Environmental Factors in Breast Cancer

Supplement to ***Cancer***

Environmental Pollutants and Breast Cancer

Epidemiologic Studies

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Laboratory research has shown that numerous environmental pollutants cause mammary gland tumors in animals; are hormonally active, specifically mimicking estrogen, which is a breast cancer risk factor; or affect susceptibility of the mammary gland to carcinogenesis. An assessment of epidemiologic research on these pollutants identified in toxicologic studies can guide future research and exposure reduction aimed at prevention. The PubMed database was searched for relevant literature and systematic critical reviews were entered in a database available at URL: www.silentspring.org/sciencereview and URL: www.komen.org/environment (accessed April 10, 2007). Based on a relatively small number of studies, the evidence to date generally supports an association between breast cancer and polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) in conjunction with certain genetic polymorphisms involved in carcinogen activation and steroid hormone metabolism. Evidence regarding dioxins and organic solvents is sparse and methodologically limited but suggestive of an association. Methodologic problems include inadequate exposure assessment, a lack of access to highly exposed and unexposed populations, and a lack of preclinical markers to identify associations that may be obscured by disease latency. Among chemicals identified in toxicologic research as relevant to breast cancer, many have not been investigated in humans. The development of better exposure assessment methods is needed to fill this gap. In the interim, weaknesses in the epidemiologic literature argue for greater reliance on toxicologic studies to develop national policies to reduce chemical exposures that may be associated with breast cancer. Substantial research progress in the last 5 years suggests that the investigation of environmental pollutants will lead to strategies to reduce breast cancer risk. ***Cancer*** **2007;109(12 Suppl):2667–711.** © *2007 American Cancer Society.*

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RATIONALE

Laboratory research provides evidence that environmental pollutants may contribute to breast cancer risk by damaging DNA, promoting tumor growth, or increasing susceptibility by altering mammary gland development. Although to our knowledge most chemicals have never been tested for these effects, 216 potential mammary carcinogens have been identified in animals.[1] In vitro assays have identified approximately 250 chemicals that mimic or interfere

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with estrogen,[2] which stimulates proliferation of estrogen-sensitive breast cancer cells in laboratory studies[3] and presumably underlies many of the established breast cancer risk factors.[4] In an emerging area of research into developmental toxicity, animal studies show that maternal exposure during pregnancy to atrazine or bisphenol A affects differentiation of the mammary glands in the offspring, which remain in a less differentiated state that is more susceptible to carcinogen exposure.[5–7]

If these mechanisms similarly affect humans, reducing or eliminating chemical exposures could have substantial public health benefits, because breast cancer is the mostly commonly diagnosed invasive cancer in women and the leading cause of cancer death in women ages 25 to 60 years.[8] Furthermore, exposure to the chemicals identified as animal mammary carcinogens and estrogen mimics is substantial; these compounds are widely detected in human tissues and in environments, such as homes, where women spend time.[9,10] Compounds of interest include, for example, benzene from gasoline, polycyclic aromatic hydrocarbons (PAHs) from vehicle exhaust and air pollution, disinfection products from chlorinated drinking water, polychlorinated biphenyls (PCBs), dioxin, chlorinated solvents, and some pesticides.[1,11]

We reviewed epidemiologic research, with an emphasis on the last 5 years, to investigate how well the field has addressed questions raised by the laboratory studies. Our goals were to summarize and integrate findings for the most frequently studied pollutants, identify methodologic challenges, and recommend directions for future research. As background for this assessment, we first introduce key methodologic issues that underlie our evaluations of the epidemiologic literature.

EXPOSURE ASSESSMENT METHODS

Designing meaningful exposure measures is 1 of the most significant challenges in translating mechanistic observations from the laboratory, in which exposure parameters are known and controlled, to epidemiologic studies. The goal in epidemiologic breast cancer studies is to observe the chemical agent(s), pathway (ingestion, inhalation, dermal absorption), dose, timing with respect to disease latency, and timing with respect to possible critical periods of development, and, when quantification is difficult, to at least correctly rank study participants' exposures.

Unfortunately, the exposure assessment strategies that underlie current knowledge regarding breast cancer risk are ill suited to studies of environmental pollutants. Most of what is known regarding risk factors relies on self-reported exposures (e.g., family history, number of births, age at first full-term pregnancy, alcohol use, physical activity), and the clearest findings concerning effects of exogenous chemicals come from clinical trials of pharmaceuticals in which exposure is specified and controlled (e.g., tamoxifen, hormone replacement therapy). In contrast, individuals cannot self-report their exposure to ambient environmental pollutants, and self-reports on chemical exposures from consumer products are subject to multiple forms of bias, including incomplete recall, differential recall between cases and controls, influences of social desirability, and poor reporting of exposure from products used by others. With regard to clinical trials, the intentional exposure of individuals to possible toxicants with no benefit to those individuals does not meet standard ethical guidelines for research on humans.

The predominant exposure assessment strategies in studies of environmental pollutants and breast cancer are job history, residential location in combination with models derived from environmental monitoring, and biomarkers in blood and adipose tissues. Although each of these methods has strengths, none of these methods can be considered a 'gold standard.'

Job histories and residential histories have the potential to assess exposure at multiple points in time, to integrate exposures across time, and to integrate exposures to real-world chemical mixtures. However, misclassification results from errors in modeling, incomplete historical information both for the individual and the setting, and missing or incomplete information regarding behaviors that modify exposure (e.g., use of protective gear at work or amount of time spent outside). The assessment of mixtures, for example, in ambient air, leaves questions concerning which chemical or group of chemicals are responsible for observed effects. Geographic location with respect to an accidental exposure, for example, the industrial explosion at Seveso, Italy, can be a uniquely valuable exposure assessment tool because the agent, relative dose, and timing of exposure are likely to be known and to differ markedly from a comparison population. The collapse of the World Trade Center in 2001 and flooding in New Orleans in 2005 are examples in which the chemical exposure is complex, and environmental sampling after the incident is needed for future studies to develop indicators of exposure based on where children and adults were located during and after these incidents. More generally, the development of geographic information systems (GIS)—computer mapping database technologies for linking locations

with environmental data—will expand exposure assessment opportunities if the underlying environmental monitoring data accrue through regulatory and environmental tracking programs.

