HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2024 August 15.

Published in final edited form as:

Int J Cancer. 2023 August 15; 153(4): 775–782. doi:10.1002/ijc.34487.

Serum perfluorooctane sulfonate and perfluorooctanoate and risk of postmenopausal breast cancer according to hormone receptor status: An analysis in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Vicky C. Chang[1,*], **Jongeun Rhee**[1,*], **Sonja I. Berndt**[1], **Steven C. Moore**[2], **Neal D. Freedman**[2], **Rena R. Jones**[1], **Debra T. Silverman**[1], **Gretchen L. Gierach**[3], **Jonathan N. Hofmann**[1,†], **Mark P. Purdue**[1,†]

[1]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

[2]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

[3]Integrative Tumor Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

Abstract

Per- and polyfluoroalkyl substances (PFAS) are highly persistent endocrine-disrupting chemicals that may contribute to breast cancer development; however, epidemiologic evidence is limited. We investigated associations between prediagnostic serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and postmenopausal breast cancer risk, overall and by hormone receptor status, in a nested case-control study of 621 cases and 621 matched controls in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. PFOS and PFOA levels were determined based on serum metabolomic profiling performed using ultra-performance liquid chromatography-tandem mass spectrometry. We used multivariable conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each PFAS and breast cancer risk, overall, by estrogen receptor (ER) or progesterone receptor (PR) status, and by joint ER/PR status. We found little evidence of association between PFOS

Correspondence: Vicky C. Chang, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. chidan.chang@nih.gov.

*Co-first authors.

†Co-senior authors.

AUTHOR CONTRIBUTIONS

Conceptualization: Vicky C. Chang, Jongeun Rhee, Debra T. Silverman, Gretchen L. Gierach, Jonathan N. Hofmann, Mark P. Purdue; *Methodology*: Vicky C. Chang, Jongeun Rhee, Steven C. Moore, Debra T. Silverman, Gretchen L. Gierach, Jonathan N. Hofmann, Mark P. Purdue; *Formal analysis*: Vicky C. Chang, Jongeun Rhee, Jonathan N. Hofmann, Mark P. Purdue; *Writing – original draft*: Vicky C. Chang, Jongeun Rhee, Jonathan N. Hofmann, Mark P. Purdue; *Writing – review & editing:* Vicky C. Chang, Jongeun Rhee, Sonja I. Berndt, Steven C. Moore, Neal D. Freedman, Rena R. Jones, Debra T. Silverman, Gretchen L. Gierach, Jonathan N. Hofmann, Mark P. Purdue. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

ETHICS STATEMENT

The PLCO Cancer Screening Trial was approved by institutional review boards at the National Cancer Institute and each of the 10 participating study centers. All participants provided written informed consent.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

or PFOA and breast cancer risk overall. However, in subtype-specific analyses, we observed statistically significant increased risks of ER+, PR+, and ER+/PR+ tumors for the third vs. lowest quartile of serum PFOS (ORs [95% CIs]=1.59 [1.01–2.50], 2.34 [1.29–4.23], and 2.19 [1.21–3.98], respectively) and elevated but non-statistically significant ORs for the fourth quartile. Conversely, for PFOA, modest positive associations with ER−, PR−, ER+/PR−, and ER−/PR− tumors were generally seen in the upper quartiles. Our findings contribute evidence supporting positive associations between serum PFOS and hormone receptor-positive tumors, and possibly between PFOA and receptor-negative tumors. Future prospective studies incorporating tumor hormone receptor status are needed to better understand the role of PFAS in breast cancer etiology.

Keywords

breast cancer; hormone receptor status; per- and polyfluoroalkyl substances (PFAS); perfluorooctane sulfonate (PFOS); perfluorooctanoate (PFOA)

1 INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a group of highly persistent synthetic chemicals manufactured since the 1940s and used in a wide range of industrial applications and consumer products.[1] Nearly the entire U.S. population has detectable levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA)—two of the most common PFAS—in their blood.[2] In 2014, the International Agency for Research on Cancer (IARC) classified PFOA—the only PFAS evaluated by IARC to date—as “possibly carcinogenic to humans” (Group 2B), based in part on limited epidemiologic evidence of associations with kidney and testicular cancers.[3,4] As endocrine-disrupting chemicals with potential estrogenic properties, some PFAS, including PFOS and PFOA, have also been suggested to play a role in the development of breast cancer,[5] although the epidemiologic evidence is relatively inconsistent and inconclusive.[6] Recently, based on a growing body of literature since the IARC evaluation, a 2022 report by the U.S. National Academies of Sciences, Engineering, and Medicine stated that there is “limited or suggestive” evidence of an association between PFAS exposure and breast cancer risk.[7] It should however be noted that most studies evaluating these associations to date relied on model-estimated exposure levels or PFAS measurements in blood collected after breast cancer diagnosis.[6]

