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Polychlorinated Biphenyls Exposure and Breast Cancer Risk:

A Meta-Analysis of the Epidemiologic Evidence

Ye Sun

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Holster Scholars. Mentor: Dr. Keith Bellizzi. University of Connecticut

Introduction:

Polychlorinated biphenyls (PCBs) are a family of structurally related and highly toxic chlorinated aromatic hydrocarbons. PCBs were once largely produced and widely used during the middle of the 20th century in industry as dielectric fluids in transformers and capacitors, organic diluents, plasticizers, adhesives, flame retardants and in several other industrial applications. By the 1970s, estimated global production of PCBs was around 1.5 million tons where the US was the largest product of an estimated 600,000 tons [1]. However, in the mid 1970's concerns about the toxicity of PCBs and potential impact on humans and wildlife led to its production and use being banned or restricted in Western Europe and North America in the late 1970s and onwards [2]. PCBs are persistent environmental pollutants and they bioaccumulate in the food chain. With long half-lives of around 10-15 years [3], PCBs has been found to accumulate in body fat found in adipose tissue, blood plasma and milk fat [4]. Additionally, PCBs are persistent in older transformers and other appliances and are vulnerable to released into the environment.

In recent years PCBs, much like other organochlorine chemicals like dichlorodiphenyltrichloroethane (DDT), have been observed to act as "endocrine disruptors", which have been shown to mimic or block endogenous hormones [5]. This observation raised concern about the potential risk of hormone dependent cancers like breast cancer. However, the exact mechanism in which PCBs may affect estrogenic activities is unclear due to the structural differences between congeners. PCBs occur in complex mixtures of the 209 structurally different congeners, a reason why most reports represent data on total PCBs levels

as means of measuring PCB exposure. However, experimental *in vitro* have observed different structure-activity relationships between different congeners and intrinsic differences in chemical properties [6]. PCB congeners have been found to exhibit a wide range of estrogenic and anti-estrogenic properties based on their chlorination patterns [7]. Additionally, congeners differ based on their environmental persistence or resistance to metabolism in organisms [8]. Certain PCB congeners have also been found to CYP1A and CYP2B inducers [9]. Thus, Wolff et al 1997 proposed to organize congeners based on these properties [10]. Based on these differing chemical characteristics, different PCB congeners within different groups may exhibit differing effects on breast cancer risk.

Evaluation of the impact of PCBs on the environment and health has been complicated and often-times limited. Given the ability of PCBs to mimic reproductive hormones and the estrogenic effects on breast cancer, it has been postulated to affect the risk of breast cancer. However, epidemiological evidence has been mixed due to various methods used to evaluate risk and estimate PCB exposure. Some epidemiologic studies showed associations between levels PCBs and breast cancer [9, 11-15], but the results have not been seens in other studies.

In this paper, we conducted a meta-analysis and systematic review of the epidemiological studies on the relationship between environmental exposure to PCBs and the risk of breast cancer.

Materials and Methods

A systematic search of MEDLINE, Pubmed, and Embase databases were conducted for relevant epidemiologic studies. Using search terms "polychlorinated biphenyls", "breast cancer", "organochlorine", and MeSH terms "polychlorinated bisphenyls", "risk factor", and "Environmental Pollutants", we identified 38 related epidemiological studies that were written in English and published up to April, 2011. The articles were then reviewed to determine if they meet parameters set for analyses: the study must be a case-control or cohort study with more than 50 cases; and report measures of association of risk (odds ratio or risk ratio) with confidence intervals for breast cancer risk.

From the previous parameters, 14 articles were excluded. Four articles were excluded because there was no measure of association between PCB exposure and breast cancer [16-19]. Three articles were excluded because there was no measure of risk associated with breast cancer [20-22]. Three articles were eliminated because they reported less than 50 cases [23-25]. Two articles were also excluded because no confidence interval was reported [9, 26]. One was excluded because it reported on the risk of cancer reoccurrence [27]. Another was eliminated because it reported on cancer survivorship instead of cancer risk [28]. In the remaining 24 articles, 21 contained data on total PCB exposure, which is the sum of the total number of congeners evaluated in the study. Three articles contained additional data on specific congener exposure and evaluated other variables associated with PCB exposure like ER status [29-31].

From each article, the following study characteristics was extracted: primary author, year published, year(s) from which biological specimen were taken, study location (country and

when applicable, area within US), epidemiologic design (case control, cohort, hospital-based, population-based), biological specimen used for evaluation, controlled variables adjusted for in analysis, number of cases and controls, levels of partitions used for measure of exposure, the measure of association/risk (OR or RR) along with the 95% confidence interval (CI). After data was extracted, relevant information was entered into analyses table using the Comprehensive Meta-Analysis software (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ). The program required for each study the adjusted relative risk and 95% CI and subsequently calculated the summary estimate of risk by combining the effect sizes for each study. Two different odds ratios were entered for one study that reported separate estimates from population-based controls and hospital-based controls [11]. The same was done for an article that reported different estimates from two different periods of time from which samples were taken [32]. Analyses were performed using the inverse of variance method for the fixed-effects model and the DerSimonian and Laird method for the random-effects model. Due to the fact that the studies analyzed did not sample from a homogenous population, the random-effects model was used for analyses, although both the fixed-effects model and the random-effects model yielded similar results.

In order to identify any possible heterogeneity within the studies analyzed, we calculated the Q-statistic as outlined by Cochran [33]. Additional heterogeneity analyses were conducted with additional subgroups to identify any possible significant difference between studies and results due to study type and biological sample from which PCB levels were measured. Additional tests of heterogeneity were undertaken to test any differences between

estrogen receptor tumor statuses and progesterone receptor tumor statuses as a result of PCB exposure. Lactation was also evaluated as a potential confounding factor. Lastly, we used the funnel plot to visually identify any possible publication bias along with Egger's regression test to quantify any possible bias. Additionally, due to the differences in toxicity and chemical structure between congeners, congener-specific meta-analyses were also conducted. Summary estimates of risk were calculated for congeners 118, 138, 153, 156, 170, 180, 183, and 187.

