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Topic 3.2

Organochlorine compounds and breast cancer risk*

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Abstract: A number of epidemiologic studies on organochlorines (OCs) and breast cancer risk have been published. The majority (n = 18) measured OCs in adipose tissue, primarily from mammary biopsies in cancer cases and controls with benign breast disease, and studied incident disease. Seven of these studies each included fewer than 50 cases and controls and had limited capacity for covariate adjustment. Eleven studies used serum samples collected from 6 months to 25 years prior to diagnosis. An additional 13 studies (2 with some overlap) used serum collected at or after diagnosis. Regardless of the medium used to measure OC levels, studies conducted to date do not provide consistent evidence that any of the OCs examined thus far play a role in the initial breast cancer risk. This paper provides a compound specific review with discussion of how the lack of evidence for adverse effects might be explained by factors related to study design, or by variation in risk across subgroups.

The sum of the evidence does not implicate any OC compound as significantly related to risk of occurrence of breast cancer. The evidence base is greatest for dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE). Limited research has been done on individual polychlorinated biphenyls (PCBs) and their isomers. The studies of OC exposure reflect current exposure levels of chemicals banned as long ago as 20 years. Although the information is extremely limited and not without major design flaws, the association between OCs and disease severity and progression is interesting and worthy of further examination.

More studies are needed on OCs other than DDTs in developing countries where use is more recent or continuing, especially given that most estrogenic OCs are not persistent. It is possible that other pathways may be involved, including activity related to cytochrome P450 (CYP) and glutathione-*S*-transferase (GST); there is limited research to date on this hypothesis. In developed countries, a body mass index (BMI)/weight loss model may warrant further analysis, perhaps using existing data.

OC exposures cannot reliably be related to trends in breast cancer incidence, as other known risk factors for breast cancer, such as childbearing and lactation, have changed along with OC residues during this timeframe. Changes in screening and treatment over time also complicate making such links. Ecologic data relating high-exposure countries to high breast cancer mortality rates do not suggest a strong link. Breast cancer rates are not generally higher in parts of the world with high DDE levels. Countries with relatively similar levels of PCBs, such as Great Britain and Japan, have very different breast cancer rates.

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As OCs are present in the environment as mixtures of correlated isomers and metabolites, it may be difficult to distinguish possible causal links from associations in which measured compounds are merely markers of other underlying exposures. For highly correlated compounds, traditional adjustment strategies may not be feasible. More complex analytical strategies may help to isolate potentially relevant isomers.

INTRODUCTION

Although a variety of other compounds, including pharmaceutical agents (e.g., oral contraceptives, tamoxifen) and phytoestrogen-containing foods (e.g., soybeans, cabbage) may mimic or modulate estrogen activity, chemicals produced for industrial or agricultural use have been the primary focus of research on endocrine disruptors and human health [1]. These chemicals, known as organochlorine compounds (OCs), comprise a diverse group of compounds, including: (i) pesticides (e.g., DDT, aldrin, dieldrin, chlordane, heptachlor epoxide, hexachlorocyclohexane, hexachlorobenzene, methoxychlor); (ii) industrial chemicals (e.g., PCBs used in lubricants, coolants, sealants, and pesticides; mirex used as a fire retardant coating and a pesticide); and (iii) breakdown products of these chemicals. OCs are lipophilic and persist in the environment. Thus, despite the bans, exposure to many OC isomers and metabolites endures decades later as a result of residues in soil, water, dust, and foods, most notably in fat-containing animal products such as meats, fish, and dairy products [2–4]. Environmental exposure to these organochlorines has been postulated to increase the risk of breast cancer through potential estrogenic activity [5–7]. Not all OCs possess estrogenic activity, and some, depending upon the internal milieu, may have antiestrogenic or anticarcinogenic effects [8–14]. Nonetheless, OCs may also increase the risk of breast cancer via other mechanisms, including promotion of tumor growth [15–17] and modulation of enzyme activity [8,18,19].

Peak use of most OC chemicals occurred in the 1950s and 1960s, some three decades after their introduction [20,21]. Most were banned in the United States and other industrialized countries in the early 1970s (DDT) or late 1970s (PCBs, mirex, benzene hexachloride [BHC], and hexachlorobenzene [HCB]) [4,22]. Use of a number of these chemicals continues in many developing countries. OC levels in human tissues and foods in these countries are several times higher than in the United States and Europe [2,23].

Data from North America and Europe indicate that residues of most OCs in human adipose tissue, breast milk, and serum have declined substantially over the past 20 years, but that more persistent isomers and metabolites are still present in detectable amounts [4,24–28]. DDT-related isomers appear to have decreased more rapidly than PCBs and some other OCs such as HCB [24,28]. Given their ubiquitous presence in the environment and the continued use of some OCs in developing countries, it is of interest to determine whether these compounds are indeed related to the risk of breast cancer. Early studies yielded conflicting results. They also generated hypotheses that might help to explain inconsistencies, such as the possibility of variation related to subgroups defined by tumor estrogen receptor (ER) status [29], lactation history [22], or ethnicity, perhaps as a result of higher exposure [30]. This paper will assess whether various aspects of study design may be related to inconsistent results, and will review whether studies published to date support the hypotheses related to at-risk subgroups. We emphasize compounds that have been the focus of most research to date, namely: (i) DDT-related compounds, including DDE, a common persistent metabolite of found in the food chain and the environment; and (ii) PCBs. We also review the more limited evidence available for several other OCs.

OVERVIEW OF RESULTS

Epidemiologic studies of OCs and breast cancer risk published to date are summarized in Table 1. The majority (n = 20; seven of which incorporate populations at least partially included in other reports)

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Table 1 Studies on organochlorines and breast cancer: Design and summary results.

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
1A. ADIPOSE TISSUE, RETROSPECTIVE (Studies with >50 cases/controls)							
Aronson et al., 2000 (Canada) [50; see also 43]	Hospital-based *Cases*: Incident in situ or invasive BC *Controls*: BBD, biopsy. Frequency matched-age.	1995–97	217/213	80.5 % overall [sufficient tissue for 81.3 cases, 100 % controls]	Excluded: wt Δ. (ER status included in [14])	– PCBs: 2a (105, 118, 156); 2b (170); 3 (180) OTHER: Mirex in parous/never-lactated	DDT, DDE PCBs: 1b (187); 2b (138); 3 (99, 153, 183) OTHER: CN, TN, OCD, HCB, b-HCH
Bagga et al., 2000 (US) [34]	HMO-based *Cases*: Any BC *Controls*: Breast reduction surgery	1995–96	73/73	Not reported.	Excluded: lactation hx, wt Δ, dietary fat, OC/HRT use, ER status. (ORs age-adj.)		DDT, DDD, DDE
Holford et al., 2000 (US) [83; data = 57]	See [85]	1994–97	304/186	See [57]	See [57]	PCBs: 3 (180, 183)	PCBs: 1b (187); 2a (74, 118, 156); 2b (138, 170); 3 (153, 180, 183)
Lucena et al., 2001 (Spain) [84]	Hospital-based *Cases*: Any BC *Controls*: BBD	1997	65/69	n/a	Results not shown except PCB 28.	PCBs: U (28)	PCBs: 1b (187); 2 (118, 170); 3 (153, 180, 183); U (52, 101, 138, 188).
Stellman et al., 2000 (US) [32]	Hospital-based *Cases*: Incid. invasive (n = 199) or in situ (33) *Controls*: BBD [<4 % atypia] (n = 250) + non-breast surgery (n = 73) w/ adipose tissue from other sites.	1994–96	232/323	95 % overall [adipose tissue from 86 %]	Excluded: wt Δ, dietary fat. Age- & BMI-adjusted means presented, & detailed analysis of DDE, PCBs and total OCs.	*p,p*-DDT PCBs: 2a (74); 2b (138); 3 (183) OTHER: OCD	*o,p*-DDT, *p,p*-DDE PCBs: 1b (187); 2a (118, 156, 167); 2b (170); 3 (99, 146, 153, 172, 178, 180) OTHER: TN, b-HCH, HCB

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Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
1A. ADIPOSE TISSUE, RETROSPECTIVE (Studies with >50 cases/controls)							
van't Veer et al., 1997 (5 countries, Europe) [56]	Pop'n.-based (2 ctries.) Hospital (3 ctries.) *Cases*: Incident, postmenopausal BC *Controls*: Matched-age, ctr, menopausal status. All adipose = buttocks.	1991–92	265/341	75–97 % cases 22–91 % ctrls. (varied by ctr.) [adipose tissue from 91 %cases, 98 % ctrls.]	Excluded: lactation hx, dietary fat, ER status; stable wt = eligibility requirement	–	DDE
Woolcott et al., 2001 (Canada) [43; data = 50]	Hospital-based *Cases*: Incident BC, sufficient tissue *Controls*: BBD. Matched-age, study site.	See [50]	See [50]	See [50]	Excluded: wt Δ	DDE (in ER+ tumors only)	*p*,*p*-DDT PCBs: Σ estimated as (138+153] x 5.2 ≈ arochlor; 1 (187); 2 (118, 156, 170); 3 (99, 153, 180, 183); U (138). OTHER: CN, TN, HCB, Mirex, b-HCH
Zheng 1999a (US) [57; see also 52,58–60,83]	Hospital-based *Cases*: Incident primary BC w/ surgery *Controls*: Incident proliferative BBD excl. atypical hyperplasia	1994–97	304/186	79 % cases, 74 % controls	Excluded: wt Δ, ER status; perhaps OC/HRT use.	–	DDT, DDE
Zheng 1999b (US) [58; data = 57]	See [57]	See [57]	See [57]	See [57]	See [57]	–	OTHER: b-benzene hexachloride (b-BHC) (ns OR in nulliparous)
Zheng 1999c (US) [59; data = 57]	See [57]	See [57]	See [57]	See [57]	See [57]	–	HCB
Zheng 2000a (US) [52; data = 57]	See [57]	See [57]	See [57]	See [57]	See [57]	–	PCBs: 1b (187); 2a (74, 118, 156); 2b (138, 170); 3 (153, 180, 183)

Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
1A. ADIPOSE TISSUE, RETROSPECTIVE (Studies with >50 cases/controls)							
Zheng 2000b (US) [52; data = 57]	See [57]	See [57]	See [57]	See [57]	See [57]	–	OTHER: TN, OCD
1B. ADIPOSE TISSUE, RETROSPECTIVE (Studies with <50 cases/controls)							
Charles et al., 2001 (US) [44]	Hospital-based *Cases*: Any *Controls*: BBD	1987–89	46/21	n/a	Unadjusted means	*o,p′*-DDE	*o,p′*-DDT, *p,p′*-DDT, *p,p′*-DDE PCBs: 1a (49, 52, 70); 1b (101, 177, 187); 2a (105, 118, 156, 169); 2b (138, 170); 3 (153, 180, 183, 187); U (137, 110, 189)
Dewailly et al., 1994 (Canada) [29]	Hospital-based *Cases*: Incident BC *Controls*: BBD	1991–92	20/17 *[Cases: 9 = ER+ 9 = ER–]*	n/a	Age-adjusted ORs (DDE) & unadjusted means only. [Similar wt Δ, parity; cases > age, < lactation reported]	DDE (in ER+ only) PCBs: 3 (99) in ER+ OTHER: TN in ER-, Mirex in ER+	– PCBs: Σ; 1b (187); 2a (105, 118, 156); 2b (138, 170); 3 (153, 180, 183) OTHER: HCB, b-HCH, OCD
Falck et al., 1992 (US) [39]	Hospital-based; stored specimens *Cases*: Incident BC *Controls*: BBD	1987	20/20	n/a	Age-adjusted ORs (DDE, PCBs) & unadjusted means only [Similar BMI; cases > age]	DDE (ns after adjust for smoking) PCBs: Σ	DDT – OTHER: HCB, TN, Σ(HCE+OCD)
Guttes et al., 1998 (Germany) [85]	Hospital-based *Cases*: Any BC (levels measured both in & distant from tumor) *Controls*: BBD	1993–94	45/20	n/a	Age-adjusted means only. *[Cases > age; other potential confounder data n/a]*	DDE PCBs: 2 (118); 3 (153)	DDT PCBs: 2a (156); 2b (138, 170); 3 (180) OTHER: b-HCH, HCB

