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Plasma perfluoroalkyl substances and breast cancer risk in Brazilian women: a case–control study

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Abstract

Background Per- and polyfluoroalkyl substances (PFAS) are persistent environmental pollutants, and have been detected in human blood. Although PFAS may increase the risk of breast cancer in humans, findings from previous epidemiological studies on the link between PFAS and breast cancer are controversial. Additionally, most studies of PFAS to date did not distinguish between isomers. Here, we examined the association of PFAS exposure and breast cancer risk in Brazilian women, who represent a racially and ethnically diverse group.

Methods We conducted a case-control study of 471 women with breast cancer and 471 matched controls attending hospitals in São Paulo, Brazil from 2001 to 2006. Plasma concentrations of PFAS congeners were measured using in-port arylation gas chromatography–isotope dilution mass spectrometry with electron capture negative ionization. Linear and branched PFAS isomers were isolated and quantified separately. We derived multivariable-adjusted odds ratios and 95% confidence intervals for breast cancer and hormone-receptor subtypes according to plasma PFAS concentration.

Results In overall analyses, higher plasma concentrations of n-perfluoroheptane sulfonate (n-PFHpS), perfluoro-3-methyl-heptane sulfonate (3 m-PFOS), and n-perfluorononanoic acid were significantly associated with increased risk of breast cancer. Adjusted odds ratios for low, medium, and high n-PFHpS concentrations were 1.00, 1.28, and 2.00 (95% confidence interval = 1.15, 3.48), respectively (P for trend = 0.015). Furthermore, plasma 3 m-PFOS concentration and total perfluorooctanoic acid concentration were significantly associated with increased risk of breast cancer among mixed-ethnicity women. In Caucasian women, a higher plasma perfluoro-4-methyl-heptane sulfonate concentration was also associated with increased risk of breast cancer. Increased plasma n-PFHpS concentration was significantly associated with higher risk of hormone receptor-positive breast cancer but not with increased risk of hormone receptor-negative breast cancer.

Conclusions Several plasma PFAS appear to increase the risk of breast cancer. Our findings suggest the importance of isomer analysis, subgroup analysis by ethnicity, and breast cancer subtype analysis for accurately characterizing this risk.

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Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals characterized by a fluorinated carbon chain and oil- and water-repellent properties [1]. PFAS have been used widely in industrial applications and consumer products, such as fire-fighting foam, waterproof spray, food packaging, nonstick cookware, cosmetics, and textiles [1]. PFAS are widely found throughout the environment [2], including groundwater, and are extremely resistant to degradation [3]. Humans encounter PFAS through multiple routes, such as drinking water [4, 5], indoor air, dust, meat, eggs, dairy products, and seafood [6, 7], and they are present in human blood at detectable levels [8–11]. The serum elimination half-life of PFAS spans from 2 to 8 years [12, 13].

The carcinogenicity of PFAS has attracted attention. In November 2023, the International Agency for Research on Cancer (IARC) categorized perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) into Group 1 (carcinogenic to humans) and Group 2B (possibly carcinogenic to humans), respectively [14]. However, IARC has not evaluated the carcinogenicity of other PFAS, including perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), or perfluorononanoic acid (PFNA), and further epidemiological evidence is needed.

Breast cancer is the most frequent female cancer worldwide [15]. PFAS can interact with hormone receptors [3] and induce breast cancer in humans [16]. However, a previous epidemiological evaluation of the association between PFAS and breast cancer yielded inconsistent and inconclusive results [17]. Additionally, research on PFAS beyond PFOS, PFOA, PFHxS, and PFNA is limited. For example, little research has examined PFHpS [18, 19]. PFAS isomer analysis in most previous studies is insufficient, apart from a single case–control study in Japan [19]. Furthermore, all previous studies examined the association between PFAS exposure and breast cancer risk in countries or areas in the Northern Hemisphere [18–27], and no study has been conducted in the Southern Hemisphere. Nevertheless, given variations in lifestyle, breast cancer incidence, types and levels of PFAS exposure, endogenous hormone levels, and other risk factors, the association between PFAS exposure and breast cancer risk likely differs across countries, regions, and ethnicities. There may also be interethnic differences in the effects of PFAS. For example, an association between PFAS and breast cancer may be more likely to occur in non-Japanese Brazilian women who already have lower bioavailable estradiol levels [28] because a higher estradiol level may mask the weak effects of PFAS on breast cancer.

Here, we conducted a multiethnic case–control study to examine the association of plasma PFAS concentrations and risk of breast cancer in Brazilian women.

Materials and methods

Study design and participants

This study was conducted under a multicenter case-control hospital-based design among Brazilian women who lived in São Paulo, Brazil [29]. Eligible cases included women aged 20–74 years who were newly diagnosed with invasive breast cancer confirmed through histological examination. The survey was conducted at the time of admission for the first treatment of breast cancer patients and included only incident cases. Case patients were recruited from a consecutive series of women who visited eight hospitals in São Paulo between 2001 and 2006, with a total of 472 case patients participating (participation rate = 97%). They consisted of 413 cases of infiltrating duct carcinoma, 35 cases of lobular carcinoma, 8 cases of intraductal papillary adenocarcinoma with invasion, 4 cases of mucinous adenocarcinoma, and others. Eligible control subjects were chosen from cancer-free patients who attended the same hospital. Cases and controls were matched 1:1 for age (within 5 years) and ethnicity during the study period. Primary reasons for visiting a hospital among the control group included health check-up (52%; mainly representing cervical screening for asymptomatic individuals); treatment for gynecological (13%; 64% of which were uterine myoma), urological (8%), or dermatological conditions (6%); clinical examination (8%); and others [30]. The major centers participating in our study were specialized in providing women's health services. Of the candidate control group, 22 patients declined to participate (participation rate = 96%), and written informed consent was obtained from 472 matched pairs. The plasma specimen was missing for one breast cancer case; after exclusion of this matched case–control set, 471 matched case–control pairs remained for analysis. This study was performed in accordance with the tenets of the Declaration of Helsinki and its later amendments. The study protocol was reviewed and approved by Comissão Nacional de Ética em Pesquisa (Brasília, Brazil), the institutional review board of the National Cancer Center (Tokyo, Japan), the Research Ethics Committee, Faculty of Medicine, Juntendo University (Tokyo, Japan), and the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (Kyoto, Japan).

Data collection

Using a structured questionnaire, trained interviewers conducted in-person interviews to collect information on smoking habit, physical activity, medical history, menstrual and reproductive history, family history of cancer, and demographics. Dietary habits were assessed using a semiquantitative food frequency questionnaire (FFQ) consisting of 118 items which was specifically prepared and validated for the Brazilian population [31]. Breast cancer patients were interviewed and underwent blood sampling after diagnosis but before their initial treatment for breast cancer. Information on estrogen receptor (ER) and progesterone receptor (PR) status in breast cancer tissue from affected patients was extracted from their medical records [29].

