Distribution of Organohalogen and Synthetic Musk Compounds in Breast Adipose Tissue of Breast Cancer Patients in Ulster County, New York, USA

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Abstract

We determined the concentrations of 98 halogenated organic compounds and synthetic musks in breast fat tissues of 50 breast cancer patients (age range: 34–77 years) collected during 1996–1998 in Ulster County, New York, USA. Polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated biphenyl 153 (PBB-153), polybrominated diphenyl ethers (PBDEs), and synthetic musk compounds (SMCs) were analyzed in breast fat tissues, and 46 analytes were found at a detection frequency of $\geq 65\%$ and at concentrations in the decreasing order of OCPs > PCBs > SMCs > PBDEs > PBB-153. PCBs (median: 323 ng/g wet wt) and dichlorodiphenyltrichloroethanes (DDTs, median: 293 ng/g wet wt) were the major compounds found in breast fat tissues. Among PCB congeners, hexa- and hepta-chlorobiphenyls (60% of total PCBs) were the abundant ones. p,p'-DDE accounted for more than 99% of the total DDT concentrations. The concentrations of SMCs and PBDEs were 1–2 orders of magnitude lower than those of PCBs and DDTs. 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-r-2-benzopyran (median: 33 ng/g wet wt) was the most abundant SMC, whereas BDE-47 (median: 4.5 ng/g wet wt) was the most dominant PBDE congener present in breast tissues. A significant correlation ($p < 0.05$) between women's age and concentrations of DDTs, chlordanes, hexachlorobenzene and PCBs in breast tissues was found. Concentrations of PCBs, PBDEs, OCPs, and SMCs were not significantly different between malignant and benign tumor cases. This study adds baseline information on target tissue burdens of persistent organic contaminants in breast cancer patients.

Graphical Abstract
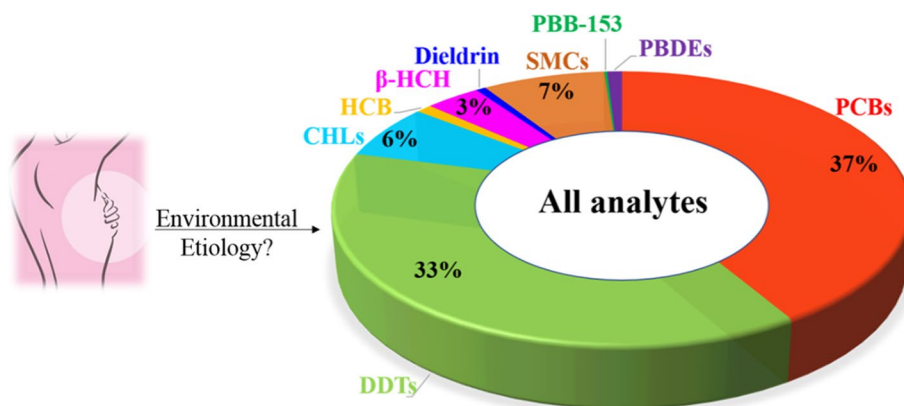
Breast cancer is the most frequently diagnosed cancer (11.6% of the total cancer cases) in females throughout the world and is the leading cause of cancer death in more than 100 countries (Bray et al. 2018). Approximately 2.1 million newly diagnosed breast cancer cases have been estimated in

2018 worldwide and the United States accounts for 15.7% of the total number of cases (BCS 2018; Bray et al. 2018). Some of the known risk factors of breast cancer include hereditary, menstruation, reproductive history, nutrition, anthropometry, breastfeeding, and physical activity (Engmann et al. 2017). As breast cancer stems from prolonged and endogenous hormonal imbalance, exposure to environmental pollutants can perturb hormone homeostasis by mimicking and interfering with hormonal function and thus can modify breast cancer risk (Bray et al. 2018; Lichtenstein et al. 2000; Wielsøe et al. 2017).

Organohalogen compounds (OCs), particularly, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethanes (DDTs), and polybrominated diphenyl ethers (PBDEs), are endocrine disruptors, and exposure to these chemicals among populations is widespread (Leng et al. 2016). Despite the ban on their production and use several decades ago, exposures to OCs continue due to their persistence in the environment. Numerous studies have reported on exposure of humans to legacy lipophilic OCs since the 1980s, but very few have reported on their occurrence in breast tissue from breast cancer patients (Golden and Kimbrough 2009). Scientific evidence linking OC exposure to breast cancer is inconclusive. A review of data published during 2003–2009 found no evidence of association between PCB exposure and breast cancer (Golden and Kimbrough 2009). Two recent studies reported an increase in breast cancer risk from PCB exposures but not from organochlorine pesticides (OCPs), polybrominated biphenyl (PBB), and PBDEs (Leng et al. 2016; Wielsøe et al. 2017). Another study reported a significant positive association between PBDE exposure and breast cancer in Chinese women (He et al. 2018). Most studies linking breast cancer and OC exposure relied on chemical measurements made in serum, because it was thought that this matrix is a proxy for body burdens (He et al. 2018; Leng et al. 2016; Wielsøe et al. 2017). Relying on such proxies, such as serum, can be a source of inconsistent findings in epidemiologic studies.

