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Polychlorinated biphenyls and their association with survival following breast cancer

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Abstract

Background—Polychlorinated biphenyls (PCBs) are hypothesized to influence breast carcinogenesis due to their persistence and potential to induce estrogenic and anti-estrogenic effects. Whether PCBs influence survival following breast cancer is unknown.

Methods—A population-based cohort of women diagnosed with first primary invasive or *in situ* breast cancer in 1996–1997 and with blood-measured PCBs (n=627) collected shortly after diagnosis was followed for vital status through 2011. After 5 and 15 years we identified 54 and 187 deaths, respectively, of which 36 and 74 were breast cancer-related. Using Cox regression, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for mortality for baseline PCB concentrations, individually and as estrogenic (ΣGroup 1B: PCB101, PCB174, PCB177, PCB187, PCB199), anti-estrogenic (ΣGroup 2A: PCB66, PCB74, PCB105, PCB118; Σ2B: PCB138, PCB170), and cytochrome P450 enzyme-inducing (ΣGroup 3: PCB99, PCB153, PCB180, PCB183, PCB203) groups.

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AUTHORS' CONTRIBUTIONS

HP Jr, MSW and MDG developed the study hypothesis and study plan. MSW, SLT, AIN, and MDG were responsible for obtaining funding and conducting data collection for the parent and ancillary studies that generated the data for the current study. SME and NKK assisted with collection, processing and preliminary analyses of the data used in the current study. HP Jr. conducted the statistical analyses for the current study, under the guidance of LSE and MDG. HP Jr. and MDG drafted the manuscript, and all authors aided in data interpretation and approved the final version of this manuscript.

Results—The highest PCB174 tertile was associated with an increase in all-cause (HR=2.22, 95%CI: 1.14–4.30) and breast cancer-specific (HR=3.15, 95%CI: 1.23–8.09) mortality within 5 years of diagnosis and remained associated with breast cancer-specific mortality (HR=1.88, 95%CI: 1.05–3.36) at 15 years. At 5 years, the highest tertile of PCB177 was positively associated with all-cause mortality (HR=2.12, 95%CI: 1.05–4.30). At 15 years, the highest tertiles of ΣGroup 2A congeners and PCB118 were inversely associated with all-cause mortality (HR=0.60, 95%CI: 0.39–0.83; HR=0.63, 95%CI: 0.43–0.92, respectively).

Conclusions—In this first US study of PCBs and breast cancer survival, PCBs were associated with mortality in biologically plausible directions. The investigation of other, structurally similar, chemicals may be warranted.

Keywords

Polychlorinated biphenyls; PCBs; organochlorine compounds; breast cancer; survival

1. BACKGROUND

Breast cancer is the most common cancer diagnosed among women and the second leading cause of death from cancer in the United States (US) [1]. Five-year survival following breast cancer diagnosis is high estimated at 90% [2], yet approximately 40,000 deaths are attributed to breast cancer annually [1]. Early detection through the use of mammography and access to high quality surgery and therapies contribute to this high survival rate [3]. Patient and tumor characteristics are established prognostic factors [4,5], but whether environmental chemicals influence survival after breast cancer diagnosis has received limited scientific attention [6,7]. Given the known effectiveness of tamoxifen and related anti-estrogenic drugs in reducing the likelihood of breast cancer progression [8], potential candidates include other exogenous compounds that influence estrogen or other biologically relevant pathways involved in breast cancer progression. One possibility is a group of environmental toxins, the polychlorinated biphenyls (PCBs).

PCBs are a class of 209 synthetic chemicals distinguished by degree and pattern of chlorination. Their hypothesized role in influencing breast carcinogenesis is due to their ubiquity, lipophilicity and persistence (biological half-lives ranging from 2–15 years [9]), abundance in breast tissue [10], and their potential to induce estrogenic and anti-estrogenic effects in human breast cells [11] and to induce cytochrome P450 enzymes [12,13]. Due to their non-flammability and chemical stability, PCBs were used worldwide in many industrial and commercial applications, including electrical and hydraulic equipment and as plasticizers. In the US, PCBs were manufactured from 1929 until their ban in 1979 [14]. Although levels detected in the general population have decreased since their ban [15] exposure to these chemicals continues, primarily through diet and through redistribution of PCBs present in the environment [16].

