Levels of Circulating Polychlorinated Biphenyls and Mammographic Breast Density

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Abstract. *Background: Polychlorinated biphenyls (PCBs) are ubiquitous chemicals found in the environment that accumulate in body fat and exhibit endocrine-disrupting properties. These compounds are therefore suspected of influencing breast cancer risk, but results from studies are inconsistent. To further clarify the role of PCBs in the etiology of breast cancer, the present study aimed to examine the relation of 24 PCB congener levels, which were considered individually and in combinations, with mammographic density, one of the risk factors most strongly associated with breast cancer. Materials and Methods: Plasma PCB levels were measured by gas chromatography coupled to mass spectrometry in 106 post-menopausal women for whom mammographic density was measured using a computer-assisted method. Results: Spearman correlation coefficients adjusted for potentially confounding factors (r_s) show that while levels of total PCBs do not appear to be correlated with the percentage mammographic density (r_s=–0.19, p=0.08), an increase in the plasma levels of congeners nos. 153, 183, 196 and combined Wolff group 3 PCBs is negatively correlated with the percentage mammographic density (r_s=–0.24, p=0.03; r_s=–0.30, p=0.004; r_s=–0.22, p=0.04; and r_s=–0.22, p=0.04 respectively). Conclusion: Our results suggest that an increase in the plasma levels of some PCB congeners, in particular cytochrome P450 1A1 inducers, is associated with lower mammographic density in post-menopausal women.*

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Key Words: Polychlorinated biphenyl, PCB, organochlorine, mammographic breast density, breast cancer.

Polychlorinated biphenyls (PCBs) are chemical compounds used in electrical equipment until their production was banned in Western Europe and North America in the 1970s (1). They represent a large class of stable chemicals that includes 209 different congeners, and their improper disposal over decades has resulted in their widespread distribution in the environment. Their stability has led to their bioaccumulation in ecosystems and exposure of humans mainly *via* food intake, particularly fish (2). The presence of PCBs in human serum, plasma or adipose tissue has been reported in several studies over the past decades (3-6).

Depending on their chlorine pattern, PCB congeners display estrogenic or anti-estrogenic activity and some can induce cytochrome *P450* enzymes involved in the metabolism of estrogens (7). Because epidemiological evidence has shown that several breast cancer risk factors are estrogen-dependent (8), and since PCBs possess the ability to mimic or inhibit estrogen activity, researchers have examined the relation between total circulating or adipose tissue levels of PCBs and breast cancer risk, but most of these studies yielded null results (9). However, when PCB congeners were assessed individually, some observed that higher levels of certain PCBs were associated with high breast cancer risk (5, 6, 10-13), whereas negative (10, 11, 14) or null associations (15-17) were found by others. In contrast, those who considered PCBs in groupings according to Wolff's classification found protective effects (14, 15), although one study found null results (10) and another an increased risk (12).

Mammographic density (MD) is increasingly used as a biomarker of breast cancer risk (18) because of its strong relation to the risk of this disease (19, 20). MD refers to the proportion of the breast that appears light on a mammography, which represents epithelial or stromal tissue. The link between

MD and breast cancer is not well-understood but does seem to be related to estrogens. For instance, in addition to the proliferative effect on fibroglandular cells of the breast by endogenous or exogenous estrogens (21), several breast cancer risk factors related to estrogens such as parity, age at first birth, age at menopause, hormone replacement therapy (HRT) or use of chemopreventive agents such as tamoxifen, are also associated with MD (22, 23). Because PCBs are believed to influence estrogen metabolism and may be related to breast cancer risk, it is plausible that plasma levels of PCBs could have an effect on MD. To our knowledge, the relation between PCB levels and MD has not been investigated to date. The aim of the present study was to evaluate the association of circulating levels of PCB congeners, individually and combined, with MD among post-menopausal women.