Adipose fat tissue has been suggested as a preferred matrix to signify steady-state concentrations of lipophilic chemical accumulated in bodies over time, as measurements in serum may be influenced by surges in blood lipid content (Johnson-Restrepo et al. 2005; Petreas et al. 2011). In addition, the concentrations of persistent organic pollutants (POPs) in serum can be affected by the volume of adipose tissue pool (Lee et al. 2017). Studies have suggested that adipose tissue is the repository for POPs in humans (Artacho-Cordón et al. 2015; Lee et al. 2017). Breast tissue also contains a significant amount of fat and can be a repository for the accumulation of lipophilic chemicals. Measurement of POPs in breast fat tissue of breast cancer patients may provide information on chemical burden in target tissues and the etiology of the disease. Nevertheless, it is challenging to obtain breast tissue for epidemiologic studies due to the invasiveness of sample collection.

In this study, 98 OCs and synthetic musk compounds (SMCs) were determined in archived breast adipose tissue collected from 43 malignant and 7 benign breast cancer patients during 1996–1998 in Ulster County, New York, USA. The objectives of this study were to investigate the concentrations and profiles of OCs and SMCs in breast fat samples of breast cancer patients, to compare chemical concentrations measured in breast cancer patients with those reported for other populations, and to evaluate chemical exposure in benign and malignant cases by logistic regression analysis after adjusting for confounders.

Materials and Methods

Sample Collection

Breast adipose tissue samples ($n = 50$) were collected from breast cancer patients with both malignant and benign breast disease, who underwent open breast surgical procedures during 1996–1998 at Benedictine Hospital in Kingston, New York, USA. These samples were archived in a freezer at Wadsworth Center, New York State Department of Health (NYSDOH). The samples were devoid of personal identifiers. Forty-three samples (86%) were from malignant breast cancer patients, and seven samples (14%) were benign cases. The donors were predominantly white females aged between 34 and 77 years, who resided in the Hudson Valley, and represented a wide range of demographic characteristics (Table S1). Information pertaining to reproductive history, menopausal status, age at first menstrual cycle, use of birth control pills, hormone prescription, gynecology procedures, fibroids, ovarian cysts or ectopic pregnancy, and alcohol and cigarette consumption were obtained. Among 50 women, 7 (14%) did not complete the questionnaire. Institutional Review Board approvals were obtained from Benedictine Hospital in Kingston, New York, for the collection of the breast tissue specimens and from NYSDOH for the analysis of breast tissue samples.

Target Analytes

The target analytes were: **(1)** OCPs (number of analytes: 25) including dichlorodiphenyltrichloroethane and its metabolites (DDTs, 6), methoxychlor (1), chlordane metabolites (CHLs, 3), hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs, 4), heptachlor and β-heptachlor epoxide (2), endosulfan isomers (3), endrin and its metabolites (3), aldrin, and dieldrin; **(2)** PCBs (53 congeners); **(3)** PBDEs (12 congeners) and PBB-153 (1); and **(4)** SMCs (7).

Chemical Analysis

Analyses of OCs and SMCs in breast fat samples were performed according to the methods described elsewhere (Johnson-Restrepo et al. 2005; Moon et al. 2012a, b), with slight modifications. Breast fat samples (approximately 1–2 g) were homogenized with anhydrous sodium sulfate and spiked with surrogate standards (PCB-30 and PCB-204). Samples were extracted overnight in a Soxhlet apparatus with 400 mL of dichloromethane (DCM)/hexane (3:1, v/v). The extract was spiked with deuterated 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (d_3-AHTN; Dr. Ehrenstorfer GmbH, Augsburg, Germany), deuterated d_{10}-phenanthrene and ^{13}C-labeled PBDE congeners 28, 47, 99, 100, 118, 153, and 183 as internal standards. Sample extracts were then purified by passage through gel permeation chromatography (Davisil, 100–200 mesh, Aldrich, Milwaukee, WI), eluted with 150 mL of 15% DCM in hexane, which was concentrated to 1 mL.

PCBs and SMCs were analyzed by a gas chromatograph (Hewlett-Packed 6890) coupled with a mass selective detector (MS) (Hewlett-Packed 5973) (Johnson-Restrepo et al. 2005; Moon et al. 2012b). A DB5-MS capillary column was used for chromatographic separation of target chemicals (30 m × 0.25 mm i.d. × 0.25-μm film thickness; Restek, Bellefonte, PA). Quantification of PCB congeners was based on the external calibration standards containing known concentrations of tri- through deca-CB congeners. For the analysis of PBDEs and PBB-153, high-resolution gas chromatography (HRGC; Trace GC Ultra; Thermo Electron, Bremen, Germany) coupled with a high-resolution DFS mass spectrometry (Thermo Electron Corp.) was used (Gump et al. 2014). PBDE congeners were separated using a DB5-MS capillary column (30 m × 0.25 mm i.d. × 0.25-μm film thickness; Restek). Isotope dilution method was used to quantify PBDE concentrations in samples. Analysis of OCPs was performed by a gas chromatograph (Hewlett-Packard 5890) connected with a DB5-MS column (30 m × 0.25 mm i.d. × 0.25-μm film thickness; Restek) and a ^{63}Ni electron capture detector. Helium was used as the carrier gas and nitrogen was the makeup gas. Quantification of OCPs was by an external calibration method.