Increased PCB concentrations examined as individual congeners and as groupings have been associated with an increased risk of breast cancer in some epidemiologic studies [17–21], though most studies have shown no association. Whether PCBs impact breast cancer survival, however, remains an unexplored topic. The present study aimed to examine the

associations between 22 PCBs and survival among US women with breast cancer. We hypothesized that estrogenic congeners and those able to induce cytochrome P450 enzymes would be positively associated with mortality, particularly breast cancer-specific mortality, while the anti-estrogenic PCBs would be inversely associated with mortality.

2. METHODS

2.1 Study design and study population

The present study uses data from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of adult female residents of Nassau and Suffolk counties of New York that incorporated a prospective component among women diagnosed with breast cancer (n=1,508) to identify environmental factors associated with survival. Institutional Review Board approval was obtained from of all participating institutions and in accordance with an assurance filed with and approved by the US Department of Health and Human Services. Details of the LIBCSP have been published previously [22,23]. Briefly, between August 1, 1996, and July 31, 1997, women with a first diagnosis of invasive or *in situ* breast cancer, confirmed by a physician and medical records, were identified for inclusion using rapid-case ascertainment via active daily or weekly contact with all local hospital pathology departments.

Of the 1,508 women with breast cancer who completed the structured interview, 1,102 provided blood samples for laboratory analyses, including quantification of PCBs and lipids. The present study was restricted to 627 women with breast cancer for whom blood levels of both lipids and PCBs were available (Table S1 and Table S2) [23]. Participants included in this study were primarily white (92%) postmenopausal women (66%) with a mean age of 58 years (SD=12). Additional participant baseline characteristics are presented in Table 1.

2.2 Laboratory assays

Within three months after breast cancer diagnosis, a total of 73% of participants of the LIBCSP provided non-fasting blood samples, of which 77% were collected prior to the initiation of chemotherapy [22,24]. Selection of samples for assaying occurred as follows: (1) randomly sampled from among women with invasive breast cancer (n=415); (2) from all women with tumors initially categorized as *in situ* that were subsequently determined to be invasive (n=42); (3) from all women with *in situ* tumors (n=184); and (4) from all African-American participants who were not selected in the first three steps (n=5). Gas chromatography/electron capture detection was conducted as outlined by Brock et al. [25] to measure PCB concentrations (Table S1). Individual congener levels below the detection limit (0.07ng/ml) were imputed as the LOD/√2. To account for non-fasting variations in blood samples, total lipids were determined for use in correction of PCB concentrations [26].

2.3 Follow-up for mortality

We used the National Death Index (NDI) [27] to ascertain date and cause of death. Breast cancer-related deaths were identified using International Statistical Classification of Diseases codes 174.9 and C-50.9 listed on the death certificate. Follow-up for mortality

occurred from the date of diagnosis in 1996–1997 until December 31, 2011. The median duration of follow up was 14.73 years. Among the 627 participants included in these analyses, 54 (9%) deaths occurred within 5 years of follow-up and 187 (30%) deaths occurred within 15 years of follow-up. Of the deaths that occurred within 5 years and 15 years of diagnosis, 36 and 74, respectively, were due to breast cancer.

2.4 Interview and medical record data

After signed informed consent and permission for medical record release, all participants completed a structured interview to assess demographic characteristics and potential and established prognostic factors for breast cancer. Medical records were abstracted to obtain information on tumor characteristics (stage, tumor size, and hormone receptor status) and first course of treatment (chemotherapy, radiation therapy, hormone therapy).