In a recent nested case-control study with 194 case-control pairs of postmenopausal breast cancer in the French E3N cohort, Mancini *et al.* reported novel findings suggesting that the relationship between PFAS exposures and breast cancer may differ by tumor hormone receptor status.[8] Specifically, they observed positive associations between prediagnostic serum PFOS concentrations and both estrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumors, as well as increased risks of receptor-negative tumors associated with medium-to-low levels of PFOS and PFOA; however, the study did not evaluate associations by joint hormone receptor status, possibly due to sample size limitations.

We investigated associations between postmenopausal circulating levels of PFOS and PFOA and risk of developing breast cancer subtypes defined by tumor ER and PR status by

leveraging data from our recent serum metabolomic profiling study of 621 postmenopausal breast cancer cases and 621 matched controls within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

2 MATERIALS AND METHODS

2.1 Study design and population

The PLCO Cancer Screening Trial is a multicenter randomized trial that enrolled ~155,000 men and women 55–74 years of age across 10 study centers in the U.S. between 1993 and 2001; participants were assigned to either a screening or control arm and followed over time for cancer outcomes (<4% loss to follow-up), with blood samples collected from most (>90%) screening arm participants.[9] Details of the design and population characteristics of our nested case-control study have been reported previously.[10,11] Briefly, this study included all incident primary invasive breast cancer cases diagnosed among women in the PLCO screening arm during follow-up through November 2013 who were postmenopausal at baseline and not using menopausal hormone therapy (MHT) at baseline. Eligible cases must have also provided prediagnostic serum samples one year after baseline (i.e., all postmenopausal at blood draw). To increase the number of hormone receptor-negative cases for subtype-specific analyses, all eligible cases with ER− and/or PR− breast tumors using MHT at baseline were also included. Using incidence density sampling, controls were selected from among women who were postmenopausal at baseline, alive and cancer-free (excluding non-melanoma skin cancer) at the time of case diagnosis, and were individually matched to cases by age at baseline (±2 years), date of blood draw (±3 months), and MHT use at baseline.

Incident cancer cases were ascertained through annual questionnaires, the National Death Index, physician reports, and next-of-kin reports, with further confirmation by review of hospital records at the screening centers. Information on demographics, lifestyle, and reproductive history of all cases and controls was obtained from the baseline PLCO questionnaire, and tumor hormone receptor status of cases was ascertained based on immunohistochemistry results from hospital records.

2.2 Serum PFOS and PFOA measurements

We used a non-targeted high-resolution mass spectrometry platform at Metabolon Inc. (Durham, NC) to measure concentrations of numerous molecular compounds in prediagnostic sera, as described previously.[10–12] Briefly, serum samples were extracted with methanol to precipitate proteins and analyzed using ultra-performance liquid chromatography-tandem mass spectrometry.[12] Of the 672 compounds identified from the analysis, PFOS and PFOA were the only two identifiable PFAS measured at detectable levels using this untargeted metabolomics approach. Based on data from another ongoing study (n=335 cancer-free PLCO participants), measurements of serum PFOS and PFOA from Metabolon were strongly correlated with standard, targeted measurements of these chemicals in the same subjects by the Centers for Disease Control and Prevention (CDC) laboratory using on-line solid phase extraction liquid chromatography-isotope dilution-

tandem mass spectrometry[13] (Spearman correlation coefficient=0.76 and 0.77 for PFOS and PFOA, respectively; unpublished data).