PFAS measurements

Plasma PFAS concentrations were measured using in-port arylation gas chromatography–isotope dilution mass spectrometry with electron capture negative ionization as previously described [32]. Laboratory analyses were conducted at the Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine (Kyoto, Japan) [32]. Chemical analysis was done using 50-μL of aliquots of plasma. The targeted substances are listed in Table S1. Isotopically labeled internal standards of PFAS (EPA-533ES, Wellington Lab, Guelph, ON, Canada) were used for isotope dilution mass spectrometry. Using a capillary column, we achieved the separation and individual quantitation of both linear and branched PFAS isomers. The PFAS frequently detected (>50%) in plasma included linear PFHpS (n-PFHpS), linear and branched PFOS (n-PFOS, 3 m-PFOS, 4 m-PFOS, 5 m-PFOS, 6 m-PFOS, and 3,5 dm-PFOS), linear perfluorooctanoic acid (n-PFOA), linear perfluorononanoic acid (n-PFNA), linear perfluorodecanoic acid (n-PFDA), and linear perfluorododecanoic acid (n-PFDoDA). In this study, n-PFOA and perfluoro-4-methyl-heptanoic acid (4 m-PFOA) were not chromatographically separated, and were combined for analysis. The prefix "n-" denotes a straight-chain isomer, while branched isomers are identified by a numerical prefix such as 3–4 m. Measurement was done by laboratory analysts who were unaware of the case-control status. Plasma samples from both cases and matched controls were tested in the same batches to reduce measurement bias. For PFAS with values below the limits of detection (LODs), we substituted the LOD divided by the square root of two [33]. LOD varied among samples because of the varying recovery of isotopically labeled internal standards. Concentrations of total PFHxS, total PFOS, and total PFOA were determined by adding the plasma concentrations of the linear and branched isomers. Results of analyses of quality control samples are presented in Table S2.

Statistical analysis

After exclusion of pairs in which at least one woman had extremely low or high daily total energy intake (<500 kcal or ≥4000 kcal), 459 pairs were available for multivariable analysis of the FFQ. Isoflavone intake was calculated by summing the amounts of daidzein and genistein consumed. To determine these two variables, we used a food composition table of isoflavones [34, 35]. Daily intakes of other nutrients and total energy were calculated using the United States Department of Agriculture (USDA) food composition tables (Brazilian version) [36] and the Fifth Revised and Enlarged Edition of the Standard Tables of Food Composition in Japan [37] for intake regarding Japanese-specific foods. Dietary intakes of isoflavones and fish and shellfish were adjusted for total energy intake via the residual method [38].

Body mass index was determined using the body weight in kilograms divided by the square of the body height in meters. The distribution of subject characteristics was examined according to case–control status based on the Mantel–Haenszel test with matched-pair strata.

Medians, tertiles, quartiles, and 80th percentiles (80%iles) were derived based on the distribution of plasma PFAS concentrations in the control group. For PFAS with a detection frequency of <50%, odds ratios (ORs) were not computed, with the exception of total PFHxS.

We calculated ORs and 95% confidence intervals (CIs) for breast cancer based on the plasma concentration of individual PFAS using conditional logistic regression analysis with the PROC PHREG procedure and the STRATA statement in SAS, using the lowest plasma PFAS concentration category as reference. We also examined linear trends across categories of each PFAS by treating median concentration within each category as a continuous variable. Using matched case–control sets, multivariable conditional logistic regression analysis (Model 1) was adjusted for body mass index (categories: <21, 21–23.9, 24–26.9, 27–29.9, ≥30 kg/m^2), height (continuous; cm), menopausal status and age at menopause (premenopause, <48, 48–50, 51–52, ≥53 years), age at menarche (<12, 12, 13, 14, ≥15 years), age at first childbirth (nulliparous, <25, 25–26, 27–28, ≥29 years), smoking status (never-smoker, former smoker, current smoker), strenuous physical activity in the past 5 years (no, yes), moderate physical activity in the past 5 years (no, 3 days/month or less, 1–4 days/week, 5 days/week or more), family history of breast cancer (no/unknown, yes), breastfeeding duration (0, 1–6, 7–15, 16–40, ≥41 months), number of births (0, 1, 2, ≥3 [ordinal variable]), alcohol intake (non-drinker, drinker), education level (primary school diploma or lower, <11 years of education, high school diploma, university degree), calendar year of blood sampling (continuous), isoflavone intake

(continuous, energy-adjusted), and fish and shellfish intake (continuous, energy-adjusted). These variables were all either well-established or highly likely risk factors for breast cancer in women [15, 39], excluding education level, calendar year of blood sampling, isoflavone intake, and fish and shellfish intake. Educational attainment was considered as it may correlate with elevated socioeconomic status, potentially leading to increased PFAS exposure. We also considered isoflavone intake and intake of fish and shellfish given the reported inverse associations between breast cancer and both isoflavone intake [29, 40] and omega-3 fatty acids found in fish [41]. Spearman rank correlation coefficients showed that isoflavone intake was significantly associated with plasma concentrations of total PFOS, total PFOA, n-PFHpS, n-PFOS, n-PFOA, and n-PFNA (data not shown). Although calendar year of blood sampling is not a known risk factor for breast cancer, we included it here to eliminate any potential bias. To assess the independent associations of breast cancer with individual PFAS, we further controlled for other PFAS in the multivariable analysis (Model 2). Individual PFAS with a detection frequency of 50% or higher were used for adjustment (Table S1). To avoid multicollinearity, branched PFOS isomers (excluding 3,5 dm-PFOS) were not used as covariates for adjustment because they were highly correlated with each other (Table S3). We considered a history of benign breast disease to be an intermediate variable in the causal link between PFAS exposure and development of breast cancer, and did not include it as a covariate.

In addition to the main analysis, several subanalyses were performed using the same dataset, namely based on menopausal status (premenopausal, postmenopausal) and ethnicity (Caucasian, mixed, Japanese Brazilians). We divided the matched case–control sets and performed unconditional logistic regression analysis using the LOGISTIC procedure in SAS, with adjustment for matching factors (age and ethnicity) along with the other covariates included in Model 2. In the subgroup analysis of mixed-ethnicity women and Japanese Brazilians, vigorous physical activity was excluded as a covariate owing to the limited number of participants engaged in it. Furthermore, we evaluated the association between PFAS exposure and breast cancer risk based on individual hormone receptor status (ER and PR) as well as joint ER/PR status. ORs were estimated using multinomial logistic regression analysis with the SAS PROC LOGISTIC procedure, employing the generalized logit link function.