Biologic measurements have the advantages of integrating an individual's exposure from all sources and her/his physiologic response. They may, but often do not, measure chemicals in the most relevant target tissue—the mammary gland—and levels in blood, urine, or other biological compartments may not reflect localized tissue levels. If the biomarker measures a metabolite (eg, dichlorodiphenyldichloroethylene [DDE]) of the agent of interest (eg, dichlorodiphenyltrichloroethane [DDT]), individual variation in metabolism and excretion may increase exposure misclassification. To our knowledge to date, biomarkers have been developed for only a few of the chemicals of interest in breast cancer studies, and existing technologies are expensive to apply in studies large enough to reliably detect the modest risks typical of the established breast cancer risk factors. Many biomarkers are too intrusive to allow for repeated measures and most are impractical for assessing exposure across relevant time periods (eg, when research questions require assessment of exposures in the past or over long time periods, or when a chemical is quickly cleared from the body), so that carefully timed measures are needed. In addition, for biomarkers the specific source of exposure is often unclear, so associations are difficult to translate into risk reduction strategies.

OTHER RESEARCH DESIGN ISSUES

Aside from exposure measurement difficulties, studies of environmental pollutants often suffer from a variety of other threats to validity. Often, lack of an unexposed comparison group and lack of a 'high' exposed group limit the ability to observe effects. In addition, emerging research on gene–environment interactions highlights the possibility that individual differences in metabolism and excretion of pollutants and individual differences in susceptibility due to DNA repair efficiency or other mechanisms may be responsible for effects in susceptible subgroups, but these effects are obscured in analyses of the general population. In addition, because breast cancer involves multiple correlated risk factors, misspecification of models may hide causal effects. For example, variables treated as confounders, such as age at menarche and menopause, could plausibly be on the causal pathway from pollutant exposures to breast cancer.[12] Sample size and diversity of study populations have often been inadequate to explore interactions or effect modification.

With these methodological issues in mind, we set out to review and synthesize epidemiologic evidence concerning breast cancer and environmental pollutants identified as mammary carcinogens or endocrine disrupting compounds, including persistent organochlorine compounds, including PCBs, dioxins, DDT, and other pesticides; PAHs, air pollution, and traffic; chlorination byproducts and drinking water contaminants; and organic solvents and other occupational exposures.

MATERIALS AND METHODS

Study Identification and Selection

We searched the PubMed database for articles in English published in peer-reviewed journals through June 2006 for human studies of breast cancer and environmental pollutants. Search terms and dates are summarized in Table 1 and exclusion criteria are summarized in Table 2. Searches included the term "breast cancer" in combination with environmental pollutant, air pollution, traffic, combustion products, vehicle exhaust, gasoline, pesticide, drinking water, organic solvent, polycyclic aromatic hydrocarbon, PAH, benzene, diesel, polychlorinated biphenyl, PCB, organochlorine, aldrin, dieldrin, DDE, DDT, heptachlor, methoxychlor, and occupation. We also searched using "breast cancer" and each of the chemicals identified as a mammary carcinogen by the National Toxicology Program. We excluded results pertaining to tobacco smoke or dietary PAH. When there were multiple reports from the same study, we excluded earlier reports unless they provide evidence not encompassed by later reports. We examined reference lists of selected articles for additional articles.

For organochlorine pesticides we limited inclusion to articles published from 2000 onward, and for PCBs we limited inclusion to articles published from 1999 onward, because useful reviews cover earlier articles (Snedeker,[13] Moysich et al.,[14] and Negri et al.[15]), and we sought to update these reviews, minimizing redundancy.

We included "occupation" as a search term to identify studies that investigated relative risks in jobs with chemical exposures. As expected, many of the results captured in this search did not pertain to environmental pollutants. We included only studies of jobs for which existing data support a reasonable inference regarding exposure to a specific chemical or mixture that has been characterized and hypothesized to affect breast cancer. Thus, we excluded studies of workers in offices, schools, stores, and similar settings,[16] because so little is known about their chemical exposures. We further excluded studies in which the possible role of environmental pollutants was not investigated inde-

TABLE 1
Search Terms and Dates

We searched PubMed for breast cancer in combination with the following terms:

1) Classes or mixtures of environmental pollutants, articles through June 2006

Air pollution	Gasoline	Pesticide*
Combustion products	Occupation	Polycyclic aromatic hydrocarbon
Diesel	Organic solvent	Traffic
Drinking water	PAH	Vehicle exhaust
Environmental pollutant		

2) Chemicals identified as mammary carcinogens by U.S. NTP, articles through June 2006

Acronycine	1,1-Dichloroethane	Methylene chloride
Benzene	1,2-Dichloroethane	Methyleugenol
2,2-Bis(bromomethyl)-1,3-propanediol	1,2-Dichloropropane (propylene dichloride)	Nithiazide
1,3-Butadiene	Dichlorvos	5-Nitroacenaphthene
C.I. Acid Red 114	Dimethoxybenzidine dihydrochloride	Nitrofurazone
C.I. Basic Red 9 monohydrochloride	3,3′-Dimethylbenzidine dihydrochloride	Nitromethane
2-Chloroacetophenone	2,4-Dinitrotoluene	Ochratoxin A
Chloroprene	Ethylene oxide	Phenesterin
Clonitralid	Furosemide	Procarbazine hydrochloride
Cytembena	Glycidol	Reserpine
2,4-Diaminotoluene	Hydrazobenzene	Sulfallate
1,2-Dibromo-3-chloropropane	Isophosphamide	2,4-and 2,6-Toluene diisocyanate
1,2-Dibromoethane	Indium phosphide	o-Toluidine hydrochloride
2,3-Dibromo-1-propanol	Isoprene	1,2,3-Trichloropropane

3) Organochlorine pesticides, articles 2000 – June 2006

Aldrin	Dieldrin	Methoxychlor
DDE	Heptachlor	Organochlorine
DDT		

4) Polychlorinated biphenyl (PCBs), articles 1999 – June 2006

5) Occupation, articles 1995 – June 2006

PAH indicates polycyclic aromatic hydrocarbons; U.S. NTP, National Toxicology Program; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.