Quality Assurance and Quality Control

The accuracy and precision of the method were evaluated by the measurements of absolute recoveries (and standard deviation) of surrogate and internal standards. The recoveries of surrogate standards spiked into samples were $74 \pm 14\%$ (mean ± standard deviation, SD) for PCB-30 and $75 \pm 17\%$ for PCB-204. Absolute mean ± SD recoveries of ^{13}C-labeled PBDE congeners 28, 47, 99, 100, 118, 153, and 183 spiked into samples were $71 \pm 13\%$, $67 \pm 13\%$, $64 \pm 12\%$, $60 \pm 12\%$, $66 \pm 12\%$, $64 \pm 13\%$, and $70 \pm 24\%$, respectively. Mean ± SD

recoveries of d_3-AHTN and d_{10}-phenanthrene were $89 \pm 21\%$ and $82 \pm 20\%$, respectively. The reported concentrations were corrected for surrogate or internal standard recoveries. Recoveries of 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-r-2-benzopyran (HHCB), AHTN, and HHCB-lactone spiked into sample matrix presented mean ± SD recoveries at $77 \pm 11\%$, $68 \pm 4\%$, and $101 \pm 5\%$, respectively. Absolute recoveries (mean ± SD) of HCB, oxychlordane, $trans$-nonachlor, cis-nonachlor, p,p'-DDT and o,p'-DDT spiked into sample matrix were $72 \pm 4\%$, $64 \pm 8\%$, $59 \pm 9\%$, $47 \pm 14\%$, $49 \pm 11\%$, and $53 \pm 10\%$, respectively. Procedural blanks were analyzed simultaneously with every set of ten samples, as a check for interferences or contamination from laboratory materials and solvents. Trace concentrations of SMCs (0.32–107 pg/g wet wt) were found in procedural blanks; the mean concentrations found in procedural blanks were subtracted from sample values. The detection limits of individual analytes were in the ranges of 60–220 pg/g for SMCs, 1.5–1.9 pg/g for PBDEs, and 3–460 pg/g for PCBs and OCPs, on a wet weight basis.

Data Analysis

Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL). The concentrations below the LOQ were assigned a value of LOQ divided by square root of 2. Only those compounds with a detection frequency (DF) of ≥ 65% were analyzed by statistical methods. Lipid content was not determined due to the limited amount of breast tissue available for analysis. However, based on the reported lipid contents in adipose tissue of females with breast cancer (Artacho-Cordón et al. 2015), we estimated the lipid content for comparison of our results with those reported by other researchers, on a lipid weight basis. The mean (± SD) lipid content of breast adipose tissue samples was $78 \pm 10.0\%$ (Artacho-Cordón et al. 2015). Differences in the concentrations of chemicals in breast tissues of malignant and benign cases were examined by Student's t test if the data followed a normal distribution; otherwise, a nonparametric Mann–Whitney U test was applied. Pearson correlation was used to examine the strength of association between parameters. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for breast cancer risk from chemicals were determined for benign and malignant cases by binary or multivariate unconditional logistic regression models (Li et al. 2018). Values of $p < 0.05$ denoted statistical significance.

Results and Discussion

Organohalogen and Synthetic Musk Concentrations in Breast Adipose Tissue

The demographic characteristics of the study population are shown in Table S1 (supporting information). The median

age of women (range) was 61 (34–77) years. Of 50 breast cancer patients, 43 had malignant tumor and 7 had benign tumor. Thirty-seven patients had at least one child, and 33 women were postmenopausal. The median (range) age at menarche was 12 (10–16) years. Thirty-six percent of the women took birth control pills, 30% received hormonal prescription, and 34% had fibroids, ovarian cysts, or ectopic pregnancies. Fifty-two percent of the patients were smokers, and 68% were alcohol drinkers before or at the time of enrollment.

Among the 98 target compounds analyzed (Table S2), only those with a DF of ≥ 65% in breast tissue samples were discussed further. PCBs (tri- through deca-CBs), DDTs (p,p′-DDE and p,p′-DDT), CHLs (oxychlordane and trans-nonachlor), HCB, β-HCH, dieldrin, PBB-153, PBDEs (congeners 28, 47, 99, 100, and 153), and SMCs (HHCB, AHTN, and musk-xylene) were found in breast tissues at a DF in the range of 66–100% (Table 1). The concentrations (ng/g wet wt) varied widely and decreased in the order (mean/median): OCPs (627/406) > PCBs (329/323) > SMCs (92/62) > PBDEs (26/7.5) > PBB-153 (2.3/1.5) (Table 1).