We handled missing values using complete case analysis. Statistical analyses were performed using SAS v.9.4 for Windows (SAS Institute, Cary, NC, USA). *P*-values and 95% CI were calculated on a two-sided basis, with a significance threshold of 0.05.

Results

Table 1 shows the demographics and characteristics of cases and controls in the present study. Compared with the control group, case patients exhibited a higher likelihood of former or current smoking, first child at an older age, shorter breastfeeding period, and alcohol consumption. Cases were less likely to have experienced childbirth and were also less inclined to participate in moderate physical activity compared with controls. Blood samples were taken more frequently from controls than from cases in later years.

Table 2 shows ORs and 95% CIs for breast cancer by plasma PFAS concentrations in Brazilian women. Although the crude analyses revealed significant inverse associations of n-PFOS and n-PFDA with breast cancer risk, these associations disappeared after multivariable adjustment. Multivariable-adjusted analyses (Model 2) revealed that elevated plasma concentrations of n-PFHpS, 3 m-PFOS, and n-PFNA were significantly linked to higher risk of breast cancer. The adjusted ORs for low, medium, and high n-PFHpS concentrations were 1.00, 1.28, and 2.00 (95% CI = 1.15, 3.48), respectively (P for trend = 0.015). Meanwhile, total PFHxS concentration showed an inverse association with breast cancer risk.

Table 3 shows ORs and 95% CIs for breast cancer by plasma PFAS concentration, categorized by menopausal status and ethnicity. A higher plasma concentration of n-PFHpS was associated with heightened risk of premenopausal breast cancer. Significant associations were also identified in subgroup analysis by ethnicity: higher plasma concentrations of total PFOA and 3 m-PFOS were associated with increased risk among mixed-ethnicity women, while higher plasma 4 m-PFOS concentration was associated with higher risk among Caucasian women.

Table 4 shows ORs and 95% CIs for hormone receptor-defined breast cancer by plasma PFAS concentration. Higher plasma concentration of n-PFHpS was significantly associated with increased risk of double-positive (ER+/PR+) breast cancer, but was not associated with double-negative (ER−/PR−) or single-positive (ER+/PR−) subtypes. Higher plasma concentration of n-PFHpS was significantly associated with higher risk of ER + and PR + breast cancer, but was not significantly associated with risk of hormone receptor-negative breast cancer, as shown in Table S4. Similar but inverse associations were found for total PFHxS concentration.

Discussion

In this study of the association of plasma concentrations of PFAS and breast cancer risk in Brazilian women using a multiethnic case–control design, we found that n-PFHpS, 3 m-PFOS, and n-PFNA were associated with increased risk of breast cancer. Additionally, higher

Table 1 Characteristics of breast cancer cases and matched controls

		Cases ($n=471$)		Controls ($n=471$)		P^a
			Missing (n)		Missing (n)	
Age [years], mean (SD)		53.3 (10.9)	0	53.3 (10.7)	0	-
Ethnicity, n (%)			0		0	-
	Caucasian	263 (55.84)		264 (56.05)		
	Mixed	84 (17.83)		83 (17.62)		
	Black	42 (8.92)		42 (8.92)		
	Japanese Brazilian	82 (17.41)		82 (17.41)		
Age at menarche, n (%)			0		0	0.94
	< 12 years	84 (17.83)		82 (17.41)		
	12 years	92 (19.53)		100 (21.23)		
	13 years	115 (24.42)		103 (21.87)		
	14 years	83 (17.62)		94 (19.96)		
	≥ 15 years	97 (20.59)		92 (19.53)		
Age at first birth, n (%)			1		0	0.031
	Nulliparous women	236 (50.21)		263 (55.84)		
	< 25 years	42 (8.94)		48 (10.19)		
	25–26 years	39 (8.30)		36 (7.64)		
	27–28 years	91 (19.36)		71 (15.07)		
	≥ 29 years	62 (13.19)		53 (11.25)		
Age at menopause, n (%)			1		1	0.41
	Premenopausal women	187 (39.79)		173 (36.81)		
	< 48 years	111 (23.62)		124 (26.38)		
	48–50 years	80 (17.02)		72 (15.32)		
	51–52 years	39 (8.30)		46 (9.79)		
	≥ 53 years	53 (11.28)		55 (11.70)		
Height [cm], mean[b]		157.4	8	157.6	10	0.81
Body mass index [kg/m^2], n (%)			11		15	0.46
	< 21	48 (10.43)		44 (9.65)		
	21 to < 24	103 (22.39)		107 (23.46)		
	24 to < 27	129 (28.04)		140 (30.70)		
	27 to < 30	95 (20.65)		92 (20.18)		
	≥ 30	85 (18.48)		73 (16.01)		
Family history of breast cancer, n (%)		30 (6.37)	0	28 (5.94)	0	0.79
History of benign breast disease, n (%)		37 (7.86)	0	31 (6.58)	0	0.45
Number of births, n (%)			0		0	0.033
	0	62 (13.16)		53 (11.25)		
	1	67 (14.23)		58 (12.31)		
	2	138 (29.30)		116 (24.63)		
	≥ 3	204 (43.31)		244 (51.80)		
Breastfeeding duration, n (%)			1		0	0.01
	0 months	110 (23.40)		93 (19.75)		
	1–6 months	105 (22.34)		87 (18.47)		
	7–15 months	89 (18.94)		98 (20.81)		
	16–40 months	101 (21.49)		97 (20.59)		
	≥ 41 months	65 (13.83)		96 (20.38)		
Smoking status, n (%)			0		0	0.003
	Never	284 (60.30)		320 (67.94)		
	Former	114 (24.20)		106 (22.51)		
	Current	73 (15.50)		45 (9.55)		
Vigorous physical activity in the past 5 years, n (%)		21 (4.46)	0	20 (4.25)	0	0.87
Moderate physical activity in the past 5 years, n (%)			0		0	0.009
	No	419 (88.96)		389 (82.59)		
	3 days/month or less	2 (0.42)		3 (0.64)		

Table 1 (continued)