* Excluding articles prior to 2000 for organochlorine pesticides.

pendently of ionizing radiation, which is a known environmental risk factor for breast cancer.[17,18]

Confounding by established breast cancer risk factors is a particular concern in occupational studies that compare workers to general populations.[19] Because workers in professional jobs, including physicians and nurses, are not comparable to general populations of women for reproductive and other socioeconomic risk factors, we excluded studies of these jobs if they failed to control for confounding or present evidence that the comparison group was similar for reproductive risk factors.[20] For included studies, we note possible sources of confounding in the tables summarizing articles we reviewed.

Because many of the occupational studies were not specifically designed to investigate breast cancer, some have poor statistical power for this analysis. We excluded studies of female breast cancer with 5 or fewer exposed women, and studies of male breast cancer with fewer than 1 observed or expected case. In addition, we excluded studies in which the exposed group was predominantly workers with less than 1 year employment.

Data Extraction and Synthesis

We reviewed the articles to identify and evaluate the inclusion criteria for study participants, comparability of control or reference groups, the exposure measurement method, control for confounding, and the strength of observed associations. All included studies controlled for age and sex; nearly all were restricted to females.

A critical review for each study was entered in a database (available at URL: www.silentspring.org/sciencereview and URL: www.komen.org/environment; accessed April 10, 2007). We summarized the results in tables for the most-studied exposure sources. Information in the tables is taken from the text of each individual study. When determining the size of a study population, we used the number that best corresponds to the analyses reported in the summary table. We relied on adjusted relative risks if they were reported.

We evaluated studies using criteria advanced in standard epidemiologic texts.[21] Thus, we considered the validity and precision of the exposure assessment, the duration of exposure, the length of follow-up after exposure to allow for disease latency, and whether the

TABLE 2
Criteria for Excluding Articles From Review

1) Articles that did not report on an epidemiologic study with a human breast cancer outcome.
2) Review articles, commentaries, and other articles not reporting new research results.
3) Earlier reports that were superseded by more recently published results.
4) Study results concerning diet or tobacco smoke.
5) Studies of occupations (including work in offices, schools, and stores) for which existing data do not support a reasonable inference about exposure to a specific chemical or mixture that has been characterized and hypothesized to affect breast cancer.
6) Studies of occupations with likely exposure to ionizing radiation for which the environmental pollutant exposure was not assessed independently of ionizing radiation.
7) Occupational studies in which the exposure was defined as work in a nonindustrial occupation and there was no control for confounding or evidence that the exposed and comparison groups were similar for reproductive risk factors.
8) Occupational studies in which the exposed group was predominantly exposed <1 year.
9) Studies of female breast cancer with five or fewer exposed women.
10) Studies of male breast cancer with <1 observed or expected case.

range of exposures (from no or low exposure to high) provided a strong comparison. We evaluated the study population based on the inclusion of participants of age to be at risk for breast cancer, the comparability of control groups with cases, and the opportunity for selection bias. Studies were considered minimally controlled for confounding if they included reproductive history and more adequately controlled if they included body size, physical activity, pharmaceutical hormone use, alcohol use, and family history. We considered the reported strength of association and statistical confidence level. We limited the review to topics for which laboratory evidence supports a plausible hypothesis concerning a causal mechanism.

RESULTS AND DISCUSSION

We identified 152 articles reporting epidemiologic studies of environmental pollutants and breast cancer. The persistent bioaccumulative organochlorines, particularly PCBs and DDT/DDE, are by far the most studied. Current-use pesticides, PAHs, and dioxins have received some attention. With the exception of 1 study of an accidental exposure to perchloroethylene in drinking water[22] and an ecologic assessment of Toxics Release Inventory data,[23] studies of organic solvents are limited to occupational settings, most with exposure assessment limited to job category. Greater than half (57%) of the articles reporting original epidemiologic research used biological exposure measures; approximately 20% used geographic location. Only 7 studies gave consideration to exposures in early life; 28 analyzed risk among nonwhites.

Persistent Organochlorines

Persistent organochlorine compounds include PCBs, chlorinated dioxins and furans, and pesticides such as DDT. They are environmentally persistent and lipophilic. They are frequently detected in food, soil, and dust, concentrate up the food chain, and are found in human breast milk and adipose tissue. Residues can be readily measured in blood and breast tissue, providing a way to quantify exposure, although these measures are invasive and expensive; therefore, as a practical matter, levels cannot be measured repeatedly in an individual. One-time measurements reflect exposures, individual differences in metabolism, and behaviors that affect excretion, such as lactation and weight change.[24,25] Specific organochlorine compounds exhibit varying estrogenic and antiestrogenic activity in biological assays.[3] Positive findings for well-controlled studies in the early 1990s of associations between breast cancer risk and the insecticide DDT, its breakdown product DDE, and PCBs prompted additional study. Snedeker[13] reviewed studies of DDT/DDE and dieldrin, concluding that existing research strategies provided conflicting and mostly negative evidence. Moysich et al.[14] and Negri et al.[15] reviewed research on PCBs, concluding that evidence was conflicting and unpersuasive in 2002 through 2003. Updating the picture to 2006 provides potential insights regarding PCBs, new findings for dioxin, essentially unchanged conclusions for DDT/DDE, and a few new results for other organochlorine pesticides. A few studies tested new geographically based exposure assessment strategies and molecular epidemiologic approaches.

Polychlorinated biphenyls

PCBs were used in electrical equipment until their production was banned in the U.S. in the 1970s. Because of bioaccumulation in contaminated rivers in industrial areas, the primary source of exposure in general populations is from fish. PCBs accumulate in fat and high levels have been found in human breast milk.

Twenty-seven articles examined the association between PCBs and breast cancer in case-control and nested case-control studies (Table 3). The primary outcome was incident breast cancer, although 4 studies examined breast cancer recurrence, survival, or aggressiveness. Exposure measures included concentrations of total PCBs, congeners grouped by functional significance, and individual congeners assessed in blood or adipose tissue.