2.3 Statistical analysis

We fit conditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) relating serum PFOS or PFOA levels and breast cancer risk. ORs were estimated for breast cancer overall, by individual hormone receptor (ER and PR) status, and by joint ER/PR status. Due to small numbers, ER−/PR+ cases (n=6) and their corresponding matched controls were excluded from the joint ER/PR analyses. Levels of each PFAS, which were quantified as mass spectral peak intensities, were classified into quartiles based on the distribution among controls. In addition to conditioning on the matching factors, models were adjusted for age at blood draw, established breast cancer risk factors (age at menarche, age at first live birth and number of live births, age at menopause, duration of MHT use, first-degree family history of female breast cancer, personal history of benign breast disease, body mass index, smoking status, and vigorous physical activity), and variables whose removal resulted in a ≥10% change in the ORs (study center, race/ethnicity, and education). Models were additionally adjusted for natural log-transformed levels of PFOA (for PFOS models) or PFOS (for PFOA models); adjustment for PFOA or PFOS quartiles instead of continuous log-transformed levels yielded no meaningful changes in the results. Missing data on covariates (<2% for all variables except physical activity [8%]; Table S1) were replaced by the most frequent category among controls; for physical activity, a missing category was created. Tests for linear trend across quartiles were performed by modeling quartile-specific median PFOS or PFOA levels among controls as a continuous variable. Heterogeneity of associations across breast tumor subtypes was assessed using the Wald test for a cross-product term between hormone receptor status (ER, PR, or ER/PR status for each matched case-control pair) and serum PFOS or PFOA levels (continuous variable based on quartile-specific medians).

To explore the potential impact of duration of follow-up on our results, we conducted analyses stratified by number of years from blood draw to breast cancer diagnosis, based roughly on the median as a cutoff point (<6 and ≥6 years). Since menstruation is a route of PFAS elimination and PFAS levels are known to increase following menopause,[14,15] we also conducted analyses stratified by time since menopause (≤15 and >15 years), calculated by subtracting age at menopause (estimated using category medians) from age at blood draw. Additional sensitivity analyses were performed by excluding women who became postmenopausal ≤5 years before blood draw (10% of cases and 7% of controls).

All tests were two-sided, and statistical significance was evaluated at $P<.05$. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3 RESULTS

In this nested case-control study of 621 postmenopausal breast cancer cases and 621 controls, tumor ER, PR, and joint ER/PR status was available for 94%, 87%, and 86% of cases, respectively (participant characteristics presented in Table S1). Participants were on average 64 years of age at blood draw, and the median time from blood draw to

case diagnosis was 5.6 years. Serum PFOS and PFOA levels were moderately correlated (Spearman correlation coefficient=0.60 among controls).

We observed little evidence of association between serum PFOS or PFOA levels and postmenopausal breast cancer risk overall (Table 1). However, when we evaluated PFOS associations by hormone receptor status, we observed statistically significant elevated risks of ER+, PR+, and ER+/PR+ tumors in relation to the third vs. lowest quartile (ORs [95% CIs]=1.59 [1.01–2.50], 2.34 [1.29–4.23], and 2.19 [1.21–3.98], respectively) and elevated but slightly weaker ORs for the fourth quartile, while findings were null for hormone receptor-negative tumors (Table 2). We observed an opposite pattern of results for PFOA; associations were null for ER+, PR+, and ER+/PR+ tumors, while modest positive associations with ER−, PR−, ER+/PR−, and ER−/PR− tumors were generally seen in the upper quartiles; risk estimates were not statistically significant, with the exception of an association with PR− tumors for the third quartile (OR=2.05, 95% CI=1.06–3.94). We observed generally stronger associations in these fully-adjusted models accounting for potential confounders compared with conditional models accounting for matching factors only (Tables S2 and S3).

Associations of PFOS and PFOA with overall breast cancer risk remained null in analyses stratified by time to diagnosis or time since menopause (Table S4). However, we observed stronger positive associations between serum PFOS levels and risks of hormone receptor-positive tumors diagnosed ≥6 years after blood draw (Tables 3 and S5), including a statistically significant exposure-response trend for ER+/PR+ tumors (ORs=4.72 and 3.67 for the third and fourth quartiles, respectively; P_{trend}=.02). For PFOA, the positive association with ER− tumors was more prominent for cases diagnosed within 6 years, whereas the association with PR− tumors appeared stronger for those diagnosed ≥6 years after blood draw (Table S5); however, these results should be interpreted with caution due to limited sample sizes. In general, no notable differences by time since menopause were observed for associations with hormone receptor-positive tumors (Tables 3 and S6), while a stronger positive association between PFOA and PR− tumors was observed among those with >15 (vs. ≤15) years between menopause and blood draw ($P_{heterogeneity}$=.001; Table S6). Finally, analyses excluding women who became menopausal ≤5 years before blood draw yielded similar findings compared to our main analyses, though with stronger associations between PFOS and ER+/PR+ tumors in the upper quartiles and a statistically significant exposure-response trend (ORs [95% CIs]=2.27 [1.18–4.38] and 2.20 [1.05–4.61] for the third and fourth quartiles, respectively; P_{trend}=.03; Table S7).