		Cases ($n=471$)		Controls ($n=471$)		P^a
			Missing (n)		Missing (n)	
	1–4 days/week	29 (6.16)		52 (11.04)		
	≥ 5 days/week	21 (4.46)		27 (5.73)		
Alcohol intake, n (%)			0		0	< 0.001
	Non-drinker	61 (12.95)		102 (21.66)		
	Drinker	410 (87.05)		369 (78.34)		
Education level, n (%)			0		0	0.82
	Primary school diploma or lower	294 (62.42)		297 (63.06)		
	< 11 years of education	62 (13.16)		60 (12.74)		
	High school diploma	70 (14.86)		71 (15.07)		
	University degree	45 (9.55)		43 (9.13)		
Calendar year of blood sampling, n (%)			0		0	< 0.001
	2001	75 (15.92)		60 (12.74)		
	2002	255 (54.14)		222 (47.13)		
	2003	105 (22.29)		127 (26.96)		
	2004	17 (3.61)		26 (5.52)		
	2005	19 (4.03)		34 (7.22)		
	2006	0 (0.00)		2 (0.42)		
Total energy intake [kcal/day], mean[b, c]		1816	12	1723	12	0.21
Fish and shellfish intake [g/day], mean[b, c]		16.1	12	19.1	12	0.17
Isoflavone intake [mg/day], mean[b, c]		3.8	12	7.9	12	0.006

[a] *P* for the Mantel–Haenszel test with matched-pair strata. Not reported for matching factors (age and ethnicity)

[b] Adjusted for age (continuous)

[c] We excluded 12 pairs that included women with extremely low (< 500 kcal) or high (≥ 4000 kcal) daily total energy intakes

The sample size varied between variables because of missing information

plasma concentrations of total PFOA and 3 m-PFOS were associated with increased risk of breast cancer among mixed-ethnicity women, whereas higher plasma 4 m-PFOS concentration was associated with increased risk in Caucasian women. Higher plasma concentration of n-PFHpS was significantly associated with increased risk of hormone receptor-positive breast cancer but not with higher risk of hormone receptor-negative disease. Furthermore, total PFHxS was inversely associated with breast cancer risk. To our knowledge, this study is the first to identify significant positive associations of plasma concentrations of n-PFHpS, 3 m-PFOS, and 4 m-PFOS with breast cancer risk. These findings also indicate the importance of isomer analysis of PFAS in epidemiological studies.

We did not identify significant associations of breast cancer with n-PFHpS, 3 m-PFOS, or n-PFNA concentrations in models unadjusted for other PFAS, as presented in Table 2 (Model 1). However, after mutual adjustment for PFAS, statistically significant associations of breast cancer with n-PFHpS, 3 m-PFOS, and n-PFNA concentrations were identified (Model 2). Even when additional adjustment was performed for n-PFOS only, the associations reached statistical significance (data not shown). This is because n-PFOS showed an inverse although not significant association with breast cancer risk. On this basis, other PFAS, especially n-PFOS, might have acted as confounding factors and masked actual associations. These results also indicate the difficulty of assessing the impact of simultaneous exposure to multiple PFAS. The problem of exposure to mixtures could be viewed as a problem of confounding [42]. Such additional adjustments for PFAS have recently been used in cancer epidemiology studies for PFAS to assess independent associations [43–48].

Results of previous studies of the association between PFAS and breast cancer have been mixed. Only a few studies have evaluated associations between PFHpS and breast cancer risk, and their findings were not consistent. A case–control study in a Chinese population found a null association between PFHpS and breast cancer risk [18], whereas a case–control study in Japanese women identified many inverse associations between breast cancer and various PFAS, including n-PFHpS and total PFHxS [19]. The inverse association between total PFHxS concentration and breast cancer risk in our present study is consistent with a study in Denmark [22]. Conversely, null associations between PFHxS and breast cancer have been reported in the United States [24] and the Philippines [20], whereas a positive association was identified in Greenland [23]. The observed positive association between n-PFNA and breast cancer is inconsistent with the results of most previous studies, which did not observe a positive association between total PFNA and

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer according to plasma PFAS concentrations

PFAS[a]	Range [ng/mL]	No. of cases	No. of controls	Crude OR (95% CI)[b]	Adjusted OR (95% CI)	
					Model 1[c]	Model 2[d]
Total PFHxS						
< 80%ile	< 0.83	396	375	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
≥ 80%ile	0.83–5.74	75	96	**0.60 (0.38, 0.93)**	**0.55 (0.31, 0.98)**	**0.49 (0.26, 0.92)**
P				**0.023**	**0.044**	**0.026**
Total PFOS						
Quartile 1	< 6.39	134	117	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	6.39–9.01	124	118	0.89 (0.62, 1.27)	1.03 (0.64, 1.66)	1.00 (0.61, 1.64)
Quartile 3	9.03–12.19	107	118	0.74 (0.50, 1.10)	0.97 (0.58, 1.62)	0.90 (0.52, 1.56)
Quartile 4	12.21–90.57	106	118	0.74 (0.50, 1.09)	1.02 (0.61, 1.71)	0.91 (0.50, 1.63)
P for trend				0.13	0.95	0.72
Total PFOA						
Quartile 1	< 1.22	134	116	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.22–1.60	115	119	0.82 (0.57, 1.18)	0.89 (0.55, 1.43)	0.86 (0.52, 1.42)
Quartile 3	1.61–2.11	117	118	0.83 (0.57, 1.21)	0.95 (0.58, 1.56)	0.86 (0.51, 1.45)
Quartile 4	2.12–73.04	105	118	0.74 (0.51, 1.09)	0.85 (0.51, 1.42)	0.70 (0.39, 1.27)
P for trend				0.18	0.60	0.26
n-PFHpS						
< Median	< 0.08	236	233	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.08–0.18	111	120	0.90 (0.63, 1.29)	1.12 (0.70, 1.81)	1.28 (0.78, 2.10)
Quartile 4	0.19–1.65	124	118	1.04 (0.72, 1.49)	1.58 (0.96, 2.60)	**2.00 (1.15, 3.48)**
P for trend				0.86	0.077	**0.015**
n-PFOS						
Quartile 1	< 3.68	147	116	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	3.68–5.21	128	119	0.82 (0.57, 1.19)	0.93 (0.58, 1.49)	0.86 (0.53, 1.40)
Quartile 3	5.22–7.16	106	117	**0.65 (0.44, 0.96)**	0.80 (0.49, 1.31)	0.75 (0.44, 1.29)
Quartile 4	7.30–60.75	90	119	**0.56 (0.38, 0.82)**	0.85 (0.51, 1.40)	0.71 (0.39, 1.28)
P for trend				**0.003**	0.50	0.27
3 m-PFOS						
< Median	< 0.39	224	235	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.39–0.55	126	115	1.15 (0.84, 1.58)	1.46 (0.95, 2.25)	**1.71 (1.06, 2.77)**
Quartile 4	0.56–11.77	121	121	1.06 (0.76, 1.49)	1.36 (0.85, 2.17)	**2.12 (1.13, 3.96)**
P for trend				0.70	0.20	**0.022**
4 m-PFOS						
< Median	< 0.65	240	227	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.65–0.91	112	125	0.83 (0.59, 1.16)	0.85 (0.55, 1.32)	0.90 (0.56, 1.46)
Quartile 4	0.92–15.30	119	119	0.93 (0.66, 1.32)	1.00 (0.63, 1.59)	1.18 (0.63, 2.22)
P for trend				0.63	0.95	0.64
5 m-PFOS						
Quartile 1	< 0.70	125	116	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	0.70–1.01	120	114	0.95 (0.65, 1.37)	1.18 (0.72, 1.94)	1.15 (0.68, 1.92)
Quartile 3	1.02–1.43	121	121	0.90 (0.61, 1.33)	0.86 (0.50, 1.46)	0.79 (0.44, 1.40)
Quartile 4	1.44–25.85	105	120	0.78 (0.53, 1.17)	0.88 (0.51, 1.51)	0.74 (0.40, 1.39)
P for trend				0.20	0.36	0.16
6 m-PFOS						
Quartile 1	< 0.82	119	117	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	0.82–1.20	124	118	1.03 (0.71, 1.50)	1.13 (0.69, 1.85)	1.11 (0.66, 1.87)
Quartile 3	1.21–1.68	115	116	0.97 (0.66, 1.42)	1.04 (0.63, 1.74)	1.02 (0.59, 1.77)
Quartile 4	1.69–18.75	113	120	0.92 (0.63, 1.35)	0.99 (0.59, 1.66)	0.97 (0.53, 1.78)
P for trend				0.58	0.83	0.79
3,5 dm-PFOS						
< Median	< 0.06	205	213	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.06–0.12	148	136	1.16 (0.83, 1.61)	1.36 (0.86, 2.15)	1.37 (0.86, 2.19)