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Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
1B. ADIPOSE TISSUE, RETROSPECTIVE (Studies with <50 cases/controls)							
Hardell et al., 1996 (Sweden) [86; see also 49]	Hospital-based *Cases*: Incident BC *Controls*: BBD	1993–95	22/19	n/a	Excluded: wt Δ, dietary fat.	OTHER: Octachloro-dibenzo-*p*-dioxin (OCDD)	OTHER: Various PCDD & PCDF isomers
Liljegren et al., 1998 (Sweden) [49; data partially used in 86]	Hospital-based *Cases*: Incident invasive BC *Controls*: BBD	1993–95	43/35	n/a	Excluded: wt Δ, dietary fat.	– PCBs: 2a (77) among ER+ postmenopausal women OTHER: HCB (ER+)	DDE PCBs: Σ; 2a (126, 169) (see below: add'l unadjusted means compared)
Mussalo-Rauhamaa et al., 1990 (Finland) [41]	Hospital-based *Cases*: Any BC *Controls*: Breast tissue from accident fatalities	1985–86	44/33	n/a	Excluded: wt Δ, dietary fat, menop. status, OC use, HRT use, ER status.	OTHER: b-BHC	DDT, DDD, DDE PCBs: Σ OTHER: HCB, HCE
Unger et al., 1984 (Denmark) [42]	Hospital-based *Cases*: (i) BC deaths; (ii) Any BC *Controls*: (i) Non-cancer deaths, (ii) BBD, matched-age.	<1984	(i) 18/35 (ii) 14/21	Not reported	Excluded: lactation hx, BMI, wt Δ, dietary fat, menop. status, OC use, HRT use, ER status.	–	DDE PCBs: Σ
2. SERUM, PROSPECTIVE (nested case-control)							
Dorgan et al., 1999 (US) [33]	Volunteer serum bank; ≥4 ml samples *Cases*: Incident BC *Controls*: Matched-age, blood yr, BBD hx.	1977–89 {1977–87} [max 9.5 yr lag, medn 2.7 yr]	105/208	n/a [70 % followed only thru 1983]	Excluded: lactation hx, wt Δ, dietary fat, ER status.	– OTHER: HCB	DDT, DDE PCBs: Σ; 2a (118); 2b (138) OTHER: b-HCH, dieldrin

Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
2. SERUM, PROSPECTIVE (nested case-control)							
Helzsouer et al., 1999 [35] (US)	Volunteer serum bank (1 = 1974, 2 = 1989) *Cases*: BC incidence or death (registry, hospital, death cert.) *Controls*: Matched - age, race, menop status, blood yr.	1974/ 1989–94 {1974, 1989 or both} [max 20 yr lag]	1974: 235/235 1989: 105/105	89 % cases, 76 % controls (for fu questionnaire)	Excluded: dietary fat.	–	DDE PCBs: Σ (see below)
Hoyer et al., 1998 (Denmark) [36]	Population-based (1 = 1976–78, 2 = 1981–83) *Cases*: Invasive incident (registry) *Controls*: Matched-age, vital status	1976–92 {1976–78 & 1981–83} [max 17 yr lag]	240/477	75.7 % exam I [78.3 % fu, exam II] [sufficient serum from 89 %]	Excluded: lactation hx, wt Δ, dietary fat, OC use, HRT use, ER status.	– OTHER: Dieldrin	*p,p′*-DDT, *o,p′*-DDT, DDE PCBs: Σ (see below) OTHER: b-HCH
Hoyer et al., 2000a (Denmark) [31; subset used in 36]	Population-based *Cases*: Invasive incident w/ repeated serum available. *Controls*: Matched-age, vital status	See [33] [mean lag 8.1 yr exam 1, 4.8 yr exam 2]	155/274	See [36]	See [36]; adjustment for wt Δ included.	*p,p′*-DDT PCBs: 2b (138)	DDT Σ, *p,p*-DDE PCBs: Σ (see below); 2a (118); 3 (153, 180) OTHER: b-HCH, dieldrin
Hunter et al., 1997 (US) [74]	Nurses Health Study *Cases*: Incident BC (83 % invasive) *Controls*: Matched-age, menopause, HRT, time/ fasting status of blood	1989–92 {1989–90}	240/240	72 % [serum from 27 %; 95 % overall follow-up rate]	Excluded: wt Δ, dietary fat, OC use.	–	DDE PCBs: Σ (defined as sum of higher congeners)

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Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
			2. SERUM, PROSPECTIVE (nested case-control)				
Krieger et al., 1994 (US) [30]	Nested HMO cohort *Cases*: Incident BC diagnosed >6 mo after serum sample. Random 50/ethnic gp. *Controls*: Matched-age, ethnicity, date joined HMO, exam yr.	1964–90 {1964–90} [min 6 mo lag; max >25 yr]	150/150 (50 black, 50 white, 50 Asian)	n/a n/a	Excluded: lactation hx, wt Δ, dietary fat, OC use, HRT use, ER status.	DDE in blacks only	DDE overall, Asians, whites PCBs: Σ (ns ↑ in blacks)
Laden et al., 2001 (US) [46; subset used in 74]	Nurses Health Study *Cases*: Incident any <1992; incident post-menop. invasive >1992. *Controls*: See [23]	1989–94 {1989–90}	381/381	See [74]	See [74]	– PCBs: Σ; 2a (118); 2b (138); 3 (153) (in nulliparous only)	DDE PCBs: 3 (180) (ns ↑)
Ward et al., 2000 (Norway) [24]	Serum bank (donors, routine health exams) *Cases*: Incident BC (registry) ≥2 yr after serum collection. *Controls*: Matched-age, sample date	1975–93 {1973–91} *[min 2-yr lag]*	150/150	n/a	Excluded: lactation history, BMI, wt Δ, dietary fat, menopausal status, OC/HRT use.	–	DDT, DDE PCBs: Σ; Gps 1, 2, 3 (see below) OTHER: OCD, TN, HCE, b-HCCH. (Others had limited detection; see below)
Wolff et al., 1993 (US) [40]	NYU Wom Hlth Study *Cases*: Incident BC <6 months after enrollment. *Controls*: Matched-age, menopause, day of menstrual cycle, dates of blood samples.	1985–91 {1985–91} [max 6 mo lag]	58/171	n/a	Excluded: wt Δ, dietary fat; no OC or HRT use in past 6 mo	DDE PCBs: Σ (higher congeners)	–
Wolff et al., 2000a (US) [25; see also 40]	See [27] *Cases*: Incident BC ≥6 mo after enrollment. *Controls*: Matched-age, menopause, dates of blood samples.	1987–94 {1985–94} [min 6 mo lag; up to 9 yr]	148/295	n/a [lipid-adjusted estimates for 74 % cases, 72 % ctrls.]	Excluded: wt Δ, dietary fat; no OC or HRT use in past 6 mo.	–	DDE PCBs: Σ

Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
			3. SERUM, RETROSPECTIVE				
Dello Iacova et al., 1999 (Italy) [87]	Community *Cases*: Any BC, 1st tx, single hospital *Controls*: Ongoing cohort study, healthy	1997–98	170/195	n/a	Unadjusted means except DDE; wt Δ, OC use, HRT use, ER status excluded.	OTHER: Heptachlor (unadj. means only)	DDT, DDE OTHER: b-BHC, endrin aldeide
Demers et al., 2000 (Canada) [51]	Hosp./pop'n. controls. *Cases*: Incident 1^{ary} invasive BC *Controls*: (i) hosp. pts; (ii) insurance registry; matched-age, region.	1994–97	315/ 219-hosp 307-pop'n.	91 % cases 89 % hosp. ctrls. 47 % pop'n. ctrls.	Excluded: wt Δ, dietary fat, menop status, ER status.	–	DDT, DDE PCBs: 3 (153) OTHER: b-HCH, TN, OCD
Gammon et al., 2002 [54]	Population-based *Cases*: Incident in situ or invasive *Controls*: Frequency matched: age	1996–97	646/429	83 % cases 68 % ctrls.	Excluded: Dietary fat. (BMI current and at age 20 included as estimate of wt Δ.)	–	DDT, DDE PCBs: 2a (118), 2b (138), 3 (153, 180) OTHER: OC+TN, dieldrin
Lopez-Carillo et al., 1997 [61] (Mexico)	Hospital-based *Cases*: Any BC, ≥20 yr residents, Mexico City *Controls*: Patients; matched-age.	1994–96	141/141	81 % cases 72 % ctrls.	Excluded: wt Δ, dietary fat, OC use, HRT use, ER status.	–	*p,p*-DDT, DDE
Mendonca et al., 1999 [62] (Brazil)	Hospital-based *Cases*: Any BC *Controls*: Hospital visitors, matched-age.	1995–96	177/350	99 % cases 79 % ctrls. [serum from 92 % cases, 95 % ctrls.]	Excluded: wt Δ, dietary fat, OC use, HRT use, ER status	–	DDE
Millikan et al., 2000 (US) [45]	Population-based *Cases*: Incident invasive BC *Controls*: Population	1993–96	889/841	74 % cases 53 % ctrls. [serum from 98 %]	Excluded: wt Δ, dietary fat, ER status. (Fruit, vegetable, fish consumption included.)	– PCBs: Σ (defined as 118, 138, 153, 180) in African Americans; ns ↑ in nulliparous & low BMI gps.	DDE (ns, low BMI) PCBs: Σ in whites, Asians

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Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
			3. SERUM, RETROSPECTIVE				
Moysich et al., 1998 (US) [22; see also 76]	Population–based *Cases*: Postmenopausal incident (hospital); blood before chemo or radiation + w/in 3 mo of surgery. *Controls*: Matched-age, county of residence, date of blood draw.	1986–1991	154/191	57 % cases 47 % ctrls. [serum from 63 %]	Excluded: wt Δ, dietary fat, ER status. Fruit & vegetable intake included.	– PCBs: Σ (73 congeners, see below) in parous never lactators	DDE OTHER: Mirex, HCB
Moysich et al., 1999b (US) [76; data used in 22]	See [34] By cytochrome P450 polymorphism (drug-metabolism)	See [22]	See [22]	See [22]	See [22]	PCBs: Σ in variants of CYP1A1 with valine substitutions.	PCBs: Σ in common variant
Olaya-Contreras et al., 1998 [88] (Columbia)	Hospital-based *Cases*: *Controls*: Matched, age	1995–96	153/153	93 % overall	Excluded: wt Δ, dietary fat, OC/HRT use, ER status.	DDE	
Romieu et al., 2000 [23] (Mexico)	Population-based *Cases*: Incident *Controls*: Age-stratified random population sample	1990–95	126/120	94 % cases, 89 % ctrls.	Excluded: wt Δ, dietary fat, OC use, ER status.	DDE (if adjusted for *p,p′*-DDT)	*p,p′*-DDT
Schecter et al., 1997 [37] (Vietnam)	Hospital-based *Cases*: Incident invasive; continuous residence N. Vietnam *Controls*: BBD pts; matched-age, area of residence	1994	21/21	Not reported	Excluded: wt Δ dietary fat, menopausal status, OC use & HRT use, ER status.	–	*p,p*-DDT, total DDT, *p,p*-DDE (*p,p*-DDT ns OR)

Table 1 (*Continued*).