4 DISCUSSION

To our knowledge, this is the largest prospective study to date to evaluate associations between prediagnostic serum PFOS and PFOA levels and breast cancer risk and the first to examine these associations by joint ER/PR status. Consistent with results reported by Mancini *et al.* from the E3N study,[8] our findings from the PLCO Cancer Screening Trial suggest that higher levels of serum PFOS, but not PFOA, may be associated with elevated risks of hormone receptor-positive breast tumors among postmenopausal women, and provide novel suggestive evidence of a positive association between PFOS and double-

positive (ER+/PR+) but not single-positive (ER+/PR−) tumors. Our results suggesting positive associations between serum PFOA and hormone receptor-negative tumors were also somewhat consistent with those from Mancini *et al.*, although they observed elevated risks of ER− and PR− tumors for the second quartile of both PFOA and PFOS.[8] Taken together, these findings suggest that while PFOS and PFOA may not be associated with breast cancer overall, they may differentially affect risks of different breast cancer subtypes, thus highlighting the importance of considering hormone receptor status when evaluating the role of PFAS in breast cancer etiology.

Notably, we observed stronger positive associations between PFOS and hormone receptor-positive tumors for cases with a longer duration between blood draw and diagnosis, indicating that reverse causation is unlikely to explain our findings. These results are also consistent with the potential long latency between exposure to endocrine-disrupting chemicals (e.g., PFAS) and breast cancer occurrence[16] and further strengthened our findings, particularly for PFOS and receptor-positive tumors. Moreover, since menstruation is a route of excretion, PFAS levels increase over time following menopause,[14,15] which may complicate their associations with breast cancer. However, time since menopause appeared to have minimal impact on our main findings; in analyses excluding recently menopausal women, the observed associations were generally similar, although for ER+/PR+ tumors the association with PFOS levels in the top quartile and the exposure-response trend became statistically significant.

In vitro and *in vivo* experiments have demonstrated the ability of several PFAS, including PFOS and PFOA, to modulate hormone receptor (e.g., ER) activity and signaling,[17] which add biologic plausibility for the observed associations, especially for PFOS and hormone receptor-positive tumors. Beyond hormone receptor-mediated effects, both PFOS and PFOA have been suggested to contribute to carcinogenesis through other mechanisms, such as oxidative stress and immunosuppression.[17] It is unclear why PFOS and PFOA exhibited different patterns of associations with breast cancer subtypes. While both chemicals consist of an eight-carbon chain and have similarly long half-lives in human blood (~3–5 years),[18,19] differences in functional groups (sulfonic vs. carboxylic acid) and toxicokinetic properties may have contributed to different modes of action.[20] Experimental studies focusing on specific breast cancer subtypes are needed to further explore potential mechanisms underlying PFOS and PFOA carcinogenicity. Several previous epidemiologic studies have also evaluated associations between PFAS and breast cancer by hormone receptor status; however, they relied on post-diagnostic measurements of PFAS and reported inconsistent findings.[21–24] Furthermore, a recent case-cohort study in China measured plasma levels of six different PFAS and reported positive associations with breast cancer risk for PFOA, but not with PFOS or most other PFAS assessed; however, information on hormone receptor status was not available.[25] Additional prospective studies incorporating tumor hormone receptor status are needed to confirm findings from our study and Mancini *et al.*[8] in order to clarify the relationship between PFOS, PFOA, and breast cancer risk, and to evaluate associations with other PFAS.

A major strength of our study was the larger sample size compared to previous prospective studies of circulating PFAS and breast cancer[6,8,25] and the availability of information on

ER and PR status for most cases, which allowed us to evaluate associations with specific breast cancer subtypes defined by individual or joint hormone receptor status. Several study limitations should also be noted. First, serum PFOS and PFOA levels were not quantified using standard targeted methods, which precluded direct comparisons of absolute concentrations with other studies. However, as stated earlier, we observed strong correlations between measurements by Metabolon (untargeted metabolomics) and those by the CDC laboratory (targeted assay) among PLCO participants with PFOS and PFOA measured using both methods (unpublished data). Second, PFOS and PFOA were measured in serum samples collected at a single point in time; however, these measurements likely reflect long-term exposures given the long serum elimination half-lives of these chemicals.[18,19] Third, despite the relatively large sample size, our study had limited statistical power for analyses of rarer breast cancer subtypes, especially in stratified analyses. Finally, because all women were postmenopausal at blood draw in our study, our findings may not be generalizable to premenopausal breast cancer.

