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PFOA and ulcerative colitis

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Abstract

Introduction: PFOA (perfluorooctanoic acid) is a perfluoroalkyl substance (PFAS). Although use in the US has been phased out, PFOA persists indefinitely in the environment, and is present in the serum of virtually all people in industrialized countries. Approximately 6 million Americans drink water contaminated with PFOA above EPA-recommended levels. In a previous cohort study ($n = 32,000$), we found a strong positive exposure-response relation between PFOA serum levels and subsequent ulcerative colitis (UC) in a high-exposed population from the mid-Ohio valley, but no association with Crohn's disease. In the present study we aimed to determine if UC cases had higher levels of PFOA than did controls or Crohn's disease patients.

Methods: We measured PFOA and three other PFAS in the serum of 114 UC patients, 60 Crohn's disease patients, and 75 controls, within a year of diagnosis. We conducted regression analyses to assess the association of the PFAS with diagnosis.

Results: The mean age of subjects was 17 years. The mean year of diagnosis was 2007. Mean levels of PFAS were similar to US levels. Mean log PFOA level in UC patients was 38% higher ($p = 0.01$) than the combined group of Crohn's disease and controls. In contrast, the three other PFASs were significantly higher in controls and Crohn's patients than UC patients. The odds ratio for UC per one unit of log PFOA was 1.60 (95% CI 1.14–2.24), but the trend by quintiles was not monotonic (1, 0.84, 40.98, 33.36, 2.86).

Conclusion: We found higher serum PFOA in UC cases compared to Crohn's disease patients or controls, in contrast to other PFAS. Our research is limited by not knowing if the elevated PFOA preceded UC in this population.

Keywords

PFOA; Ulcerative colitis

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Competing financial interest

None of the authors has any competing financial interest

1. Introduction

PFOA (perfluorooctanoic acid) is a the perfluorinated compound which has been used in making commercial products such as fluoropolymer Teflon®. The half-life in humans is approximately 2.3–3.4 years (Bartell et al., 2010; Olsen et al., 2007). PFOA persists indefinitely in the environment and is present in the serum of virtually all people living in industrialized countries.

In the United States, PFOA production and use has been cut back since the signing of a consent decree in 2010 between the EPA and eight large manufactures/users, calling for a phase-out by 2015 (<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program>). Likely, this accord is partly responsible for the gradually decreasing PFOA levels in the general population, from a geometric mean of 4.0 ng/mL (Calafat et al., 2007) in 2003–2004–1.9 ng/mL in the most recent data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES, 2017).

While production is being phased out by large companies, PFOA has been found in the groundwater of over 60 U.S. communities in the last few years (personal communication, CDC's NCEH/ATSDR director Pat Breyse, 10/21/16). A recent publication calculated human exposures from EPA data on six PFAS (among them PFOA) in public drinking and estimated that 6 million people in the United States were exposed to either PFOA, PFOS, or the total of both at levels above the EPA recommended limit of 70 pg/mL or parts-*per*-trillion (Hu et al., 2016).

We have previously studied a large representative cohort of adults ($n = 32,000$) in West Virginia and Ohio, with high exposure to PFOA (mean serum level 82 ng/mL, median 28 ng/mL, in 2005) resulting from PFOA contamination of drinking water by a DuPont plant manufacturing Teflon® (Winqvist et al., 2013). The cohort was assembled from 69,000 people in six water districts with PFOA-contaminated water, who were tested for PFOA serum levels in 2005. In this cohort, the largest high-exposed PFOA cohort in the world, we estimated PFOA serum levels over time using PFOA emissions data from the DuPont plant and a fate-transport model. Predicted serum PFOA in 2005 correlated well with measured serum PFOA in 2005 (Spearman correlation 0.67), suggesting our modeled estimates were likely to be reasonably accurate. Follow-up for ulcerative colitis began at time of first exposure to PFOA-contaminated water and ended at time of disease occurrence, death, or end of follow-up in 2011. Self-reports of ulcerative colitis and other disease end-points were confirmed by medical record. Studies of this high-exposed cohort have been the source of much of our knowledge of the health effects of PFOA.