In studies of general populations, the evidence for an association between total PCBs and breast cancer risk was inconsistent, regardless of the exposure measure.[26–34] To our knowledge, no association has been

TABLE 3
Associations of Polychlorinated Biphenyls (PCBs) and Breast Cancer in Recently Reported (2000–2005) Epidemiologic Studies

Author, year Place Analysis	Odds ratio*	(95% CI)	Cases/ controls Source‡	Highest vs lowest exposure category cutpoint†	Year(s) collected sample	Comments
Nested case-control studies, PCBs in serum and primary breast cancer						
Hoyer, 2000			155/274		1976–1983	Exposure is the average of two concentrations taken at 5-y intervals.
Denmark						No OR above 1.0 was seen for 153 or 180.
PCB 118	0.9	(0.4–1.9)		NR		Highest vs lowest quartile total PCBs OR = 1.6 (0.8–3.3)
	1.1	(0.5–2.4)				
	1.9	(0.9–3.9)				
PCB 138	0.9	(0.4–1.9)		NR		
	1	(0.5–2.1)				
	2.1	(1.0–4.4)				
Hoyer, 2001			161/318		1976–1978	No evidence of increased risk among ER− tumors.
Denmark						
Total PCBs (ER+)	1.1	(0.6–1.7)		>1405 ng/ml lipid vs <811		
	0.7	(0.4–1.2)				
	1.3	(0.8–2.2)				
Hoyer, 2002			162/316		1976–1978	Nonsignificantly increased risk (highest quartile OR = 3.0) for Total PCBs among p53 variants.
Denmark						
Total PCBs	1.78	(0.43–7.41)		NR		
	3.82	(0.85–17.41)				
	3.0	(0.66–13.62)				
Laden, 2001			381/381		1989–1990	No increased risk for Total PCBs, 138, 153, or 180. No associations when limited to ER+ tumors or postmenopausal women, or within strata of age, age at menarche, age at birth of first child, number of children, history of BBD, or family history of breast cancer. Significantly elevated risk for 118, 138, and 153 among nulliparous women.
U.S.			Nurses			
PCB 118	0.68	(0.39–1.17)		>101 ng/g lipid vs <45		
	0.62	(0.36–1.06)				
	1.02	(0.59–1.77)				
	0.69	(0.39–1.22)				
Ward, 2000			150/150		1973–1990	No association for congener 99.
Norway			Blood bank			
Group 1B	0.6	NR		NR		
	0.6					
	0.5					
Group 2	0.9	NR		NR		
	0.8					
	0.8					
Group 3	0.7	NR		NR		
	0.8					
	0.6					
Wolff, 2000			148/295		1985–1991	No evidence of effect modification by menopausal status. Levels of DDE and PCBs were higher in ER− cases than in controls, but not different for ER+.
New York						
Total PCBs	1.55	(0.59–4.12)		>876 ng/g lipid vs <478		
	1.23	(0.49–3.08)				
	2.02	(0.76–5.37)				

(*continued*)

TABLE 3
(*continued*)

Author, year Place Analysis	Odds ratio*	(95% CI)	Cases/ controls Source‡	Highest vs lowest exposure category cutpoint†	Year(s) collected sample	Comments
Case-control studies of PCBs in serum and primary breast cancer						
Charlier, 2004			60/60		NR	ORs for each PCB congener were calculated while controlling for the other congeners. No association was seen for 52, 101, 138, or 180.
Belgium			Non-BBD			
PCB 153	1.8	(1.4–2.5)		NR		
Demers, 2000			315/219		1994–1997	Congener 153 was chosen as a surrogate for the highly prevalent PCBs, because it was highly correlated with the others (99, 118, 138, 156, 170, 180, 183, and 187). No differences in OC concentrations between ER+ and ER– tumors. Similar results for hospital and population controls.
Quebec, Canada			Hospital non-BC and population			
PCB 153	1.02	(0.54–1.94)		>69.3 ng/g plasma lipid vs <36.4		
	0.99	(0.5–1.93)				
	0.64	(0.33–1.23)				
	1.07	(0.54–2.12)				
Demers, 2002			314/523		1994–1997	Elevated overall risks for almost all PCB congeners. Risks were higher for pre-menopausal than post-menopausal women. When congener data from this study was grouped into "potentially anti-estrogenic and dioxin-like" congeners (74, 118, 138, 156, 170), as in Zheng et al. 2000, no association was seen.
Quebec, Canada			Hospital and population			
PCB 118	0.9	(0.58–1.39)		>221 ng/g plasma vs <9.4		
	1.12	(0.73–1.74)				
	1.6	(1.01–2.53)				
PCB 156	1.44	(0.91–2.26)		>9.8 ng/g plasma vs <5.9		
	1.44	(0.90–2.31)				
	1.8	(1.11–2.94)				
Gammon, 2002			646/429		1996–1997	Similarly nonelevated risks for 118, 138, and 180. No increased risk for the peak-4 PCBs (118, 138, 153 and 180) in subgroups of parity, breastfeeding, BMI, menopausal status, cancer state, or ER/PR status.
Long Island, NY						
PCB 153	0.75	(0.5–1.13)		>228 ng/g lipid vs <105		
	0.85	(0.57–1.27)				
	0.68	(0.45–1.03)				
	0.86	(0.56–1.32)				
Lopez-Carillo, 2002			95/95		1994–1996	
Mexico			non-BBD			
Total PCBs	0.63	(0.23–1.76)		>833 ng/g lipid vs <26		
	1.31	(0.33–5.21)				
Millikan, 2000			292/270		1993–1996	Nulliparous women and those who never breastfed showed slightly stronger associations. No differences when stratifying by menopausal or ER status. ORs for white, and especially black, women were elevated in higher tertiles of BMI. No increased risk for Total PCBs among whites.
North Carolina			African-American			
Total PCBs			456/389			
	1.35	(0.84–2.16)	White	>540 ng/g lipid vs <313		
	1.74	(1.0–3.01)	DMV + Medicare			
Pavuk, 2003			24/88		1997–1999	Results for congener groups 1, 2, and 3 were similar to those for Total PCBs.
Slovakia						
Total PCBs	0.99	(0.25–4.0)		>3688 ng/g lipid vs <1892		
	0.42	(0.10–1.82)				

(*continued*)

TABLE 3
(*continued*)