1st author, yr (place) [ref.]	Design	Years: diagnosis	# Cases/ controls	Response rate [other attrition]	Key covariates excluded?	Positive & significant associations	NS or inverse associations
			3. SERUM, RETROSPECTIVE				
Wolff et al., 2000b (US) [53]	Hospital-based *Cases*: Incident BC *Controls*: Gp1 = BBD (n = 181), gp 2 = routine screenings & minor surgeries (n = 175) no hx of BBD; matched-age, race.	1994–96	175/356 [181 ctrls. = BBD]	65 % overall	Excluded: wt Δ, dietary fat	–	*p,p*-DDT, DDE PCBs: Σ; High chlorination (Σ 118, 153, 141, 138, 183, 187, 167, 174, 177, 156, 180, 170, 201, 203); low chlorination (Σ 28, 66, 74, 99, 101) OTHER: TN
Zheng 2000c (US) [89; sample overlap with 57]	Hospital & population *Cases*: Incident BC from hospital or 1 county (tx initiated 1st) *Controls*: (1) Hospital = BBD excluding atypical hyperplasia, (2) County residents. Frequency matched-age.	1995–97	326/347-hosp. 149/155-pop'n.	Hospital: 77 % cases, 71 % cntrls. County: 74 % cases, 61 % cntrls.	Excluded: wt Δ	–	*p,p*-DDE PCBs: Σ (74, 118, 138, 153, 156, 170, 180, 183, 187)

Abbreviations: *Chemicals*: CN = *cis*-nonachlor; TN = *trans*-nonachlor; AC = a-chlordane; YC = y-chlordane; OCD = oxychlordane; HCB = hexachlorobenzene; HCE = heptachlorepoxide; b-HCH = beta-hexachlorocyclohexane; OCD = oxychlordane; PCBs = polychlorinated biphenyls; PCDDs = poly-chlorinated dibenzo-*p*-dioxins; PCDFs = poly-chlorinated di-benzofurans. *Other:* BBD = benign breast disease; BC = breast cancer; OC = oral contraceptives; HRT = hormone replacement therapy; wt Δ = weight change. ER = estrogen receptors. Conversions/estimates: mcg/kg = ng/g; mg/kg × 1000 = ng/g; mcg/g × 1000 = ng/g. Wet wt: ppb = ng/ml; ppm × 1000 = ng/ml. Midpoints used to estimate medians when not given. Other notes: *Additional PCBs examined*: Helzsouer [35] reported NS differences (not shown) in: 1b (177, 187, 201); 2a (74, 118, 156); 2b (138,170); 3 (153,180, 183, 203); U (28, 146, 172, 178, 189, 193, 194, 195, 206). Ward [24] also examined (ns): 1b (177, 187, 201) 2a (74, 105, 118, 126, 156, 157, 167, 169, 189); 2b (170); 3 (99, 146, 153, 172, 178, 180, 183, 194, 195, 206, 209); several U. Liljegren [49] showed ns mean differences for: 1a (52), 1b (101, 177, 187, 201), 2a (66, 74, 105, 118, 156), 2b (138, 170), 3 (99, 153, 183, 203/196), U (28, 47, 110, 114, 157, 128/167, 171, 172, 180, 193, 189, 194, 195, 202, 206, 207, 208, 209). *Other compounds examined*: Ward [24] found limited detection of dieldrin, aldrin, endrin, *o,p′*-DDT, Mirex, OCDD, OCDF and other dioxins; further analysis was not possible.

measured OCs in adipose tissue, primarily from mammary biopsies in cancer cases and controls with benign breast disease (BBD). Eight of these studies each included fewer than 50 cases and controls and had limited capacity for covariate adjustment. Ten studies (three with overlap in populations) used serum samples collected from 6 months to 25 years prior to diagnosis. An additional 13 studies (two with some overlap) used serum collected at or after diagnosis.

As summarized in Table 1 and detailed below, regardless of the medium used to measure OC levels, studies conducted to date do not provide consistent evidence that any of the OCs examined thus far play a role in the initial breast cancer risk. A compound-specific review follows with discussion of how the lack of evidence for adverse effects might be explained by factors related to study design, or by variation in risk across subgroups.

DDT/DDE

p,*p*′-DDT is only weakly estrogenic, but persists in the food chain [2,11,13]. Of 10 studies reporting multivariate-adjusted ORs, only one [31] found elevated risk associated with adipose or serum levels of *p*,*p*′-DDT (Table 2). Another eight studies compared mean levels of *p*,*p*′-DDT but incorporated limited covariate adjustment. One of these [32] reported significantly higher levels in cases, after adjusting for age and BMI. *o*,*p*′-DDT—a more estrogenic but less persistent isomer—has not been studied epidemiologically because even studies using serum collected in the 1970s, when levels were higher, had too few participants with detectable levels to analyze associations separately [33]. A number of studies [31,33–37] examined associations with total DDT, estimated as the sum of *p*,*p*′-DDT and several metabolites. None reported evidence of adverse effects in relation to high levels of the sum of these DDT metabolites.

Most studies of DDE have examined *p*,*p*′-DDE, the main persistent metabolite of DDT. Since this compound, which is not estrogenic, is found in foods, elevated levels may not be the result of direct exposure to *p*,*p*′-DDT [11,37,38]. Although a few studies conducted from 1992 to 1994 [29,39], in ER positive [ER+] tumors; [40] suggested possible increased risk associated with *p*,*p*′-DDE, other early exploratory studies did not find increased risk [41,42], and the majority of studies since that time have reported inverse or null associations (Table 3). Two of the three initial studies reporting elevated *p*,*p*′-DDE in subjects with breast cancer were very small (≤20 cases) and unable to conduct adequate multivariate adjustment [29,39]. Positive associations reported by [40] were based on cases diagnosed within 6 months of serum collection and were not confirmed in a follow-up using cases with similar OC levels, diagnosed >6 months after enrollment [25]. Adjustment for serum lipids, omitted in the first analysis, did not influence results of the second study.

To date, 27 moderate to large (i.e., at least 50 cases) studies with multivariate adjustment have explored associations between *p*,*p*′-DDE and breast cancer. Other than the early studies referenced above, only one other study ([23] in a Mexico City study of parous women) has reported significant positive associations overall. Two additional studies reported significant positive associations in different subgroups ([43] in ER negative [ER–] tumors; [30] in blacks but not whites or Hispanics). One small study [44], using adipose tissue samples collected from 1987 to 1989 and analyzed without adjustments did report significantly higher means of the more estrogenic but short-lived metabolite *o*,*p*′-DDE in cases than controls.

In summary, the majority of studies, regardless of medium or study size, showed no negative impact of DDT or DDE on risk of breast cancer. Risk was not more likely to be apparent in populations with higher mean concentrations of DDT or DDE. In fact, many studies show risk ratios below 1, as above 1 (as seen on Figs. 1a and 1b).

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Table 2 DDT and breast cancer risk.

1st author, year published [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean DDT		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
1A. ADIPOSE TISSUE, RETROSPECTIVE (>50 cases/controls)														
Aronson [50][a]			–	1995–97	Canada	217/213	22.0	19.3 ng/g	y	1.0	0.8	0.9	1.2	
Bagga [34][†]			–	1995–96	US	73/73	261.6	267.3 ng/g	age	–				
Stellman [32][†,1]	↑			1994–96	US	232/323	12.3	12.1* ng/g	age, bmi	–				
Woolcott [43]		ns		1995–97	Canada	217/213	23.5 = ER–	19.3 ng/g	not	–				
							21.3 = ER+		shown	–				
Zheng [57][†]			–	1994–97	US	304/186	51.8	55.6 ng/ml	y	1.0	0.8	0.6	0.8	
1B. ADIPOSE TISSUE, RETROSPECTIVE (<50 cases/controls)														
Charles [44]														
p,p′-DDT		ns		1987–89	US	43/21	102.0	77.8 ng/g	n	–				
o,p′-DDT		ns		″	″	″	15.9	10.4 ng/g	n	–				
Falck [39]		ns		1987	US	20/20	216	148 ng/g	n	–				
Guttes [85][†]			–	1993–94	Germany	45/20	30	28 ng/g	age	–				
Mussalo-Rauhamaa [41]		ns		1985–86	Finland	44/33	70	60 ng/g	n	–				
2. SERUM, PROSPECTIVE														
Dorgan [33]														
p,p′-DDT			–	1977–87	US	105/208	–	–	y	1.0	1.0	1.1	0.4	
Total DDT			–	″	″	″	–	–	y	1.0	1.1	0.3	0.8	
Hoyer [36][1]														
p,p′-DDT			–	1976–83	Denmark	240/477	pooled	141 ng/g	y	1.0	1.1	0.9	1.2	
Total DDT			–	″	″		pooled	1326 ng/g	y	1.0	0.8	0.9	0.8	
Hoyer [31]														
p,p′-DDT[1]	↑			1976–78	Denmark	155/274	pooled	144 ng/g (bs)	y	1.0	1.3	2.1	3.6*	
				1981–83				46 ng/g (fu)						
Total DDT[1]		ns					pooled	1350 ng/g (bs)	y	1.0	1.1	1.4	2.4	
								1191 ng/g (fu)						
Ward [24]			–	1973–91	Norway	150/150	119.5	137.7 ng/g	y	1.0	0.2	0.5	0.3	

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Table 2 (*Continued*).

1st author, year published [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean DDT		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
3. SERUM, RETROSPECTIVE														
Dello Iacova [87][1]		ns		1997–98	Italy	170/195	2.47	1.77 ng/ml	n	–				
Demers [51]														
Pop'n. controls			–	1994–97	Canada	315/307	12.7	11.0 ng/g	y	1.0	0.6	0.5	0.7	0.8
Hosp. controls			–	″	″	315/219	12.7	12.5 ng/g	y	1.0	0.9	1.1	1.1	1.4
Gammon [54]			–	1996–97	US	633/418	69.0	69.3 ng/g	y	1.0	0.7	1.0	1.2	1.2
Lopez-Carillo [61]			–	1994–96	Mexico	141/141	62	85 ng/g	n	–				
Romieu [23]			–	1990–95	Mexico	126/120	150	230 ng/g	n	–				
Premenopausal			–	″	″	56/64	220	130 ng/g	n	–				
Postmenopausal		ns		″	″	64/62	250	180 ng/g	n	–				
Schecter [37][2]														
p,p′-DDT		ns		1994	Vietnam	21/21	2.33	2.37 ng/ml	y	1.0	2.2	1.2		
Total DDT			–	″	″		15.90	20.95 ng/ml	y	1.0	0.4	1.1		
Wolff [53][†]			–				30	28 n/g	y	1.0	1.2	1.3		

DDT = *p,p*-DDT unless otherwise noted; total DDTs are sum of several isomers. Statistical significance defined as $p < 0.05$/CI excludes null or $p < 0.10$. bs = baseline; fu = follow-up.