PCBs and OCPs

PCBs accounted for 37% of the sum concentrations of all chemicals measured (median: 323 ng/g wet wt or 441 ng/g lipid wt) followed by DDTs (33% of all chemicals measured, median: 293 ng/g wet wt or 388 ng/g lipid wt) in breast adipose samples (Fig. 1; Table 2). The concentrations of other OCs, such as CHLs (median: 51 ng/g wet wt or 68 ng/g

Table 1 Concentrations (ng/g wet wt) of organohalogen and synthetic musk compounds in human breast tissue ($n = 50$) from Ulster County, New York, USA, during 1996–1998

	DF (%)	Mean	SD	Percentiles				
				Min	25th	Median	75th	Max
Tri-CB	86	2.2	1.8	0.0	1.3	2.0	3.0	7.7
Tetra-CB	100	17	10	2.9	7.2	18	26	37
Penta-CB	100	39	25	6.4	17	39	53	106
Hexa-CB	100	133	82	24	70	118	174	333
Hepta-CB	100	77	44	13	40	74	101	186
Octa-CB	98	41	27	0.0	21	36	54	128
Nona-CB	90	14	11	0.0	5.1	12	21	39
Deca-CB	86	5.8	5.2	0.0	1.6	4.5	10	16
∑ PCBs	**100**	**329**	**181**	**59**	**170**	**323**	**466**	**808**
p,p′-DDE	100	515	504	11	127	292	872	2380
p,p′-DDT	66	4.7	21	0.0	0.0	0.8	2.2	146
∑ DDTs	**100**	**520**	**510**	**11**	**127**	**293**	**874**	**2390**
Oxychlordane	100	26	13	3.2	15	27	32	62
Trans-nonachlor	100	24	12	4.2	15	21	31	54
∑ CHLs	**100**	**50**	**23**	**7.4**	**30**	**51**	**66**	**101**
HCB	100	8.7	3.8	2.2	6.1	8.0	11	17
β-HCH	100	36	27	6.4	17	28	49	136
Dieldrin	98	8.7	10	0.0	3.3	5.0	9.4	56
∑ OCPs	**100**	**627**	**529**	**62**	**254**	**406**	**1030**	**2500**
PBB-153	84	2.3	3.0	0.0	0.6	1.5	2.8	16
BDE-28	100	0.7	1.1	0.0	0.1	0.2	0.9	5.0
BDE-47	100	14	27	0.1	1.8	4.5	15	149
BDE-99	96	3.4	7.2	0.0	0.4	0.9	3.1	46
BDE-100	96	3.6	8.5	0.0	0.3	0.7	3.0	48
BDE-153	96	4.6	11	0.0	0.2	0.7	1.7	48
∑ PBDEs	**100**	**26**	**51**	**0.1**	**2.9**	**7.5**	**24**	**288**
HHCB	100	49	50	3.4	25	33	52	320
AHTN	96	8.4	7.0	0.1	2.8	6.6	11	33
Musk-xylene	98	34	39	0.0	14	22	40	236
∑ SMCs	**100**	**92**	**75**	**13**	**52**	**62**	**103**	**437**

Bold values represent the sum of individual compounds for each chemical group

DF detection frequency, SD standard deviation

lipid wt), β-HCH (median: 28 ng/g wet wt or 37 ng/g lipid wt), HCB (median: 8.0 ng/g wet wt or 11 ng/g lipid wt), and dieldrin (median: 5.0 ng/g wet wt or 6.6 ng/g lipid wt) were 1–2 orders of magnitude lower than those of PCBs and DDTs (Table 2).

The concentrations of target compounds measured in this study were compared with those reported for human adipose samples from Americas, Europe, Asia, and Africa during 1993–2016 (Table 2). The concentrations measured in our study were comparable to those reported for breast tissue from California, USA, during the mid-1990s (Petreas et al. 2004, 2011; She et al. 2002). Since 1993, four studies have reported concentrations of PCBs and OCPs in breast adipose tissue of breast cancer patients (Artacho-Cordón et al. 2015; Kalantzi et al. 2009; Petreas et al. 2004, 2011). PCBs and/or DDTs were major compounds found in breast tissues in all of those four studies. PCB concentrations measured in our study (New York) were similar to those reported for California women, but our DDTs concentrations were fourfold lower than those measured from California (Petreas et al. 2004).

Of all the human adipose tissues analyzed thus far, 26 of 27 studies reported PCBs and DDTs as the dominant compounds (Table 2). Whereas PCBs are elevated in Americas and Europe, adipose tissues from Asian countries showed the predominance of DDTs and HCHs (Kunisue et al. 2007; Nakata et al. 2002; Qin et al. 2010; Tan et al. 2008). It is worth noting that the concentrations of PCBs and OCPs in human fat samples have been decreasing globally (Table 2), following the regulations on their production and use (Malarvannan et al. 2013). It is also worth noting that our samples were collected two decades ago and that the current levels in breast tissues can be lower than what was measured in this study. The concentrations of PCBs, DDTs, chlordanes, HCHs, and dieldrin were lower by 68, 80, 85, 56, and 14% in adipose tissue collected in 2013–2014 than those found in our study (Ploteau et al. 2016, 2017).