2.5 Statistical analyses

Continuous concentrations of lipid-corrected PCBs were divided into 3 groups based on the 33^{rd} and 67^{th} percentiles as cutpoints (Table S2). We also summed groups of wet-weight PCB congeners as proposed by Wolff and colleagues [28] to examine whether functional groupings were differentially associated with breast cancer survival. Summing moles per gram of lipid gave similar results as summing wet-weights; therefore, we present analyses using summed wet-weights. Seven (PCBs 52, 110, 167, 172, 178, 193, and 200) of the 29 detected PCBs were reported by the laboratory with too low a frequency or too few samples were above the limits of detection (Table S1), and were not considered further. We did not have measurements of congeners in Groups 1A (PCBs 44, 49, and 52), which are estrogenic, but not persistent, thus we were unable to examine this functional grouping. Because not all congeners were available for our analyses, each of the groups comprised the following congeners [28]: Group 1B (101, 174, 177, 187, and 199) which are potentially estrogenic and persistent; Group 2A (66, 74, 105, and 118) which are potentially anti-estrogenic and persistent; Group 2B (138, 170) which are potentially anti-estrogenic and dioxin-like and persistent, Group 3 (99, 153, 180, 183, and 203) which induce expression of the cytochrome P450 enzymes CYP1A1 and CYP2B. Additionally, in summing groups, we imputed missing lipid-corrected congeners based on the available same-group congeners using multiple linear regression rather than assigning a zero value to the missing congener or setting the total sum to missing. To correct for artificially minimized standard errors for the estimates produced when using imputations, the standard errors were inflated back to the lower sample-size level. This imputation strategy reduced the amount of missing PCB group data in the following manner: Group 1B from 6.2% to 0.2%; Group 2A from 20.1% to 2.2%; Group 2B from 8.1% to 0.0%; and Group 3 from 6.7% to 0.0%. Several of the estimates obtained from this imputed data set were different from those obtained from the data set in which participants with missing values were simply dropped (Table S3); however the conclusions and interpretations were not materially different.

We used multivariable Cox models [29] to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between tertiles of individual and summed lipid-corrected PCB concentrations with all-cause and breast cancer-specific mortality at 5 and 15 years after diagnosis. The proportional hazards assumption was assessed using exposure

interactions with time and Schoenfeld residuals [29]. Two violations of the proportional hazards assumptions were observed for PCB15 and PCB174 in relation to 15-year all-cause mortality. Including the interaction terms for time (≤5 years and >5 years) yielded similar results to those obtained when the interactions were excluded from the models; therefore, results excluding the interaction terms are presented. Tests for trend used continuous natural log-transformed lipid-corrected concentrations in Cox regression models.

Possible confounders were selected based on previous studies of organochlorine compounds, including organochlorine pesticides and PCBs and breast cancer incidence and survival [4,30] and directed acyclic graphs [31]. These included age at diagnosis (5-year age groups), education (categorical), body mass index (BMI; continuous), and parity/lactation (nulliparous, parous/never lactated, and parous/ever lactated). Tumor characteristics and treatment were not included as a covariate in the models since these characteristics are potential causal intermediates in the association between PCBs and breast cancer survival [32]. We present age-only-adjusted results in the Supplemental Material (Table S4 and Table S5).

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

3. RESULTS

3.1 5-Year all-cause and breast cancer-specific mortality

As shown in Table 2, after adjusting for potential confounders, PCB174 and PCB177 were associated with a two-fold increase in 5-year all-cause mortality (third tertile versus first, HR=2.22, 95%CI: 1.14–4.30, P_{Trend}=0.07; HR=2.12, 95%CI: 1.05–4.30, P_{Trend}=0.02). No other PCB congeners were associated with 5 year all-cause mortality (Table 2 and Table S6).

Similarly, PCB174 was associated with a two- to three-fold increased hazard of breast cancer-specific mortality for the second and third tertiles (HR=2.14, 95%CI: 0.81–5.64; HR=3.15, 95%CI: 1.23–8.09, P_{Trend}=0.09, Table 2). We also observed and elevated hazard for the middle tertile of the sum of Group 3 congeners (HR=2.77, 95%CI: 1.06–7.25), though the highest tertile was attenuated in relation to breast cancer-specific mortality (HR=1.57, 95%CI: 0.49–5.01).

3.2 15-Year all-cause and breast cancer-specific mortality

For 15-year all-cause mortality, we observed decreased hazards for PCB118 (second tertile versus first, HR=0.78, 95%CI: 0.54–1.12; third tertile versus first, HR=0.63, 95%CI: 0.43–0.92) and the sum of Group 2A congeners (third tertile versus first, HR=0.60, 95%CI: 0.39–0.83), but the trends were not significant (P_{Trends}>0.30, Table 3). No other PCB congeners were associated with 15-year all-cause mortality (Table 3 and Table S6).

For 15-year breast-cancer specific mortality, we observed and increased hazard of mortality for PCB174 and PCB177, consistent with those seen for 5-year breast cancer mortality, but weaker with risk less than two-fold. For PCB 174, the HRs increased monotonically (second

tertile versus first, HR=1.27, 95%CI: 0.69–2.32; third tertile versus first, HR=1.88, 95%CI: 1.05–3.36, P_{Trend}=0.12). PCB177 showed a stronger trend with an apparent threshold effect (second tertile versus first, HR=1.79, 95%CI: 1.00–3.23; third tertile versus first, HR=1.71, 95%CI: 0.93–3.15, P_{Trend}=0.02, Table 3).