[1]Medians vs. means.

[2]Means are wet wt rather than lipid basis.

[a–e]Supplementary analysis gave similar results when stratified by: a: pre/post-menopausal; b-ER status; c: lactation/parity group; d: BMI group.

[†]Other notes: Zheng [57] are age- and lipid-adjusted means; Wolff [53]: Results similar for blacks, hispanics, and whites.

Table 3 DDE and breast cancer risk.

1st author, year published [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean DDE		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
1A. ADIPOSE, RETROSPECTIVE: STUDIES WITH >50 CASES/CONTROLS														
Aronson [50][a,c]		ns		1995–97	Canada	217/213	693	596 ng/g	y	1.0	1.0	0.9	1.6	
Bagga [34][†]		ns		1995–96	US	73/73	800*	709 ng/g	age					
Stellman [32][†1,b]			–	1994–96	US	232/323	419	374 ng/g	y	1.0	1.1	0.7		
van't Veer [56]			–	1991–92	Europe	265/341	1350	1510 ng/g	y	1.0	1.1	0.7	0.5*	
Woolcott [43; = 50]														
ER+			–	″	″	″	638	596 ng/g	y	1.0	0.9	1.1		
ER–	↑			1995–97	Canada	217/213	906	596 ng/g	y	1.0	0.8	2.4*		
Zheng [57][†,1]			–	1994–97	US	304/186	736.5	784.1 ng/ml	y	1.0	1.3	0.9	0.9	
1B. ADIPOSE, RETROSPECTIVE: STUDIES WITH <50 CASES/CONTROLS														
Charles [44]														
p,p′-DDE		ns		1987–89	US	43/21	1472.3	1387.7 ng/g	n	–				
o,p′-DDE	↑			″	″	″	1.4	0.5 ng/g	n	–				
Dewailly [29]														
ER+	↑			1991–92	Canada	9/17	2132*	765 ng/g	age					
ER–			–	″	″	″	609	765 ng/g	age					
Falck [39]	↑			1987	US	20/20	2200*	1487 ng/g	age					
Guttes [85][†]	↑			1993–94	Germany	45/20	805*	496 ng/g	age					
Liljegren [49][a,b]			–	1993–95	Sweden	43/35	767	1026 ng/g	y	1.0	0.4			
Mussalo-Rauhamaa [41]			–	1985–86	Finland	44/33	96	98 ng/g	n					
Unger (i) [42]			–	<1984	Denmark	18/35	< detection	197 ng/g	n					
Unger (ii)			–	″	″	14/21	123	125 ng/g	n					
2. SERUM, PROSPECTIVE														
Dorgan [33]			–	1977–87	US	105/208	–	–	y	1.0	0.9	0.4	0.8	
Helzsouer '74 [35][a,b]			–	1974	US	235/235	1698.9	1920.3 ng/g	y	1.0	1.2	1.0	0.9	0.7
ER+			–	″	″	″	–	–	y	1.0	0.9	0.8		
ER–		ns		″	″	″	–	–	y	1.0	1.1	1.7		

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Table 3 (*Continued*).

1st author, year published [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean DDE		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
2. SERUM, PROSPECTIVE														
Helzsouer '89 [35]-All			–	1989	US	105/105	1311.9	1586.3 ng/g	y	1.0	1.2	0.6		
Premenopausal		ns		〃	〃	〃	–	–	y	1.0	4.3	1.4		
Postmenopausal		ns		〃	〃	〃	–	–	y	1.0	1.6	0.5		
ER+		ns		〃	〃	〃	–	–	y	1.0	2.3	0.6		
ER–			–	〃	〃	〃	–	–	y	1.0	0.7	0.2		
Hoyer [36][1]			–	1976–83	Denmark	240/477	pooled	1183 ng/g	y	1.0	0.8	0.8	0.9	
Hoyer [31][1]			–	〃	〃	155/274	pooled	1197 ng/g (bs) 1169 ng/g (fu)	y	1.0	1.0	0.8	1.4	
Hunter [74][1,2]			–	1989–90	US	240/240	6.01	6.97 ng/ml	y	1.0	0.8	0.5	0.7	0.7
Laden [46][1,c,d]			–	〃	〃	381/381	768	817 ng/g	y	1.0	1.0	0.5	0.9	0.8
Krieger [30][1]-All			–	1964–90	US	150/150	43.3	43.1 ng/ml	y	1.0	1.3	1.3		
White		ns		〃	〃		35.7	35.0 ng/ml	y	1.0	1.9	2.4		
Black	↑			〃	〃		49.2	43.4 ng/ml	y	1.0	2.3	3.9*		
Asian			–	〃	〃		45.1	50.8 ng/ml	y	1.0	0.9	0.7		
Ward [24][b]			–				1230	1260 ng/g	y	1.0	0.7	1.0	1.2	
Wolff [40][1]	↑						11.0	7.7* ng/ml	y	1.0	1.7	4.4*	2.3	3.7*
Wolff [25][b]			–				977	1097 ng/g	y	1.0	0.8	0.6	1.3	
3. SERUM, RETROSPECTIVE														
Dello Iacova [87]			–	1997–98	Italy	170/195	9.55	8.98 ng/ml	y	1.0	0.8	1.2		
Demers [51]														
Pop'n. controls			–	1994–97	Canada	315/307	509	480 ng/g	y	1.0	0.8	1.1	0.9	1.0
Hosp. controls		ns		〃	〃	315/219	509	463 ng/g	y	1.0	0.9	0.7	1.5	1.4
Gammon [54][a,b,c,d]			–	1996–97	US	643/427	672	646 ng/g	y	1.0	0.9	0.9	0.9	1.2
Lopez-Carillo [61][a]			–	1994–96	Mexico	141/141	563	506 ng/g	y	1.0	0.6	0.8		
Mendonca [62][2]			–	1995–96	Brazil	177/350	5.1	4.8 ng/ml	y	1.0	1.0	1.3	1.1	0.8
Millikan [45][a,b,c,e]			–	1993–96	US	889/841	1960 660	1690 (Black) 760 (White) ng/g	y	1.0	1.1	1.1		
Black, BMI <25.0		ns							y	1.0	2.7	3.8		
White, BMI <25.0			–						y	1.0	0.7	0.9		

Table 3 (*Continued*).

1st author, year published [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean DDE		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
3. SERUM, RETROSPECTIVE														
Moysich [76] – All			–				11.5	10.8 ng/g	y	1.0	1.0	1.3		
Never lactated, parous		ns					13.2	10.8 ng/g	y	1.0	2.0	1.8		
Ever lactated			–				10.4	10.4 ng/g	y	1.0	0.8	1.3		
Olaya-Contreras [88]	↑			1995–96	Columbia	153/153	3.30	2.50 ng/ml	y	1.0	1.2	2.0*		
Premenopausal		ns		″	″	60/60	3.02	2.1 ng/ml	y	1.0	1.4	2.5		
Postmenopausal		ns		″	″	93-93	3.45	3.0 ng/ml	y	1.0	1.1	1.9		
Romieu [23] – All	↑			1990–95	Mexico	126/120	3840	2510 ng/g	y	1.0	1.2	2.3	3.8*	
Premenopausal		ns		″	″	56/64	2400	1930 ng/g	y	1.0	1.4	2.5	2.4	
Postmenopausal		ns		″	″	64/62	5100	3120 ng/g	y	1.0	1.1	2.4	5.3	
Schecter [37][2]			–	1994	Vietnam	21/21	12.17	16.67 ng/ml	y	1.0	0.5	1.1		
Wolff [53][b,e]			–	1994–96	US	175/356	610	660 ng/g	y	1.0	0.8	0.9		
Zheng [89][†,b,c]			–	1995–97	US	475/502	460.1	456.2 ng/g	y	1.0	1.1	1.0		

DDE = *p,p*-DDE unless otherwise noted. Statistical significance defined as $p < 0.05$/CI excludes null or $p < 0.10$. bs = baseline fu = follow-up

[1]Medians rather than means.

[2]Means are wet weight rather than lipid basis.

[a–e]Supplementary analysis found no meaningful differences when stratified by: a: pre/post-menopausal; b: ER status; c: lactation/parity group; d: BMI group; e: ethnic groups.

[†]Other notes: Stellman [32] are age/BMI-adjusted means. Zheng [57] are age- and lipid-adjusted means.

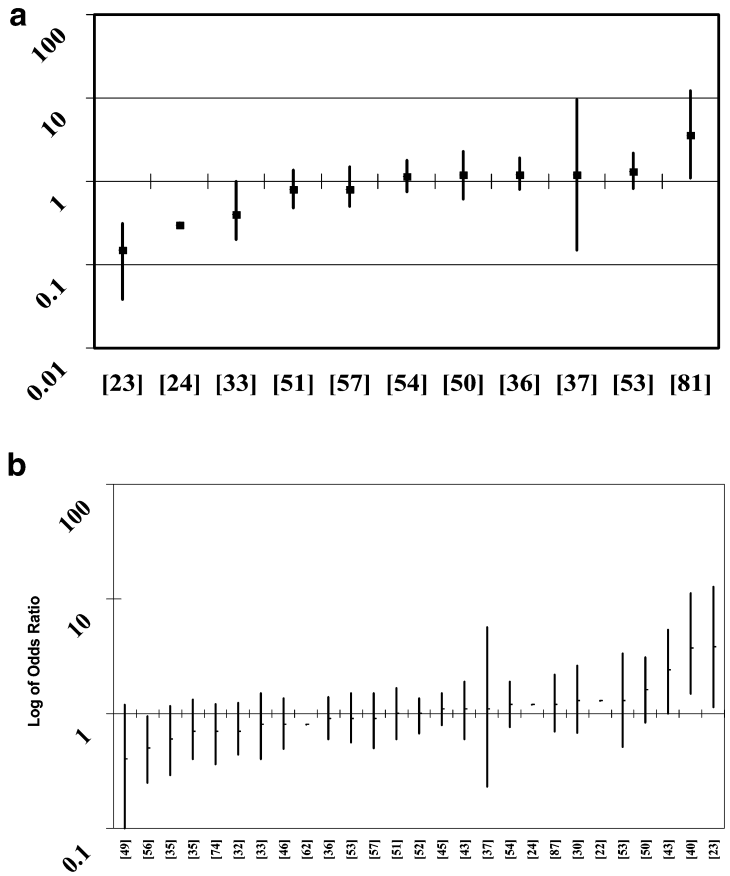

Fig. 1 (a) DDT and breast cancer risk. (b) DDE and breast cancer risk.

PCBs

Four of 17 published studies on total PCBs and breast cancer risk reported significant positive associations (Table 4). The report of Wolff et al. [40] showed a significant positive association that was not replicated in the follow-up study [25]. In the three other studies, elevated risk was limited to various diverse population subgroups (Moysich et al. [22] in parous never-lactators; Millikan et al. [45] in blacks, particularly if obese; Laden et al. [46] in nulliparous women).

