possibility of reverse causation

Many previous studies have reported the potential exposure and absorption routes for PFASs [14,15]. These routes include diet, indoor air/dust, tap water, food packaging, inhalation, dermal exposure, carpets, and consumer goods [15]. Additionally, a recent study reported that wastes from electronic products ('e-waste') could be an essential source of PFAS exposure [16]. If patients with cancer who recovered from their disease were intensively exposed to PFASs, which caused increased serum concentrations of PFASs in these patients, the reported exposure routes should be associated with cancer recovery. However, we could not consider the association between these exposure routes and cancer diagnosis/recovery status. One possible hypothesis is that during their medical treatment, the patients with cancer could have been intensively exposed to PFASs during transfusion, routine fluid infusion, injection, or any other medical procedure such as bone marrow biopsy.

To exclude this possibility, the authors restricted the diagnostic time of cancer to 10 years prior to the survey. This is further explained in subsection 3.5.

3.3. Descriptive analysis

Table 1 presents the results of the descriptive analysis. Regarding brain cancer, 12913, two, and 5321 participants reported no history of brain cancer, a history of brain cancer, or an NA response, respectively. The mean ages of the participants with no history and those with a history of brain cancer were 48.25 and 74.00, respectively. Among the participants with no history of brain cancer, 6203 and 6710 were men and women, respectively. Among participants with a history of brain cancer, two were men, and none were women. The median and mean values of PFOA for participants with no history and those with a history of brain cancer were 2.50 and 3.19 and 5.50 and 5.50, respectively. The median and mean values of PFOS for participants with no history and those with a history of brain cancer were 8.20 and 12.96 and 15.85 and 15.85, respectively. The median and mean values of the PFHxS for the participants with no history and those with a history of brain cancer were 1.44 and 2.15 and 8.00 and 8.00, respectively. The median and mean values of PFNA for participants with no history and those with a history of brain cancer were 0.90/1.16 and 1.19/1.19, respectively.

For esophageal cancer, 12914, three, and 5319 participants reported no history of esophageal cancer, a history of esophageal cancer, or an NA response, respectively. The mean ages of the participants with no history and those with a history of esophageal cancer were 48.25 and 57.00, respectively. Among the participants with no history of esophageal cancer, 6204 and 6710 were men and women, respectively. Among the participants with a history of esophageal cancer, two and one were men and women, respectively. The median and mean values of PFOA for participants with no history and those with a history of esophageal cancer were 2.50 and 3.19 and 6.30 and 6.97, respectively. The median and mean values of PFOS for participants with no history and those with a history of esophageal cancer were 8.20 and 12.96 and 33.20 and 34.93, respectively. The median and mean values of PFHxS for participants with no history and those with a history of esophageal cancer were 1.44 and 2.15 and 1.10 and 1.07, respectively. The median and mean

values of PFNA for the participants with no history and those with a history of esophageal cancer were 0.90/1.16 and 1.80/2.73, respectively.

For lung cancer, 12911, 27, and 5298 participants reported no history of lung cancer, a history of lung cancer, or an NA response, respectively. The mean ages of the participants with no history or a history of lung cancer were 48.24 and 68.33, respectively. Among the participants with no history of lung cancer, 6202 and 6709 were men and women, respectively. Among the participants with a history of lung cancer, 15 and 12 were men and women, respectively. The median and mean values of PFOA for participants with no history and those with a history of lung cancer were 2.50 and 3.19 and 3.60 and 3.60, respectively. The median and mean values of PFOS for participants with no history and those with a history of lung cancer were 8.20 and 12.96 and 15.50 and 20.02, respectively. The median and mean values of PFHxS for participants with no history and those with a history of lung cancer were 1.44 and 2.15 and 2.20 and 3.17, respectively. The median and mean values of PFNA for participants with no history and those with a history of lung cancer were 0.90 and 1.16 and 1.10 and 1.53, respectively.