In conclusion, our study findings contribute to evidence supporting a positive association between serum PFOS levels and hormone receptor-positive breast tumors, and possibly between PFOA and hormone receptor-negative tumors. Future prospective studies should seek to incorporate tumor hormone receptor status where possible to better evaluate these highly persistent chemicals as potential breast carcinogens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors thank the PLCO participants, the NCI study management team and staff at Information Management Services, Inc., Westat, Inc., Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., and American Type Culture Collection. We thank Nathan Appel of Information Management Services, Inc. for creating the dataset analyzed for this project.

FUNDING INFORMATION

This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI), National Institutes of Health.

DATA AVAILABILITY STATEMENT

Data from the PLCO Cancer Screening Trial are available from the National Cancer Institute Cancer Data Access System (https://cdas.cancer.gov/plco/) upon application and approval. Further information is available from the corresponding author upon request.

Abbreviations:

CDC	Centers for Disease Control and Prevention
CI	confidence interval
ER	estrogen receptor

IARC	International Agency for Research on Cancer
MHT	menopausal hormone therapy
OR	odds ratio
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoate
PFOS	perfluorooctane sulfonate
PLCO	Prostate, Lung, Colorectal and Ovarian
PR	progesterone receptor

REFERENCES

1. Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, Lohmann R, Ng CA, Trier X, Wang Z. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ Sci Process Impacts 2020;22:2345–2373. [PubMed: 33125022]
2. Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect 2007;115:1596–1602. [PubMed: 18007991]
3. Benbrahim-Tallaa L, Lauby-Secretan B, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Bouvard V, Guha N, Mattock H, Straif K, International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. Lancet Oncol 2014;15:924–925. [PubMed: 25225686]
4. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 110. Some Chemicals Used as Solvents and in Polymer Manufacture Lyon: International Agency for Research on Cancer; 2017.
5. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. Environ Res 2018;160:152–182. [PubMed: 28987728]
6. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res 2021;194:110690. [PubMed: 33385391]
7. National Academies of Sciences, Engineering, and Medicine. Guidance on PFAS Exposure, Testing, and Clinical Follow-up. Washington, DC: The National Academies Press; 2022.
8. Mancini FR, Cano-Sancho G, Gambaretti J, Marchand P, Boutron-Ruault MC, Severi G, Arveux P, Antignac JP, Kvaskoff M. Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort. Int J Cancer 2020;146:917–928. [PubMed: 31008526]
9. Hayes RB, Sigurdson A, Moore L, Peters U, Huang WY, Pinsky P, Reding D, Gelmann EP, Rothman N, Pfeiffer RM, Hoover RN, Berg CD, PLCO Trial Team. Methods for etiologic and early marker investigations in the PLCO trial. Mutat Res 2005;592:147–154. [PubMed: 16054167]
10. Playdon MC, Ziegler RG, Sampson JN, Stolzenberg-Solomon R, Thompson HJ, Irwin ML, Mayne ST, Hoover RN, Moore SC. Nutritional metabolomics and breast cancer risk in a prospective study. Am J Clin Nutr 2017;106:637–649. [PubMed: 28659298]
11. Moore SC, Playdon MC, Sampson JN, Hoover RN, Trabert B, Matthews CE, Ziegler RG. A metabolomics analysis of body mass index and postmenopausal breast cancer risk. J Natl Cancer Inst 2018;110:588–597. [PubMed: 29325144]
12. Evans AM, Bridgewater BR, Liu Q, Mitchell MW, Robinson RJ, Dai H, Stewart SJ, DeHaven CD, Miller LAD. High resolution mass spectrometry improves data quantity and quality as

compared to unit mass resolution mass spectrometry in high-throughput profiling metabolomics. Metabolomics 2014;4:132.