Results

Table 1 describes the 21 studies analyzed for meta-analysis. All studies evaluated the risk of breast cancer in relations to exposure to total PCBs by partitioning exposure into tertiles, quartiles, or quintiles. All studies were case-control studies, eight of which were prospective nested case-control studies [13, 32, 34-39], nine were retrospective case-control studies where subjects were selected from hospitals [11, 40-47], and five were retrospective case-control studies where subjects were chosen from a selected population [11, 14, 15, 48-49]. One study included both population-based and hospital-based controls, thus both study statistics from the different controls were reported and analyzed [11]. Four studies used breast adipose tissue samples to derive the concentration of PCBs [39, 45-47], and seventeen studies used serum samples for PCB concentrations [11-15, 29-32, 34-49].

Different studies had different variables adjusted for or matched controls and cases for in the risk ratios reported (See Appendix A for the full list for each study). All studies adjusted for age. Most studies adjusted for history of breast cancer, age of menarche, and usage of

hormone replacement therapy, which have all been identified as potential factors that influence breast cancer risk [50].

Figure 1 shows the results of meta-analyses on the association between PCB exposure levels and breast cancer risk. The summary estimate of risk for all studies was found to be 0.98 (95% CI 0.87-1.10). Overall, however, after conducting the Q-statistic test for heterogeneity, we found that there was no significant heterogeneity in results from the studies. The Q-value was found to be 17.46 with degrees of freedom (df) of 23 and a P-value of 0.74. Additional tests for possible publication bias were conducted. Figure 2 shows a funnel plot plotting the standard error against the log OR. From the overall symmetrical shape, it can see seen visually that there is little publication bias. Though Itoh et al 2009 shows potential publication bias, using the Egger's test and the Begg and Mazumdar rank correlation test, we found that it was insignificant. Kendall's tau value with continuity correlation was found to be -0.15 with a P-value of 0.30. Egger's test found an intercept value of -0.43 with a P-value of 0.44. Therefore, publication bias was insignificant.

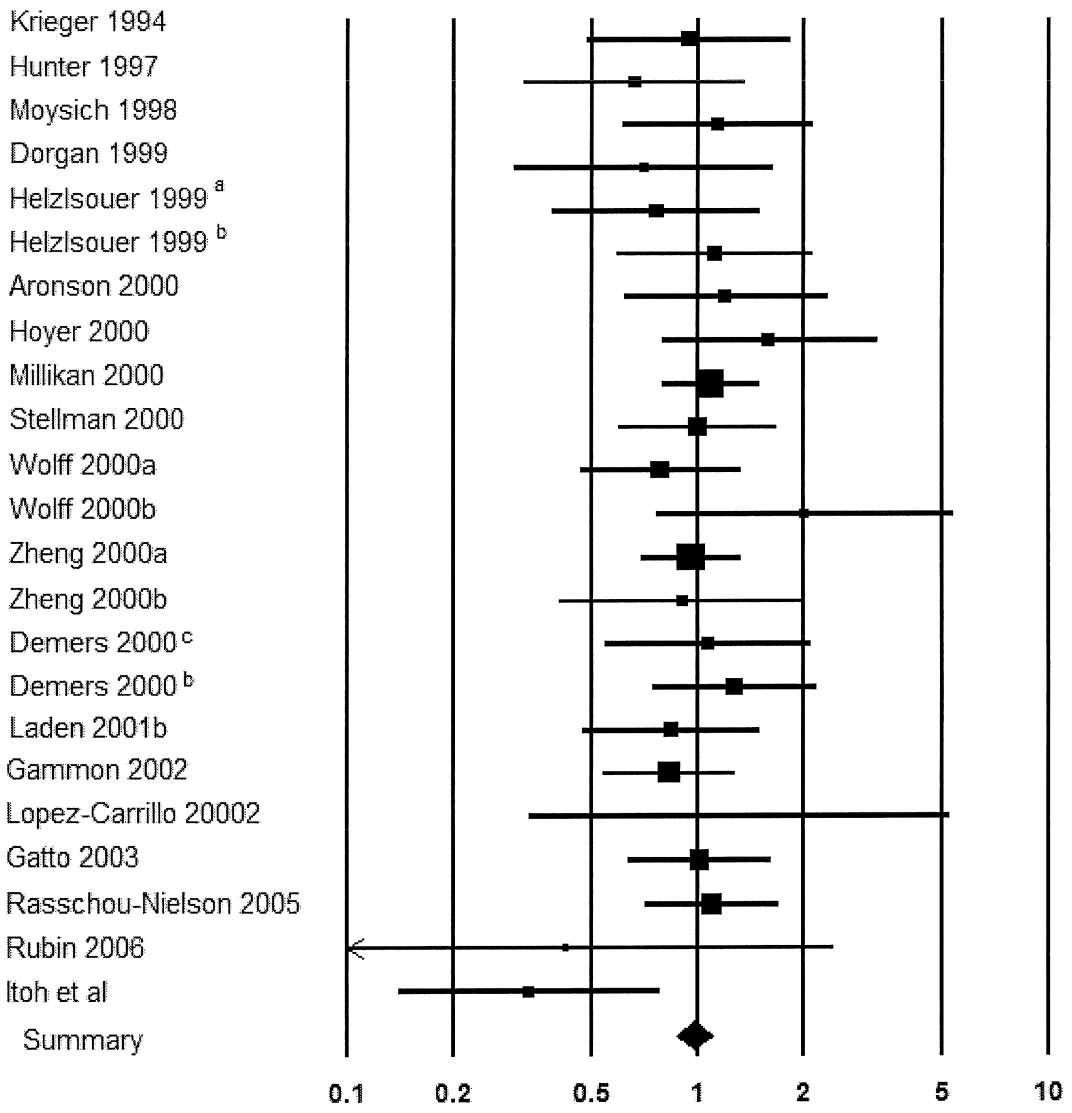


Figure 1. Cumulative meta-analysis of all studies. Summary OR = 0.978 (95% CI: 0.868-1.102)

[a]Samples taken in 1974. [b]Samples taken in 1989. [c]Controls are hospital-based. [d]Controls were population-based.