For melanoma, 12909, 44, and 5283 participants reported no history of melanoma, a history of melanoma, or an NA response, respectively. The mean ages of the participants with no history and those with a history of melanoma were 48.24 and 69.30, respectively. Among the participants with no history of melanoma, 6202 and 6707 were men and women, respectively. Among the participants with a history of melanoma, 30 and 14 were men and women, respectively. The median and mean values of PFOA for participants with no history and those with a history of melanoma were 2.50 and 3.19 and 3.80 and 4.43, respectively. The median and mean values of PFOS for participants with no history and those with a history of melanoma were 8.20 and 12.95 and 14.45 and 19.27, respectively. The median and mean values of PFHxS for participants with no history and those with a history of melanoma were 1.44 and 2.15 and 2.30 and 3.25, respectively. The median and mean values of PFNA for participants with no history and those with a history of melanoma were 0.90 and 1.16 and 1.31 and 1.49, respectively.

For prostate cancer, 12909, 138, and 5189 participants reported no history of prostate cancer, a history of prostate cancer, or an NA response, respectively. The mean ages of the participants with no history and those with a history of prostate cancer were 48.24 and 71.58, respectively. Among the participants with no history of prostate cancer, 6199 and 6710 were men and women, respectively. Among the participants with a history of prostate cancer, 138 were men and none were women. The median and mean values of PFOA for participants with no history and those with a history of prostate cancer were 2.50 and 3.19 and 3.20 and 3.81, respectively. The median and mean values of PFOS for participants with no history and those with a history of prostate cancer were 8.20 and 12.95 and 17.15 and 22.57, respectively. The median and mean values of PFHxS for participants with no history and those with a history of prostate cancer were 1.44 and 2.15 and 2.07 and 2.74, respectively. The median and mean values of PFNA for participants with no

Table 2

Adjusted odds ratios calculated from multivariate logistic regression when diagnosis time restricted to 10 years before the survey time.