Author, year Place Analysis	Odds ratio*	(95% CI)	Cases/ controls Source‡	Highest vs lowest exposure category cutpoint†	Year(s) collected sample	Comments
Rubin, 2006			63/63		1981–1987	
Alaska						
Total PCBs	0.56	(0.11–2.74)		NR		
	0.42	(0.07–2.38)				
Wolff, 2000			175/355		1994–1996	No differences when stratifying by race, BMI, age, parity/lactation, or menopausal status. HPCB levels were non-significantly elevated in ER+ tumors.
New York			BBD and non-BBD/ cancer			
HPCB	0.88	(0.52–1.5)		>799 ng/g lipid vs <80		HPCBs: sum of 118, 153, 141, 138, 183, 187, 167, 174, 177, 156, 180, 170, 201, 203
	0.78	(0.45–1.3)				
LPCB	1.47	(0.84–2.6)		>163 ng/g lipid vs <85		LPCBs: sum of 28, 66, 74, 99, 101
	0.96	(0.53–1.7)				
Zheng, 2000			475/502		1995–1997	Total PCBs = sum of 74, 118, 138, 153, 156, 170, 180, 183, 187. No elevated ORs by parity or breast-feeding status. Modest elevation for the Group 1 congeners (1.45; 0.99–2.11) for the middle tertile, less for Group 2 and none for Group 3.
Connecticut			Hospital (BBD)+ population			
Total PCBs	1.04	(0.76–1.45)		>800 ng/g lipid vs <605		
	0.95	(0.68–1.32)				
Nested case-control studies of PCBs in adipose tissue and primary breast cancer						
Raaschou-Nielsen, 2005			409/409		1993–1997	Postmenopausal women only. Total PCB concentrations were higher among less advanced tumors (by size and lymph node involvement). ORs were lower among ER– tumors than ER+, and were often below 1. Significantly reduced risks were seen for the highest quartiles of 118, 138, and 153 among ER– breast cancers. No risks were significantly elevated, although the highest quartile risks did reach 1.6 for 187 and 183, and 1.4 for 201, 138, and 153. No elevated risks were seen for 118, 156, 170, 99, and 180.
Denmark						
Total PCBs	0.9	(0.6–1.4)		>1,024 ng/g lipid vs < 672		
	0.7	(0.5–1.1)				
	1.1	(0.7–1.7)				
Case-control studies of PCBs in adipose tissue and primary breast cancer						
Aronson, 2000			217/213		1995–1997	Linear trends not reaching significance were seen for 99 and 138. Associations for 105 and 118 were stronger for premenopausal women, but for 170 and 180 the only significant ORs are for the second tertiles among post-menopausal women (3.27 and 2.43, respectively, with lower values in the highest category). No association for 153, 156, 183, or 187. Most PCB congeners were more highly associated with ER– tumors than ER+ (although ORs did not reach significance). Congener 180 was significantly associated with PR- tumors in the third quartile, but not the highest. Total PCBs were slightly more highly associated with higher grade tumors (highest quartile OR = 1.5, vs 1.2 for lower grade tumors, neither significant). (Woolcott et al., 2001)
Ontario, Canada			BBD			
PCB 105	1.16	(0.62–2.14)		>13ng/g vs <4.2		
	2.03	(1.12–3.68)				
	3.17	(1.51–6.68)				
PCB 118	1.25	(0.68–2.29)		>50 ng/g vs <17		
	1.88	(1.0–3.55)				
	2.31	(1.11–4.78)				

(*continued*)

TABLE 3
(*continued*)

Author, year Place Analysis	Odds ratio*	(95% CI)	Cases/ controls Source‡	Highest vs lowest exposure category cutpoint†	Year(s) collected sample	Comments
Woolcott, 2001			217/213		1995–1997	See Comments in Aronson et al, 2000
Ontario, Canada			BBD			
Lucena, 2001			69/65		1997	No elevated risk for 101, 118, 138, 153, 170, 180, 183, 187, or 188. Unspecified higher risk for 52.
Spain			BBD			
PCB 28	9.6	(3.77–24.2)		NR		
McCready, 2004			70/69		1995–1997	OR for 118 is 1.7 (0.69–4.21), and 1.48 for 183. No elevation for 138, 153, 156, 170, 180, or 187. Results for CYP1A1-M2/PCB interactions are not presented.
Toronto, Canada			Hospital excision biopsy patients			
PCB 99	2.4	(0.95–6.04)		NR		
PCB 105	2.5	(1.02–6.13)		NR		
Rusiecki, 2004			244/186		1994–1997	Among postmenopausal women, increased risk of ER+/PR+ tumors was seen with increasing levels of BZ-183. All comparisons stratified by joint ER/PR status. No elevated risks for any ER/PR combination for congeners 187, 74, 118, 138, 156, 170, 153, or 180. Among postmenopausal women, an association only for ER+/PR+ tumors for BZ-183 (highest tertile OR = 2.4, 1.0–6.0).
New Haven, CT			BBD			
PCB 183 (ER+PR-)	1.1	(0.4–2.9)		>14.48 ng/g lipid vs <9.8		
	1.6	(0.6–3.9)				
Stellman, 2000			232/323		1994–1996	No substantial changes when stratified by ER+/ER−. Sum of 74, 99, 118, 138, 146, 153, 156, 167, 170, 172, 178, 180, 183, 187. None were significantly elevated except for 156 and 183.
Long Island, NY			BBD and non-BBD			
Total PCBs	1.06	(0.67–1.69)		>332.24 ng/g vs <181.2		
	1.01	(0.6–1.69)				
PCB 156	1.9	(1.1–3.0)		>13.6 ng/g vs <5.88		
	1.5	(0.9–2.5)				
PCB 183	1.3	(0.8–2.1)		>5.67 ng/g vs <3.16		
	2	(1.2–3.4)				
Zheng, 2000			304/186		1994–1997	No associations for Total PCBs, overall, or by parity, BMI, breastfeeding status, menopausal status, or by congener grouping. No elevated risks for the individual congeners 187, 74, 118, 138, 153, 170, 180, or 183. Holford et al (2000), in revised analysis of these results, adjusted for collinearity between congeners, found that adverse effects were limited to 180 and 183, while 156 was protective.
New Haven, CT			BBD			
PCB 156	0.9	(0.6–1.5)		>26.2 ng/g lipid vs <15.6		
	0.7	(0.4–1.1)				
Holford, 2000						See comments in Zheng et al., 2000.
New Haven, CT						
Case-case studies of PCBs in adipose tissue and breast cancer recurrence						
Muscat, 2003			224 cases		1994–1996	ORs for most PCB congeners were elevated, ORs >2 for 118, 138, 153, 167, 183, and 187.
Long Island, NY						
Total PCBs	0.9	(0.3–2.6)		NR		
	2.9	(1.02–8.2)				