Table 1. Study characteristics of prospective and retrospective studies on PCBs and breast cancer risk.

Prim. Author	Year	Country	Type of Specimen	Type of Study	No. of Cases	No. of Controls	Partition	OR/RR + Additional Data
Krieger et al. (1994)	1964-1971	California, USA	Serum	NCC[a]	150	150	Tertile	0.94 (0.48-1.84)
Hunter et al. (1997)	1976-1992	Massachusetts, USA	Serum	NCC	230	230	Quintile	0.66(0.37-1.40)
Dorgan et al. (1999)	1977-1987	Missouri, USA	Serum	NCC	104	206	Quartile	0.7 (0.3-1.5)
Helzlsouer et al. (1999)	1974	Maryland, USA	Serum	NCC	235	235	Quintile	1.12 (0.59-2.15)
	1989	Maryland, USA	Serum	NCC	105	105	Tertile	0.76 (0.38-1.51)
Hoyer et al. (2000b)	1981-1983	Denmark	Serum	NCC	155	274	Quartile	1.6 (0.8-3.3)
Wolff et al. (2000b)	1985-1991	New York, USA	Serum	NCC	110	213	Quartile	2.02 (0.76-5.37)
Laden et al. (2001b)	1997-2001	11 States , USA	Serum	NCC	370	370	Quintile	0.84 (0.47-1.52)
Rasschou-Nielson et al. (2005)	1993-1997	Denmark	Breast Adipose Tissue	NCC	365	365	Quartile	1.1 (0.7-1.7)
Wolff et al. (2000a)	1994-1996	New York, USA	Serum	CCH[b]	140	300	Tertile	0.78(0.45-1.3)
Zheng et al. (2000a)	1995-1997	Connecticut, USA	Serum	CCH	475	502	Tertile	0.96 (0.68-1.32)
Demers et al. (2000)[d]	1994-1997	Canada	Serum	CCH	314	218	Quintile	1.07 (0.54-2.12)

[a]Prospective nested case control [b] Retrospective case-control study (hospital-based).

Table 1. Continued.

Prim. Author	Year	Country	Type of Specimen	Type of Study	No. of Cases	No. of Controls	Partition	OR/RR + Additional Data
Gammon et al. (2002)	1996-1997	Long Island, New York, USA	Serum	CCH	646	429	Tertile	0.83 (0.52-1.29)
Lopez-Carrillo et al. (2002)	1994-1996	Mexico	Serum	CCH	95	95	Tertile	1.31 (0.33-5.31)
Itoh et al. (2009)	2001-2005	Japan	Serum	CCH	349	349	Quartile	0.33 (0.14-0.78)
Aronson et al. (2000)	1995-1997	Canada	Breast Adipose Tissue	CCH	217	213	Quartile	1.15 (0.58-2.25)
Stellman et al. (2000)	1994-1996	Long Island, New York, USA	Breast Adipose Tissue	CCH	232	223	Tertile	1.01 (0.6-1.69)
Zheng et al. (2000b)	1994-1997	Connecticut, USA	Breast Adipose Tissue	CCH	304	186	Tertile	0.7 (0.4-1.1)
Moysich et al. (1998)	1986-1991	New York, USA	Serum	CCP[c]	154	131	Tertile	1.14 (0.61-2.15)
Millikan et al. (2000)	1993-1996	North Carolina, USA	Serum	CCP	748	659	Tertile	1.09 (0.79–1.52)
Demers et al. (2000)[d]	1994-1997	Canada	Serum	CCP	314	205	Quintile	1.45 (0.82-2.58)
Gatto et al. (2007)	1994-1998	5 states, USA	Serum	CCP	355	327	Quintile	1.01 (0.63, 1.63)
Rubin et al. (2006)	1981-1987	Alaska, USA	Serum	CCP	63	63	Tertile	0.42 (0.07-2.38)

[c] Retrospective case-control study (population-based). [d] Both results with population-based and hospital-based controls were reported, and are analyzed separately.

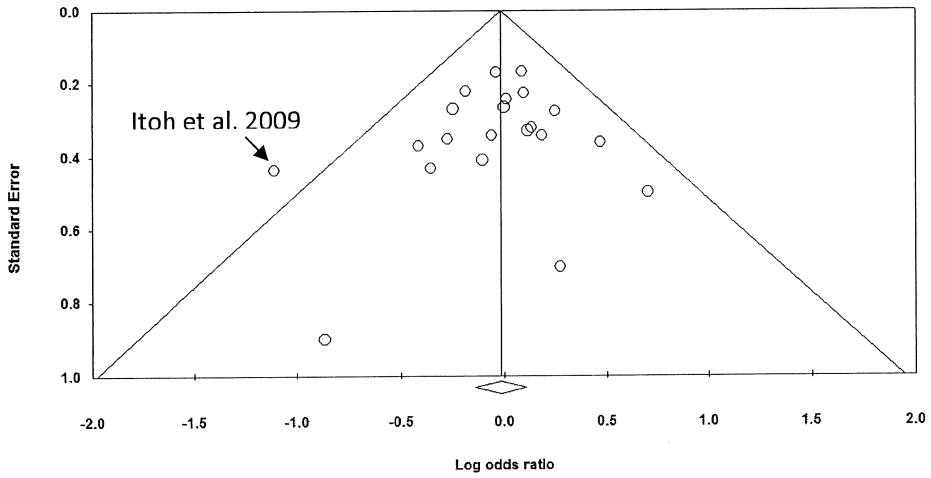


Figure 2. Funnel plot outlining possible publication bias.