Adjusted OR (95 % CI)	PFOA	PFOS	PFHxS	PFNA
Bladder cancer	0.96 (0.60–1.62)	1.00 (0.69–1.50)	1.05 (0.66–1.70)	0.87 (0.53–1.45)
Blood cancer	9.19 (0.73–189.07)	3.9 (0.65–22.26)	3.67 (0.42–34.15)	4.17 (0.43–47.86)
Bone cancer	1.22 (0.26–6.10)	0.68 (0.20–2.14)	1.56 (0.36–7.02)	0.73 (0.11–3.83)
Brain cancer*	4.09 (0.69–35.39)	1.72 (0.49–7.84)	**8.16 (2.98–68.89)***	1.69 (0.32–10.37)
Breast cancer	1.15 (0.87–1.54)	1.03 (0.84–1.28)	0.85 (0.66–1.09)	1.09 (0.83–1.45)
Cervix cancer	1.32 (0.80–1.83)	1.20 (0.87–1.67)	1.26 (0.88–1.80)	1.24 (0.82–1.88)
Colon cancer	0.89 (0.64–1.28)	1.03 (0.79–1.37)	0.80 (0.59–1.10)	1.11 (0.79–1.58)
Esophageal cancer*	**5.10 (1.18–17.34)***	**3.97 (1.24–11.42)***	0.63 (0.23–2.07)	3.43 (0.88–10.33)
Gallbladder cancer	Cannot be calculated			
Kidney cancer	0.94 (0.56–1.67)	0.86 (0.58–1.32)	0.91 (0.54–1.59)	0.66 (0.38–1.20)
Larynx cancer	1.43 (0.32–9.63)	1.25 (0.40–4.90)	0.92 (0.25–4.75)	1.19 (0.24–6.80)
Leukemia	2.03 (0.69–5.57)	1.16 (0.54–2.68)	1.02 (0.43–2.53)	0.67 (0.28–1.81)
Liver cancer	1.20 (0.47–3.74)	0.84 (0.45–1.91)	2.03 (0.75–5.57)	0.81 (0.31–2.34)
Lung cancer	1.02 (0.64–1.70)	1.33 (0.90–2.03)	1.13 (0.72–1.81)	1.54 (0.93–2.54)
Lymphoma/Hodgkin's disease	1.13 (0.57–2.37)	1.44 (0.82–2.55)	0.76 (0.43–1.41)	1.36 (0.68–2.73)
Melanoma*	**1.65 (1.07–2.58)***	1.12 (0.83–1.54)	**1.55 (1.07–2.25)***	1.37 (0.92–2.04)
Mouth/tongue/lip cancer	1.51 (0.45–6.94)	1.48 (0.54–4.67)	0.68 (0.25–2.32)	1.5 (0.38–6.18)
Nervous system	1.34 (0.18–23.41)	1.89 (0.31–30.42)	3.34 (0.38–33.57)	0.51 (0.07–6.48)
Ovarian cancer	0.70 (0.41–1.25)	0.82 (0.53–1.31)	0.64 (0.37–1.13)	0.67 (0.37–1.28)
Pancreatic cancer	0.57 (0.23–1.87)	0.61 (0.29–1.50)	0.97 (0.34–3.06)	0.57 (0.20–1.84)
Prostate cancer*	1.10 (0.86–1.42)	**1.21 (1.00–1.48)***	1.08 (0.86–1.36)	**1.27 (1.00–1.62)***
Rectal cancer	0.36 (0.11–1.67)	0.51 (0.19–1.73)	0.37 (0.10–1.62)	0.38 (0.09–1.82)
<u>**Non-melanomatous skin cancer**</u>	<u>**1.24 (0.99–1.56)**</u>	1.08 (0.92–1.28)	1.14 (0.94–1.40)	1.06 (0.85–1.31)
Skin cancer, unknown histologic type	1.18 (0.87–1.63)	0.97 (0.78–1.23)	0.85 (0.65–1.12)	0.90 (0.67–1.22)
Soft tissue (muscle or fat) cancer	Cannot be calculated			
Stomach cancer	0.72 (0.25–2.78)	0.57 (0.26–1.41)	0.75 (0.26–2.63)	0.86 (0.25–3.49)
Testis cancer	2.13 (0.66–7.30)	2.27 (0.92–4.92)	0.76 (0.32–2.04)	1.53 (0.49–5.15)
Thyroid cancer	1.14 (0.63–2.15)	1.18 (0.75–1.91)	0.85 (0.51–1.46)	1.31 (0.73–2.36)
Uterus cancer	1.19 (0.68–2.12)	1.09 (0.72–1.69)	0.83 (0.52–1.35)	1.33 (0.78–2.26)

Adjusted OR (95 % CI): odds ratio with a 95 % confidence interval, calculated by the logistic regression PFOA: perfluorooctanoic acid. PFOS: perfluorooctanesulfonic acid. PFHxS: perfluorohexanesulfonic acid. PFNA: perfluorononanoic acid.

* and bold: statistically significant with an increased odds ratio.

Underline and bold: statistically insignificant with a lower bound of confidence interval over 0.95.

history and those with a history of prostate cancer were 0.90 and 1.16 and 1.24 and 1.46, respectively.

For non-melanomatous skin cancer, 12909, 142, and 5185 participants reported no history of non-melanomatous skin cancer, a history of non-melanomatous skin cancer, or an NA response, respectively. The mean ages of participants with no history and those with a history of non-melanomatous skin cancer were 48.24 and 67.01, respectively. Among participants with no history of non-melanomatous skin cancer, 6201 and 6708 were men and women, respectively. Among the participants with a history of non-melanomatous skin cancer, 80 and 62 were men and women, respectively. The median and mean values of PFOA for participants with no history and those with a history of non-melanomatous skin cancer were 2.50 and 3.19 and 3.15 and 3.99, respectively. The median and mean values of PFOS for participants with no history and those with a history of non-melanomatous skin cancer were 8.20 and 12.95 and 12.20 and 17.22, respectively. The median and mean values of PFHxS for participants with no history and those with a history of non-melanomatous skin cancer were 1.44 and 2.15 and 2.00 and 2.67, respectively. The median and mean values of PFNA for participants with no history and those with a history of non-melanomatous skin cancer were 0.90/1.16 and 0.98/1.29, respectively.