(*continued*)

TABLE 3
(*continued*)

Author, year Place Analysis	Odds ratio*	(95% CI)	Cases/ controls Source‡	Highest vs lowest exposure category cutpoint†	Year(s) collected sample	Comments
Nested case-case studies of breast cancer survival, serum						
Hoyer, 2000			195 cases		1976–1978	Exposure is the average of two concentrations taken at 5-y intervals. The OR presented is the risk of dying (age adjusted). Only ORs below 1 were seen when exposure was based on 1 blood concentration.
Denmark						
Total PCBs	1.62	(0.78–3.38)		>1374 ng/g lipid vs <794		
	1.49	(0.70–3.18)				
	1.44	(0.68–3.05)				
Hoyer, 2001			161/318		1976–1978	The OR presented is the risk of dying. No ORs above 1 for ER– tumors.
Denmark						
Total PCBs (ER+)	1.5	(0.6–3.4)		>1405 ng/ml lipid vs <811		
	1.0	(0.4–2.3)				
	2.5	(1.1–5.7)				
Case-case studies of breast cancer aggressiveness, serum						
Demers, 2000			315		1994–1997	Congener 153 was chosen as a surrogate for all the highly prevalent PCBs because it was highly correlated with the others (99, 118, 138, 156, 170, 180, 183, and 187). The ORs shown are for lymph-node involvement. The highest exposure OR for tumor size was 1.49 (0.77–2.86).
Quebec, Canada						
PCB 153	1.22	(0.61–2.43)		>61.7 ng/g plasma lipid vs <43.0		
	2.12	(1.05–4.30)				

NR indicates information not reported; OR, odds ratio; PCB, polychlorinated biphenyl; ER, estrogen receptor; +, positive; -, negative; BBD benign breast disease; DDE, dichlorodiphenyldichloroethylene; BC, breast cancer; OC, organochlorine; BMI, body mass index; PR, progesterone receptor; DMV, Department of Motor Vehicles; HPCB, higher chlorinated PCBs; LPCB, lower chlorinated PCBs; HCFA, Healthcare Finance Administration (currently, Center for Medicare and Medicaid Services); WT wildtype.

* OR for increasing exposure categories (except reference), adjusted for potential confounding factors.

† All units are presented in lipid-adjusted ng/g, except ng/mL.

‡ Source is population-based unless otherwise specified.

observed in studies that used a PCB congener grouping suggested by Wolff et al.,[27] based on enzyme induction and other toxicological aspects.[14,33,35,36] Results have been inconsistent for individual congeners (including BZ 99, 105, 118, 138, 153, 156, 180, 183, and 187) and interpretation is complicated due to the fact that biological levels of these congeners are highly correlated. When Holford et al.[35] controlled for colinearity using logistic ridge regression, adverse effects were limited to congeners 180 and 183. Many studies have stratified by menopausal status, estrogen receptor status, and parity/lactation, again yielding inconsistent results.[36]

A number of recent studies have focused on the effect of genetic polymorphisms on the association between PCB exposure and breast cancer risk (Table 4). The most consistent evidence is for a modifying effect of a polymorphism in the *CYP1A1* gene on the association between PCB levels and risk (Fig. 1). Three studies have found a higher breast cancer risk associated with higher PCB exposures among postmenopausal white women with the *CYP1A1*-m2 genetic variant (also referred to as the exon 7 variant).[38–40] Cytochrome P4501A1 (*CYP1A1*) is induced by PCBs and involved in metabolism of steroid hormones and polycyclic aromatic hydrocarbons in humans.[39,41] Li et al.[42] found a nonsignificant risk increase among premenopausal women with the *CYP1A1*-m2 variant, but not among postmenopausal women, based on smaller numbers than in the other studies. The *CYP1A1*-m2 variant is present in 10% to 15% of the white population[39,40] and in a larger proportion of African Americans.[42] Another small study demonstrated a nonsignificant risk elevation among women with the *CYP1A1*-m1 variant genotype and high PCB levels.[43]

Another potential gene–environment interaction was reported by Hoyer et al.[44] Among women with variants of the p53 suppressor gene, the highest quartile of total PCB exposure was associated with increased risk of breast cancer (odds ratio [OR] = 3.0; 95% confidence interval [95% CI], 0.66–13.62). In an investigation of other possible mechanisms of susceptibility, results from a case-control study nested in a prospective cohort did not reveal modifying effects of the *GSTM1*, *GSTT1*, *GSTP1*, *COMT*, and *CYP17* genotypes on the association between PCB levels and breast cancer risk.[45]

Three studies have related PCB exposure to breast cancer recurrence or survival. Muscat et al.[46] found that high PCB levels were associated with an increased risk of breast cancer recurrence (OR = 2.9; 95% CI, 1.02–8.2) (Table 3), Hoyer et al.[47] reported that high PCB levels are significantly associated with risk of death among women with estrogen receptor-positive (ER+) tumors (highest tertile OR = 2.5; 95% CI, 1.1–5.7), and Demers et al.[36] found that higher levels of PCB 153 were associated with more aggressive breast cancer. These studies are of particular interest because the shorter time interval between exposure and outcome increases confidence in the validity of the exposure measure and suggests the possibility that ongoing exposures may have health implications.