4. DISCUSSION

In this first population-based study of US women with breast cancer of PCBs and survival, we observed a two- to three-fold increased risk of 5-year all-cause and breast cancer-specific mortality for two estrogenic and biologically persistent congeners, PCB174 and PCB177. For 15-year breast cancer mortality, we observed similar elevated risks for these congeners, but not for total 15-year mortality. We observed similarly elevated hazards of mortality for PCB180 and PCB183, which are biologically persistent CYP1A1 and CYP2B inducers, in a threshold effect pattern. In contrast, PCB118 and the sum of Group 2A congeners, which are anti-estrogenic and moderately persistent, were inversely associated with all-cause mortality after 15 years, but not after 5 years. Group 1B includes PCB174 and PCB177, which are characterized by having a vacant, non-chlorinated 4-position on one of the phenyl rings. Trends were similar for other congeners in this group except for PCB101, which has the shortest half-life in this group, and PCB187. Structurally, Group 2A congeners have all 4- and 4′-positions chlorinated, but every congener has at least one unchlorinated 2-position and group 2B congeners have the 6- and 6′-positions unchlorinated. Group 3 congeners are highly chlorinated all with 2- and 2′-positions chlorinated and one or more 5-position chlorinated.

To date, only one study has been published on the association between polychlorinated biphenyls and breast cancer survival [6,7]. In the first study of 195 Danish women [6], though multiple PCBs were measured, only the results examining the total sum of 27 PCBs were reported in their study, which were somewhat elevated (HR=1.45, 95%CI: 0.69–3.06). In contrast to their study, we did not examine the total sum of the PCBs given that different congeners have different potential for estrogenic and anti-estrogenic activity and combining all PCBs would, thus, potentially mask the underlying associations. Instead we used functional groupings [28], which distinguish PCBs as estrogenic (Group 1), anti-estrogenic, immunotoxic, and dioxin-like (Group 2), and phenobarbital and CYP1A1 and CYP2B inducers (Group 3). In the study reported here, we observed associations in directions that are biologically plausible based on these groupings. Although the mechanism by which PCBs may affect survival is uncertain, our findings support biological mechanisms related to: a) the estrogenic and anti-estrogenic potential of these compounds; and b) the potential adverse effects of metabolites of PCBs, including hydroxylated PCBs and methyl sulfone PCBs, which resemble natural hormones [33].

This study has several strengths. We measured PCB exposures in blood, which are established and widely used measures of PCB burden [16,33]. Samples were collected from participants within a few months following diagnosis of their first primary breast cancers and before most had begun chemotherapy [24]. Participants were followed using the NDI, which accurately captures vital status [34]. As a limitation, we were not able to examine all PCB congeners and groupings of interest including those proposed to be estrogenic, but not

persistent (Group 1A). Multiple comparisons could have resulted in spurious results; however, because in this study we examined the associations between environmental agents known to exert physiologic effects, real associations are to be expected and, therefore, adjustments are unwarranted [35]. Another limitation of this study is that we only had one measurement of PCBs taken close to diagnosis and we were unable to examine changes in PCB levels over time and the association between changes in PCB concentrations and survival; however, because of the long biological half-lives of PCBs the associations observed up to 15 years after diagnosis of breast cancer are plausible. Regarding measurement error of the outcome, determination of breast cancer-related deaths based on the death certificate may have resulted in outcome misclassification [36]. However, this misclassification is likely to be non-differential with respect to PCB levels, which would attenuate the risk estimates for breast cancer-specific mortality [37].

5. CONCLUSIONS

In the study reported here, we show that estrogenic PCB congeners may adversely affect short-term and long-term survival following a diagnosis of breast cancer. Furthermore, in our study anti-estrogenic congeners were inversely associated with all-cause mortality. Given the limited research on the associations between environmental exposures and breast cancer survival conducted to date, our findings require replication. Future studies should consider associations with additional PCB congeners as well as additional organochlorine compounds. Because of the worldwide ubiquity and persistence of these chemicals together with the high incidence and prevalence of breast cancer, understanding, whether these and other structurally similar environmental contaminants affect survival requires attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

PCBS are ubiquitous and persistent contaminants.