Supplementary Material A provides the results of the descriptive analyses for two additional confounding variables (educational level and parity) when the diagnosis time was confined to 10 years before the survey. Supplementary Material B provides the results of the descriptive analyses with no restrictions on diagnosis time.

3.4. Check for linearity assumption of logistic regression

Supplementary Material C provides generalized additive model plots for the association between the serum concentrations of the four PFASs and the corresponding logit values to check the linearity assumption of logistic regression. The plots for only six cancers (brain, esophageal, lung, melanomatous skin, prostate, and non-melanomatous skin cancers) with a statistically significant OR (provided in subsection 3.5) are provided.

3.5. Multivariate logistic regression

Table 2 provides the OR of each cancer calculated from the multivariate logistic regression when the time of diagnosis was confined to 10 years prior to the survey. For brain cancer, the OR for each one-unit increase in the natural logarithm of serum PFHxS was 8.16 (95 % CI 2.98–68.89). For esophageal cancer, the odd ratio for each one unit increase of natural logarithm of serum PFOA and PFOS

Table 3
Adjusted odds ratios calculated from multivariate logistic regression when diagnosis time restricted to 10 years before the survey time, with education level and parity adjusted.

Adjusted OR (95 % CI)	PFOA	PFOS	PFHxS	PFNA
Bladder cancer	1.25 (0.47–4.20)	1.18 (0.56–2.88)	0.97 (0.38–2.70)	0.85 (0.33–2.31)
Blood cancer	Cannot be calculated			
Bone cancer	Cannot be calculated			
Brain cancer	Cannot be calculated			
Breast cancer	0.95 (0.71–1.30)	0.97 (0.77–1.23)	0.81 (0.61–1.07)	0.95 (0.70–1.30)
Cervix cancer	1.27 (0.83–2.00)	1.28 (0.91–1.82)	1.33 (0.91–1.95)	1.26 (0.82–1.95)
Colon cancer	0.90 (0.58–1.46)	1.07 (0.75–1.60)	0.88 (0.57–1.37)	1.26 (0.77–2.10)
Esophageal cancer	Cannot be calculated			
Gallbladder cancer	Cannot be calculated			
Kidney cancer	1.79 (0.65–6.06)	1.25 (0.61–2.93)	1.66 (0.63–4.65)	1.35 (0.50–3.78)
Larynx cancer	Cannot be calculated			
Leukemia	1.45 (0.26–10.83)	0.69 (0.20–2.96)	0.61 (0.13–3.27)	0.59 (0.13–3.70)
Liver cancer	Cannot be calculated			
Lung cancer*	1.23 (0.51–3.04)	**2.62 (1.24–5.83)***	0.97 (0.45–2.12)	**2.38 (1.00–5.52)***
Lymphoma/Hodgkin's disease	2.09 (0.54–7.08)	2.24 (0.72–7.83)	1.93 (0.61–5.79)	1.54 (0.42–5.68)
<u>Melanoma</u>	**<u>2.23 (0.97–5.63)</u>**	0.92 (0.54–1.67)	1.64 (0.83–3.34)	1.29 (0.63–2.85)
Mouth/tongue/lip cancer	Cannot be calculated			
Nervous system cancer	Cannot be calculated			
Ovarian cancer	0.67 (0.36–1.36)	0.78 (0.46–1.38)	0.73 (0.38–1.47)	0.63 (0.31–1.35)
Pancreatic cancer	Cannot be calculated			
Prostate cancer	Cannot be calculated			
Rectal cancer	Cannot be calculated			
Non-melanomatous skin cancer	1.18 (0.83–1.71)	0.99 (0.76–1.3)	1.1 (0.80–1.51)	1.11 (0.78–1.60)
Skin cancer, unknown histologic type	1.17 (0.69–2.04)	0.93 (0.64–1.39)	0.86 (0.55–1.38)	0.83 (0.51–1.39)
Soft tissue (muscle or fat) cancer	Cannot be calculated			
Gastric cancer	16.2 (0.72–8521.52)	2.34 (0.26–36.82)	6.53 (0.38–290.00)	6.79 (0.49–292.14)
Testis cancer	Cannot be calculated			
Thyroid cancer	1.42 (0.62–3.29)	1.30 (0.69–2.56)	1.01 (0.49–2.09)	1.15 (0.52–2.62)
Uterus cancer	1.08 (0.58–2.09)	0.91 (0.57–1.48)	0.72 (0.42–1.24)	1.08 (0.59–2.00)