Among PCB congeners, hexa- and hepta-chlorobiphenyls accounted for 60% of the total PCB concentrations (Fig. 1), which is similar to that reported in earlier studies of human adipose samples (Achour et al. 2017; Moon et al. 2012a; Artacho-Cordón et al. 2016; Mustieles et al. 2017). PCB-153
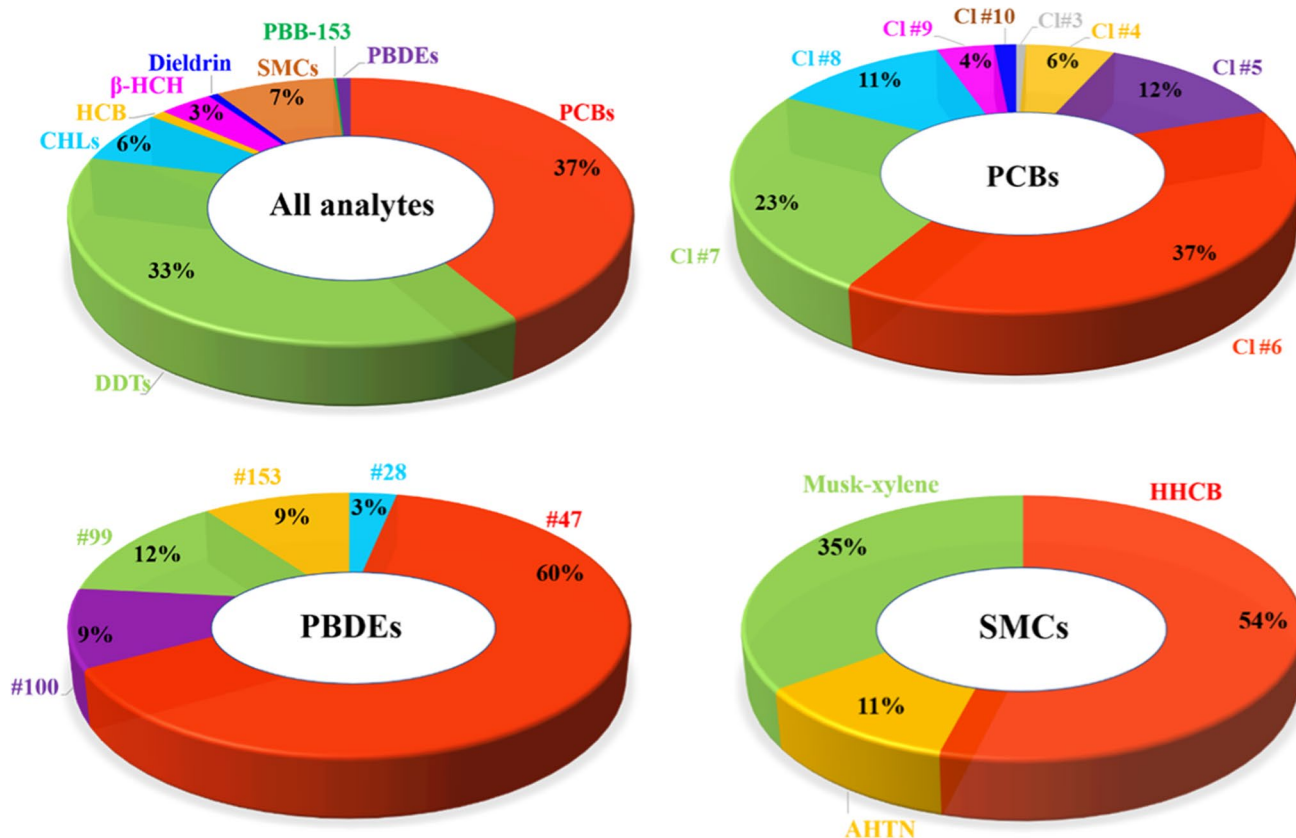
Fig. 1 Distribution profiles of organohalogen and synthetic musk compounds in human breast tissue (based on median concentrations) from Ulster County, New York, USA

Table 2 International comparison of concentrations of organohalogen and synthetic musk compounds in human adipose fat samples