Table 2 (continued)

PFAS[a]	Range	No. of	No. of	Crude OR (95% CI)[b]	Adjusted OR (95% CI)	
	[ng/mL]	cases	controls		Model 1[c]	Model 2[d]
Quartile 4	0.13–5.78	118	122	1.02 (0.72, 1.44)	1.14 (0.72, 1.81)	1.26 (0.77, 2.07)
P for trend				0.98	0.70	0.42
n-PFOA + 4 m-PFOA						
Quartile 1	< 0.89	135	117	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 2	0.89–1.23	115	118	0.84 (0.59, 1.20)	0.92 (0.58, 1.46)	0.88 (0.54, 1.44)
Quartile 3	1.24–1.74	114	117	0.83 (0.57, 1.20)	0.97 (0.59, 1.59)	0.86 (0.51, 1.47)
Quartile 4	1.76–72.80	107	119	0.77 (0.53, 1.11)	0.92 (0.55, 1.52)	0.76 (0.43, 1.37)
P for trend				0.19	0.79	0.39
n-PFNA						
< Median	< 0.19	241	235	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.19–0.27	115	111	0.97 (0.68, 1.39)	1.45 (0.90, 2.33)	1.65 (0.99, 2.77)
Quartile 4	0.28–3.89	115	125	0.80 (0.51, 1.25)	1.68 (0.89, 3.15)	**2.19 (1.05, 4.56)**
P for trend				0.35	0.094	**0.033**
n-PFDA						
< Median	< 0.09	244	224	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.09–0.13	131	126	0.92 (0.67, 1.25)	1.00 (0.66, 1.51)	1.00 (0.65, 1.55)
Quartile 4	0.14–2.26	96	121	**0.64 (0.43, 0.94)**	0.87 (0.51, 1.48)	0.72 (0.38, 1.34)
P for trend				**0.030**	0.64	0.37
n-PFDoDA						
< Median	< 0.05	206	212	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.05–0.07	117	120	1.03 (0.72, 1.46)	1.23 (0.77, 1.97)	1.31 (0.81, 2.11)
Quartile 4	0.08–3.03	148	139	1.15 (0.79, 1.68)	1.31 (0.80, 2.15)	1.35 (0.81, 2.25)
P for trend				0.46	0.29	0.26

For total PFHxS, women were dichotomized by 80%iles because of low detection frequency

[a] Medians, quartiles, and 80%iles are based on the distribution of plasma PFAS concentrations among controls

[b] Analyses were performed using conditional logistic regression models of matched case–control sets

[c] Conditional logistic regression models adjusted for body mass index, height, menopausal status and age at menopause, age at menarche, age at first childbirth, smoking status, strenuous physical activity in the past 5 years, moderate physical activity in the past 5 years, family history of breast cancer, breastfeeding duration, number of births, alcohol intake, education level, calendar year of blood sampling, isoflavone intake, and fish and shellfish intake

[d] Additionally adjusted for all other PFAS congeners (natural log-transformed concentration) with a detection frequency of 50% or higher (Table S1), excluding combinations of PFAS congeners with a Spearman rank correlation coefficient of 0.70 or higher to avoid multicollinearity. The branched PFOS isomers (excluding 3,5 dm-PFOS) were not used as covariates for adjustment because they were highly correlated with each other (Table S2)

Bold font indicates a statistically significant association

In the analyses of Models 1 and 2, we excluded 12 pairs that included women with extremely low (< 500 kcal) or high (≥ 4000 kcal) daily total energy intake. Owing to missing covariates, 447 cases and 443 controls were finally used in Model 1 and 2 analyses

breast cancer [16, 18]. The proportion of n-PFNA relative to total PFNA ranged from 58.1 to 98.6% among cases and from 43.0 to 97.0% among controls in the present study. Such variations may change their associations with the risk of breast cancer. A case–control study in a Chinese population also reported null associations of breast cancer with 3 m-PFOS and 4 m-PFOS exposure [18]. The lack of a significant association between total PFOS and breast cancer is consistent with the results of a previous meta-analysis [16]. The observed significant positive association between total PFOA and breast cancer risk in mixed-ethnicity women is also consistent with the result of a previous meta-analysis [16]. It is difficult to explain some inconsistencies in results between studies by differences in PFAS exposure. PFAS exposure levels among women living in São Paulo, Brazil have not always been high, as previously reported [10], while concentrations in our present Brazilian women were lower than those in Japanese women living in Nagano Prefecture for all PFAS excluding branched PFOS isomers, as presented in Table S5. Other discrepancies in results across studies might be partially due to variations in the adjustment variables used in each study.