Materials and Methods

Study population and data collection. The population of this study has been described in detail elsewhere (4). In summary, 110 women were recruited at a mammography screening clinic located in Quebec City between July 2003 and March 2004. Women were eligible if they were post-menopausal with no history of cancer at any site, had not taken hormonal derivatives within three months prior to mammography, had never used tamoxifen or raloxifen, had no breast surgery and no endocrine system disease. Women agreeing to participate provided informed consent. The Research Ethics Committee of the Centre Hospitalier Universitaire de Québec (Quebec, QC, Canada) reviewed and approved this study (# DR-002-1025). Breast cancer risk factors were documented by a face-to-face interview. Anthropometric measurements were also recorded and blood samples collected. Four women were excluded from analyses because of missing mammogram film.

Mammographic breast density assessment. A craniocaudal view of a randomly chosen breast was evaluated for each woman after all mammograms were digitized using a Kodak Lumiscan85 digitizer (Eastman Kodak Company, Rochester, NY, USA) at 260 μm per pixel. Breast tissue density (as a percentage) and the absolute amount of dense tissue (absolute density in cm^2) were assessed by one trained author (C.D.), with a computer-assisted method (24). The reviewer did not have any information regarding women's status or medical history. The intra-class correlation coefficients (n=106 duplicate images) were 0.98 and 0.97 for percentage and absolute density, respectively.

Laboratory analysis. The method for PCB analysis was followed as previously described (4). Samples were analyzed by gas chromatography-electron capture negative ionisation mass spectrometry. Plasma lipid levels were determined by enzymatic methods and calculated according to the equation proposed by Akins *et al*. (25). The accuracy of analytical procedures was verified through the quantification of the NIST standard reference material (SRM) 1589a (National Institute of Standards and Technology, Gaithersburg, MD, USA) and participation in international inter-laboratory comparison programs. Furthermore, the precision was monitored by analyzing 15 samples from a control serum pool. The limit of detection (LOD) ranged from 3 to 5 ng/l, depending on the PCB congener.

Statistical analysis. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and a *p*-value of less than 0.05 was considered statistically significant. Correlation between continuous levels of plasma lipid-adjusted PCBs [24 congeners individually, PCB groupings or total PCBs (sum of the 24 congeners)] and continuous measures of MD were evaluated with Spearman correlation coefficients (r_s) and their *p*-value in univariate and multivariate-adjusted models. For PCB congeners significantly correlated to MD ($p<0.05$) in the fully-adjusted model and for the other congeners in Wolff group 3, multivariate-adjusted means of MD were assessed according to the tertiles of each PCB level using generalized linear models. MD data were square-root transformed for normalizing their skewed distribution. Results are presented as back-transformed values. Multivariate analyses were adjusted for potential confounders identified *a priori* which are listed in the table footnotes. Waist circumference was used in these analyses because this measure of body size most strongly correlated with MD. These analyses were also performed with crude PCB levels (not plasma lipid-adjusted) and results remained similar (data not shown). The latter analyses were similarly adjusted in multivariate models except that plasma lipid was also included as a covariate.

Results

Population characteristics are described in Table I. The mean age at time of mammography was 58.2 years [standard deviation (SD)=5.6 years] and mean waist circumference was 85.6 cm (SD=12.8 cm). The mean percentage and absolute MD was 26.7% (SD=21.2%) and 31.4 cm^2 (SD=23.2 cm^2) respectively.

Median plasma lipid-adjusted levels of PCB congeners detected in more than 50% samples are presented in Table I. The three congeners with highest levels in plasma samples were PCB 153, PCB 180 and PCB 138 with median levels of 39.9, 33.7 and 23.3 ng/g lipid respectively.

Correlations between PCB levels and MD are presented in Table II. Among all congeners, an increase in the plasma levels of congeners 153, 183, 196 and combined Wolff group 3 PCBs was negatively correlated with MD. The other congeners when analyzed individually, in groupings or as the sum of all 24 congeners (total PCBs) did not show any significant correlation with MD.