PCBs have the potential to induce estrogenic and antiestrogenic effects.

How PCBs influence survival following breast cancer diagnosis is unknown.

PCBs were associated with mortality in biologically plausible directions.

PCBs may adversely impact survival following breast cancer.

Table 1

Distribution of the selected baseline characteristics of the LIBCSP women diagnosed with breast cancer in 1996–1997 and with PCB measurements.

	n (%)
Age	
<35–44	102 (16%)
45–54	160 (26%)
55–64	163 (26%)
65–74	152 (24%)
75+	50 (8%)
Income[a]	
<$15,000–$24,999	123 (20%)
$25,000–$49,999	186 (30%)
$50,000–$90,000+	316 (51%)
Education[a]	
<HS-HS graduate	275 (44%)
Some college/-College graduate	250 (40%)
Post college	99 (16%)
Parity/Lactation history	
Nulliparous	66 (11%)
Parous/never lactated	347 (55%)
Parous/ever lactated	214 (34%)
Menopausal status[a]	
Pre-menopausal	210 (34%)
Post-menopausal	405 (66%)
Tumor characteristics[a]	
Invasive	447 (71%)
Tumor size (≥2cm)	99 (31%)
ER^+ or PR^+	272 (78%)
Treatment[a]	
Chemotherapy	158 (35%)
Radiation therapy	261 (58%)
Hormone therapy	244 (55%)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997 and followed-up through December 31, 2011.

[a]Missing: income=2; education=3; menopausal status=12; tumor size=303; ER/PR status=276; chemotherapy=179; radiation therapy=178; hormone therapy=182

TABLE 2

Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between blood levels of lipid-corrected PCBs and **5-year mortality** in the LIBCSP women diagnosed with breast cancer in 1996–1997.

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
Wolff Group 1B (Potentially estrogenic, persistent)										
ΣGroup 1B – The 4- or 4′-position is unchlorinated on one phenyl ring										
Tertile 1	19	189	1			14	194	1		
Tertile 2	19	190	0.90	(0.47–1.72)		10	199	0.68	(0.30–1.54)	
Tertile 3	16	193	0.73	(0.35–1.51)	0.46	12	197	0.90	(0.39–2.09)	0.12
PCB101 – 2,2′,4,5,5′										
Tertile 1	17	179	1			11	185	1		
Tertile 2	16	181	0.84	(0.42–1.68)		12	185	1.04	(0.46–2.38)	
Tertile 3	18	178	1.01	(0.52–1.98)	0.87	11	185	0.96	(0.41–2.22)	0.70
PCB174 – 2,2′,3,3′,4,5,6′										
Tertile 1	14	194	1			6	202	1		
Tertile 2	14	195	1.05	(0.50–2.21)		13	196	2.14	(0.81–5.64)	
Tertile 3	26	183	2.22	(1.14–4.30)	0.07	17	192	3.15	(1.23–8.09)	0.09
PCB177 – 2,2′,3,3′,4′,5,6										
Tertile 1	12	196	1			8	200	1		
Tertile 2	19	190	1.72	(0.83–3.56)		14	195	1.83	(0.76–4.37)	
Tertile 3	23	186	2.12	(1.05–4.30)	0.02	14	195	1.94	(0.81–4.65)	0.09
PCB187 – 2,2′,3,4′,5,5′,6										
Tertile 1	22	186	1			14	194	1		
Tertile 2	16	193	0.68	(0.35–1.31)		11	198	0.83	(0.37–1.86)	
Tertile 3	16	193	0.63	(0.31–1.25)	0.89	11	198	0.87	(0.38–2.03)	0.32
PCB199 – 2,2′,3,3′,4′,5,5′,6										
Tertile 1	16	192	1			11	197	1		
Tertile 2	14	195	0.96	(0.46–2.02)		10	199	1.11	(0.46–2.69)	
Tertile 3	24	185	1.53	(0.75–3.15)	0.23	15	194	1.98	(0.83–4.72)	0.05
Wolff Group 2A (Potentially anti-estrogenic, persistent)										