Examining total PCBs may mask variation in congener-specific effects, as some of the 209 congeners are thought to be estrogenic (type 1a), while others appear to be antiestrogenic (types 2a and b), or to have no estrogenic activity (type 1b, based on groupings proposed by Wolff and Toniolo [8]; Wolff et al. [47]). Net effects of PCB mixtures may vary depending on relative concentrations of these different congeners [47,48]. The low-chlorination, potentially estrogenic congeners of group 1a are not persistent, as they are readily metabolized and eliminated [48]. However, the two studies [44,49] reporting means for congeners in this group did not find significant differences between cases and controls (Table 5). Given their rapid elimination, retrospective studies may not be reliable for assessing any long-term effects of these congeners. The prospective studies have had few subjects with detectable levels of 1a congeners [33].

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Table 4 Total PCBs and breast cancer risk.

1st author [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean PCB Σ		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
IA. ADIPOSE TISSUE, RETROSPECTIVE (>50 CASES)														
Stellman [32][†,1,b]			–	1994–96	US	232/323	294.7	257.1 ng/g	y	1.0	1.1	1.0		
Woolcott [43; data = 50]														
ER+			–	″	″	″	920		y	1.0	1.3	1.3		
ER–		ns		1995–97	Canada	217/213	1,020	870 ng/g	y	1.0	1.1	1.7		
Zheng [60][†,a,b,c]			–	1994–97	US	304/186	494.1	478.6 ng/g	y	1.0	0.6	0.7		
IB. ADIPOSE TISSUE, RETROSPECTIVE (< 50 CASES)														
Dewailly [29]														
ER+			–	″	″	″	404.7	397.0 ng/g	age	–				
ER–			–	1991–92	Canada	9/17	331.5	397.0 ng/g	age	–				
Falck [39]	↑			1987	US	20/20	1965*	1395 ng/g	age	–				
Liljegren [49][a,b]														
All			–	1993–95	Sweden	43/35	1205	1149 ng/g	y	1.0	0.7			
Postmenop, ER+		ns		″	″	″	–	–	y	1.0	1.8			
Mussalo-Rauhamaa [41]			–	1985–86	Finland	44/33	1050	1300 ng/g	n	–				
Unger [42] (i)		ns		<1984	Denmark	18/35	6470	5120 ng/ml	n					
Unger [42] (ii)			–	14/21	123	125 ng/g	3890	3930 ng/ml	n					
II. SERUM, PROSPECTIVE														
Dorgan [33]		ns		1977–87	US	105/208	–	–	y	1.0	0.7	1.1	0.7	
Helzsouer 1974 [35][b]														
All			–	1974	US	235/235	735.3	663.6 ng/g	y	1.0	1.4	0.9	1.1	1.1
Premenopausal		ns		″	″	″	–	–	y	1.0	0.7	2.2		
Postmenopausal			–	″	″	″	–	–	y	1.0	0.7	0.6		
Helzsouer 1989 [35][a,b]														
All			–	1989	″	105/105	327.7	332.9 ng/g	y	1.0	0.8	0.8		
Premenopausal		ns		″	″	″	–	–	y	1.0	1.5	2.1		
Postmenopausal			–	″	″	″	–	–	y	1.0	0.8	0.7		
Hoyer [36][1]			–	1976–84	Denmark	240/477	pooled	1100 ng/g	y	1.0	0.9	0.8	1.1	
Hoyer [31][1]			–	″	″	155/274	pooled	1102 ng/g (bs) 979 ng/g (fu)	y	1.0	0.8	0.8	1.6	

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Table 4 (*Continued*).

1st author [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean PCB Σ		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
II. SERUM, PROSPECTIVE														
Hunter [74][†,1,2,b]			–	1989–90	US	240/240	5.1	5.2 ng/ml	y	1.0	0.6	0.5	0.5	0.7
Laden [46][b,d]														
All			–	1989–94	US	381/381	544	543 ng/g	y	1.0	0.7	0.8	0.9	0.8
Nulliparous	↑						–		y	1.0	0.8	5.3*	–	–
Krieger [30][2]														
All			–	1964–90	US	150/150	4.4	4.8 ng/ml	y	1.0	1.2	0.9		
White			–	″	″	50/50	3.6	4.2 ng/ml	y	1.0	1.0	0.5		
Black		ns		″	″	50/50	4.8	4.5 ng/ml	y	1.0	1.7	2.2		
Asian			–	″	″	50/50	4.9	5.6 ng/ml	y	1.0	1.2	0.8		
Ward [24][b]			–	1973–91	Norway	150/150	776.1	806.6 ng/g	y	1.0	0.6	0.8	0.5	
Wolff [40][1]	↑			1985–91	US	58/171	8.0	6.7 ng/ml	y	1.0	5.2*	7.0*	4.1	4.4
Wolff [25][b]		ns		1985–94	US	148/295	683	663 ng/g	y	1.0	1.6	1.2	2.0	
III. SERUM, RETROSPECTIVE														
Millikan [45][†,a,b]														
All			–	1993–96	US	889/841	560 (black) 380 (white)	510 ng/g 380 ng/g	y	1.0	1.3	1.1		
Black	↑			″	″		–	–	y	1.0	1.4	1.7*		
Black, BMI >30	↑			″	″		–	–	y	1.0	1.7	4.3*		
White			–	″	″		–	–	y	1.0	1.3	1.0		
White, BMI >30		ns		″	″		–	–	y	1.0	2.0	1.5		
Moysich [22][2,†]														
All			–	1986–91	US	154/191	4.3	4.1 ng/g serum	y	1.0	0.7	1.1		
Never lact, parous	↑			″	″		4.6	4.0 ng/g serum	y	1.0	1.7	2.9*		
Ever lactated			–	″	″		4.3	4.3 ng/g serum	y	1.0	0.4	0.7		
Lo chlor, never lact.	↑			″	″		–	–	y	1.0	0.7	3.6		
Hi chlor, never lact.			–	″	″		–	–	y	1.0	0.5	1.5		
Wolff [53][b,e]														
HPCB			–	1994–96	US	175/356	600	620 ng/g	y	1.0	0.9	0.8		
LPCBs		ns		″	″		110	110 ng/g	y	1.0	1.5	1.0		

Table 4 (*Continued*).

1st author [ref.]	+ve	ns	–ve	Years	Place	# Cases/ controls	Mean PCB Σ		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
III. SERUM, RETROSPECTIVE														
Zheng [89][†,2,b,c]														
All			–	1994–97	US	304/186	733.1	747.6 ng/ml	y	1.0	1.0	1.0		
Nulliparous		ns		″	″				y	1.0	1.5	0.8		

HPCBs = high-chlorination PCBs; LPCBs = low-chlorination PCBs. Statistical significance defined as $p < 0.05$/CI excludes null or $p < 0.10$.

[1]Medians presented rather than means.

[2]Means are wet weight rather than lipid basis.

[a–e]Supplementary analysis found no meaningful differences when stratified by: a: pre/post-menopausal; b: ER status; c: lactation/parity group; d: BMI group; e: ethnic groups.

[†]Other notes: Millikan [45] found lower ORs in low-moderate chlorination congeners than in high chlorination congeners; as well as NS > risk in nulliparous. Moysich [22] reported higher ORs in low-moderate chlorination congeners, particularly among parous women who never lactated (cite OR). Stellman [32] are age/BMI-adjusted means. Zheng [89] present age- and lipid-adjusted means. Helzsouer [35] examined the following PCBs individually and by group; results were NS and not shown: 1b (177, 187, 201); 2a (74, 118, 156); 2b (138,170); 3 (153,180,183, 203); U (28, 146, 172,178, 189,193, 194, 195, 206). Hoyer [36] – PCBs are sum of: 1 (177, 187, 201); 2 (74, 105, 118, 156, 170, 189); 3 (99, 146, 153, 172, 178, 180,183, 194, 195, 206); U (28, 52, 56, 66, 101, 110, 138, 193, 203).

Table 5 Individual PCB congeners and breast cancer risk.

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
Σ, gp1	*Serum, prospective*								
	None	–	–	None	–	–	Ward [24]	62.6	65.0 ng/g
49 (1a)	*Adipose tissue*								
	None	–	–	None	–	–	Charles [44]	0.5	1.0 ng/g
52 (1a)	*Adipose tissue*								
	None	–	–	Charles [44]	2.9	2.0 ng/g	Liljegren [49]	0.8	0.8 ng/g
70 (1a)	*Adipose tissue*								
	None	–	–	Charles [44]	3.7	2.0 ng/g	None	–	–
101 (1b)	*Adipose tissue*								
	None	–	–	Charles [44]	4.6	3.8 ng/g	None	–	–
177 (1b)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	14.5	14.0 ng/g
							Charles [44]	7.5	6.7 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	12.1	12.4 ng/g
187 (1b)	*Adipose tissue*								
	None	–	–	Charles [44]	29.4	24.7 ng/g	Aronson [50]	25.7	24.2 ng/g
				Stellman [32]	16.2	12.8 ng/g	Dewailly [29] [ER+/–]	19.4/18.7	20.4 ng/g
				Woolcott [43] ER+	27.1	24.2 ng/g	Liljegren [49]	54.9	55.9 ng/g
				Woolcott [43] ER–	25.3				
							Zheng [60]	28.8	ng/g pooled
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	37.2	38.2 ng/g
							Zheng [89]	61.5	ng/g pooled
201 (1b)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	21.2	21.6 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	14.0	14.7 ng/g

Table 5 (*Continued*).

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
Σ, gp2	*Adipose tissue*								
	None	–	–	None	–	–	Zheng [60]	269.9	ng/g pooled
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	165.2	169.8 ng/g
	Serum, retro.								
	None	–	–	None	–	–	Zheng [89]	247.0	ng/g pooled
74 (2a)	*Adipose tissue*								
	Stellman [32]	29.6	26.7 ng/g	None	–	–	Liljegren [49]	17	18 ng/g
							Zheng [60]	307	ng/g pooled
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	27.0	28.7 ng/g
77 (2a)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	5.2	4.9 pg/g
105 (2a)	*Adipose tissue*								
	Aronson [50]	7.1	6.3 ng/g				Charles [44]	17.7	19.6 ng/g
							Dewailly [29]	7.3/3.9 [ER+/–]	6.0 ng/g
							Liljegren [49]	8	7 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	11.1	11.2 ng/g
118 (2a)	*Adipose tissue*								
	Aronson [50] [in premenopausal]	30.3	24.7 ng/g, (all)	Charles [44]	55.1	46.5 ng/g	Dewailly [29]	37.7/19.1 [ER+/–]	34.9 ng/g
	Guttes [85]	81	65 ng/g	Stellman [32]	30.4	24.0 ng/g	Liljegren [49]	41	35 ng/g
							Zheng [60]	44.1	ng/g pooled
	Serum, prospective								
	Laden [46] [in nulliparous]	67	68 ng/g (all)	Hoyer [31]	63.9/42.5 [bs/fu]	ng/g pooled	Dorgan [33]	75	ng/g pooled
							Ward [24]	50.7	52.8 ng/g
	Serum, retrospective								
	None	–	–	None	–	–	Gammon [54]	55.1	56.4 ng/g

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Table 5 (*Continued*).