Using cumulative exposure to PFOA prior to diagnosis in Cox regression models, we found a strong association between cumulative serum PFOA exposure and ulcerative colitis (UC; $n = 151$), a serious auto-immune disease which was confirmed by medical records (Steenland et al., 2013). Relative risks by increasing quartile of cumulative PFOA exposure were 1.00, 1.76, 2.73, 2.86 (test for linear trend $p = 0.0001$). This association was specific for UC; it was not seen for Crohn's disease nor for other auto-immune diseases, suggesting a unique role for PFOA in the molecular pathology of UC.

Plausible mechanisms linking PFOA and risk of UC may include shifts in the balance of tissue macrophages towards an anti-inflammatory M2 phenotype and/or a TH2-like response to specific antigens (DeWitt et al., 2012). Experimental findings also suggest PPAR-gamma activation may lead to reprogramming of tissue macrophages towards an M2 anti-inflammatory phenotype, which may contribute to decreased vaccine efficacy or immunosuppression in diseases dependent on cytotoxic T-cell responses (Dewitt et al., 2012). Other studies suggest PFOA may induce shifts in the TH1/TH2 balance, increasing production of TH2-like cytokines involved in hypersensitivity responses (Dewitt et al., 2012). One TH2-type cytokine (IL-13) is thought to play a unique and critical role in UC in gut mucosal inflammatory response (Mannon and Reinisch, 2012), but PFOA-related effects on IL-13 expression have not been described. Ultimately, the context of the microbial environment may be especially relevant in explaining PFOA-related effects on UC. One study's findings that PFOA leads to both systemic neutropenia and increased lipopolysaccharide-related cytokine release in other cell populations (e.g., macrophages) (Qazi et al., 2009) suggests a general increase in host susceptibility to infections (Dewitt et al., 2012). Together, these findings suggest that the unique relationship of PFOA and UC we observed in this study (i.e., compared with a lack of clear associations with Crohn's or any of the other autoimmune diseases examined) may be due to altered response to infectious exposures and other unique aspects of lower gastrointestinal toxicity that may not be reflected by systemic or other organ-specific immune effects. The hypothesis that infections trigger the onset of UC is further supported that HLA (human leukocyte antigen) is a dominant genetic determinate that explains the vast majority of genetic susceptibility in UC. Compared to UC, HLA plays much less significant role in CD may explain the lack of association ((Cho and Brant, 2011; Goyette et al., 2015)).

We have now further explored this association in a population of patients with UC or Crohn's disease, as well as controls, who were seen at Emory University in Atlanta, Georgia, from 2009 to 2015. We hypothesized that UC cases would have higher PFOA than both controls and Crohn's disease patients, although the effects of disease on PFOA levels are not clear, and a preferable design would have measured the PFAS prior to diagnosis.

2. Methods

Cases were recruited from those coming to clinics at Egleston Hospital on Emory campus, or other Emory Healthcare outpatient clinics, and who volunteered for research, from 1999 through 2012. Standard criteria were used to establish a diagnosis of either UC or Crohn's disease. Comprehensive demographic, clinical, laboratory, and serologic values were obtained either at the time of enrollment or by retrospective chart review. All stored blood samples from UC and Crohn's disease patients dating from late 2004 or early 2005 were used for this study. Controls were chosen among non-diseased friends and family of cases, who were asked to enroll in a research study of African-Americans, regarding the genetics of inflammatory bowel disease (Huang et al., 2015). Stored blood samples from these controls were available through the Emory Gastroenterology Department at the time we began the present study. For both cases and controls, we used all the stored samples which were available at the time we began this study. Cases and controls in the present study were

independent of the prior cohort study in the mid-Ohio valley, and were a priori assumed to have lower serum levels of serum PFASs compared to that high-exposed cohort.