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
ΣGroup 2A – The 4- and 4′-positions are chlorinated on both phenyl rings and one phenyl ring has an unchlorinated 2-position										
Tertile 1	19	185	1			14	190	1		
Tertile 2	17	188	0.82	(0.39–1.72)		10	195	0.75	(0.28–1.96)	
Tertile 3	17	187	0.71	(0.33–1.52)	0.95	12	192	0.92	(0.38–2.26)	0.51
PCB66 – 2,3′,4,4′										
Tertile 1	14	156	1			7	163	1		
Tertile 2	19	152	1.24	(0.62–2.49)		14	157	1.95	(0.78–4.86)	
Tertile 3	12	159	0.80	(0.37–1.73)	1.00	8	163	1.08	(0.39–2.99)	0.38
PCB74 – 2,4,4′,5										
Tertile 1	20	184	1			16	188	1		
Tertile 2	14	191	0.65	(0.32–1.31)		9	196	0.59	(0.25–1.36)	
Tertile 3	19	186	0.83	(0.42–1.64)	0.50	11	194	0.75	(0.33–1.72)	0.40
PCB105 – 2,3,3′,4,4′										
Tertile 1	14	191	1			11	194	1		
Tertile 2	17	188	1.27	(0.62–2.60)		11	194	1.06	(0.46–2.46)	
Tertile 3	23	182	1.59	(0.81–3.11)	0.27	14	191	1.34	(0.61–2.98)	0.52
PCB118 – 2,3′,4,4′,5										
Tertile 1	18	190	1			12	196	1		
Tertile 2	19	190	1.02	(0.53–1.95)		11	198	0.98	(0.43–2.23)	
Tertile 3	17	192	0.70	(0.34–1.45)	0.93	13	196	1.22	(0.51–2.92)	0.13
Wolff Group 2B (Potentially anti-estrogenic, limited dioxin activity, persistent)										
ΣGroup 2B – The 6- and 6′-positions are unchlorinated										
Tertile 1	20	188	1			11	197	1		
Tertile 2	16	192	0.75	(0.38–1.50)		13	195	1.20	(0.53–2.71)	
Tertile 3	18	190	0.76	(0.38–1.52)	0.37	12	196	1.20	(0.49–2.89)	0.90
PCB138 – 2,2′,3,4,4′,5′										
Tertile 1	18	175	1			11	182			
Tertile 2	16	177	0.77	(0.38–1.53)		13	180	1.18	(0.52–2.68)	
Tertile 3	16	177	0.74	(0.36–1.51)	0.51	11	182	1.11	(0.46–2.67)	0.73
PCB170 – 2,2′,3,3′ ′,4,4′,5										

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
Tertile 1	19	188	1			11	196	1		
Tertile 2	20	187	1.09	(0.57–2.07)		14	193	1.47	(0.66–3.28)	
Tertile 3	15	192	0.70	(0.34–1.45)	0.34	11	196	1.18	(0.49–2.87)	0.85
Wolff Group 3 (CYP1A1 and CYP2B inducers, biologically persistent)										
ΣGroup 3 – The 2- and 2′- and 4 and 4′-positions are chlorinated and the 5 or 5′-position is chlorinated										
Tertile 1	16	193	1			8	201	1		
Tertile 2	23	186	1.49	(0.74–3.00)		18	191	2.77	(1.06–7.25)	
Tertile 3	15	194	0.84	(0.36–1.98)	0.90	10	199	1.57	(0.49–5.01)	0.14
PCB99 – 2,2′,4,4′,5										
Tertile 1	14	183	1			9	188	1		
Tertile 2	18	180	1.24	(0.61–2.54)		14	184	1.57	(0.67–3.68)	
Tertile 3	16	182	0.99	(0.47–2.07)	0.55	8	190	0.96	(0.36–2.56)	0.77
PCB153 – 2,2′,4,4′,5,5′										
Tertile 1	17	190	1			9	198	1		
Tertile 2	23	185	1.38	(0.72–2.64)		17	191	2.25	(0.99–5.15)	
Tertile 3	14	194	0.69	(0.32–1.46)	0.95	10	198	1.30	(0.50–3.36)	0.13
PCB180 – 2,2′,3,4,4′,5,5′										
Tertile 1	18	191	1			9	200	1		
Tertile 2	17	192	0.95	(0.47–1.89)		14	195	2.00	(0.83–4.83)	
Tertile 3	19	190	1.02	(0.49–2.12)	0.94	13	196	2.16	(0.84–5.57)	0.15
PCB183 – 2,2′,3,4,4′,5′,6										
Tertile 1	12	195	1			7	200	1		
Tertile 2	21	187	1.82	(0.89–3.73)		15	193	2.29	(0.93–5.64)	
Tertile 3	21	187	1.66	(0.80–3.42)	0.07	14	194	2.17	(0.86–5.48)	0.03
PCB203 – 2,2′,3,4,4′,5,5′,6										
Tertile 1	16	193	1			10	199	1		
Tertile 2	19	190	1.37	(0.69–2.73)		13	196	1.66	(0.71–3.88)	
Tertile 3	19	190	1.12	(0.53–2.35)	0.17	13	196	1.82	(0.73–4.53)	0.07