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
126 (2a)	*Adipose tissue*								
	Liljegren [49] [>postmen, ER+]	0.237	0.164 ng/g (postmen)				Ward [24]	0.164	0.166 ng/g
138 (2b)	*Adipose tissue*								
	Stellman [32]	28.7	21.7 ng/g	Aronson [50]	73.8	66.8 ng/g	Zheng [60]	83.9	ng/g pooled
				Guttes [85]	228	194 ng/g	Dewailly [29]	78.1/59.6 [ER+/–]	70.1 ng/g
				Woolcott [43] ER+	71.7	66.8 ng/g	Liljegren [49]	235	234 ng/g
				Woolcott [43] ER–	81.8				
	Serum, prospective								
	Laden [46] [in nulliparous]	95	97 ng/g (all)	None	–	–	Dorgan [33]	94	ng/g pooled
	Hoyer [31] [bs only]	176.1	ng/g	Charles [44]	94.8	84.7 ng/g			
	Serum, retrospective								
	None	–	–	None	–	–	Gammon [54]	82.1	84.9 ng/g
156 (2a)	*Adipose tissue*								
	Aronson [50]	18.6	17.2 ng/g	Stellman [32]†	11.2	9.1 ng/g	Zheng [60]	21	ng/g pooled
				Woolcott [43] ER+	18.3	17.2 ng/g	Charles [44]	2.2	17.6 ng/g
				Woolcott [43] ER–	20.1				
							Dewailly [29]	15.7/16.8 [ER +/–]	17.9 ng/g
							Guttes [85]	61	76 ng/g
							Liljegren [49]	26	24 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	15.5	16.6 ng/g
157 (U)	*Serum, prospective*								
	None	–	–	None	–	–	Ward [24]	3.8	3.7 ng/g
67 (2a)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	10	9 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	6.4	6.7 ng/g

Table 5 (*Continued*).

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
69 (2a)	*Adipose tissue*								
	None	–	–	Liljegren [49]	0.118	0.105 ng/g	Charles [44]	0.6	0.7 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	0.080	0.084 ng/g
170 (2b)	*Adipose tissue*								
170 (2b)	Aronson [50] [postmenopausal]	34.3	32.0 ng/g (all)	Charles [44]	27.3	22.5 ng/g	Dewailly [29]	30.6/28.2 [ER+/–]	36.7 ng/g
				Woolcott [43] ER+	33.8	32.0 ng/g	Guttes [85]	245	267 ng/g
				Woolcott [43] ER–	36.1				
							Liljegren [49]	106	105 ng/g
							Stellman [32]	13.5	11.2 ng/g
							Zheng [60]	33.2	ng/g pooled
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	49.2	52.0 ng/g
189 (U)	*Adipose tissue*								
	None	–	–	None	–	–	Charles [44]	1.9	1.8 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	3.02	2.79 ng/g
Σ, gp3	*Serum, retro.*								
	None	–	–	None	–	–	Zheng [89] (Σ 153, 180)	256.g	ng/g pooled
99 (3)	*Adipose tissue*								
	Aronson [50]	19.5	17.7 ng/g	Stellman [32]	19.3	13.9 ng/g	Liljegren [49]	19.1	19.4 ng/g
	Dewailly [29]	31/15 [ER+/–]	20.5 ng/g	Woolcott [43] ER+	18.9	17.7 ng/g			
				Woolcott [43] ER–	21.9				
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	25.7	28.8 ng/g
146 (3)	*Adipose tissue*								
	None	–	–	Stellman [32]	9.2	6.9 ng/g	Ward [24]	21.8	23.4 ng/g

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Table 5 (*Continued*).

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
153 (3)	*Adipose tissue*								
	Guttes [85]	624*	505 ng/g	Charles [44]	129.2	110.7 ng/g	Aronson [50]	105.2	98.3 ng/g
				Stellman [32]	76.1	63.1 ng/g	Dewailly [29]	100/82.2 [ER+/–]	95.6 ng/g
				Woolcott [43] ER+	102.8	98.3 ng/g	Liljegren [49]	289	291 ng/g
				Woolcott [43] ER–	114.6				
	Serum, prospective								
	Laden [46] [nulliparous]	107	106 ng/g	None	–	–	Hoyer [31]	223/204 [bs/fu]	ng/g (pooled)
							Ward [24]	183.4	195.6 ng/g
	Serum, retro.								
	None	–	–	None	–	–	Demers [51] [pop'n/hosp ctrls.]	58.7	55.6/53.3 ng/g
							Gammon [54]	151.7	153.2 ng/g
172 (3)	*Adipose tissue*								
	None	–	–	Stellman [32]	2.4	1.6 ng/g	Liljegren [49]	11	11 ng/g
	Serum, prospective								
	None	–	–				Ward [24]	6.41	6.93 ng/g
178 (3)	*Adipose tissue*								
	None	–	–	Stellman [32]	3.9	3.0 ng/g	Ward [24]	8.4	8.5 ng/g
180 (3)	*Adipose tissue*								
	Aronson [50] [postmenopausal]	71.9	65.7 ng/g (all)	Charles [44]	77.6	65.1 ng/g	Dewailly [29]	74.6/80.0 [ER+/–]	86.2
				Guttes [85]	375	301 ng/g	Liljegren [49]	204	198 ng/g
				Stellman [32]	42.4	33.7 ng/g			
				Woolcott [43] ER+	71.4	65.7 ng/g			
				Woolcott [43] ER–	75.0				
	Serum, prospective								
	None	–	–	Laden [46] [nulliparous]	74	75 ng/g (all)	Gammon [54]	79.7	78.6 ng/g
							Hoyer [31]	85.8/82.2 [bs/fu]	ng/g (pooled)
							Ward [24]	107.7	115.8 ng/g

Table 5 (*Continued*).

PCB # (GRP)	+ve, Significant 1st author, yr	Mean: cases	Controls	+ve, NS 1st author, yr	Mean: cases	Controls	Inverse/none 1st author, yr	Mean: cases	Controls
183 (3)	*Adipose tissue*								
	Stellman [32]	5.8	4.0 ng/g	Charles [44]	13.8	10.7 ng/g	Aronson [50]	10.3	9.5 ng/g
				Dewailly [29]	10/6.8 [ER+/–]	7.5 ng/g	Liljegren [49]	25	25 ng/g
				Woolcott [43] ER+	9.9	9.5 ng/g			
				Woolcott [43] ER–	11.8				
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	16.2	16.4 ng/g
194 (3)	*Adipose tissue*								
							Liljegren [49]	28	30 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	17.2	18.3 ng/g
195 (3)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	6	7 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	4.84	5.43 ng/g
206 (3)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	8	7 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	5.20	5.61 ng/g
209 (3)	*Adipose tissue*								
	None	–	–	None	–	–	Liljegren [49]	8	9 ng/g
	Serum, prospective								
	None	–	–	None	–	–	Ward [24]	3.97	4.52* ng/g

Group 1b PCBs are weak phenobarbital inducers and are more persistent. Published studies have not reported positive associations of these congeners as a group [24] or individually (multivariate results—[24,50–52]; means—[29,32,43,49]).

Congeners in group 2a are thought to be antiestrogenic and immunotoxic; those in group 2b appear to have limited dioxin activity. The highly persistent congeners in group 3 are thought to induce cytochrome P450 and phenobarbital activity. No studies have reported elevated risk associated with the sum of the congeners from these groups. A few studies have reported elevated risk associated with individual congeners in each group (e.g., PCBs 118, 138, 99), but results have been inconsistent (Table 5).

Two studies compared PCB congeners classified as high- vs. low-chlorination in relation to breast cancer and again found ambiguous results. Wolff et al. [53] reported evidence of elevated risk only for low-chlorination congeners. In contrast, Millikan et al. [45] reported greater risk associated with high-chlorination congeners.

Other OCs

The few studies examining other OCs in relation to breast cancer risk have, for the most part, found no association (Table 6). No studies have reported significant increased risk associated with chlordane metabolites, including *cis*-nonachlor (CN), *trans*-nonachlor (TN), oxychlordane (OXY), and heptachlor epoxide (HCE) [24,43,50–54]. Mixed results have been reported for dieldrin, mirex, HCB, and HCH (or b-BHC; see Table 6). No studies on endosulfan were found.

STUDY DESIGN FACTORS

Adipose tissue vs. blood

As OCs are lipophilic, adipose tissue sample stores are thought to provide a better index of long-term exposure than blood-based measures. Strong correlations between adipose tissue and lipid-adjusted serum levels of DDE have been reported in some (r = 0.8, [55]) but not all (r = 0.4, [64]) studies. Similar, low correlations between adipose and lipid-adjusted serum levels of PCBs have been seen (e.g., r = 0.4 for PCB 153; [55]).

Differences in these measures do not, however, appear to explain study inconsistencies, as results using each medium have been heterogeneous. For example, significant positive associations with DDE and breast cancer were reported for: (i) one of six reports from large studies using adipose tissue samples; (ii) two of 10 studies using prospective serum samples; and (iii) none of 10 studies based on retrospective serum (Table 2).

Study populations—using benign breast disease (BBD) controls

Most studies based on adipose tissue used BBD patients as controls because it is more difficult to obtain adipose tissue samples from disease-free subjects (Table 1). If OCs contribute to the risk of BBD, this strategy may bias results toward the null. However, studies using alternative control groups also failed to observe positive associations. Using patients presenting for breast reduction surgery, Bagga et al. [34] found null associations for various DDTs. Inverse associations with DDE were reported by van't Veer et al. [56] in a study based on gluteal adipose tissue samples and population-based controls. Studies that excluded [57–60] or limited [32] the proportion of BBD controls with evidence of atypia found no strong evidence of adverse effects. Wolff et al. [53] also found no difference in results between BBD and non-BBD non-cancer controls, suggesting that the predominance of BBD controls is not the reason for lack of a measurable detrimental effect.

Table 6 Other organochlorines and breast cancer.

1st author [ref.]	+ve	ns	–ve null	Years	Place	# Cases/ controls	Mean		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
I. CHLORDANE METABOLITES														
Cis-nonachlor: *Adipose*														
Aronson [50][a]			–	1995–97	Canada	217/213	6.0	6.0 ng/g	y	1.0	0.8	0.5	0.8	
Woolcott [43; data = 50][†]														
ER+			–	″	″	″	5.9	6.0 ng/g	y	1.0	0.9	0.7		
ER–			–	″	″	″	6.2	″	y	1.0	0.5	0.5		
Trans-nonachlor: *Adipose*														
Aronson [50][a]			–	″	″	″	40.4	41.1 ng/g	y	1.0	0.9	0.7	0.8	
Woolcott[†] [43; data = 50]														
ER+			–	″	″	″	39.1	41.1 ng/g	y	1.0	0.8	0.5		
ER–			–	″	″	″	43.3		y	1.0	1.0	1.0		
Zheng [52][a,b,c]			–	1994–97	US	304/186	55.5	58.1 ng/g	y	1.0	1.2	0.7	1.1	
Serum, prospective														
Ward [24]				1973–91	Norway	150/150	117	104 ng/g	y	1.0	1.0	0.9	1.0	
Serum, retrospective														
Demers [51][†]														
Pop'n. controls		ns		1994–97	Canada	315/307	16.6	16.0 ng/g	y	1.0	0.8	1.5	0.7	1.2
Hosp. controls		ns		″	″	315/219	″	16.7 ng/g	y	1.0	1.3	1.5	0.6	0.7
Wolff [53][e]				??	US	175/356	0.035	0.036 ng/g	y	1.0	1.0	0.7		
Oxychlordane: *Adipose*														
Aronson [50][a]			–	1995–97	Canada	217/213	30.4	30.5 ng/g	y	1.0	0.7	0.6	0.6	
Zheng [52][a,b,c]			–	1994–97	US	304/186	36.4	38.0 ng/g	y	1.0	0.7	0.7	0.7	
Serum, prospective														
Ward [24]			–	1973–91	Norway	150/150	10.0	10.9 ng/g	y	1.0	1.0	1.0	0.9	
Serum, retrospective														
Demers [51]														
Pop'n. controls		ns		1994–97	Canada	315/307	12.9	12.2 ng/g	y	1.0	1.1	1.0	1.3	1.5
Hosp. controls			–	″	″	315/219	″	13.0 ng/g	y	1.0	1.1	1.0	0.8	0.6
Heptachlor epoxide: *Serum, prospective*														
Ward [24]		ns		1973–91	Norway	150/150	7.1	8.5 ng/g	y	1.0	1.5	1.8	1.0	

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Table 6 (*Continued*).