Country	Collection year	Tissue type	n	Gender	Age (range)	PCBs	DDTs	CHLs	HCB	HCHs	dieldrin	SMCs	PBB-153	PBDEs	References
Americas															
USA/CA[a,c]	1995–1998	Breast/abdominal tissue	23	F	28–62	–	–	–	–	–	–	–	–	41	She et al. (2002)
USA/CA[a,c]	1995–1998	Breast biopsy	152	F	28–85	265	–	–	–	–	–	–	–	47	Petreas et al. (2011)
USA/CA[a,d]	1995–1998	Breast/abdominal tissue	21	F	41–59	404	1166	143	59	120	24	–	–	91	Petreas et al. (2004)
USA/NY[b,c]	1996–1998	Breast biopsy	50	F	34–77	323	293	51	8.0	28	5.0	62	1.5	7.5	This study
USA/NY[a,c]						441	388	68	11	37	6.6	82	2.0	10	
USA/NY[a,c]	2003–2004	Subcutaneous fat	52	F, M	18–51	110	–	–	–	–	–	–	–	77	Johnson-Restrepo et al. (2005)
USA/NY[b,c]	2003–2004	Subcutaneous fat	49	F, M	18–51	–	–	–	–	–	–	94	–	–	Kannan et al. (2005)
USA/NY[a,c]						–	–	–	–	–	–	186	–	–	
Brazil[a,c]	2004–2005	Breast fat	25	F	40–71	51	–	–	–	–	–	–	–	1.5	Kalantzi et al. (2009)
Bolivia[a,e]	2010	Adipose tissue	112	F, M	18–70	212	427	–	26	–	–	–	–	–	Arrebola et al. (2012)
Europe															
Denmark[a,c]	1993–1997	Buttock biopsy	402	F	50–64	872	505	–	–	–	–	–	–	–	Vaclavik et al. (2006)
Belgium[a,c]	1996–1998	Subcutaneous fat	46	F	24–42	335	450	–	–	5.9	12.5	–	–	–	Pauwels et al. (2000)
Finland[a,c]	1997–1999	Appendicitis	420	F, M	13–81	437	–	–	–	–	–	–	–	–	Kiviranta et al. (2005)
Belgium[a,c]	2001–2003	Abdominal fat (autopsy)	100	F, M	2–91	585	–	–	–	–	–	–	–	–	De Saeger et al. (2005)
Belgium[a,c]	2001–2003	Abdominal fat (autopsy)	53	F, M	19–84	605	–	–	–	–	–	–	–	5.3	Naert et al. (2006)
Turkey[a,d]	2002–2007	Adipose tissue	46	M	21–64	367	619	–	113	304	–	–	–	–	Çok et al. (2010)
Spain[a,c]	2003	Adipose tissue	20	F	24–81	–	–	–	–	–	–	–	0.3	2.9	Fernandez et al. (2007)
Spain[a,c]	2003	Adipose tissue	20	F	24–81	687	–	–	–	–	–	–	–	–	Fernandez et al. (2008)
Spain[a,c]	2003–2004	Adipose tissue	271	F, M	52[d]	494	97	–	14	10	–	–	–	–	Artacho-Cordón et al. (2016)
Spain[a,c]	2003–2004	Adipose tissue	387	F, M	52[c]	486	93	–	15	11	–	–	–	–	Mustieles et al. (2017)
Belgium[a,d]	2003–2005	Mesenteric (autopsy)	25	F, M	9–70	490	–	–	–	–	–	–	–	5.3	Covaci et al. (2008)
Italy[a,d]	2005–2006	Adipose tissue	12	F, M	0–81	1550	2040	84	152	74	<5	493	–	11	Schiavone et al. (2010)
Czech Republic[a,c]	2007	Subcutaneous fat	98	F, M	17–60	595	510	–	72	17.5	–	–	–	3.1	Pulkrabová et al. (2009)
Belgium[a,d]	2009–2012	Subcutaneous fat	52	F, M	18–57	276	153	11	10	18	–	–	–	2.7	Malarvannan et al. (2013)
Spain[a,c]	2012–2014	Breast fat	103	F	47–62[f]	198	194	–	67	–	–	–	–	–	Artacho-Cordón et al. (2015)
France[a,c]	2013–2014	Subcutaneous fat	99	F	34[d]	137	74	9.3	10	16	5.5	–	0.21	2.1	Ploteau et al. (2016)
		omental fat	51			148	84	11	11	16	5.8	–	0.24	2.0	
France[a,c]	2013–2014	Adipose tissue	93	F	18–45	142	75	9.5	11	17	5.7	–	0.20	3.7	Ploteau et al. (2017)

Table 2 (continued)

Country	Collection year	Tissue type	n	Gender	Age (range)	PCBs	DDTs	CHLs	HCB	HCHs	dieldrin	SMCs	PBB-153	PBDEs	References
Asia															
China[a,c]	2001	Breast biopsy	5	F	48–91	71	4400	27	50	5100	–	–	–	–	Nakata et al. (2002)
Japan[a,c]	2003–2004	Mesenteric (autopsy)	28	F, M	25–109	915	1200	245	31	655	–	–	–	5.8	Kunisue et al. (2007)
Singapore[a,c]	2004–2006	Abdominal fat	88	F	18–40	45	394	0.14	19	51	–	–	–	4.9	Tan et al. (2008)
Hong Kong[a,d]	2006–2007	Adipose tissue	48	F	28–54	110	1770	–	22	231	–	–	–	9.7	Qin et al. (2010)
Korea[a,c]	2007–2008	Omental fat	53	F	40–68	250	190	14	7.4	11	–	–	–	11	Moon et al. (2012a)
Korea[a,c]	2007–2008	Omental fat	43	F	40–68	–	–	–	–	–	–	104	–	–	Moon et al. (2012b)
China[a,c]	2014–2016	Breast/abdominal tissue	374	F	52[d]	–	–	–	–	–	–	–	–	95	He et al. (2018)
Africa															
Tunisia[a,c]	2014	Adipose tissue	40	F, M	20–85	100	343	–	10	10	–	–	–	–	Achour et al. (2017)