Table III lists associations of Wolff group 3 PCBs with MD. Increasing tertile levels of PCB 153 were associated with a lower percentage MD (31.9%, 24.8% and 22.0%; r_s=–0.24, p=0.03). A negative correlation was also observed for PCB 183 levels with percentage MD (r_s=–0.30, p=0.004), and the mean percentage MD according to increasing tertile levels of PCB 183 were 32.8%, 23.8% and 21.8%, respectively. Increasing tertile levels of PCB 196 were also associated with a lower percentage MD (29.7%, 27.5% and 21.6%; r_s=–0.22, p=0.04). Although no other group 3 congener was associated with MD, levels of combined Wolff group 3 PCBs were negatively correlated with the percentage MD (r_s=–0.22, p=0.04) and the mean percentage MD in relation to the first to the third tertiles

Table I. *Characteristics of the study population (N=106).*

Age (years)	
At mammography, mean (SD)	58.2 (5.6)
At menarche, mean (SD)	12.8 (1.7)
At first full-term pregnancy[a], mean (SD)	25.3 (4.3)
At menopause, mean (SD)	51.7 (4.3)
Waist circumference (cm), mean (SD)	85.6 (12.8)
Number of full-term pregnancies[a], mean (SD)	2.5 (1.1)
Lactation (weeks)[a], mean (SD)	17.4 (29.7)
Contraceptive use %	82.1
Number of years since cessation of HRT[b], mean (SD)	2.9 (4.0)
Family history of breast cancer %	29.3
Personal history of breast biopsies %	23.6
Ex- or current smoker %	55.7
Alcohol intake (drinks/day), mean (SD)	0.5 (0.6)
Mammographic density (%), mean (SD)	26.7 (21.2)
Mammographic density (cm^2), mean (SD)	31.4 (23.2)

Congeners[c]	Median[d]	Interquartile range[d]		CV
	Q2	Q1	Q3	
PCB 74	9.05	6.06	13.8	17
PCB 99	6.22	4.12	9.52	18
PCB 105	1.99	1.30	3.08	8
PCB 118	11.0	7.62	16.4	6
PCB 138	23.3	16.7	31.0	7
PCB 146	3.88	2.96	5.40	7
PCB 153	39.9	31.6	54.8	6
PCB 156	4.55	3.27	6.16	6
PCB 163	14.7	10.5	20.4	11
PCB 167	1.46	0.97	1.92	13
PCB 170	10.7	8.22	14.8	5
PCB 172	1.45	1.08	1.99	6
PCB 177	1.57	1.17	2.28	11
PCB 178	1.85	0.88	2.71	12
PCB 180	33.7	25.4	45.8	5
PCB 183	2.77	1.80	3.65	11
PCB 187	7.20	5.36	10.4	13
PCB 194	6.13	4.60	8.33	9
PCB 195	1.18	0.89	1.58	10
PCB 196	1.91	1.38	2.68	12
PCB 199	2.33	1.64	3.13	10
PCB 203	3.99	2.89	5.33	9
PCB 206	2.09	1.63	3.03	12
PCB 209	1.05	0.79	1.54	11
Group 1	8.71	6.50	12.5	-
Group 2	64.4	45.2	83.3	-
Group 3	88.9	67.5	120	-
PCBs	202	159	270	-

CV, Coefficient of variation of 15 blind duplicates. HRT, hormone replacement therapy. [a]In parous women (n=80). [b]Among women who used HRT (n=68). [c]Only congeners detected in more than 50% samples are listed. [d]Lipid-adjusted concentrations (ng/g lipids) of PCB congeners; a value equal to one half of the limit of detection was attributed to non-detected values to calculate median. Group 1 according to Wolff's classification includes congeners 177 and 187. Group 2 includes congeners 74, 105, 118, 138, 156, 167 and 170. Group 3 includes congeners 99, 153, 180, 183, 196 and 203.

were 33.0%, 22.1% and 23.2% respectively. Similarly, although not always statistically significant, increasing levels of congeners nos. 153, 183, 196 and combined Wolff group 3 PCBs were associated with a lower absolute MD.

Discussion

This cross-sectional study showed that while the plasma levels of total PCBs and most of the individual PCB congeners evaluated did not seem to relate to MD, levels of congeners 153, 183, 196 and combined Wolff group 3 PCBs were inversely associated with MD among post-menopausal women. To our knowledge, the relation of PCBs with MD had not been assessed to date.