1st author [ref.]	+ve	ns	–ve null	Years	Place	# Cases/ controls	Mean Cases	Mean Controls	Adjusted?	ORs 1	2	3	4	5
I. CHLORDANE METABOLITES														
Oxychlordane + *trans*-nonachlor: *Serum, retrosp.*														
Gammon [54]: All[a,b,d]			–	1996–97	US	597/397	97.6	95.9 ng/g	y	1.0	0.9	1.0	1.2	1.0
Nulliparous		ns		″	″	″	–	–	y	1.0	2.4	2.8		
II. DIELDRIN:														
Serum, prospective														
Dorgan [33]			–	1977–87	US	105/208			y	1.0	0.7	0.8	0.7	
Hoyer [36][1]	↑			1976–83	Denmark	240/477	pooled	24 ng/g	y	1.0	1.6	2.0*	2.1*	
Ward [24]														
Serum, retrospective														
Gammon [54]			–	1996–97	US	597/397	97.6	95.9 ng/g	y	1.0	0.9	1.0	1.2	1.0
III. MIREX														
Adipose														
Aronson [50][a] – All			–	1995–97	Canada	217/213	9.0	9.9 ng/g	y	1.0	1.2	1.4	1.2	
Never lactators, parous	↑			″	″	″	–	–	y	1.0	2.6	1.9	4.2*	
Ever lactators, parous			–	″	″	″	–	–	y	1.0	1.5	0.9	0.3	
Serum, retrospective														
Moysich [22][†,2] – All			–	1986–91	US	154/191	0.043	0.037 ng/g serum	y	1.0	1.4			
Parous, never lactated		ns			″	″	0.083	0.046 ng/g serum	y	1.0	2.4			
IV. HEXACHLOROBENZENE:														
Adipose														
Aronson [50][a]			–	1995–97	Canada	217/213	32.0	30.1 ng/g	y	1.0	1.0	0.8	1.2	
Liljegren [49] – All			–	1993–95	Sweden	43/35	73	48 ng/g		1.0	1.3			
Premenopausal			–	″	″	″	33	35 ng/g		–				
Postmenopausal		ns		″	″	″	87	56 ng/g	y	1.0	1.9			
ER–		ns		″	″	″	–	–	y	1.0	2.0			
ER+	↑			″	″	″	–	–	y	1.0	7.1*			
Zheng [59][a,b] – All			–	1994–97	US	304/186	21.0	19.1	y	1.0	0.7	0.7	0.9	
Nulliparous		ns		″	″	″			y	1.0	0.5	2.1		

Table 6 (*Continued*).

1st author [ref.]	+ve	ns	–ve null	Years	Place	# cases/ controls	Mean		Adjusted?	ORs				
							Cases	Controls		1	2	3	4	5
IV. HEXACHLOROBENZENE:														
Serum, retrospective														
Dorgan [33]	↑			1977–87	US	105/208	73 (est)	ng/g pooled	y	1.0	2.5*	1.9	2.3*	
Moysich-postmen [22][2,†]			–	1986–91	US	154/192	0.41	0.42 ng/g serum	y	1.0	0.6	0.8		
Parous, never lactated							0.45	0.39 ng/g serum	y	1.0	1.3	1.8		
V. HEXACHLOROCYCLOHEXANE (b-HCH/b-BHC):														
Adipose tissue														
Aronson [50][a]			–	1995–97	Canada	217/213	43.1	41.5 ng/g	y	1.0	0.7	1.0	0.7	
Zheng [58][a,b] – All			–	1994–97	US	304/186	27.1	26.3 ng/g	y	1.0	0.7	0.8	0.6	
Nulliparous		ns		″	″	″			y	1.0	1.4	3.1		
Woolcott[†] [43; data = 1]														
ER–			–	″	″	″	56.2	41.5 ng/g	y	1.0	0.8	1.4		
ER+			–	″	″	″	39.3	″	y	1.0	0.8	0.7		
Serum, prospective														
Dorgan [33]			–	1977–87	US	105/208	–	–	y	1.0	0.5*	0.5*	0.6	
Hoyer [36][1]			–	1976–83	Denmark	240/477	pooled	119 ng/g	y	1.0	1.1	1.4	1.4	
Hoyer [31][1]			–	1976–83	Denmark	155/274	pooled	119 (bs) ng/g 60 (fu)	y	1.0	1.3	1.2	1.2	
Ward [24]			–	1973–91	Norway	150/150	60.0	63.4 ng/g	y	1.0	1.0	0.7	0.7	
Serum, retrospective														
Demers [51]														
Pop'n. controls			–	1994–97	Canada	315/307	21.1	19.4 ng/g	y	1.0	0.6	0.6	0.9	0.8
Hosp. controls			–	″	″	315/219	″	17.5 ng/g	y	1.0	0.7	0.9	0.7	0.8

Statistical significance defined as $p < 0.05$/CI excludes null or $p < 0.10$.

[1]Medians presented rather than means.

[2]Means are wet weight rather than lipid basis.

[a–e]Supplementary analysis found no meaningful differences when stratified by: a: pre/post-menopausal; b: ER status; c: lactation/parity group; d: BMI group; e: ethnic groups.

[†]Other notes: Moysich [22] found elevated ns ORs for HCB only in parous women who never lactated. Zheng [52,58,59] are age- and lipid-adjusted means.

Hoyer [36] –Results not shown for mirex, aldrin, endrin, AC, YC, heptachlor, heptachlor oxide, OCD, TN, y-HCH, HCB—presumed NS.

Timing of exposure measurement vs. use of OC chemicals

The majority of studies in industrialized countries have measured OC residues in biological samples collected from adults in the 1980s and 1990s, well after most source chemicals were banned. Given half-life estimates on the order of 7 to 11 years for DDE and PCBs [53], residues measured in these studies may largely reflect exposure to persistent but less estrogenic OCs (such as *p*,*p*′-DDE and high-chlorination PCB congeners), rather than long-term exposure to estrogenic but less persistent compounds such as DDT, dieldrin, and low-chlorination PCBs [11,13,48]. Therefore, recent measures of OCs may not be good estimates of past exposure to estrogenic compounds.

Direct estimates using samples obtained closer to the period when chemical sources remained in use should be more reliable for identifying any adverse effects of less persistent OCs, as long as samples were stable and analytic measures were sensitive enough. In industrialized countries, four of five prospective studies used blood collected as early as the 1960s and 1970s. These did not find overall adverse effects of DDTs, PCBs, or several other OCs [24,30,33,35]. Concentrations of DDE and DDT in these samples were relatively high (Tables 2 and 3). The one study showing effects that examined *p*,*p*′-DDT in a population-based Danish study [31] used repeated serum measures and adjusting for weight change. No other studies have incorporated repeated measures of OC exposure, and few have included measures of weight change (see Table 1).

Of the studies examining associations between DDT, DDE, and breast cancer risk in countries where use of DDT continues (Table 2), some based in Mexico City [23,61] and in Vietnam [37] found lower mean levels of *p*,*p*′-DDT in breast cancer cases vs. controls. No association between DDE and breast cancer in hospital-based case-control studies were noted in Vietnam [37], Mexico City [61], or in a population-based study in Brazil [62]. An anomalous result was seen in a population-based study of parous women in Mexico City [23] that reported strong and significant positive associations with DDT-adjusted levels of serum DDE. The authors hypothesized that adjusting for DDT provided better estimates of long- vs. short-term exposure to DDE. It is not clear whether they limited their adjustment model to low-persistence DDT isomers. Without this adjustment, multivariate associations were not significant (OR for highest vs. lowest quartile 2.16, CI 0.85–5.50 vs. 3.81, CI 1.14–2.8).

It is surprising that, although timeframes for the Mexico City studies overlapped (1990 to 1995 for Romieu et al. [23]; 1994 to 1996 for Lopez-Carillo et al. [61]), serum DDE was five times higher in the study reporting positive associations (lipid-adjusted means in cases/controls were 3840/2510 vs. 563/506 nanograms per gram [ng/g]). It is not clear to what extent discrepancies between the two Mexico City studies may reflect true differences in DDT and DDE exposure, metabolism, temporal changes, or differences in laboratory techniques.

Mobilization and elimination of OCs—weight change, adiposity, and lactation

A number of factors, including body fat burden, weight changes, and lactation history, may influence the dilution, mobilization, and elimination of fat schedule substances stored in the body [25,31,63,64].

Weight loss over a 5-year period was associated with significant declines in DDE and several PCBs, while weight gain was associated with larger increases in PCBs as compared to weight-stable subjects [31]. Self-reported losses or gains of >5 pounds in the past year was associated with significantly lower levels of DDE as compared to weight-stable women when examined cross-sectionally [63].

Greater adiposity may result in more dilute residues, particularly in adipose tissue [25,53,65]. Wolff and Anderson [65] proposed a pharmacokinetic model in which one or two half-lives after significant uptake elimination may become more complete in lean subjects than in those with a greater adipose tissue reservoir. Under this model, BMI should be treated as a modifier rather than as a confounder.

Lactation may also influence OC body burden, as breast milk is thought to be an important route of excretion of OCs. High concentrations of OC residues are detected in breast milk, and lactation has been associated with lower OCs [40,64,66]. Indeed, Wolff et al. [40] reported that adjusting for lacta-

tion status increased coefficients for DDE exposure by 57 % (from 0.051 ± 0.022 to 0.080 ± 0.030). Limited data also suggest that higher DDE is associated with reduced duration of breastfeeding [67], and several studies found that OCs were associated with higher risk of breast cancer among nulliparous women, or parous women who never breastfed than lactators ([22]–HCB; [50]–Mirex; [45,46]–total PCBs; [54]–chlordane). These findings are consistent with the hypothesis that breastfeeding may help to reduce the OC burden during a period of increased susceptibility to breast cancer.

Dietary confounders

Few studies have included dietary covariates (see Table 1). Dietary fat may be a confounder, given that fat-containing foods are important sources of exposure to persistent OC metabolites [3]. However, results of studies that adjusted for fat intakes did not differ from those that did not [50,52,57–59]. Furthermore, the role of dietary fat in breast cancer is unclear [68]. Dietary phytoestrogens may modify or confound associations, perhaps by inhibiting estrogenic action of OCs [69,70] A number of dietary phytoestrogens (e.g., genistein) appear to be more potent estrogens than typical OCs [71]. No studies to date have reported accounting for dietary phytoestrogens, whose role in breast cancer etiology is also uncertain [72,73].

Consideration of adjustment for these variables is essential for approximating cumulative or past exposure based on single measures of OC residues. While most studies have adjusted for BMI, few have accounted for lactation history or weight change (see Table 1 for details) [29,31,35,56]. No study has simultaneously considered all three factors.