13. Kato K, Kalathil AA, Patel AM, Ye X, Calafat AM. Per- and polyfluoroalkyl substances and fluorinated alternatives in urine and serum by on-line solid phase extraction-liquid chromatography-tandem mass spectrometry. Chemosphere 2018;209:338–345. [PubMed: 29935462]
14. Rickard BP, Rizvi I, Fenton SE. Per- and poly-fluoroalkyl substances (PFAS) and female reproductive outcomes: PFAS elimination, endocrine-mediated effects, and disease. Toxicology 2022;465:153031. [PubMed: 34774661]
15. Upson K, Shearston JA, Kioumourtzoglou MA. An epidemiologic review of menstrual blood loss as an excretion route for per- and polyfluoroalkyl substances. Curr Environ Health Rep 2022;9:29–37. [PubMed: 35267175]
16. Eve L, Fervers B, Le Romancer M, Etienne-Selloum N. Exposure to endocrine disrupting chemicals and risk of breast cancer. Int J Mol Sci 2020;21:9139. [PubMed: 33266302]
17. Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM. Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. Int J Environ Res Public Health 2020;17:1668. [PubMed: 32143379]
18. Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 2007;115:1298–1305. [PubMed: 17805419]
19. Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 2018;75:46–51. [PubMed: 29133598]
20. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM. Per- and polyfluoroalkyl substance toxicity and human health review: Current state of knowledge and strategies for informing future research. Environ Toxicol Chem 2021;40:606–630. [PubMed: 33017053]
21. Wielsøe M, Kern P, Bonefeld-Jørgensen EC. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environ Health 2017;16:56. [PubMed: 28610584]
22. Hurley S, Goldberg D, Wang M, Park JS, Petreas M, Bernstein L, Anton-Culver H, Nelson DO, Reynolds P. Breast cancer risk and serum levels of per- and poly-fluoroalkyl substances: A case-control study nested in the California Teachers Study. Environ Health 2018;17:83. [PubMed: 30482205]
23. Tsai MS, Chang SH, Kuo WH, Kuo CH, Li SY, Wang MY, Chang DY, Lu YS, Huang CS, Cheng AL, Lin CH, Chen PC. A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. Environ Int 2020;142:105850. [PubMed: 32580117]
24. Itoh H, Harada KH, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Yokoyama K, Zhu J, Harada Sassa M, Tsugane S, Iwasaki M. Serum perfluoroalkyl substances and breast cancer risk in Japanese women: A case-control study. Sci Total Environ 2021;800:149316. [PubMed: 34392213]
25. Feng Y, Bai Y, Lu Y, Chen M, Fu M, Guan X, Cao Q, Yuan F, Jie J, Li M, Meng H, Wang C, Hong S, Zhou Y, Zhang X, He M, Guo H. Plasma perfluoroalkyl substance exposure and incidence risk of breast cancer: A case-cohort study in the Dongfeng-Tongji cohort. Environ Pollut 2022;306:119345. [PubMed: 35472559]

Novelty and Impact

Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are synthetic chemicals with widespread use in industrial applications and consumer products. They also are endocrine disruptors with suspected links to cancer. Here, the authors investigated potential associations between prediagnostic serum PFOS and PFOA levels and risk of breast cancer subtypes among postmenopausal women. No association was found between PFOS or PFOA and breast cancer risk overall. However, PFOS levels were positively associated with hormone receptor-positive breast tumors, and modest positive associations were observed between PFOA levels and receptor-negative tumors. The findings warrant further investigation in studies incorporating breast tumor hormone receptor status.

TABLE 1.

Odds ratios (95% confidence intervals) for the associations between serum PFOS and PFOA levels and risk of postmenopausal breast cancer (N = 621 cases and 621 controls)

PFAS[a]	$n_{controls}$	n_{cases}	Model 1[b]	Model 2[c]
PFOS				
Quartile 1	156	145	1.00 (Ref)	1.00 (Ref)
Quartile 2	155	158	1.19 (0.83–1.70)	1.21 (0.84–1.74)
Quartile 3	155	167	1.35 (0.97–1.90)	1.39 (0.96–1.99)
Quartile 4	155	151	1.12 (0.79–1.59)	1.17 (0.77–1.79)
P_{trend}[d]			.61	.58
PFOA				
Quartile 1	156	147	1.00 (Ref)	1.00 (Ref)
Quartile 2	155	148	0.92 (0.65–1.31)	0.91 (0.64–1.30)
Quartile 3	155	162	1.09 (0.77–1.55)	1.07 (0.73–1.55)
Quartile 4	155	164	1.06 (0.75–1.50)	1.01 (0.66–1.55)
P_{trend}[d]			.62	.83

Abbreviations: MHT, menopausal hormone therapy; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

[a]Quartiles are based on the distribution of PFOS or PFOA levels among controls.

[b]Conditional logistic regression models adjusted for age at blood draw (continuous; years), study center (Upper Midwest [Wisconsin and Minnesota], West/South [Colorado, Hawaii, Missouri, Utah, and Alabama], East [Washington DC, Michigan, and Pennsylvania]), race/ethnicity (non-Hispanic White, non-Hispanic Black, other), education (high school graduate or less, post-high school training or some college, college graduate or postgraduate), age at menarche (<12, 12–13, ≥14 years), age at first live birth and number of live births (nulliparous, <20 years and ≥1 birth, 20–29 years and 1–2 births, 20–29 years and ≥3 births, ≥30 years and ≥1 birth), age at menopause (<45, 45–49, 50–54, ≥55 years), duration of MHT use (never, ≤1, 2–5, 6–9, ≥10 years), first-degree family history of female breast cancer (no/unknown, yes), personal history of benign breast disease (no/unknown, yes), body mass index (<25, 25 to <30, ≥30 kg/m^2), smoking status (never, former, current), and vigorous physical activity (<1, 1–3, ≥4 hours/week, missing). Models conditioned on case-control matched pairs, with controls individually matched to cases on age at baseline (±2 years), date of blood draw (±3 months), and MHT use at baseline.