Additional analyses were conducted with subgroups in the total number of studies. Table 1 shows combined effect size for studies that used serum or adipose tissue as the biological specimen from which PCB levels were measured along with combined effecti sizes for studies that were prosepctive nested case-control, retrospective population-based case-control or retrospective hospital-based case-control studies. From the 17 studies that used serum as means of measuring PCB levels, the combined OR was 0.97 and the 4 studies that used adipose as means of measuring PCB levels, the combined OR was 1.06. Using the Q-statistic test, we tested for any heterogeneity between the two subgroups, and the Q value came to be 0.37 with a df of 1 and P-value of 0.54, which means there is insignificant heterogeneity. When looking to see if there is any heterogeneity between subgroups of different types of stuides, the combined OR for prospective nested case-control studies was 1.00, retrospective case-control hospital-based was 0.90 and retrospective case-control population-based was 1.09. Again, using the Q-statistic test, no significant heterogeneity was detected with a Q value of 1.80, a df of 2 and a P-value of 0.41.

Table 2. Summary of overall ORs for breast cancer risk and total PCB exposure levels stratefied by selected factors.

	No. Studies	Combined Effect Size	CI 95% Lower	CI 95% Upper	Q value	df (Q)	P-value
Overall	21[a]	0.98	0.87	1.10			
Specimen							
Serum	17	0.97	0.85	1.11			
Adipose	4	1.06	0.80	1.41			
Heterogeneity					0.37	1	0.54
Type of Study							
Prospective Nested Case Control	8	1.00	0.80	1.24			
Retrospective Case Control-Hospital based	9[a]	0.90	0.75	1.08			
Retrospective Case Control-Population based	5[a]	1.09	0.87	1.36			
Heterogeneity					1.80	2	0.41
ER Status							
ER-	5	0.90	0.57	1.43			
ER+	5	1.19	0.94	1.52			
Heterogeneity					1.11	1	0.29
ER/PR Status							
ER+/PR+	3	0.74	0.52	1.07			
ER+/PR-	3	0.48	0.21	1.10			
ER-/PR+	2	0.93	0.25	3.47			
ER-/PR-	3	0.47	0.32	0.69			
Heterogeneity					3.69	3	0.30
Lactation							
Ever Lactated	5	0.90	0.69	1.17			
Never Lactated	5	1.11	0.80	1.54			
Heterogeneity					0.93	1	0.34

[a]A total of 21 studies were used for analysis. However, because Demers et al 2000 contributed separate estimates with both hospital-based and population-based controls, they are considered separately.

Additional analyses was conducted to find any possible heterogeneity between different subgroups in the studies analyzed. First, in looking at possible differences in outcome, we looked to find any association between PCB exposure and estrogen receptor (ER) and progesterone receptor (PR) tumor status. Meta-analyses were performed first on studies that presented results based only on ER status, and then on studies that presented results based on both ER and PR statuses. Figure 3 shows the forest graph for the meta-analysis looking at the association between PCB exposure and breast cancer based only on ER status. Figure 4 shows the meta-analysis looking at the association between PCB exposure and breast cancer based on ER/PR statuses. Table 2 shows meta-analysis results along with results of Q statistic test for heterogenity that were conducted to assess any possible differences between different tumor statuses.

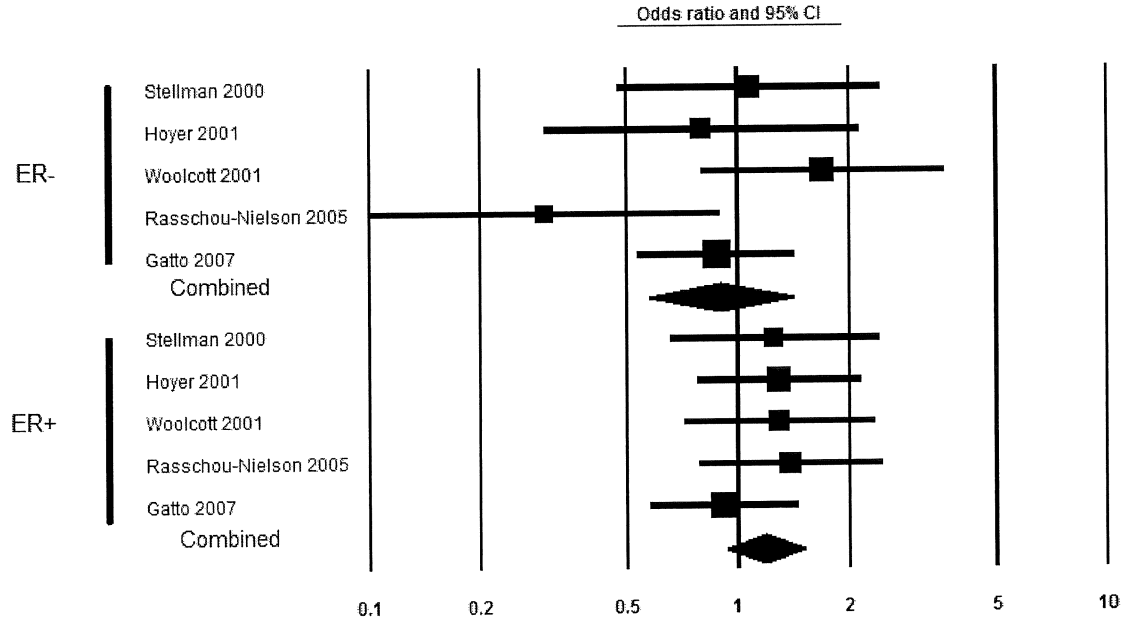


Figure 3. Meta-analysis on association between total PCB exposure and breast cancer stratified by ER status.