Since MD is a strong and independent breast cancer risk factor and because both share common estrogen-related determinants, it is interesting to compare our results to those of breast cancer risk. Our observation of no association of total plasma PCBs levels and MD seems to agree with null results found by most who evaluated the association between total PCB levels and breast cancer risk (10, 11, 13, 15-17, 26, 27). When assessed individually, PCB 153 levels showed an inverse (14) or positive (6) association with breast cancer risk; however this congener did not appear to influence the risk of this disease in most studies (5, 12, 13, 16, 17, 28). Similarly, levels of PCB 183 did not seem to be related to the risk of this cancer in several studies (5, 14, 17) but was associated with an increased risk in one study (13). Therefore, our findings of lower MD with higher plasma levels of PCB 153 and PCB 183 do not reflect results from other studies, although inconsistent, on breast cancer. PCB 196 has not been discussed in the literature regarding its relation to breast cancer risk.

The three congeners that appear to influence MD are all part of the same group (group 3) according to the classification proposed by Wolff *et al*. (7). This PCB congener grouping is based on structural, biological and pharmacokinetic considerations. For example, congeners in group 2 present potentially anti-estrogenic effects and are moderately persistent, whereas those in group 3 are biologically persistent and some are inducers of enzyme cytochrome-*p450 1A1* (CYP1A1). This enzyme participates in estrogen catabolism and transforms estradiol into catechol estrogens which bind to estrogen receptor with less affinity compared to estradiol, making them less potent mitogenic agents (29). Moreover, CYP1A1 protein levels were shown to be lower in malignant than in normal breast tissue (30). Therefore, induction of the activity of this enzyme by group 3 PCBs could, in part, explain the observed inverse association between some group 3 PCBs (or all combined) (p=0.04), and MD, since MD reflects the extent of proliferation of fibroglandular cells (31). However, CYP1A1 also participates in the metabolism of carcinogenic substances

Table II. *Correlations between plasma concentrations of polychlorinated biphenyls and mammographic density.*