[c]Adjusted for all Model 1 covariates and additionally for natural log-transformed levels of PFOA (for the PFOS model) or PFOS (for the PFOA model).

[d]Tests for linear trend across quartiles performed by modeling quartile-specific median values of PFOS or PFOA among the controls as a continuous variable.

TABLE 2.

Odds ratios (95% confidence intervals) for the associations between serum PFOS and PFOA levels and risk of postmenopausal breast cancer according to hormone receptor status

	ER status			PR status			ER/PR status[a]			
PFAS[b]	**ER+ (n = 435)**	**ER− (n = 147)**	**P_{het} [c]**	**PR+ (n = 299)**	**PR− (n = 241)**	**P_{het} [c]**	**ER+/PR+ (n = 291)**	**ER+/PR− (n = 98)**	**ER−/PR− (n = 138)**	**P_{het} [c]**
PFOS										
Quartile 1	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	
Quartile 2	1.26 (0.81–1.95)	0.98 (0.39–2.47)		1.55 (0.90–2.67)	1.00 (0.52–1.92)		1.46 (0.84–2.54)	0.79 (0.19–3.38)	1.01 (0.38–2.63)	
Quartile 3	**1.59 (1.01–2.50)**	1.13 (0.49–2.62)		**2.34 (1.29–4.23)**	0.91 (0.50–1.64)		**2.19 (1.21–3.98)**	0.32 (0.08–1.32)	1.12 (0.48–2.62)	
Quartile 4	1.29 (0.77–2.15)	0.52 (0.18–1.55)		1.79 (0.92–3.48)	0.61 (0.29–1.31)		1.89 (0.97–3.69)	0.32 (0.06–1.86)	0.60 (0.19–1.83)	
P_{trend} [d]	.39	.20	.71	.14	.15	.66	.08	.12	.34	.25
PFOA										
Quartile 1	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	
Quartile 2	1.07 (0.68–1.66)	0.84 (0.36–1.95)		1.14 (0.66–1.96)	0.90 (0.47–1.70)		1.14 (0.66–1.97)	1.40 (0.32–6.11)	0.90 (0.38–2.10)	
Quartile 3	1.01 (0.64–1.61)	2.08 (0.85–5.07)		1.02 (0.57–1.83)	**2.05 (1.06–3.94)**		0.99 (0.55–1.80)	1.88 (0.55–6.42)	2.23 (0.90–5.54)	
Quartile 4	1.03 (0.61–1.75)	1.63 (0.63–4.20)		0.77 (0.39–1.52)	1.48 (0.75–2.93)		0.81 (0.40–1.62)	1.63 (0.45–5.87)	1.62 (0.62–4.23)	
P_{trend} [d]	.96	.19	.30	.31	.15	.21	.41	.50	.21	.44

Notes: Odds ratios and 95% confidence intervals were estimated from conditional logistic regression models adjusted for age at blood draw (continuous; years), study center (Upper Midwest [Wisconsin and Minnesota], West/South [Colorado, Hawaii, Missouri, Utah, and Alabama], East [Washington DC, Michigan, and Pennsylvania]), race/ethnicity (non-Hispanic White, non-Hispanic Black, other), education (high school graduate or less, post-high school training or some college, college graduate or postgraduate), age at menarche (<12, 12–13, ≥14 years), age at first live birth and number of live births (nulliparous, <20 years and ≥1 birth, 20–29 years and 1–2 births, 20–29 years and ≥3 births, ≥30 years and ≥1 birth), age at menopause (<45, 45–49, 50–54, ≥55 years), duration of MHT use (never, ≤1, 2–5, 6–9, ≥10 years), first-degree family history of female breast cancer (no/unknown, yes), personal history of benign breast disease (no/unknown, yes), body mass index (<25, 25 to <30, ≥30 kg/m^2), smoking status (never, former, current), vigorous physical activity (<1, 1–3, ≥4 hours/week, missing), and natural log-transformed levels of PFOA (for PFOS models) or PFOS (for PFOA models). Models conditioned on case-control matched pairs, with controls individually matched to cases on age at baseline (±2 years), date of blood draw (±3 months), and MHT use at baseline.