[a] Adjusted for age at diagnosis, education, body mass index, and parity/lactation history.

[b] Natural log-transformed.

TABLE 3

Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between blood levels of lipid-corrected PCBs and **15-year mortality** in the LIBCSP women diagnosed with breast cancer in 1996–1997.

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
Wolff Group 1B (Potentially estrogenic, persistent)										
ΣGroup 1B – The 4- or 4′-position is unchlorinated on one phenyl ring										
Tertile 1	58	150	1			27	181	1		
Tertile 2	63	146	0.98	(0.67–1.43)		19	190	0.72	(0.39–1.31)	
Tertile 3	65	144	0.92	(0.63–1.35)	0.93	28	181	1.16	(0.65–2.05)	0.22
PCB101 – 2,2′,4,5,5′										
Tertile 1	54	142	1			22	174	1		
Tertile 2	62	135	1.15	(0.79–1.66)		19	178	0.86	(0.46–1.60)	
Tertile 3	58	138	1.14	(0.78–1.66)	0.73	29	167	1.33	(0.76–2.33)	0.42
PCB174 – 2,2′,3,3′,4,5,6′										
Tertile 1	66	142	1			19	189	1		
Tertile 2	61	148	0.95	(0.70–1.35)		24	185	1.27	(0.69–2.32)	
Tertile 3	59	150	1.09	(0.77–1.56)	0.90	31	178	1.88	(1.05–3.36)	0.12
PCB177 – 2,2′,3,3′,4′,5,6										
Tertile 1	59	149	1			18	190	1		
Tertile 2	62	147	1.12	(0.78–1.61)		30	179	1.79	(1.00–3.23)	
Tertile 3	65	144	1.18	(0.82–1.69)	0.35	26	183	1.71	(0.93–3.15)	0.02
PCB187 – 2,2′,3,4′,5,5′,6										
Tertile 1	64	144	1			30	178	1		
Tertile 2	52	157	0.69	(0.47–1.00)		20	189	0.70	(0.39–1.25)	
Tertile 3	70	139	0.86	(0.60–1.25)	0.27	24	185	0.90	(0.50–1.61)	0.99
PCB199 – 2,2′,3,3′,4′,5,5′,6										
Tertile 1	56	152	1			27	181	1		
Tertile 2	55	154	0.88	(0.60–1.30)		21	188	0.88	(0.49–1.59)	
Tertile 3	76	133	1.04	(0.70–1.56)	0.70	26	183	1.26	(0.68–2.32)	0.29
Wolff Group 2A (Potentially anti-estrogenic, persistent)										