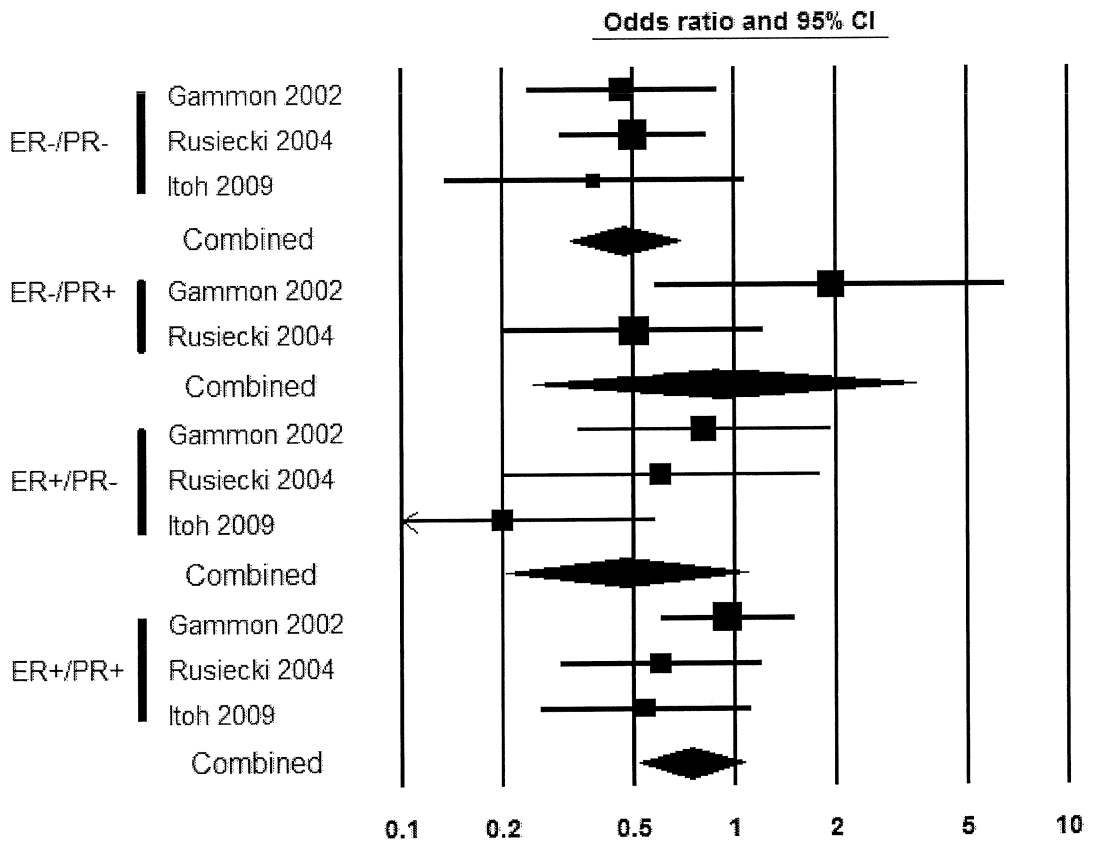


Figure 4. Meta-analysis on the association between PCB exposure and breast cancer stratefied by ER/PR statuses.

Additional analysis was conducted looking at lactation as a possible factor. Figure 5 shows the meta-analysis on the association between PCB exposure and breast cancer stratefied by lactation, with patient populations divided between ever lactated and never lactated. Table 2 shows the estimat esummary effect size along with the Q statistic for heterogeneity looking at any possible differences between the two results.

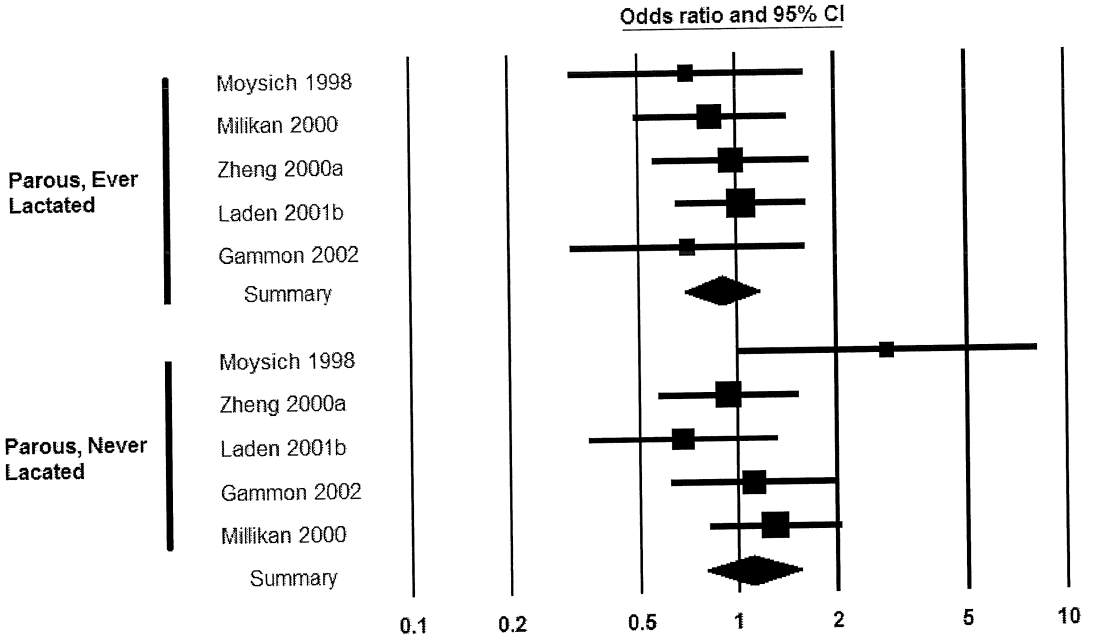


Figure 5. Meta-analysis on association between PCB exposure and breast cancer risk stratified by lactation status.