Bold indicates statistical significance at $P < .05$.

Abbreviations: ER, estrogen receptor; MHT, menopausal hormone therapy; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PR, progesterone receptor.

[a] ER−/PR+ cases were not analyzed due to small numbers (n = 6).

[b] Quartiles are based on the distribution of PFOS or PFOA levels among controls.

[c] *P*-values for heterogeneity of associations across tumor subtypes, estimated using a Wald test for a cross-product term between hormone receptor status (ER, PR, or ER/PR status for each matched case-control pair) and serum PFOS or PFOA levels (continuous variable based on quartile-specific median values).

[d] Tests for linear trend across quartiles performed by modeling quartile-specific median values of PFOS or PFOA among the controls as a continuous variable.

TABLE 3.

Odds ratios (95% confidence intervals) for the associations between serum PFOS and PFOA levels and risk of ER+/PR+ breast cancer, stratified by time to diagnosis or time since menopause

	Time from blood draw to diagnosis			Time from menopause to blood draw		
PFAS[a]	**<6 years (n = 152)**	**≥6 years (n = 139)**	P_{het} [b]	**≤15 years (n = 146)**	**>15 years (n = 145)**	P_{het} [b]
PFOS						
Quartile 1	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
Quartile 2	1.40 (0.61–3.19)	1.48 (0.59–3.73)		1.42 (0.34–5.99)	1.27 (0.42–3.81)	
Quartile 3	2.02 (0.86–4.73)	**4.72 (1.66–13.47)**		2.45 (0.40–15.13)	3.28 (0.93–11.56)	
Quartile 4	1.28 (0.47–3.42)	**3.67 (1.20–11.25)**		2.72 (0.45–16.56)	1.89 (0.53–6.80)	
P_{trend} [c]	.66	**.02**	.45	.25	.26	.36
PFOA						
Quartile 1	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
Quartile 2	1.14 (0.49–2.66)	1.31 (0.53–3.24)		1.47 (0.31–7.02)	1.00 (0.34–2.92)	
Quartile 3	1.39 (0.58–3.30)	1.02 (0.36–2.91)		2.41 (0.36–16.10)	0.92 (0.29–2.86)	
Quartile 4	1.50 (0.52–4.38)	0.53 (0.17–1.70)		0.36 (0.03–3.75)	0.81 (0.20–3.28)	
P_{trend} [c]	.48	.15	.46	.22	.74	.81

Notes: Odds ratios and 95% confidence intervals were estimated from conditional logistic regression models adjusted for age at blood draw (continuous; years), study center (Upper Midwest [Wisconsin and Minnesota], West/South [Colorado, Hawaii, Missouri, Utah, and Alabama], East [Washington DC, Michigan, and Pennsylvania]), race/ethnicity (non-Hispanic White, non-Hispanic Black, other), education (high school graduate or less, post-high school training or some college, college graduate or postgraduate), age at menarche (<12, 12–13, ≥14 years), age at first live birth and number of live births (nulliparous, <20 years and ≥1 birth, 20–29 years and 1–2 births, 20–29 years and ≥3 births, ≥30 years and ≥1 birth), age at menopause (<45, 45–49, 50–54, ≥55 years), duration of MHT use (never, ≤1, 2–5, 6–9, ≥10 years), first-degree family history of female breast cancer (no/unknown, yes), personal history of benign breast disease (no/unknown, yes), body mass index (<25, 25 to <30, ≥30 kg/m^2), smoking status (never, former, current), vigorous physical activity (<1, 1–3, ≥4 hours/week, missing), and natural log-transformed levels of PFOA (for PFOS models) or PFOS (for PFOA models). Models conditioned on case-control matched pairs, with controls individually matched to cases on age at baseline (±2 years), date of blood draw (±3 months), and MHT use at baseline.

Bold indicates statistical significance at $P < .05$.

Abbreviations: ER, estrogen receptor; MHT, menopausal hormone therapy; PFAS, per- and polyfluoroalkyl substances; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PR, progesterone receptor.

[a]Quartiles are based on the distribution of PFOS or PFOA levels among controls.

[b]*P*-values for heterogeneity of associations across strata, estimated using a Wald test for a cross-product term between time to diagnosis or time since menopause and serum PFOS or PFOA levels (continuous variable based on quartile-specific median values).

[c]Tests for linear trend across quartiles performed by modeling quartile-specific median values of PFOS or PFOA among the controls as a continuous variable.