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
ΣGroup 2A – The 4- and 4′-positions are chlorinated on both phenyl rings and one phenyl ring has an unchlorinated 2-position										
Tertile 1	63	141	1			29	175	1		
Tertile 2	57	148	0.66	(0.44–0.99)		24	181	0.84	(0.45–1.55)	
Tertile 3	65	139	0.60	(0.39–0.83)	0.59	21	183	0.72	(0.37–1.42)	0.86
PCB66 – 2,3′,4,4′										
Tertile 1	48	122	1			16	154	1		
Tertile 2	57	114	1.16	(0.79–1.71)		27	144	1.71	(0.92–3.19)	
Tertile 3	52	119	1.10	(0.74–1.63)	0.74	18	153	1.10	(0.55–2.16)	0.45
PCB74 – 2,4,4′,5										
Tertile 1	55	149	1			27	177	1		
Tertile 2	59	146	0.83	(0.56–1.21)		25	180	0.93	(0.53–1.62)	
Tertile 3	71	134	0.91	(0.62–1.34)	0.57	22	183	0.86	(0.47–1.57)	0.76
PCB105 – 2,3,3′,4,4′										
Tertile 1	58	147	1			29	176	1		
Tertile 2	53	152	0.83	(0.57–1.22)		20	185	0.71	(0.40–1.26)	
Tertile 3	74	131	1.17	(0.83–1.67)	0.46	25	180	0.92	(0.54–1.59)	0.73
PCB118 – 2,3′,4,4′,5										
Tertile 1	62	146	1			26	182	1		
Tertile 2	55	154	0.78	(0.54–1.12)		24	185	0.93	(0.53–1.63)	
Tertile 3	70	139	0.63	(0.43–0.92)	0.32	24	185	0.96	(0.51–1.79)	0.39
Wolff Group 2B (Potentially anti-estrogenic, limited dioxin activity, persistent)										
ΣGroup 2B – The 6- and 6′-positions are unchlorinated										
Tertile 1	62	146	1			26	182	1		
Tertile 2	55	153	0.72	(0.49–1.05)		23	185	0.86	(0.48–1.55)	
Tertile 3	70	138	0.80	(0.55–1.16)	0.09	25	183	1.00	(0.55–1.81)	0.91
PCB138 – 2,2′,3,4,4′,5′										
Tertile 1	57	136	1			27	166	1		
Tertile 2	57	136	0.77	(0.52–1.12)		18	175	0.65	(0.35–1.19)	
Tertile 3	64	129	0.79	(0.54–1.16)	0.09	27	166	1.07	(0.60–1.89)	0.81
PCB170 – 2,2′,3,3′,4,4′,5										

	All-cause Mortality					Breast Cancer-specific Mortality				
PCB	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**	**Deaths**	**Censored**	**HR_{Adj}[a]**	**95% CI**	**P_{Trend}[b]**
Tertile 1	64	143	1			27	180	1		
Tertile 2	57	150	0.82	(0.57–1.19)		25	182	0.97	(0.56–1.70)	
Tertile 3	65	142	0.82	(0.55–1.20)	0.29	22	185	0.88	(0.48–1.61)	0.42
Wolff Group 3 (CYP1A1 and CYP2B inducers, biologically persistent)										
ΣGroup 3 – The 2- and 2′- and 4 and 4′-positions are chlorinated and the 5 or 5′-position is chlorinated										
Tertile 1	58	151	1			22	187	1		
Tertile 2	63	146	0.93	(0.62–1.39)		31	178	1.63	(0.89–3.00)	
Tertile 3	66	143	0.85	(0.56–1.28)	0.52	21	188	1.13	(0.57–2.26)	0.51
PCB99 – 2,2′,4,4′,5										
Tertile 1	46	151	1			18	179	1		
Tertile 2	59	139	1.14	(0.77–1.70)		27	171	1.57	(0.85–2.90)	
Tertile 3	69	129	1.11	(0.75–1.64)	0.99	23	175	1.39	(0.73–2.64)	0.69
PCB153 – 2,2′,4,4′,5,5′										
Tertile 1	57	150	1			23	184	1		
Tertile 2	64	144	0.96	(0.66–1.39)		29	179	1.39	(0.79–2.43)	
Tertile 3	65	143	0.82	(0.55–1.21)	0.38	22	186	1.07	(0.57–2.00)	0.57
PCB180 – 2,2′,3,4,4′,5,5′										
Tertile 1	59	150	1			26	183	1		
Tertile 2	57	152	0.82	(0.56–1.20)		22	187	0.97	(0.53–1.76)	
Tertile 3	71	138	0.93	(0.62–1.39)	0.73	26	183	1.29	(0.69–2.41)	0.63
PCB183 – 2,2′,3,4,4′,5′,6										
Tertile 1	56	151	1			22	185	1		
Tertile 2	62	146	1.05	(0.73–1.52)		25	183	1.21	(0.68–2.16)	
Tertile 3	66	142	0.99	(0.69–1.43)	0.80	26	182	1.34	(0.75–2.41)	0.13
PCB203 – 2,2′,3,4,4′,5,5′,6										
Tertile 1	56	153	1			25	184	1		
Tertile 2	55	154	1.03	(0.70–1.52)		22	187	1.01	(0.56–1.83)	
Tertile 3	76	133	1.11	(0.74–1.65)	0.35	27	182	1.42	(0.77–2.62)	0.11

[a] Adjusted for age at diagnosis, education, body mass index, and parity/lactation history.

[b] Natural log-transformed.