POSSIBLE HIGH-RISK SUBGROUPS

Menopausal status: It has been suggested that postmenopausal women because of low circulating estrogen levels may be more susceptible to risk factors that influence the hormonal milieu [72]. A few studies have observed stronger associations in post-menopausal than in pre-menopausal women for DDT ([23] for DDT) or total PCBs ([49], especially if ER+). The majority of studies have not found strong associations among postmenopausal women for DDT/DDE [22,25,30,32,33,45,49,50,53, 54,56,57,60,61,74], total PCBs [22,25,32,45,53,60] or other OCs such as HCB, mirex, and chlordane metabolites [22,40,50,52,54,58,59]. In fact, several studies found stronger associations among premenopausal than postmenopausal women for DDE [35], total PCBs [35], and selected PCB congeners [50].

Assessing the significance of any differences in risk by menopausal status is complicated by differences in exposure patterns of younger vs. older women. A cohort effect in older women having experienced greater childhood and lifetime exposures may be responsible for what might be considered an age-related or lifetime accumulation effect when compared with younger women. Among younger women, whose exposure during peak use of these chemicals was limited to childhood and adolescence, adult OC residues may largely reflect ongoing food-borne exposure to persistent metabolites. Direct exposure to industrial and agricultural chemicals in the past likely explains why OC levels are higher in older than in younger women (e.g., [27]). However, exposure in postmenopausal women may have been qualitatively different from that in younger women: during peak chemical use in the 1950s and 1960s, these women were adults.

ER status

Consistent with the hypothesis that the hormones may be more involved in the etiology of ER+ than ER– tumors [75], Dewailly et al. [29] found that DDE, PCB 99, and *trans*-nonachlor were associated with ER+ but not ER– tumors (see Tables 3, 4, and 7). Liljegren et al. [49] also found significantly higher risk associated with HCB and several PCBs (77, 126, 169) among ER+ tumors, especially in

postmenopausal women. Other studies have not confirmed these findings. Woolcott et al. [43] found somewhat stronger associations between DDE, total PCBs, *trans*-nonachlor, b-HCH, and several PCB congeners in ER– tumors (see Tables 3–5). Although Helzsouer et al. [35] found higher associations with DDE in ER+ tumors using serum collected in 1989, associations were higher in ER– tumors using serum from 1974. Numerous studies reported similar associations with DDE [24,25,45,49,52–54,74], PCBs [24,25,35,45,52–54,60,74], and other OCs [43,52,54,58,59] regardless of ER status.

Ethnicity and threshold effects: Krieger et al. [30] and Millikan et al. [45] reported somewhat stronger associations between serum DDE, total PCBs, and breast cancer risk among African Americans than other ethnic groups (whites and Asians). They hypothesized that the higher associations might be attributable at least in part to higher exposure levels. Yet there were no differences in associations among African Americans, whites, and Hispanics in a report by Wolff et al. [53], in which OC levels were similarly elevated among blacks. There was also no association with breast cancer risk in other studies in whites with similar serum OC levels [25,35]. However, associations between breast cancer and DDE were significant in the studies with the highest serum levels [23], after adjustment for DDT) and adipose levels [29,39]. Research in multiethnic settings with high levels of DDE is needed to confirm this hypothesis.

Genetic polymorphisms

In addition to mimicking estrogen activity, OCs are inducers of detoxification and drug-metabolizing enzymes [76,77]. Variation in genotypes for drug-metabolism genotypes such as cytochrome P4501A1 (CYP1A1) and detoxification enzymes such as glutathione-*S*-transferase μ (GSTM1) may be associated with susceptibility to OCs. Moysich et al. [76] found elevated breast cancer risk among subjects with high total PCBs and either heterozygous (isoleucine: valine) or homozygous valine subtypes for CYP1A1. Compared to the isoleucine homozygous group with low PCBs, this group was 2.9 times more likely to have breast cancer after multivariate adjustment (95 % CI 1.2–7.5). For the isoleucine homozygous group with high PCB exposure, the OR was 1.08 (CI 0.6–1.9). However, Helzsouer et al. [35] did not find strong evidence of modified susceptibility to the effects of DDE or total PCBs associated with polymorphisms in GSTM1, GSTT1, GSTP1, COMT, or CYP17.

OCCUPATIONAL STUDIES

Few studies on occupational exposure and breast cancer among women have been published. Both the exposure route and the estrogenicity of isomers to which women are exposed occupationally are likely to differ substantially from food-borne exposure to persistent OCs. Studies of pesticide workers have not reported an increased breast cancer incidence or mortality cancer associated with this industry ([78,79]; earlier studies reviewed by Adami et al. [80]). While farmworking per se was not associated with increased risk, Duell et al. [21] reported increased risk of breast cancer associated with women who were present in fields during or shortly after pesticide application (OR = 1.8, 95 % CI = 1.1–2.8). Risk was also elevated among women who reported not using protective clothing while applying pesticides (OR = 2.0; 95 % CI = 1.0–4.3) but not among those who reported using protective clothing (OR = 0.8; 95 % CI = 0.4–1.8). As no consistent exposure-related effects are seen in other studies, this may reflect other farm-based exposures or characteristics of the lifestyle, rather than OC exposure.

OCS AND BREAST CANCER SEVERITY AND PROGRESSION

Although laboratory data suggest that OCs may act as tumor promoters [16], the hypothesis that OCs may be related to the progression rather than the incidence of breast cancer has been explored in very few studies, so less is known on this topic [51]. Associations with various measures of stage, aggressiveness, and tumor markers have been reported in six studies to date (see Table 7). These studies—all

Table 7 Organochlorines and breast cancer survival, severity, and progression.

	DDT	DDE	PCBs	Other compounds
I. Survival	*ns* ↑	*null*	*mixed*	*mixed*
Hoyer et al., 2000b [81] – *Serum, prospective*				
	OR = 1.6 ns (*q4 vs. 1*) OR = 2.1* (#138, gp2b) (*q4 vs. 1*)	OR = 1.1 ns (*q4 vs. 1*)	OR = 0.9 ns (ΣPCBs)	Dieldrin: OR = 2.6* HCB: OR = 0.7 ns (*q4 vs. 1*)
II. Severity, among cases	*ns* ↑	↑	↑	↑
Demers [51] – *Serum, retrospective*				
Tumor ≥ v <2cm	OR = 1.6 ns (*q3 vs. 1*)	OR = 1.6 ns (*q3 vs. 1*)	OR = 1.5 ns (# 153, gp3) (*q3 vs. 1*)	TN: OR = 2.3* b-HCH: OR = 2.3* OCD: OR = 1.7 ns (*q3 vs. 1*)
Lymph yes/ no	OR = 1.5 ns (*q3 vs. 1*)	OR = 2.9* (*q3 vs. 1*)	OR = 2.1* (#153, gp3) (*q3 vs. 1*)	TN: OR = 2.0 ns b-HCH: OR = 2.0* OCD: OR = 2.3* (*q3 vs. 1*)
III. Severity at diagnosis	–	ns ↑/-ve	ns ↑/-ve	
Woolcott [43] – *Adipose, retrospective*				
Tumor < 2cm vs. none	–	OR = 1.6 ns (*q3 vs. 1*)	OR = 1.5 ns (Σ PCBs) OR = 0.9 ns (#187, gp1b) (*q3 vs. 1*)	
Tumor ≥ 2cm vs. none	–	OR = 1.1 ns (*q3 vs. 1*)	OR = 1.5 ns (Σ PCBs) OR = 1.6 ns (#187, gp1b) (*q3 vs. 1*)	
Tumor grade I/II vs. none	–	OR + 1.1 ns	OR = 1.2 ns (Σ PCBs)	
Tumor grade III vs. none		OR = 1.4 ns	OR = 1.5 ns (Σ PCBs)	
Zheng [89] – *Serum, retrospective. Means (adj. age & lipids)*				
Tumor grade I/II	–	Mean = 455.9 ng/ml	719.8 ng/ml (Σ PCBs)	
Tumor grade III/IV	–	Mean = 402.1 ng/ml	638.9 ng/ml (Σ PCBs)	
IV. Tumor markers (cases)	*ns* ↑	*mixed*		
Wolff et al. [53] – *Serum, retrospective.Means (adjusted for age, race, menopausal status)*				
erbB-2–	33 ng/g	740 ng/g	590 ng/g (HPCBs)	– –
erbB-2+	35 ng/g	800 ng/g	600 ng/g (HPCBs)	– –
p53–	35 ng/g	730 ng/g	600 ng/g (HPCBs)	
p53+	30 ng/g	820 ng/g	580 ng/g (HPCBs)	

[†]Notes: Demers [51]: Stronger associations also found for DDE using combined tumor size and lymph node involvement as marker of severity. Millikan [45] also examined associations stratified by stage at diagnosis and reported no differences in associations (results not shown). Zheng [52] also reported no association between TN and OCD and breast cancer histology or stage at diagnosis (data not shown).

conducted in industrialized countries using recent OC samples—have not reported associations between DDT/DDE and breast cancer survival, stage, aggressiveness, or tumor marker (p53 or erbB-2) [45,51,53,81]. Positive associations with PCBs and various measures of progression, severity, or survival have been reported in some studies [51,81], but weak or null associations have been reported in other [43,45,52,53] studies. Gammon et al. [54] did not find positive associations between stage at diagnosis (in situ vs. invasive disease) and concentrations of DDE, PCBs, or chlordane. Limited data suggest that other OCs may be associated with severity [51] and survival [81]. More data are needed before conclusions can be drawn, but this is an area deserving further study.

SUMMARY AND RECOMMENDATIONS

The sum of the evidence does not implicate any OC compound as significantly related to risk of occurrence of breast cancer. The evidence base is greatest for DDT and DDE. More limited research has been done on individual PCBs and their isomers. The studies of OC exposure reflect current exposure levels of chemicals that may have been banned for 20 years. Despite long half-lives (of 10 years) in adipose tissue, samples were generally collected 30 years after the peak exposure times. However, given ongoing exposure to persistent, nonestrogenic metabolites in foods, it is not certain that ranking of exposures using these samples is an accurate measure of past exposure to those compounds thought to increase risk.

More studies are needed on OCs other than DDTs in developing countries where use is more recent or continuing, especially given that most estrogenic OCs are not persistent. The possibility that OC exposure in excess of certain thresholds may be related to risk cannot be ruled out based on existing data. It is possible that other pathways that influence susceptibility may be involved, including activity related to CYP and GST; limited research is available to date on this hypothesis. Additionally, the BMI/weight loss model may warrant further analysis, perhaps using existing data.

OC exposures cannot reliably be related to trends in breast cancer incidence, as other known risk factors for breast cancer, such as childbearing and lactation. Changes in screening and treatment over time also complicate making such links. Ecologic data relating high-exposure countries to breast cancer mortality rates do not suggest a strong link. As noted by Rogan [82], "in general, breast cancer rates are not higher in parts of the world with high DDE levels (the People's Republic of China, India, and Guatemala), and countries with relatively similar levels of PCBs (Great Britain and Japan) have very different breast cancer rates."

Although the information is extremely limited and not without major design flaws, the association between disease severity and progression is interesting and worthy of further examination.

As OCs are present in the environment as mixtures of correlated isomers and metabolites, it may be difficult to distinguish possible causal links from associations in which measured compounds are merely markers of other underlying exposures. Few studies [23,36,40,52,83] have reported adjusting for other OCs. For highly correlated compounds, traditional adjustment strategies may not be feasible. More complex analytical strategies, such as those used by Holford et al. [83], may help to isolate potentially relevant isomers.

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