In the current study we measured PFOA in the serum of study participants, as well as three other PFAS detected ubiquitously in the serum of US residents: perfluorooctane sulfonate (PFOS), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA)). Serum samples (100 µL) were spiked with isotopically labeled internal standards and mixed. Proteins were denatured by the addition of formic acid and the resulting supernatant was applied to Isolute C18 cartridges. The supernatant was pulled through the cartridges to waste. The cartridges were washed with water:isopropanol and eluted with methanol and concentrated to dryness. The concentrate was re-suspended in mobile phase for analysis using high-performance liquid chromatography with tandem mass spectrometry. Quantification was achieved using isotope dilution calibration. The limits of detection were 0.08 ng/mL or lower enabling detection of levels similar to US population levels. The relative standard deviations were less than 10%. NIST samples analyzed concurrently with unknown samples were within the target range. Further, the method and laboratory are certified by the German External Quality Assessment Scheme (G-EQUAS) proficiency testing program.

We conducted standard linear regression analyses with PFOA and other PFAS as the outcome variable and diagnostic category as a predictor variable, while controlling for age, gender, race (white/non-white, Hispanic/Asians considered non-white), and calendar year of sampling, variables which differed between UC patients and either Crohn's disease patients or controls (Table 1). The PFAS were log transformed for these analysis. We also conducted logistic regression in which UC was the outcome, and the referents were either controls or a combined population of controls and Crohn's disease subjects. In these models we included covariates for age, gender, and race. The controls were almost all African-American, collected via a study focused on that group. We have used white vs. non-white in our coding of race; the non-white were largely African-Americans. This lack of whites among controls made adequate control for race difficult when comparing the UC cases to controls alone, motivating the use of a combined referent population of controls and Crohn's disease subjects.

3. Results

Table 1 provides descriptive results for the study population. As noted, the controls were largely non-white. Blood samples were collected one or two years after diagnosis. Most participants were diagnosed as teenagers, with 80% being diagnosed at 21 years or younger. The mean and median levels of PFAS are similar to those seen nationally in NHANES (Calafat et al., 2007). The distribution of PFAS was generally right skewed, as can be seen via the difference between means and medians. As noted for linear regression analyses with PFAS as outcomes, we used a natural log transformation of the PFAS to make them approximately normal. Figs. 1 and 2 illustrate the effect of log transformation on PFOA.

Table 2 shows the linear regression results for the regression of PFAS on diagnostic groups, controlling for gender, age, race, and sample year. For PFHxS, PFNA, and PFOS, controls

and Crohn's disease patients generally had higher levels than the UC patients, as noted by the positive coefficients in the table, most of which were statistically significant at the $p = 0.05$ level. However, for PFOA the UC cases had higher levels than the controls or the Crohn's disease patients, as we had hypothesized, the difference being significant for UC cases vs the Crohn's disease patients. As the controls and Crohn's disease patients had similar PFOA levels compared to UC cases after adjusting for covariates (with coefficients of -0.29 and -0.33), we combined these groups in further analyses in Table 3a, 3b.

Table 3a shows the analysis of log PFOA regressed on the combined control/Crohn's disease group. The UC patients had 38% ($\exp(.32)$) higher PFOA levels ($p = 0.01$), adjusting for covariates. No covariates were statistically significant predictors at the $p = 0.05$ level. After dropping 4 outliers with studentized-t values above 2.0 (Table 3b), the model fit better (R square 0.20 vs 0.14), and the UC patients again had significantly higher levels of PFOA (20% higher), although not as marked as in Table 3a.

Table 4 shows the categorical distribution of UC cases vs. the combined control/Crohn's disease group. An excess of UC cases are found in quintiles 3 and 4, but not in quintile 5. Table 5 shows the logistic regression results for UC patients vs the combined control/Crohn's disease group. Using a continuous variable for log of PFOA, there was an increased odds of 1.60 ($p = 0.007$, 95% CI 1.14–2.24) for having a diagnosis of UC for every unit of log PFOA. However, in categorical analyses seen at the bottom of Table 5, as expected from Table 4, there is no monotonic increasing risk of UC by quintile of PFOA: the excess risk of a UC diagnosis was confined to quintiles 3 and 4 vs quintile 1, while in the highest PFOA quintile the risk drops off.

4. Discussion

We found that higher PFOA was associated with higher risk of UC vs a diagnosis of Crohn's disease or being a control, as we had hypothesized. However, that increased risk did not show a monotonic increase with increasing levels of PFOA. These results are consistent with our prior cohort study in a high-exposed population in the mid-Ohio valley showing that UC cases had higher levels than non-cases, which was not true for Crohn's disease in the mid-Ohio valley.