Lastly, in order to look at the effects of specific PCB congeners on breast cancer risk, PCB congeners 187, 118, 138, 156, 170, 153, 180, and 183 were analyzed. Each congener was organized into groups as proposed by Wolff and Toniolo, 1993 [9]. Group I represents portentially estrogenic congeners. Figure 6 shows the meta-analysis and result for congener 187 which is a Group I congener that acts as a persistent potentially estrogenic chemical. Figure 7 shows the meta-analysis and results for congeners 118, 138, 156, and 170, which are Group II congeners that act as potentially antiestrogenic and dioxin-like chemicals. Lastly, Figure 8 shows the meta-analysis and results for congeners 153, 180, and 183, which are Group III congeners that act as biologically persistent CYP1A and CYP2B inducers. Table 3 shows the meta-analysis results for the individual congeners grouped into congener groups. A Q-statistic test for

heterogeneity was performed to test for any differences amongst the groups, but a nonsignificant P-value of 0.63 was found.

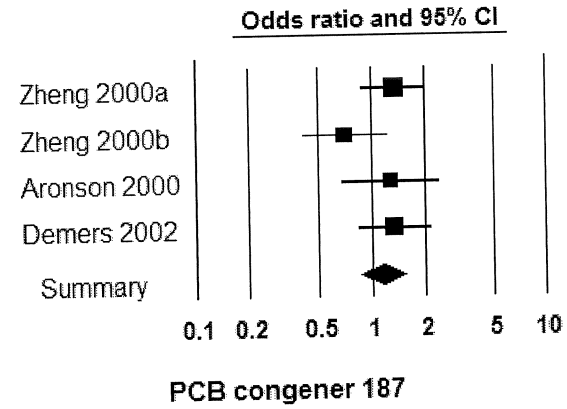
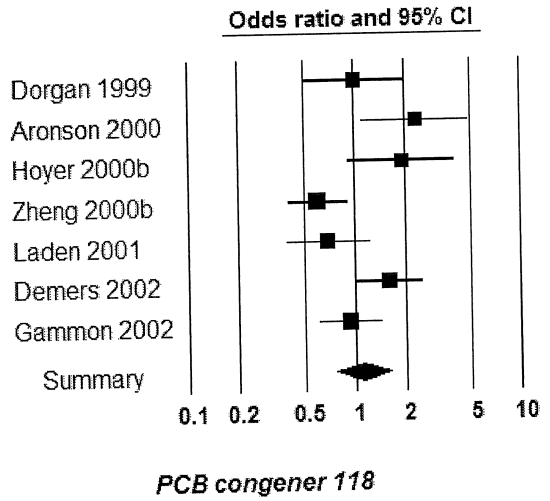
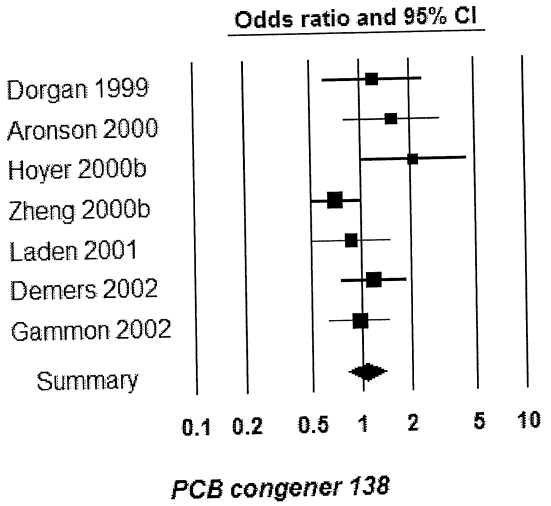
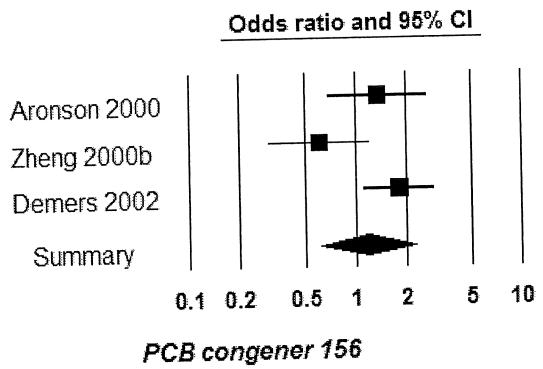


Figure 6. Specific congener result for Group I potentially estrogenic congeners.







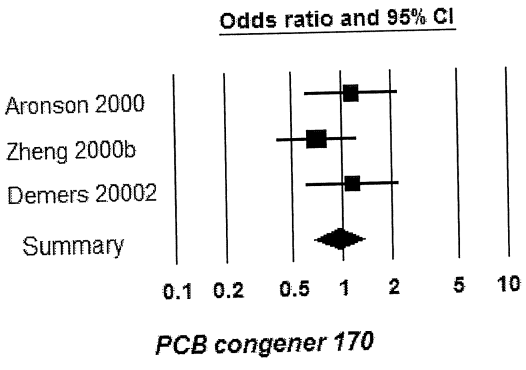


Figure 7. Specific congener results for Group II potentially antiestrogenic and immunotixic, dioxinlike congeners.