Adjusted OR (95 % CI): odds ratio with a 95 % confidence interval, calculated by the logistic regression.
PFOA: perfluorooctanoic acid. PFOS: perfluorooctanesulfonic acid. PFHxS: perfluorohexanesulfonic acid. PFNA: perfluorononanoic acid.
* and bold: statistically significant with an increased odds ratio.
Underline and bold: statistically insignificant with a lower bound of confidence interval over 0.95.

were 5.10 (95 % CI 1.18–17.34) and 3.97 (95 % CI 1.24–11.42), respectively. For melanoma, the OR for each one-unit increase of natural logarithm of serum PFOA and PFHxS were 1.65 (95 % CI 1.07–2.58) and 1.55 (95 % CI 1.07–2.25), respectively. For prostate cancer, the OR for each one-unit increase of natural logarithm of serum PFOS and PFNA were 1.21 (95 % CI 1.00–1.48) and 1.27 (95 % CI 1.00–1.62), respectively. For non-melanomatous skin cancer, the OR for each one-unit increase of natural logarithm of serum PFOS was 1.24 (95 % CI 0.99–1.56).

Table 3 provides the OR of each cancer calculated from multivariate logistic regression when the time of diagnosis was confined to 10 years prior to the survey, with educational level and parity adjusted. For lung cancer, the OR for each one-unit increase of natural logarithm of serum PFOS and PFNA were 2.62 (95 % CI 1.24–5.83) and 2.38 (95 % CI 1.00–5.52), respectively. For melanoma, the odd ratio for each one-unit increase in the natural logarithm of serum PFOA was 2.23 (95 % CI 0.97–5.63).

Supplementary Material D provides the ORs calculated from the multivariable logistic regression with no restriction on diagnosis time and no adjustment for educational level and parity. By comparing Table 2 and Supplementary Material D, it can be concluded that several cancers with a decreased OR with statistical significance without restriction of diagnosis time were neutralized to an equivocal OR with statistical insignificance after restricting the time of diagnosis to 10 years prior to the survey (rectal cancer for PFOA and stomach cancer for PFHxS). The stomach and rectum are the first and final parts of the gastrointestinal tract, respectively, which can affect the absorption of PFASs through the gastrointestinal lumen [4]. These results reflect that after cancer surgery, the absorption of PFASs through the stomach or rectum is reduced. Therefore, possible reverse causation was corrected by restricting the time of diagnosis. Esophageal cancer also showed similar results: equivocal ORs with statistical insignificance before restricting the time of diagnosis; however, increased ORs with statistical significance after restricting the time of diagnosis. Although the esophagus is not a major organ for absorption, a similar phenomenon is expected to occur in esophageal cancers. Similar results were obtained for prostate cancer. However, because prostate cancer is not a part of the gastrointestinal tract, a slightly different pathophysiological background is required to explain these results, which necessitates further research.