CA California, *NY* New York, – not available

[a]ng/g lipid wt; [b]ng/g wet wt; [c]median value; [d]mean value; [e]geometric mean; [f]25th–75th percentiles

(median: 50 ng/g wet wt) was the most dominant congener, followed by PCB-138 (median: 41 ng/g wet wt) and PCB-180 (median: 34 ng/g wet wt) (Table S2). *p,p′*-DDE, a major metabolite of DDT, accounted for more than 99% of the total DDT concentrations, which is in agreement with that of previous studies and suggests historical exposures to this pesticide rather than current exposure (Achour et al. 2017; Malarvannan et al. 2013). Among chlordane compounds, oxychlordane (median: 27 ng/g wet wt) and *trans*-nonachlor (median: 21 ng/g wet wt) (Table S2) were the major metabolites found in breast tissue. Among HCH isomers, only β-HCH (median: 28 ng/g wet wt) was found in our breast tissue samples, probably due to its higher persistence and bioaccumulation over other HCH isomers (Petreas et al. 2004; Schiavone et al. 2010). It is worth noting that human adipose fat samples from Asian countries presented higher concentrations of HCHs than those from North American and European countries (Kunisue et al. 2007; Nakata et al. 2002; Petreas et al. 2004; Pauwels et al. 2000) (Table 2). Dietary sources, especially animal origin foods (fish, dairy products and meat), are the main sources of PCB and OCP exposure in the general population (Batt et al. 2017; Gasull et al. 2011).

PBDEs

The total PBDE concentrations in breast adipose tissue ranged from 0.1 to 288 ng/g wet wt, with a median value of 7.5 ng/g wet wt (Table 1). A comparison of measured concentrations of PBDEs in adipose tissues worldwide revealed that samples from the United States had the highest concentrations, followed by those from Asian and European countries (Covaci et al. 2008; Malarvannan et al. 2013; Moon et al. 2012a; Petreas et al. 2004) (Table 2).

Among PBDE congeners analyzed, BDE-47 (median: 4.5 ng/g wet wt) was the dominant congener, accounting for 60% of total PBDEs, followed by BDE-99, BDE-100, BDE-153, and BDE-28 (median: 0.2–0.9 ng/g wet wt) (Table 1). Elevated concentrations of BDE-47 have been reported in human adipose tissues from the United States (Johnson-Restrepo et al. 2005; Petreas et al. 2004), Europe (Naert et al. 2006; Schiavone et al. 2010), and Asia (Qin et al. 2010; Tan et al. 2008) (Table 2). Nevertheless, some European studies presented BDE-153 as the dominating congener in human adipose samples. BDE-209 was reported to be the prominent congener in adipose tissue from a French and Korean female population (Moon et al. 2012a; Ploteau et al. 2017). The congener profiles of PBDEs in human tissues were similar between breast and other adipose samples. Indoor dust ingestion and diet are major sources of PBDE exposure in humans (Bramwell et al. 2016).

SMCs

The concentrations of SMCs in breast adipose tissues were one order of magnitude lower than those of PCBs and DDTs and accounted for 7% of the total concentrations of target chemicals measured in the study (Table 1; Fig. 1). Synthetic musks can originate from sources, such as deodorants and antiperspirants, which are commonly applied under arm and near breasts. The sum concentrations of HHCB, musk-xylene, and AHTN in breast tissue samples ranged from 13 to 437 (median: 62) ng/g wet wt (Table 1). Only a few studies have reported SMC concentrations in human adipose samples. Our values for samples collected during 1996–1998 were lower than those reported for adipose fat samples collected from New York City in 2003–2004 (Kannan et al. 2005), Korean females in 2007–2008 (Moon et al. 2012b), and Italian samples in 2007–2008 (Schiavone et al. 2010) (Table 2).

HHCB (54%) was the predominant SMC followed by musk-xylene (35%) and AHTN (11%) in breast tissue samples (Fig. 1). Due to their toxicity, nitro musks, such as musk xylene, have been replaced with polycyclic musks, HHCB, and AHTN. However, musk-xylene and musk-ketone continue to be used in personal care products and other household cleaning products (Taylor et al. 2014). HHCB was found in 100% of human breast tissue samples analyzed at concentrations that ranged from 3.4 to 320 (median: 33) ng/g wet wt. AHTN was found in 96% of the samples analyzed at concentrations that ranged from 0.1 to 33 (median: 6.6) ng/g wet wt. The higher concentrations of HHCB than of AHTN suggest greater usage rates of the former, which is in line with what was reported earlier (Kannan et al. 2005; Moon et al. 2012b; Schiavone et al. 2010). For example, production/import volume of HHCB (1–10 million lbs) in the United States was 20–100-fold higher than that of AHTN (0.01–0.5 million lbs) in 1990–1994 (SGP 2013). HHCB was found at higher concentrations in household commodities and cosmetics than AHTN (Nakata et al. 2015; Reiner and Kannan 2006).