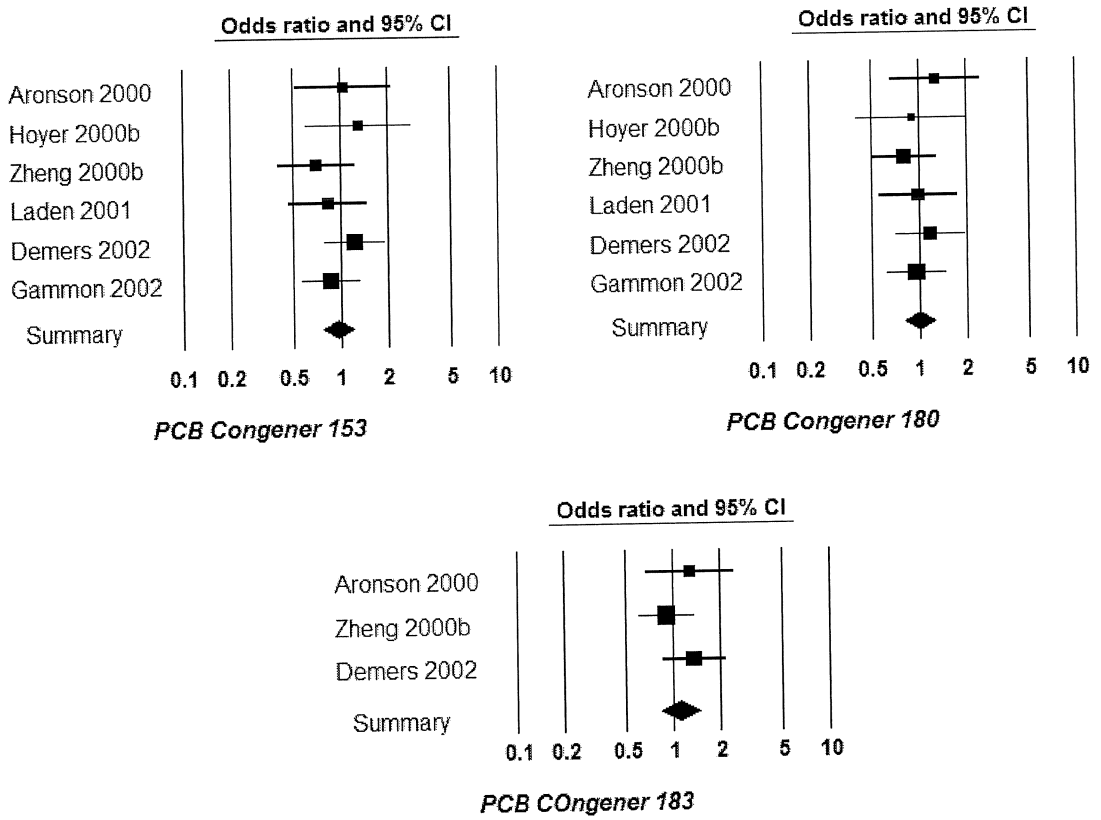


Figure 8. Specific congener results for Group III are biologically persistent CYP1A and CYP2B inducers

Table 3. Meta-analyses of individual PCB congeners and associated breast cancer risk.

	No. Studies	Combined Effect Size	CI 95% Lower	CI 95% Upper	Q value	df (Q)	P-value
Group I, Combined	4	1.14	0.85	1.53			
Congener 187	4	1.14	0.85	1.53			
Group II, Combined		1.08	0.90	1.29			
Congener 118	7	1.10	0.76	1.61			
Congener 138	7	1.06	0.81	1.38			
Congener 156	3	1.17	0.62	2.23			
Congener 170	3	0.94	0.66	1.34			
Group III, Combined		1.00	0.87	1.14			
Congener 153	6	0.95	0.76	1.19			
Congener 180	6	0.99	0.79	1.23			
Congener 183	3	1.10	0.84	1.46			
Heterogeneity					0.87	2	0.65

Discussion:

The results of the meta-analysis of 21 studies showed that there was no evidence for an association between PCB exposure levels and breast cancer risk. The summary effect size for total PCB exposure was found to be 0.98 (95% CI 0.87-1.10), and all summary ORs found for individual PCB exposure levels showed no evidence of an association. Analyses were undertaken to see if differences in methodology may alter results. A factor considered was the time period after the onset of breast cancer that exposure levels were taken. However, as seen in Table 2, there was no significant difference between results from retrospective and prospective studies, which means the time of exposure taken does not affect results. Additional methodological differences in study type (hospital-based vs population-based) and biological specimen used for PCB detection were evaluated and shown to not contribute any significant differences in reported effect sizes. However, one confounding factor that was not evaluated was how many PCB congeners were detected to calculate the total PCB level. Studies varied from using 73 congeners [13] to using only 14 congeners [46] to calculate total PCB levels. Another factor that may affect results was the lack of a consistent gradient of PCB exposure levels. All calculated ORs used for meta-analysis were taken from the measure of association estimated for the highest vs lowest level of exposure. However, studies varied in number of partitions used to divide the exposure levels, and lacked a standardized gradient of exposure. One possible explanation for no associations found could be that though serum and adipose tissue may provide a comprehensive estimate of a woman's lifetime body burden, it is impossible to evaluate body burden at critical periods of exposure (e.g. pre-natal, puberty), and

hard to evaluate the timing of exposure, which would be optimal when evaluating for the risk of breast cancer.

When evaluating different subgroups within the studies, lactation was studied as a possible confounding factor. Lactation has been shown to decrease body burden levels of PCBs [51] and longer period of lactation has been shown to be associated with a decreased risk of breast cancer [52]. Amongst the studies analyzed, one study, Moysich et al, 1998 suggested that amongst women who never lactated, there was increased risk of breast cancer with increasing serum PCBs level (See Figure 5) [15]. However, from the meta-analysis results in Table 2, it can be seen that such results were not replicated in other studies. The summary effect size for women who never lactated was 1.11 (95% CI 0.80-1.54) and in women who ever lactated, the summary effect size was 0.90 (95% CI 0.69-1.17), with no significant heterogeneity between the two groups.