4. Discussion

In this study, the OR of brain cancer for one unit increase in ln (PFHxS) was 8.16 (95 % CI 2.98–68.89). The OR of esophageal cancer for one unit increase of ln (PFOA) and ln (PFOS) were 5.10 (95 % CI 1.18–17.34) and 3.97 (95 % CI 1.24–11.42), respectively. The OR of melanoma for one unit increase of ln (PFOA) and ln (PFHxS) were 1.65 (95 % CI 1.07–2.58) and 1.55 (95 % CI 1.07–2.25), respectively. The OR of prostate cancer for one unit increase of ln (PFOS) and ln (PFNA) were 1.21 (95 % CI 1.00–1.48) and 1.27 (95 % CI 1.00–1.62), respectively. The OR of lung cancer for one unit increase of ln (PFOS) and ln (PFNA) were 2.62 (95 % CI 1.24–5.83) and 2.38 (95 % CI 1.00–5.52), respectively.

4.1. Prior research on the relationship between PFASs and each type of cancer

Supplementary Material E summarizes previous studies stratified by cancer type. Vieira et al. found that, when compared to the unexposed subpopulation, the adjusted odds relative to brain cancer for the subpopulations with low (3.7–12.8 ng/mL), medium (12.9–30.7 ng/mL), and high (30.8–109 ng/mL) serum PFOA concentrations were, respectively, 1.5 (95 % CI 0.8–2.7), 1.8 (95 % CI 1.1–3.2), and 0.6 (95 % CI 0.2–1.6) [17]. Although the present study reported a statistically significant OR for PFHxS, the OR for PFOA showed an increased point estimate. If the sample size increases in future studies, this study will also show a statistically significant increase in risk estimates. Elevated glioma grades were linked to increased serum concentrations of perfluorooctane sulfonamide (PFOSA), PFOA, and PFOS, according to Xie et al. The pathogenic molecular markers of gliomas, Ki-67 and P53, have been found to positively correlate with serum PFOA concentrations [18]. This can be a biological background for carcinogenicity.

For the relationship between PFAS exposure and esophageal cancer, Messmer et al. reported a relative risk (RR) of 1.71 (95 % CI 1.10–2.65) for residents in Merrimack, New Hampshire, in an ecological study. Around this town, at least 65 square miles of drinking water were contaminated by PFAS emissions from a plastic coating industrial source. This study also showed a statistically significant increase in RR. The relatively low magnitude of the point estimate might have been caused by the design of that ecological study [19].

Lundin et al. reported a standardized mortality ratio (SMR) of 1.2 (95 % CI 0.5–2.3), 1.0 (95 % CI 0.7–1.4), and 0.8 (95 % CI 0.5–1.1) for the ever definite, ever probable, and never exposure group to PFOA, respectively, regarding the association between PFAS exposure and lung cancer [20]. Although these SMRs were not statistically significant, the tendency of increasing point estimates agrees with this study's results. If the sample size of this study were increased, the results might show statistically significant confidence intervals. The present study showed statistically significant OR for the PFOS and PFNA levels. However, in this study, only the SMR associated with PFOA was calculated. Examining the relationship between PFOS/PFNA and lung cancer will require more research.

When comparing cohort members who have ever worked in high-exposure jobs to PFOS to those who have only worked in PFOS-non-exposed jobs, Alexander et al. reported SMRs of 2.62 (95 % CI 0.32–9.46) and 1.38 (95 % CI 0.03–7.67) for melanoma, respectively, in relation to the general population [21]. Although this study showed a statistically significant increased OR for PFOA and PFHxS, future studies should show a statistically significant association with PFOS with increased sample sizes. Steenland et al. reported that the RR of melanoma for serum PFOA quartile 2, 3, and 4 subgroups compared to quartile one subgroup was 0.85 (95 % CI 0.27–2.71), 1.10 (95 % CI 0.34–3.58), and 0.75 (95 % CI 0.21–2.67), respectively, when a latency of ten years was used [22]. The equivocal RRs without statistical significance can be explained by the possible effects of having healthy workers in this study. Another possible explanation could be the insufficient sample size.