The pathways linking PFAS exposure with breast cancer remain largely unexplored. However, the mechanisms might be revealed by analysis of the association between PFAS and risk of hormone receptor-specified breast cancer. With regard to n-PFHpS and total PFHxS, a hormone receptor-mediated mechanism has been suggested. Future epidemiological studies to evaluate the role of PFAS in the development of breast cancer must incorporate tumor hormone receptors. Furthermore, we previously found that serum PFAS concentrations, including n-PFHpS, n-PFNA, total PFHxS, and total PFOA, were

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer according to plasma PFAS concentrations by menopausal status and ethnicity

PFAS[a]	Range [ng/mL]	Adjusted OR (95% CI)				
		Menopausal status		Ethnicity		
		Premenopausal[b] (181 cases, 164 controls)	Postmenopausal[c] (266 cases, 279 controls)	Caucasian[d] (249 cases, 246 controls)	Mixed[e] (78 cases, 76 controls)	Japanese Brazilian[e] (79 cases, 80 controls)
Total PFHxS						
< 80%ile	< 0.83	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
≥ 80%ile	0.83–5.74	0.80 (0.34, 1.87)	0.66 (0.39, 1.11)	0.84 (0.47, 1.51)	0.53 (0.15, 1.88)	0.65 (0.17, 2.46)
P		0.60	0.12	0.56	0.32	0.52
Total PFOS						
Tertile 1	< 7.34	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	7.34–11.08	1.23 (0.65, 2.35)	0.75 (0.45, 1.26)	0.76 (0.46, 1.25)	1.48 (0.45, 4.86)	0.66 (0.17, 2.65)
Tertile 3	11.11–90.57	1.12 (0.47, 2.63)	0.69 (0.39, 1.19)	0.87 (0.48, 1.57)	0.65 (0.18, 2.34)	0.65 (0.12, 3.44)
P for trend		0.78	0.21	0.67	0.48	0.71
Total PFOA						
Tertile 1	< 1.34	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	1.34–1.91	0.79 (0.42, 1.51)	0.85 (0.51, 1.40)	0.68 (0.40, 1.16)	1.33 (0.46, 3.81)	1.82 (0.57, 5.84)
Tertile 3	1.92–73.04	0.85 (0.40, 1.81)	0.88 (0.52, 1.49)	0.96 (0.54, 1.71)	**5.05 (1.31, 19.49)**	0.93 (0.26, 3.31)
P for trend		0.67	0.75	0.84	**0.015**	0.72
n-PFHpS						
< Median	< 0.08	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.08–0.18	1.38 (0.74, 2.60)	1.01 (0.63, 1.63)	0.90 (0.55, 1.46)	2.55 (0.85, 7.66)	0.83 (0.21, 3.28)
Quartile 4	0.19–1.65	**2.42 (1.07, 5.47)**	1.51 (0.92, 2.49)	1.74 (0.97, 3.14)	2.60 (0.77, 8.79)	1.14 (0.38, 3.45)
P for trend		**0.031**	0.12	0.12	0.079	0.82
n-PFOS						
Tertile 1	< 4.13	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	4.13–6.48	0.75 (0.40, 1.40)	0.89 (0.54, 1.47)	0.84 (0.51, 1.39)	1.32 (0.40, 4.37)	0.29 (0.07, 1.25)
Tertile 3	6.50–60.75	0.89 (0.41, 1.97)	0.75 (0.43, 1.31)	0.95 (0.53, 1.69)	0.67 (0.19, 2.40)	0.26 (0.05, 1.47)
P for trend		0.76	0.30	0.88	0.47	0.24
3 m-PFOS						
< Median	< 0.39	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.39–0.55	2.03 (1.03, 4.03)	1.24 (0.75, 2.04)	1.51 (0.91, 2.52)	**3.74 (1.02, 13.66)**	0.73 (0.21, 2.54)
Quartile 4	0.56–11.77	1.50 (0.62, 3.65)	1.66 (0.91, 3.02)	1.72 (0.90, 3.30)	**7.85 (1.24, 49.88)**	2.41 (0.57, 10.28)
P for trend		0.30	0.096	0.095	**0.031**	0.25
4 m-PFOS						
< Median	< 0.65	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.65–0.91	1.75 (0.85, 3.58)	0.86 (0.52, 1.42)	0.89 (0.52, 1.54)	2.88 (0.77, 10.79)	0.49 (0.14, 1.70)
Quartile 4	0.92–15.30	1.44 (0.56, 3.69)	1.24 (0.69, 2.24)	**2.18 (1.11, 4.30)**	2.18 (0.47, 10.13)	1.07 (0.24, 4.74)
P for trend		0.30	0.41	**0.029**	0.35	0.82
5 m-PFOS						
Tertile 1	< 0.80	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	0.80–1.27	**2.17 (1.17, 4.04)**	0.64 (0.37, 1.13)	1.03 (0.61, 1.72)	0.71 (0.21, 2.35)	2.36 (0.59, 9.40)
Tertile 3	1.28–25.85	2.02 (0.86, 4.72)	0.61 (0.34, 1.11)	1.22 (0.66, 2.25)	0.51 (0.14, 1.84)	1.86 (0.31, 11.05)
P for trend		0.060	0.19	0.49	0.31	0.82
6 m-PFOS						
Tertile 1	< 0.93	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	0.93–1.46	1.71 (0.94, 3.11)	0.78 (0.46, 1.32)	1.03 (0.62, 1.71)	0.83 (0.26, 2.65)	2.21 (0.62, 7.83)
Tertile 3	1.47–18.75	1.50 (0.71, 3.17)	0.90 (0.51, 1.57)	1.26 (0.70, 2.24)	0.77 (0.23, 2.55)	2.33 (0.51, 10.58)
P for trend		0.27	0.93	0.42	0.68	0.42
3,5 dm-PFOS						

Table 3 (continued)