Dioxin

Tetrachlorodibenzo-*p*-dioxin (TCDD) is classified by the International Agency for Research on Cancer (IARC) as a human carcinogen, based on an increase in cancers at all sites, and has multiple endocrine effects (reviewed in Steenland et al.,[48] and Kogevinas[49]). TCDD is a reference chemical for mixtures of dioxins and furans produced by combustion and other processes involving chlorine. Primary sources of dioxin in the environment are waste incineration, pulp and paper manufacturing, and other industrial processes. Primary sources of exposure are dietary fat, particularly milk, fish, and meat.[49] Schecter et al.[50] estimated that nursing babies exceed the U.S. and European standards for safe dose in their first year of life. Occupational exposure occurs in production of phenoxy herbicides and chlorophenols.

Evidence regarding dioxin and breast cancer comes from cohorts of community residents exposed by a 1976 industrial accident in Seveso, Italy, and contamination from a chemical plant in Chapaevsk, Russia; cohorts of workers exposed during production of herbicides; and 2 small case-control studies of women referred for breast surgery (Table 5).

The most recent report from the Seveso accident includes 981 women who were infants to 40 years of age at the time of the accident and lived in the 2 most contaminated zones (A and B).[51] TCDD was measured in serum collected between 1976 and 1981 and standardized to represent 1977 levels. Results showed a 2-fold increase in breast cancer incidence in 1976 to 1998 associated with a 10-fold increase in serum TCDD, based on 15 cases in a cohort of 981. These women are still young for breast cancer diagnosis, so future reports will continue to be informative. Earlier follow-ups assessed exposure by zone of residence and showed nonsignificantly lower breast cancer incidence through 1986 among older women (RR = 0.7; 95% CI, 0.3–1.5)[52] and lower mortality through 1991.[53]

In Chapaevsk Russian women, Revich et al.[54] reported elevated breast cancer mortality (standardized morbidity ratio [SMR] = 2.1; 95% CI, 1.6–2.7) among women living near the chemical plant com-

TABLE 4
Genetic Polymorphisms, Polychlorinated Biphenyls (PCBs), and Breast Cancer Risk

Author, year Place Analysis[§]	Odds ratio*	(95% CI)	Cases/controls Source[‡]	Highest vs lowest exposure category cutpoint[†]	Year(s) collected sample	Comments
***CYP1A1*-m2 polymorphisms, PCBs in serum, and primary breast cancer**						
Moysich, 1999			154/192		1986–1991	Postmenopausal white women. Main effect for *CYP1A1*-m2 OR = 1.79 (0.91–3.55) in this group. Serum drawn postdiagnosis.
US			RMV and HCFA			
WT/WT - PCB high	1.08	(0.62–1.89)	case-control	>3.73 ng/g vs <3.73		
Variant - PCB low	0.88	(0.29–2.70)				
Variant - PCB high	2.93	(1.18–7.45)				
Laden, 2002			367/367		1989–1990	Postmenopausal women. Main effect for *CYP1A1*-m2 OR = 0.88 (0.58–1.33) pre- and postmenopausal women. Serum sampled 0–4 years before diagnosis.
US			nurses nested case-control			
WT/WT - PCB med	1.0	(0.63–1.60)		>670 ng/g lipid vs <470		
WT/WT - PCB high	0.97	(0.57–1.67)				
Variant - PCB low	0.52	(0.20–1.36)				
Variant - PCB med	1.29	(0.51–3.21)				
Variant - PCB high	2.78	(0.99–7.82)				
Zhang, 2004			374/406		1994–1997	Postmenopausal white women. Main effect for *CYP1A1*-m2 OR = 2.1 (1.1–3.9) overall; OR = 2.4 (1.1–5.0) among postmenopausal women. High PCB levels and m2 variant of *CYP1A1* OR = 3.6 (1.5–8.2) for pre-and post-menopausal women combined. Serum sampled postsurgery.
New Haven, CT			hospital (BBD)+ population			
WT/WT - PCB high	1.1	(0.8–1.6)		>611 ng/g lipid vs <611		
Variant - PCB low	1.8	(0.7–4.5)	case-control			
Variant - PCB high	4.3	(1.6–12.0)				
Li, 2005			242/242		1993–1996	Premenopausal white women. ORs among postmenopausal white women were < 1. Higher odds-ratios were seen when the PCB concentration cutpoints from Moysich et al. and Laden et al. were used for this data. The main effect for *CYP1A1*-m2 among premenopausal white women was OR = 0.7 (0.3–1.9). serum (sampled postdiagnosis).
North Carolina			African-American			
WT/WT - PCB high	0.6	(0.4–1.0)	370/357	>0.35 ng/ml lipid vs <0.35		
Variant - PCB low	0.3	(0.1–0.8)	White			
Variant - PCB high	2.1	(0.4–10.6)	RMV & HCFA case-control			
***CYP1A1* m1 variant, PCBs in breast tissue, and primary breast cancer**						
McCready, 2004			68/52		1995–1997	PCB 180 and PCB 187 showed significant interaction terms with *CYP1A1*-m1 genotype
Canada			Hospital based			
Variant - PCB low vs WT/WT - PCB low	0.79	(0.41–1.52)	case-control	NR		
Variant - PCB high vs WT/WT - PCB high	2.7	(0.68–10.70)				
***CYP17, COMT, GSTM1, GSTT1, GSTP1*, PCBs in serum, and primary breast cancer**						
Helzlsouer, 1999			109/113		1974–1989	No modifying effects of *GSTM1, GSTT1, GSTP1, COMT, and CYP17* genotypes. Confidence intervals for ORs were not reported. Trend tests were not significant
USA			CLUE II	334–2008 ng/g lipid vs 14–192		
			Nested case control			
***p*53, PCBs in serum, and primary breast cancer**						
Hoyer, 2002			162/316		1976–1978	Nonsignificantly increased risk (highest quartile OR = 3.0) for Total PCBs among p53 variants.
Denmark						
Total PCBs	1.78	(0.43–7.41)		NR		
	3.82	(0.85–17.41)				
	3.0	(0.66–13.62)				

BBD indicates benign breast disease; CI, confidence interval; ER, estrogen receptor, HCFA, Healthcare Finance Administration (currently, Center for Medicare and Medicaid Services); NR, information not reported; OR, odds ratio; PCB, polychlorinated biphenyl; RMV, registry of motor vehicles; WT, wildtype.

* OR for increasing exposure categories (except reference), adjusted for potential confounding factors.