		r_s (*p*)[a]					
		Percentage density (%)			Absolute density (cm^2)		
Compound Wolff groupings	N[b]	Crude	Adjusted[c]	Adjusted[d]	Crude	Adjusted[c]	Adjusted[d]
Group 1							
PCB 177	106	–0.02 (0.82)	–0.13 (0.18)	–0.17 (0.12)	–0.09 (0.36)	–0.14 (0.14)	–0.13 (0.23)
PCB 187	106	0.13 (0.20)	–0.10 (0.32)	–0.16 (0.15)	0.02 (0.86)	–0.10 (0.32)	–0.11 (0.32)
Group 1[e]	106	0.09 (0.34)	–0.11 (0.26)	–0.17 (0.13)	–0.002 (0.99)	–0.11 (0.28)	–0.11 (0.29)
Group 2							
PCB 74	105	–0.03 (0.75)	0.02 (0.88)	–0.02 (0.88)	–0.004 (0.97)	0.02 (0.85)	0.01 (0.91)
PCB 105	106	0.01 (0.89)	0.04 (0.67)	–0.007 (0.95)	0.05 (0.58)	0.07 (0.47)	0.05 (0.67)
PCB 118	106	–0.01 (0.92)	–0.006 (0.95)	–0.06 (0.58)	0.02 (0.85)	0.03 (0.80)	–0.005 (0.96)
PCB 138	106	–0.08 (0.42)	–0.18 (0.06)	–0.21 (0.05)	–0.14 (0.16)	–0.18 (0.06)	–0.16 (0.13)
PCB 156	106	0.17 (0.09)	–0.02 (0.84)	–0.09 (0.42)	0.04 (0.65)	–0.06 (0.58)	–0.09 (0.43)
PCB 167	106	0.04 (0.69)	–0.09 (0.34)	–0.14 (0.19)	–0.01 (0.88)	–0.08 (0.42)	–0.08 (0.44)
PCB 170	106	0.15 (0.12)	–0.08 (0.40)	–0.10 (0.36)	0.02 (0.82)	–0.10 (0.31)	–0.07 (0.50)
Group 2[f]	106	0.002 (0.98)	–0.09 (0.35)	–0.13 (0.21)	–0.05 (0.63)	–0.09 (0.35)	–0.09 (0.39)
Group 3							
PCB 99	93	–0.17 (0.11)	–0.16 (0.14)	–0.13 (0.25)	–0.15 (0.16)	–0.13 (0.21)	–0.13 (0.28)
PCB 153	106	0.05 (0.61)	–0.18 (0.07)	**–0.24 (0.03)**	–0.04 (0.72)	–0.15 (0.13)	–0.15 (0.15)
PCB 180	105	0.17 (0.09)	–0.07 (0.47)	–0.09 (0.40)	0.04 (0.65)	–0.08 (0.44)	–0.05 (0.67)
PCB 183	106	–0.08 (0.41)	**–0.29 (0.003)**	**–0.30 (0.004)**	–0.17 (0.07)	**–0.28 (0.005)**	**–0.24 (0.02)**
PCB 196	106	0.03 (0.74)	**–0.24 (0.01)**	**–0.22 (0.04)**	–0.09 (0.33)	**–0.24 (0.01)**	–0.19 (0.08)
PCB 203	106	0.15 (0.12)	–0.10 (0.31)	–0.12 (0.28)	0.03 (0.76)	–0.10 (0.30)	–0.08 (0.49)
Group 3[g]	106	0.05 (0.64)	–0.18 (0.06)	**–0.22 (0.04)**	–0.05 (0.62)	–0.17 (0.09)	–0.17 (0.13)
Not classified							
PCB 146	106	0.13 (0.18)	–0.09 (0.34)	–0.20 (0.06)	0.04 (0.69)	–0.07 (0.47)	–0.12 (0.27)
PCB 163	106	0.12 (0.20)	–0.06 (0.53)	–0.13 (0.23)	0.06 (0.56)	–0.03 (0.75)	–0.06 (0.61)
PCB 172	106	0.18 (0.07)	–0.07 (0.46)	–0.12 (0.26)	0.07 (0.49)	–0.06 (0.56)	–0.07 (0.55)
PCB 178	106	0.18 (0.06)	–0.09 (0.38)	–0.12 (0.25)	0.04 (0.67)	–0.10 (0.31)	–0.10 (0.38)
PCB 194	106	0.20 (0.04)	–0.05 (0.59)	–0.04 (0.74)	0.08 (0.43)	–0.05 (0.59)	–0.001 (0.99)
PCB 195	106	0.04 (0.72)	–0.19 (0.05)	–0.18 (0.10)	–0.08 (0.43)	–0.20 (0.04)	–0.14 (0.19)
PCB 199	105	0.18 (0.06)	–0.009 (0.93)	–0.009 (0.94)	0.06 (0.54)	–0.04 (0.70)	–0.006 (0.95)
PCB 206	106	0.08 (0.43)	–0.14 (0.16)	–0.14 (0.20)	–0.01 (0.89)	–0.13 (0.20)	–0.08 (0.44)
PCB 209	106	0.06 (0.53)	–0.18 (0.06)	–0.18 (0.09)	0.005 (0.96)	–0.11 (0.25)	–0.10 (0.37)
Total PCB	106	0.05 (0.61)	–0.15 (0.14)	–0.19 (0.08)	–0.04 (0.71)	–0.14 (0.17)	–0.14 (0.21)

[a]Spearman correlation coefficient and *p*-value of the non-parametric testing of the strength of the linear association between compound and mammographic density entered as continuous variables. N, Number of women for crude [b] and adjusted [c] analyses; for model [d], 4 women were lost. Models adjusted for [c] age at mammography (years) and waist circumference (cm); [d] age at mammography (years), waist circumference (cm), age at menarche (years), age at menopause (years), age at first birth (years), number of full-term pregnancies, breastfeeding (total number of weeks), hormonal contraceptive used (yes/no), number of years since cessation of replacement hormonal therapy (years), smoking status (current and ever/never), alcohol consumption (number of drinks/day), breast cancer in a first degree relative (yes/no), breast biopsy (yes/no). Sum of congeners [e] 177 and 187; [f] 74, 105, 118, 138, 156, 167 and 170; [g] 99, 153, 180, 183, 196 and 203.