PFAS[a]	Range	Adjusted OR (95% CI)				
	[ng/mL]	Menopausal status		Ethnicity		
		Premenopausal[b] (181 cases, 164 controls)	Postmenopausal[c] (266 cases, 279 controls)	Caucasian[d] (249 cases, 246 controls)	Mixed[e] (78 cases, 76 controls)	Japanese Brazilian[e] (79 cases, 80 controls)
< Median	< 0.06	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.06–0.12	0.94 (0.53, 1.69)	1.24 (0.78, 1.98)	1.29 (0.80, 2.09)	1.56 (0.59, 4.15)	0.52 (0.16, 1.70)
Quartile 4	0.13–5.78	0.82 (0.42, 1.63)	1.24 (0.75, 2.05)	1.18 (0.69, 2.01)	1.31 (0.41, 4.20)	0.81 (0.27, 2.42)
P for trend		0.58	0.44	0.58	0.65	0.72
n-PFOA + 4 m-PFOA						
Tertile 1	< 1.00	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	1.00–1.54	0.86 (0.45, 1.64)	0.70 (0.42, 1.16)	0.79 (0.46, 1.35)	0.50 (0.17, 1.46)	2.01 (0.60, 6.73)
Tertile 3	1.55–72.80	0.97 (0.46, 2.04)	0.79 (0.47, 1.33)	0.97 (0.55, 1.73)	3.00 (0.79, 11.44)	1.24 (0.35, 4.37)
P for trend		0.93	0.60	0.91	0.051	0.88
n-PFNA						
< Median	< 0.19	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.19–0.27	1.01 (0.52, 1.95)	1.31 (0.79, 2.15)	0.88 (0.50, 1.55)	1.43 (0.51, 4.03)	0.88 (0.26, 2.97)
Quartile 4	0.28–3.89	0.74 (0.34, 1.62)	0.95 (0.54, 1.65)	0.79 (0.41, 1.53)	1.17 (0.32, 4.21)	0.36 (0.08, 1.55)
P for trend		0.49	0.90	0.49	0.70	0.16
n-PFDA						
< Median	< 0.09	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.09–0.13	1.03 (0.53, 1.98)	0.97 (0.60, 1.55)	1.35 (0.81, 2.26)	0.55 (0.17, 1.81)	1.55 (0.47, 5.11)
Quartile 4	0.14–2.26	0.46 (0.19, 1.09)	0.94 (0.53, 1.68)	0.56 (0.29, 1.06)	1.47 (0.38, 5.68)	2.73 (0.56, 13.39)
P for trend		0.12	0.83	0.17	0.65	0.22
n-PFDoDA						
< Median	< 0.05	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.05–0.07	1.11 (0.56, 2.20)	1.20 (0.74, 1.93)	1.03 (0.60, 1.76)	2.85 (0.88, 9.18)	0.63 (0.20, 1.96)
Quartile 4	0.08–3.03	1.38 (0.74, 2.58)	1.25 (0.76, 2.05)	1.10 (0.66, 1.84)	1.44 (0.48, 4.31)	2.58 (0.74, 8.96)
P for trend		0.31	0.37	0.72	0.47	0.12

For total PFHxS, women were dichotomized by 80%iles because of low detection frequency

[a] Medians, tertiles, quartiles, and 80%iles are based on the distribution of plasma PFAS concentrations among controls

[b] The adjustment variables used in this analysis are essentially the same as in Model 2 in Table 2. However, we additionally adjusted for age (continuous) and ethnicity (Caucasian, mixed, Black, Japanese Brazilian), while we did not adjust for age at menopause

[c] The adjustment variables used in this analysis are essentially the same as in Model 2 in Table 2. However, we additionally adjusted for age (continuous) and ethnicity (Caucasian, mixed, Black, Japanese Brazilian)

[d] The adjustment variables used in this analysis are essentially the same as in Model 2 in Table 2. However, we additionally adjusted for age (continuous)

[e] The adjustment variables used in this analysis are essentially the same as in Model 2 in Table 2. However, we additionally adjusted for age (continuous), while vigorous physical activity was not used as a covariate because of the small number of participants engaged in vigorous physical activity. Education level was used as an ordinal variable (continuous)

Bold font indicates a statistically significant association

Subgroup analysis for Black ethnicity was not performed because of the small sample size

significantly associated with elevated global DNA methylation level in peripheral blood leukocytes among Japanese women [11]. Such global methylation is associated with changes in cancer risk [49].

The mechanisms underlying ethnic variation in the association of breast cancer risk with total PFOA, 3 m-PFOS, and 4 m-PFOS remain unidentified. The plasma concentration of 4 m-PFOS in Caucasian women was not higher than that in women of other ethnicities, as presented in Table S6, while plasma concentrations of total PFOA and 3 m-PFOS in mixed-ethnicity women were not higher than those in women of other ethnicities (Table S6). Variations in PFAS exposure do not explain the differences in the observed associations. Interethnic differences in susceptibility to these PFAS may be present. As hypothesized in the Introduction, there were significant associations between breast cancer risk and PFAS among non-Japanese Brazilians but not among Japanese Brazilians.

The present study's strengths include the high reliability of plasma PFAS concentrations as exposure markers for PFAS owing to their prolonged elimination half-lives in human blood. A previous study of serial blood sampling and measurement of PFAS 5 years apart reported

Table 4 Odds ratios (ORs) and 95% confidence intervals (CIs) for hormone receptor-defined breast cancer by plasma concentrations of perfluoroalkyl substances

PFAS[a]	Range	Adjusted OR (95% CI)[b]		
	[ng/mL]	Joint ER/PR status		
		ER + and PR+ (139 cases, 443 controls)	ER + and PR– (58 cases, 443 controls)	ER– and PR– (94 cases, 443 controls)
Total PFHxS				
< 80%ile	< 0.83	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
≥ 80%ile	0.83–5.74	**0.48 (0.25, 0.93)**	0.86 (0.37, 2.02)	0.51 (0.22, 1.20)
P		**0.028**	0.73	0.12
Total PFOS				
Tertile 1	< 7.34	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	7.34–11.08	0.97 (0.55, 1.69)	0.84 (0.40, 1.75)	0.88 (0.47, 1.64)
Tertile 3	11.11–90.57	1.31 (0.67, 2.55)	0.63 (0.25, 1.59)	0.70 (0.32, 1.53)
P for trend		0.39	0.33	0.37
Total PFOA				
Tertile 1	< 1.34	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	1.34–1.91	0.74 (0.42, 1.29)	0.94 (0.43, 2.03)	0.70 (0.37, 1.33)
Tertile 3	1.92–73.04	1.00 (0.55, 1.80)	1.24 (0.53, 2.86)	0.94 (0.47, 1.88)
P for trend		0.81	0.56	0.98
n-PFHpS				
< Median	< 0.08	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.08–0.18	1.29 (0.74, 2.24)	1.18 (0.57, 2.45)	1.11 (0.60, 2.05)
Quartile 4	0.19–1.65	**2.55 (1.41, 4.59)**	1.87 (0.81, 4.30)	1.46 (0.71, 3.00)
P for trend		**0.002**	0.15	0.31
n-PFOS				
Tertile 1	< 4.13	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	4.13–6.48	0.97 (0.56, 1.68)	0.92 (0.44, 1.92)	0.85 (0.47, 1.55)
Tertile 3	6.50–60.75	1.42 (0.74, 2.71)	0.79 (0.32, 1.93)	0.60 (0.28, 1.31)
P for trend		0.24	0.60	0.20
3 m-PFOS				
< Median	< 0.39	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.39–0.55	1.12 (0.64, 1.96)	1.74 (0.82, 3.70)	1.83 (0.96, 3.50)
Quartile 4	0.56–11.77	1.17 (0.58, 2.36)	1.92 (0.70, 5.28)	1.94 (0.86, 4.41)
P for trend		0.67	0.20	0.11
4 m-PFOS				
< Median	< 0.65	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.65–0.91	0.92 (0.51, 1.66)	0.97 (0.42, 2.22)	1.21 (0.63, 2.33)
Quartile 4	0.92–15.30	1.37 (0.69, 2.75)	1.94 (0.73, 5.17)	1.25 (0.53, 2.91)
P for trend		0.37	0.19	0.58
5 m-PFOS				
Tertile 1	< 0.80	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	0.80–1.27	1.38 (0.77, 2.45)	0.91 (0.41, 2.01)	1.00 (0.53, 1.88)
Tertile 3	1.28–25.85	1.22 (0.62, 2.40)	0.99 (0.40, 2.47)	0.81 (0.37, 1.75)
P for trend		0.70	0.99	0.55
6 m-PFOS				
Tertile 1	< 0.93	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	0.93–1.46	1.43 (0.81, 2.55)	0.78 (0.36, 1.69)	1.16 (0.63, 2.13)
Tertile 3	1.47–18.75	1.85 (0.97, 3.51)	1.09 (0.47, 2.55)	0.83 (0.40, 1.73)
P for trend		0.070	0.73	0.53
3,5 dm-PFOS				
< Median	< 0.06	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.06–0.12	1.05 (0.63, 1.74)	1.21 (0.60, 2.43)	1.23 (0.69, 2.20)
Quartile 4	0.13–5.78	0.95 (0.54, 1.67)	1.16 (0.52, 2.58)	0.97 (0.49, 1.92)
P for trend		0.84	0.72	0.95
n-PFOA + 4 m-PFOA				