In contrast, in our population studied here, for the other 3 PFAS, controls and Crohn's disease cases had significantly higher levels in their serum than did the UC cases. It is possible that PFOA was elevated in UC cases prior to their disease occurrence, if PFOA is indeed a risk factor for UC. Alternatively, it is also possible that the disease itself also affects serum PFOA levels in UC cases, but in a manner contrary to its effect on the other 3 PFAS. Although our earlier cohort study found that PFOA levels were higher for cases before the disease developed, we need more longitudinal data on PFOA exposure and subsequent risk of UC to help clarify this puzzle.

One possible explanation for our findings is that cases in our study had blood samples taken earlier than controls (mean 2008 vs. 2011). National survey data (NHANES) shows that PFOA levels have been dropping over time (NHANES, 2017). Furthermore, controls in our

study were almost all non-white, and NHANES data also show that whites have higher levels of PFOA than non-whites. However, there are several reasons to believe that neither of these factors can explain our results. First, analyses in Table 2, Table 3a, 3b are adjusted for year of sample, so year of sample will not confound our results (it is worth noting for example, that PFOS has dropped much more sharply over time than PFAS, but UC cases had lower levels of PFOS than controls – consistent with the adjustment for year of sample controlling for time-related changes in PFAS). Furthermore, UC cases had higher PFOA levels than Crohn's disease cases, which were sampled on the average in the same year. With regard to race, controls were almost all non-white, so adjustment for race in the model for UC cases vs. controls is unlikely to be effective. However, we note that the higher levels of PFOA we saw in UC cases vs. controls were not seen for PFHxS, a PFAS where whites also had more markedly higher levels in NHANES than non-whites (eg, 34% higher for PFHxS, compared to 22% for PFOA, in 2010); yet UC cases had a highly significant decrease in PFHxS compared to controls. We also note that a similar excess of PFOA in UC cases vs controls was also seen in UC cases vs. Crohn's disease, the latter being similar in race distribution to UC cases.

Another possibility that might explain our findings is that IBD results in lower kidney function, and that in turn causes higher PFAS levels (ie, reverse causality, which has been documented in the case of PFOA and kidney function by Watkins et al. (2013). Corica and Romano (2016) have pointed to the general problem of renal involvement in IBD, although noting that it is rare. While we did not have data on glomerular function in our study population, to adjust directly, there are several lines of reasoning that argue against this reverse causality possibility. First, we found only PFOA to be elevated in UC cases vs Crohn's disease/controls, not the other PFASs – yet all would be expected to be increased in the serum if excreted less due to worse glomerular function (Watkins et al., 2013). Second, if reverse causality were an issue for IBD patients, then it would be expected to affect our Crohn's disease patients as well as our UC patients, yet the UC cases had higher PFOA than did the Crohn's cases. Finally, to further investigate, we obtained serum creatinine data on 97 UC cases, 794 Crohn's cases, and 178 controls from a cohort study of pediatric IBD cases (the RISE study, see Kugathasan et al., 2017 for more details). After calculating the eGFR using the formula for children (https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/children-conventional-units), we found that only about 5% of these study groups had abnormally low eGFR (< 75), and that there were no significant differences in abnormally low GFR between either UC cases and Crohn's cases ($p = 0.55$), or between UC cases and controls ($p = 0.20$) (data not shown).

In conclusion, the pathogenesis of inflammation in UC and Crohn's disease are very similar. The finding of PFOA association with UC but not Crohn's disease needs further investigation. The fact that there is some evidence that PFOA is an immune suppressant, and that HLA is an important genetic determinant of UC, suggesting the infections play a role in UC etiology, lends some mechanistic support to the idea the PFOA may increase the risk of UC.

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Fig. 1.
Distribution of PFOA in study population.

Fig. 2.
Distribution of log PFOA in the study population.

Table 1

Descriptive data for the study population.