Age-Dependent Accumulation

The concentrations of OCPs and PCBs increased significantly with women's age (Fig. 2). The median concentrations of PCBs, DDTs, chlordanes, and HCB in breast adipose tissues of older women (≥ 60 years) were 1.5–2.0-fold higher than those in younger women (< 60 years; Fig. S1). The patients ≥ 60 years had a higher OC burden (Table S1). The increasing concentration of POPs with age has been reported earlier (Artacho-Cordón et al. 2015; Malarvannan et al. 2013). The relationship between age and concentrations of POPs in
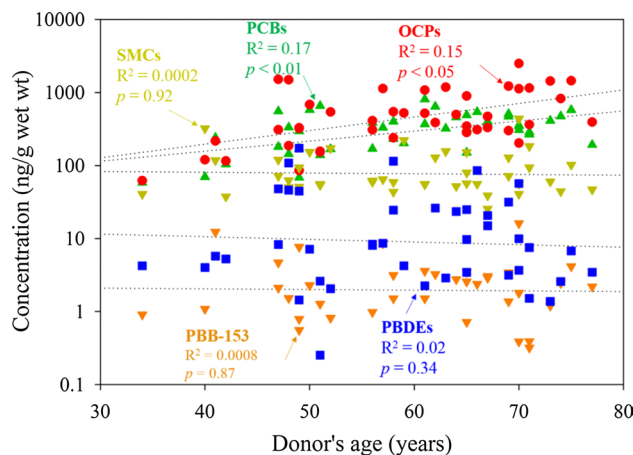
Fig. 2 Correlations between donor's age and concentrations of organohalogen and synthetic musk compounds in breast tissues from Ulster County, New York, USA

human adipose tissues was reported earlier in the United States (Johnson-Restrepo et al. 2005), Bolivia (Arrebola et al. 2012), Spain (Artacho-Cordón et al. 2015), Belgium (Covaci et al. 2008; Malarvannan et al. 2013), France (Ploteau et al. 2016), Singapore (Tan et al. 2008), Japan (Kunisue et al. 2007), and China (Nakata et al. 2002; Qin et al. 2010).

In contrast to that found for PCBs and OCPs, the concentrations of PBDEs, PBB-153, and SMCs in breast adipose tissue were not positively correlated with age (Fig. 2). When PBDE concentrations were grouped into two age groups, younger women (< 60 years) had 1.1/1.8-fold (mean/median) higher levels than those of older women (≥ 60 years; Table S1). Several earlier studies have reported the lack of age-dependent accumulation of PBDEs and SMCs in human adipose tissue (Kalantzi et al. 2009; Moon et al. 2012a, b). Higher PBDE concentrations in younger than older individuals have been reported (Petreas et al. 2011; She et al. 2002). The higher concentration of PBDEs in younger individuals may be related to lifestyle choices, which involve frequent use of electronics (Harrad et al. 2010; Watkins et al. 2011). No correlation existed among the concentrations of PBDEs and OCPs in breast tissue samples (Table S3), which was in agreement with those reported in previous results (Johnson-Restrepo et al. 2005; Petreas et al. 2011) and suggests differences in exposure sources and accumulation features of these two classes of chemicals in humans.

Comparison Between Malignant and Benign Tumor Cases

There was no significant difference in the concentrations of OCPs, PCBs, PBDEs, PBB-153, and SMCs in breast

tissue samples between malignant and benign tumor cases ($p > 0.05$; Table S4). In comparison with the first quartile concentrations of target chemicals, the ORs for breast cancer risk were ≥ 1 in the higher quartiles for most OCs, but the associations were not significant in both crude and adjusted models (Table S5). A recent study showed a significant positive association between PBDEs and breast cancer risk in women from China (He et al. 2018).

Conclusions

This is one of the very few studies that determined concentrations of PCBs, DDTs, HCHs, CHLs, HCB, PBDEs, and synthetic musks in breast adipose tissues from breast cancer patients. Our results show that OCs and SMCs are ubiquitously found in breast adipose samples, with concentrations in the decreasing order: OCPs > PCBs > SMCs > PBDEs > PBB-153. The concentrations of PCBs and DDTs accounted for 70% of the concentrations of all compounds analyzed. The concentrations of target chemicals were not significantly different between malignant and benign tumor cases. Although this is one of the very few studies that measured OCs and SMCs in target tissues of breast cancer patients, our study has several limitations. The breast adipose tissues were collected almost two decades ago. Breast lipid content was not determined due to the limited mass of sample available for chemical analysis. Our sample size is limited, which can affect our analysis of breast cancer risk from POPs exposures. Nevertheless, this study adds knowledge to the existing information on target tissue concentrations of POPs in breast cancer patients.

Compliance with Ethical Standards

Conflict of interest The authors declare no competing financial interest.

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