Looking at the possible links between ER and PR statuses and the association between PCB exposure and breast cancer risk, meta-analysis showed that there was no significant difference in ER and PR statuses as a result of total PCB exposure. From Table 2, it can be seen that studies that looked at ER/PR status showed that there was a significant inverse association found for ER-/PR- tumors with increasing concentration of total PCBs (OR=0.47, 95% CI 0.32-0.68). However, no statistical significant differences were found between the groups. When comparing only ER statuses, though a study by Rasshou-Nielson et al, 2005 showed an inverse association for ER- tumors with increasing concentration of total PCBs, the result was not found

in other studies, and the summary effect size for ER- tumors was found to be insignificant as well (OR=0.90, 95% CI 0.57-1.43) [39].

Individual meta-analyses on PCB congeners were also performed, but none found any associations between exposure level and breast cancer risk. Additionally, there were little differences between different congener groupings as proposed by Wolff et al, 1997. From the studies analyzes, two studies found significant association between PCB congener 118 exposure and breast cancer risk [31, 45]. One study found a significant association between PCB congener 138 and breast cancer risk [13], and another study found a significant association between PCB congener 156 and breast cancer [31]. All three congeners are found within the Group II potentially antiestrogenic, dioxinlike and mono-*ortho* congeners. Smaller studies have provided other additional evidence of the possible relationship between dioxin-like congeners and breast cancer risk. Liljegren et al reported an increased risk of breast cancer amongst women with higher breast adipose tissue levels of PCB 77 and PCB 169 [23]. Guttes et al also reported significantly higher concentration of PCB 118 in adipose tissue of cases [19]. However, similar results were not seen in the other studies, as the meta-analysis results did not show any significant association between any congener and breast cancer risk. Additionally, there was no significant heterogeneity between the groups. From these findings, we can see that due to the lack of evidence supporting any association between specific congeners and breast cancer, the lack of a positive or negative association between PCB exposure and breast cancer could not be due to the combined estrogenic and anti-estrogenic properties of specific congeners in the total PCB mixture.

In conclusion, from this meta-analysis, we can see that epidemiological evidence does not support any direct relation between exposure to PCB and the risk of breast cancer. However, the negative association found between ER-/PR- status and PCB exposure may warrant further investigations as the epidemiological evidence was limited. Additional analysis looking at PCB exposure at critical periods of development would also give a better understanding and measurement of PCB exposure. Overall though our findings confirm and further establish that there is no clear association between PCB exposure and breast cancer.

Appendix A. Variables matched/adjusted for in risk ratios reported

Prim. Author, year	Variables matched/adjusted
Krieger et al, 1994	Age, age at menarche, BMI, pregnancy status (ever vs never pregnant), menopause, and race
Hunter et al, 1997	Age, menopause, month of blood sample taken, postmenopausal hormone use, history of breast cancer, history of benign breast disease, age at menarche, number of children, age at birth of first child, duration of lactation, BMI
Dorgan et al, 1999	Age, height, weight, BMI, parity, age at menarche, menopause, exogenous estrogen usage, history of breast cancer, education, number of packs of cigarettes smoked per day
Helzlsouer et al, 1999	Age, BMI, age at menarche, history of breast cancer, age of first birth, duration of lactation
Hoyer et al, 2000b	Age, weight, parity, and usage of hormone-replacement therapy
Wolff et al, 2000b	Age, age at menarche, number of full pregnancies, age at first term pregnancy, family history of breast cancer, lifetime history of lactation, height, BMI, menopausal status
Laden et al, 2001b	Age, history of breast cancer, history of benign breast disease, age at menarche, BMI, number of children, age at birth of first child, duration of lactation
Rasschou-Nielson et al, 2005	Age, education, BMI, alcohol intake, number of childbirths, age at first delivery, duration of lactation, years of use of HRT, and history of benign breast disease.
Wolff et al 2000a	Age, menopause, race, BMI, lactation history, family history, parity
Zheng et al 2000a	Age, BMI, age at menarche, lifetime months of lactation, age at first pregnancy, number of live births, lifetime months of HRT, dietary fat intake, family history of breast cancer, income, race and study site
Gammon et al 2002	Age, Race, History of fertility problems, history of breast cancer
Lopez-Carrillo et al 2002	Age, age at menarche, number of children and age at first birth, lifetime months of lactation, family history of breast cancer, menopause
Itoh et al, 2009	Age, BMI, menopause, age at menopause, smoking, fish consumption, vegetable consumption, history of breast cancer, age at first childbirth, parity, age of menarche, history f breast cancer screening, history of breast feeding
Aronson et al 2000	Age, usage of HRT, ethnicity, family history of breast cancer, fat intake, alcohol intake, menopause
Stellman et al 2000	Age, BMI, hospital, race
Zheng et al, 2000b	Age, BMI, lifetime months of lactation, age at menarche, age at first pregnancy, fat consumption, race, income, family breast cancer history
Moysich et al, 1998	Age, education, history of breast cancer, parity, quetelet index, duration of lactation, age at first birth, years since first pregnancy, fruit and vegetable intake
Millikan et al, 2000	Age, menopause, parity/lactation, usage of hormone replacement

	therapy, income, race
Demers et al, 2000	Age, region of residence, BMI, duration of lactation, age at first birth, number of fertile years, history of breast cancer, history of benign breast cancer
Gatto et al, 2003	Age, BMI, lactation
Rubin et al, 2006	Age, parity, age at menarche, history of breast cancer, ethnicity, triglycerides and cholesterol levels

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