	Ulcerative colitis (n = 114)	Crohn's disease (n = 60)	Controls (n = 75)
% male	57%	53%	39%
% white	80%	87%	3%
Mean age (std dev) at diagnosis	15 (11)	16 (9)	22 (12)
Mean year of diagnosis (range)	2006 (1999–2012)	2007 (1999–2012)	n.a.
Mean year of blood sample (year)	2008 (2004–2013)	2008 (2005–2012)	2011(2010–2013)
Mean/median	3.76/2.93	3.63/1.78	2.46/1.33
PFOA (ng/mL)			
Mean/median	7.25/3.95	9.45/3.32	5.38/4.21
PFOS (ng/mL)			
Mean/median	0.99/0.43	1.81/0.54	1.24/0.91
PFNA (ng/mL)			
Mean/median	2.12/0.93	3.66/1.46	2.04/1.55
PHHxS (ng/mL)			

Table 2

Linear regression results for log of PFOA, PFOS, PFNA, and PFHxS concentrations *

PFAS compound	Diagnosis	Coefficient, change in log(PFAS) by diagnosis, with ulcerative colitis as referent	Std error coefficient	p-value	R-square model
PFOA	UC vs control	0.29	0.19	0.13	0.14
PFOA	UC vs Crohn's disease	0.33	0.14	0.02	
PFOS	UC vs control	-0.40	0.21	0.06	0.09
PFOS	UC vs Crohn's disease	0.05	0.16	0.77	
PFNA	UC vs control	-0.75	0.18	< 0.0001	0.15
PFNA	UC vs Crohn's disease	-0.26	0.13	0.05	
PFHxS	UC vs control	-1.22	0.29	< 0.0001	0.14
PFHxS	UC vs Crohn's disease	-0.45	0.19	0.02	

* Covariates in model included diagnostic category, gender, age category (< 11, 11–14, 15–19, 20+) white/non-white, and year of sample.

Table 3a

Regression of log PFOA on covariates, control/Crohn's disease combined as referent.

Variable	Coefficient, change in log(PFAS)	Std error coefficient	P-value coefficient
UC vs control/Crohn's disease combined	0.32	0.12	0.01
Age 11–14 vs < 11	0.27	0.15	0.08
Age 15–19 vs < 11	0.16	0.16	0.32
Age 20 + vs < 11	– 0.17	0.15	0.36
Female vs male	– 0.08	0.11	0.46
White vs non-white	0.15	0.15	0.31
Year of sample	– 0.02	0.02	0.36

*
R square model 0.14.

Table 3b

Regression of log PFOA on covariates, control/Crohn's disease combined as referent, without 4 outliers.

Variable	Coefficient, change in log(PFAS)	Std error coefficient	P-value coefficient
UC vs control/Crohn's disease	0.18	0.08	0.02
Age 11–14 vs < 11	0.22	0.10	0.02
Age 15–19 vs < 11	0.19	0.10	0.07
Age 20 + vs < 11	– 0.06	0.12	0.57
Female vs male	– 0.04	0.07	0.58
White vs non-white	0.17	0.09	0.07
Year of sample	– 0.03	0.02	0.08

*
R square model 0.20.

Table 4

UC cases vs combined controls/Crohn's disease, by PFOA quintile.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
UC cases	6	6	40	43	19
Controls/Crohn's Disease	43	44	10	7	31

Table 5

Logistic regression results for ulcerative colitis vs controls/Crohn's disease in relation to PFOA.

Covariate	Odds ratio	95% CI
Age1	0.82	0.39–1.72
Age2	0.95	0.43–2.08
Age3	0.62	0.24–1.62
Female vs male	0.72	0.41–1.29
white	4.20	2.12–8.34
Log(PFOA)	1.60	1.14–2.24
PFOA quintile 2 vs 1	0.81	0.22–2.93
PFOA quintile 3 vs 1	40.98	11.67–150.34
PFOA quintile 4 vs 1	33.36	11.32–119.36
PFOA quintile 5 vs 1	2.86	0.94–8.75

* Odds ratio for log PFOA for ulcerative colitis vs controls was 2.00 (1.08–3.67), while the odds ratio for log PFOA for ulcerative colitis vs Crohn's disease was 1.68 (1.07–2.32)