Concerning the link between exposure to PFAS and prostate cancer, Messmer et al. reported an RR of 1.36 (95 % CI 1.19–2.39) for

residents in Merrimack [19]. The calculated RR was slightly higher in that study than in the present study. This discrepancy may be due to the ecological study design of this study. For prostate cancer, Lundin et al. reported an SMR of 2.1 (95 % CI 0.4–6.1), 0.9 (95 % CI 0.4–1.8), and 0.4 (95 % CI 0.1–0.9) for the ever definite, ever probable, and never exposure group to PFOA, respectively [20]. Although these SMRs were not statistically significant, the tendency of increasing point estimates agrees with this study's results. If the sample size of this study were increased, the results might show statistically significant confidence intervals. The present study showed statistically significant ORs for PFOS and PFNA. However, in this study, only the SMR associated with PFOA was calculated. It will take more research to determine whether PFOS/PFNA and prostate cancer are related.

4.2. Meaning of this study

Prior studies on the relationship between PFAS exposure and cancer has concentrated on a number of cancer types, such as colorectal, lung, lymphohematopoietic, bladder, kidney, prostate, colorectal, liver, and biliary cancer [23]. However, this study revealed that PFAS exposure could possibly increase the risk of several cancers that are not commonly thought to be caused by PFAS exposure. Brain, esophageal, and melanomatous skin cancers are not generally associated with PFAS exposure. Researchers looking into the connection between PFAS exposure and cancer may choose to expand their coverage of probable cancers or retarget the cancers of interest as outcomes in light of these findings.

4.3. Limitations

This study has several potential biases. The first possibility is information bias. This study used the US NHANES datasets, which are composed of demographic data, questionnaires, examination, and laboratory data. Among these, questionnaire data could be prone to information bias if a group of participants responded with bias. If communication between the interviewing physicians and interviewed participants was unclear, several answers could be biased. For example, the distinction between benign tumors and cancer could be unclear in their conversations (breast fibroadenoma vs. breast cancer, benign thyroid nodule vs. thyroid cancer, and ovarian cyst vs. ovarian cancer). Second, there is the possibility of reverse causation. Although the authors tried to exclude reverse causation in subsection 3.2, a possible remaining causation could exist. Third, there is the possibility of confounding factors. Although the authors plotted the DAG for the potential variables, a missed confounder could exist. However, the authors did not adjust for many confounders due to the risk of collider adjustment or M-bias [24]. Fourth, a cross-sectional study, the US NHANES, was conducted. Future long-term research, such as a cohort study, is necessary to draw a reliable causal inference. Fifth, there was a possibility of selection bias. If a specific type of cancer induced by PFAS exposure progresses rapidly, this subgroup may not have been included in this analysis.

5. Conclusion

Using the US NHANES datasets, this study examined the association between exposure to four PFAS (PFOA, PFOS, PFHxS, and PFNA) and each kind of cancer. To overcome the limitations of this cross-sectional study, the authors excluded reverse causation and adjusted for potential confounders. This study found that exposure to PFHxS, PFOA/PFOS, PFOA/PFHxS, PFOS/PFNA, and PFOS/PFNA was linked to cancers of the brain, esophagus, melanomatous skin, prostate, and lung, respectively. Considering that brain, esophageal, and melanomatous skin cancers have not been targets of epidemiologic studies regarding PFAS exposure, future studies could target these cancers as outcomes of interest.

Ethics statements

This study solely used an open, anonymized data source that was available to the public, so it did not require review or permission from an ethical committee: the US National Health and Nutrition Examination Survey (NHANES), https://www.cdc.gov/nchs/nhanes/index.htm.
Every patient or participant (or their legal guardians or proxies) gave their informed consent before beginning the study.
All patients and/or participants (or their legal guardians/proxies) gave their informed consent for the release of their de-identified clinical data.

Consent for publication

Not applicable.

Data availability statement

Data associated with this study has been deposited into a publicly available repository: the US National Health and Nutrition Examination Survey (NHANES), https://www.cdc.gov/nchs/nhanes/index.htm.

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CRediT authorship contribution statement

Jinyoung Moon: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yong-seok Mun:** Writing – review & editing, Project administration.

Declaration of competing interest

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

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Appendix A. Supplementary materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24337.

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