Table 4 (continued)

PFAS[a]	Range	Adjusted OR (95% CI)[b]		
	[ng/mL]	Joint ER/PR status		
		ER + and PR+ (139 cases, 443 controls)	ER + and PR– (58 cases, 443 controls)	ER– and PR– (94 cases, 443 controls)
Tertile 1	< 1.00	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Tertile 2	1.00–1.54	0.72 (0.41, 1.27)	0.79 (0.36, 1.73)	0.68 (0.36, 1.29)
Tertile 3	1.55–72.80	1.04 (0.58, 1.88)	1.13 (0.49, 2.61)	0.80 (0.40, 1.60)
P for trend		0.67	0.64	0.63
n-PFNA				
< Median	< 0.19	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.19–0.27	1.36 (0.80, 2.33)	0.73 (0.34, 1.57)	0.76 (0.39, 1.50)
Quartile 4	0.28–3.89	1.01 (0.54, 1.90)	0.41 (0.17, 1.02)	0.70 (0.33, 1.52)
P for trend		0.88	0.053	0.33
n-PFDA				
< Median	< 0.09	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.09–0.13	0.93 (0.55, 1.59)	1.88 (0.94, 3.79)	1.09 (0.59, 2.04)
Quartile 4	0.14–2.26	0.78 (0.39, 1.54)	0.62 (0.22, 1.71)	0.91 (0.41, 2.06)
P for trend		0.47	0.63	0.88
n-PFDoDA				
< Median	< 0.05	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Quartile 3	0.05–0.07	1.29 (0.74, 2.22)	1.01 (0.46, 2.21)	1.26 (0.65, 2.43)
Quartile 4	0.08–3.03	1.12 (0.64, 1.93)	1.23 (0.58, 2.63)	1.70 (0.91, 3.18)
P for trend		0.69	0.58	0.10

For total PFHxS, women were dichotomized by 80%iles because of low detection frequency

[a] Medians, tertiles, quartiles and 80%iles are based on the distribution of plasma PFAS concentrations among controls

[b] The adjustment variables used in this analysis are essentially the same as in Model 2 in Table 2. However, we additionally adjusted for age (continuous) and ethnicity (Caucasian, mixed, Black, Japanese Brazilian)

Bold font indicates a statistically significant association

ER-/PR + breast cancer were not analyzed because of the small number of cases

relatively high intraclass correlation coefficients (e.g., interclass correlation coefficient for PFHpS of 0.90) [43]. The reliability of our measurements was additionally assured by the use of isotopically labeled internal standard substances for many PFAS. In addition, our study was specially designed to study risk factors of breast cancer, and the analysis adjusted for a number of potential confounders. Finally, nearly all of the women invited to take part in the study did so, eliminating the possibility of non-response bias.

It is also important to recognize several inherent limitations of this study. First, single-spot measurements of plasma PFAS concentrations might not always reflect pre-disease exposure levels. However, serum levels of PFAS are reported to show long elimination half-lives [12, 13] and relatively high 5-year reproducibility [43]. Although some PFAS have a long half-life, this alone is insufficient to establish temporality. Blood samples collected after diagnosis are not ideal for drawing robust conclusions about associations with disease risk, because the disease itself could impact PFAS concentration due to physiological changes during breast cancer development. Second, sample sizes in the subgroup and subtype analyses were not large. The lack of significant associations in these analyses does not guarantee that these PFAS do not affect the risk of breast cancer. Third, although considerably high participation rates among both eligible case and control subjects reduced the possibility of selection bias, the use of hospital-based controls, whose dietary habits and PFAS exposure level may have differed from those of the general population because of them being particularly conscious of their health or concerned about disease, might nonetheless have led to selection bias. If the diseases of the controls might have affected PFAS exposure level, misclassification bias cannot be ruled out. Fourth, we cannot necessarily rule out the possibility of residual confounding variables such as diabetes.

Conclusions

This study showed that plasma concentrations of several PFAS are associated with breast cancer risk in Brazilian women. Our findings suggest the importance of isomer analysis, subgroup analysis by ethnicity, and breast cancer subtype analysis for accurately characterizing this risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01168-5.

Supplementary Material 1

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Author contributions

H.I., S.T., and M.I. contributed to the conceptualization of the study. K.H.H. contributed to the methodology of laboratory analysis. H.I., K.H.H., G.S.H., Z.L., T.F., M.H.S., and M.I. contributed to the investigation. T.Y. shipped plasma samples. H.I., G.S.H., Z.L., T.F., M.H.S., and M.I. contributed to data curation. H.I. and M.I. contributed to programming (software). H.I. contributed to formal analysis, project administration, and writing the original draft. H.I., S.T., and M.I. contributed to funding acquisition. S.T. and M.I. contributed to supervision. All authors contributed to writing– review and editing.

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Data availability

The ethical guidelines set forth by Japan's Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology mandate the protection of study participants' privacy, thereby prohibiting the public release of individual data. Moreover, the informed consent obtained does not authorize public data sharing. Researchers who wish to verify or replicate our study's findings can submit a research proposal to the corresponding author. The study group board will review the proposal through a prescribed process, considering the privacy of study participants, and may grant special permission to access a minimal dataset if deemed appropriate.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by Comissão Nacional de Ética em Pesquisa (Brasília, Brazil); the institutional review board of the National Cancer Center (Tokyo, Japan); the Research Ethics Committee, Faculty of Medicine, Juntendo University (Tokyo, Japan); and the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (Kyoto, Japan). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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