such as polycyclic hydrocarbons (32), thus its effect on breast tissue could be complex. When PCBs were grouped according to Wolff's classification in analyses, group 3 PCB levels appeared to be related to a lower breast cancer risk (14, 15); however, an adverse effect (12) or no effect were also reported (10). Discrepancies between breast cancer risk studies and ours could be related to the heterogeneity in these populations' estrogen-related characteristics. For example, most of the analyses were conducted among pre-and post-menopausal women in different proportions, while ours was conducted exclusively among post-menopausal women. Reproductive history and ethnicity also differed and these are

Table III. *Associations between plasma concentrations of Wolff group 3 polychlorinated biphenyls with mammographic density.*

		Mean mammographic density[a]						
			Percentage density (%)			Absolute density (cm^2)		
PCB tertile		N[b]	Crude	Adjusted[c]	Adjusted[d]	Crude	Adjusted[c]	Adjusted[d]
PCB 99	1	31	30.1	26.0	25.9	34.7	33.2	33.2
	2	31	26.4	27.2	29.0	31.2	32.1	34.3
	3	31	21.8	20.5	21.8	26.5	26.4	27.4
	r_s^e (95% CI)		–0.17 (–0.36;0.04)	–0.16 (–0.35;0.05)	–0.13 (–0.35;0.10)	–0.15 (–0.34;0.06)	–0.13 (–0.33;0.08)	–0.13 (–0.34;0.11)
PCB 153	1	35	26.5	29.0	31.9	33.3	35.6	37.9
	2	36	25.0	24.7	24.8	29.4	29.9	30.8
	3	35	29.1	22.5	22.0	32.0	28.5	27.8
	r_s^e (95% CI)		0.05 (–0.14;0.24)	–0.18 (–0.36;0.02)	**–0.24 (–0.43;-0.03)**	–0.04 (–0.22;0.16)	–0.15 (–0.33;0.05)	–0.15 (–0.35;0.06)
PCB 180	1	35	23.1	26.5	27.7	30.3	33.4	33.5
	2	35	25.4	25.4	26.8	31.4	32.0	34.1
	3	35	31.1	23.3	23.2	31.3	26.8	27.1
	r_s^e (95% CI)		0.17 (–0.03;0.35)	–0.07 (–0.26;0.12)	–0.09 (–0.30;0.12)	0.04 (–0.15;0.23)	–0.08 (–0.27;0.12)	–0.05 (–0.26;0.17)
PCB 183	1	35	31.2	31.7	32.8	36.9	38.0	38.2
	2	36	22.0	23.5	23.8	28.2	29.7	30.9
	3	35	27.4	21.0	21.8	29.6	26.2	27.1
	r_s^e (95% CI)		–0.08 (–0.27;0.11)	**–0.29 (–0.46;-0.11)**	**–0.30 (–0.48;-0.10)**	–0.17 (–0.35;0.02)	**–0.28 (–0.44;-0.09)**	**–0.24 (–0.43;-0.03)**
PCB 196	1	35	25.2	29.8	29.7	32.6	36.9	35.9
	2	36	27.4	25.9	27.5	33.5	33.3	36.1
	3	35	27.9	20.5	21.6	28.4	23.8	24.9
	r_s^e (95% CI)		0.03 (–0.16;0.22)	**–0.24 (–0.41;-0.05)**	**–0.22 (–0.41;-0.01)**	–0.09 (–0.28;0.10)	**–0.24 (–0.41;-0.05)**	–0.19 (–0.38;0.02)
PCB 203	1	35	23.9	27.7	28.2	31.9	35.7	35.8
	2	36	26.6	24.5	26.5	31.7	31.2	33.5
	3	35	30.0	24.0	24.0	31.0	27.0	27.2
	r_s^e (95% CI)		0.15 (–0.04;0.33)	–0.10 (–0.29;0.09)	–0.12 (–0.32;0.10)	0.03 (–0.16;0.22)	–0.10 (–0.29;0.09)	–0.08 (–0.28;0.14)
Group 3[f]	1	35	28.9	31.0	33.0	36.5	39.0	40.3
	2	36	22.8	22.5	22.1	27.4	28.0	28.2
	3	35	28.9	22.7	23.2	30.9	27.0	27.6
	r_s^e (95% CI)		0.05 (–0.15;0.23)	–0.18 (–0.36;0.01)	**–0.22 (–0.41;-0.01)**	–0.05 (–0.24;0.14)	–0.17 (–0.34;0.03)	–0.17 (–0.36;0.05)

[a]Percentage and absolute density are presented as back-transformed values. N, number of women for crude [b] and adjusted [c] analyses; for model [d], 4 women were lost. Models adjusted for [c] age at mammography (years) and waist circumference (cm); [d] age at mammography (years), waist circumference (cm), age at menarche (years), age at menopause (years), age at first birth (years), number of full-term pregnancies, breastfeeding (total number of weeks), hormonal contraceptive used (yes/no), number of years since cessation of replacement hormonal therapy (years), smoking status (current and ever/never), alcohol consumption (number of drinks/day), breast cancer in a first degree relative (yes/no), breast biopsy (yes/no). [e]Spearman correlation coefficient and 95% confidence intervals (CI) of the non-parametric testing of the strength of the linear association between selected compound and mammographic density entered as continuous variables. [f] Sum of congeners 99, 153, 180, 183, 196 and 203.

all factors that influence a woman's levels of estrogen, which has an effect on MD (33). Moreover, PCBs were analysed either in serum, plasma or adipose tissue; a previous study reported a good correlation between serum and adipose tissue levels (3). Furthermore, the number of congeners included in total PCBs or PCB grouping according to Wolff's classification also varied between studies (10, 12, 14, 15).

The observed 8 to 11% difference in percentage MD between the lower and the upper tertile of PCBs is significant in terms of breast cancer risk. For example, it was shown that among healthy women at risk of developing breast cancer, those who received 54 months of tamoxifen had an absolute reduction of 6.4% in MD compared to those receiving placebo (34); in high-risk women, tamoxifen has been shown to reduce the risk of breast cancer by 30% to 50% (35, 36).

This study has several strengths. Firstly, mammograms were performed with equipment accredited by the Canadian Association of Radiology in addition to satisfying the high-quality standards of the Quebec breast cancer screening program. Secondly, quantitative measurements of MD were obtained without any information on women, using a computer-assisted method, by one reader whose reliability of reading was shown to be high. Although the density of only one breast was measured, the concordance of the measures between right and left breasts was shown to be high (37).

Thus, the misclassification of MD should be relatively small, at random, and therefore should not have biased our results. Furthermore, PCB measurements were performed under extensive-quality assurance procedures. Finally, adjustment was made for factors known or suspected to be related to MD in order to control most of the potential confounding bias.

Plasma levels of PCB congeners 153, 183, 196 and combined Wolff group 3 PCBs appear to be associated with lower MD among post-menopausal women, however, this relation should be confirmed by other studies. If confirmed, these findings may provide insight into the etiology of breast cancer, particularly into the relation between PCBs and breast cancer risk.

Funding source

This study was supported by the Canadian Breast Cancer Research Alliance (Etiology and Prevention Grant 013568). CD is a Junior Investigator of the Canadian Cancer Society (2011-700657).

Competing Financial Interest

None.

Acknowledgements

This study was supported by the Canadian Breast Cancer Research Alliance (Etiology and Prevention Grant 013568). CD is a Junior Investigator of the Canadian Cancer Society (2011-700657). We thank Jacques Brisson, Sylvie Bérubé and Marc Sinotte for their valuable contributions to the initial study.

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Received October 10, 2013
Revised November 9, 2013
Accepted November 12, 2013