† All units are presented in lipid-adjusted ng/g, except ng/mL.

‡ Source is population-based unless otherwise specified.

§ WT/WT indicates that neither copy of the *CYP1A1* gene is the m2 variant.

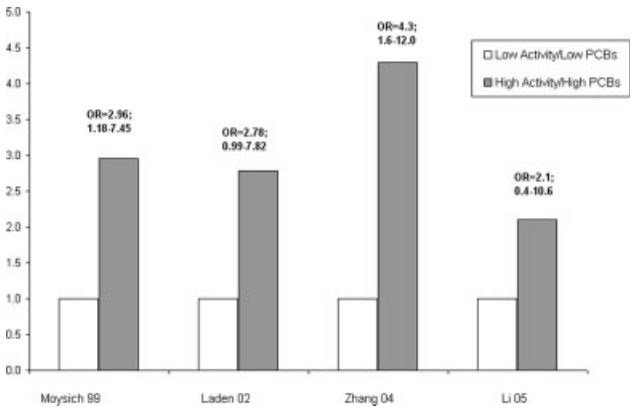

FIGURE 1. Polychlorinated biphenyls (PCBs), *CYP1A1*, and breast cancer risk. OR indicates odds ratio, followed by 95% confidence interval.

pared with surrounding regions. In a cohort of German herbicide workers, an early report by Manz et al.[54] showed elevated female breast cancer mortality, although only 7% of the women workers were in the high exposure locations. Later reports from the cohort applied a more sophisticated exposure model based on biological measures and integrating exposure over time. In the most recent report on females in this cohort, the incidence was found to be significantly elevated (standardized incidence ratio [SIR] = 1.84; 95% CI, 1.17–2.67) in comparison with the regional population.[56] A significant dose-related increased risk was observed for tertiles of exposure within the cohort. In studies based on international registers of exposed workers, the early reports showed male breast cancer mortality was elevated, but female breast cancer mortality and incidence were not.[57,58] The most recent follow-up showed a greater than 2-fold increase in both male and female breast cancer mortality, although the 95% CIs included 1.[59]

Two hospital-based case-control studies of women referred for breast surgery found no overall association between dioxin concentrations in breast tissue and diagnosis with malignant vs nonmalignant breast conditions.[60,61] However, both studies reported statistically unstable higher risk associated with 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD). Reynolds et al.[61] found that this higher risk was among nonwhite women. Exposure measurements made near the time of diagnosis/interview in these studies may not represent the etiologic period, although this limitation may be less pronounced for OCDD, which has a longer half-life than other congeners.[61] Controls with benign breast conditions may be at higher breast cancer risk than a nonhospital population, reducing the ability to detect effects in these studies.

Only 2 studies of breast cancer and dioxin[51,59] were adequately controlled for confounding by established risk factors. In the occupational studies, risk may be obscured by the failure to account for healthy worker effects and specifically confounding by physical activity on the job, which is protective. Among the occupational studies, Kogevinas et al.[59] allowed comparison between exposed women and a similarly employed nonexposed group and Flesch-Janys et al.[56] compared risk across exposures within the cohort; both strategies reduce potential confounding. Comparisons of occupationally exposed women with general populations are problematic because women factory workers likely differ from white and pink-collar workers and nonemployed women with regard to many factors related to breast cancer. In the occupational and Russian cohorts, exposures to multiple chemicals mean that disease effects may not be specific to dioxin.

DDT/DDE in serum and adipose tissue

Twenty-five reports from case-control studies and nested case-control studies published in 2000 to June 2006 examined associations between serum or adipose levels of DDT or DDE and breast cancer (Table 6). DDE levels are considered a measure of exposure to DDT and to DDE from food and the environment, with DDE being the predominant exposure in the U.S. since 1972, when DDT was banned.[13] A few studies show elevated risk. In hospital-based case-control studies, Charlier et al.[62] reported higher risk in European whites with detectable DDT (OR = 5.64; 95% CI, 1.81–17.65) or DDE (OR = 2.21; 95% CI, 1.41–3.48)[63] in serum, and Romieu et al.[64] found evidence of a dose-response association (*P*-trend = .02) with DDE in serum (highest compared with lowest quintile OR = 3.81; 95% CI, 1.14–12.8) in Mexico City. Most studies did not support an association of DDE and breast cancer overall or stratified by menopausal status, tumor hormone receptor status, parity, breastfeeding, or body mass index. The largest of the organochlorine studies, the Long Island population-based case-control study, found no association,[65] and 2 meta-analyses covering greater than 20 studies did not demonstrate an elevated risk.[29,66] In light of these findings, additional study of incident breast cancer in association with biological measures of DDE/DDT levels near the time of diagnosis is not a promising avenue. Further analysis of risk in subgroups characterized by polymorphisms that affect metabolism and detoxification is an active area of investigation that may be informative, although it has not yielded consistent findings to date. Three studies conducted between 2000 and 2006 investigated DDT and DDE

TABLE 5
Epidemiologic Studies of Dioxins and Breast Cancer

Author, year Breast cancer outcome Subgroup	Exposure	Study type, population	Confounders considered?	Relative risk (95% CI) deaths/cases	Comment
Seveso, Italy, female residents cohort					
Bertazzi, 1989 (AJE) Female mortality 1976–1986 Zone A (closest) Zone B Zone R	Residence in area contaminated by TCDD in a 1976 industrial accident	Residents in the exposed zones in 1976–1986 and aged 20–74 at follow-up compared with surrounding districts	No	 RR 1.06 (0.1–7.5) 1 death RR 0.87 (0.4–2.1) 5 deaths RR 0.64 (0.4–0.9) 28 deaths	Mortality is an insensitive indicator. Follow-up is short.
Bertazzi, 1993 Female incidence 1977–1986 < 45 years > 45 years	Residence in area contaminated by TCDD in a 1976 industrial accident	Residents in the exposed zones in 1976–1984 compared with surrounding districts	No	 RR 0.9 (0.3–2.9) RR 0.7 (0.3–1.5).	
Bertazzi, 1997 Female mortality 1976–1991 Zone A (closest) Zone B Zone R	Residence in area contaminated by TCDD in a 1976 industrial accident	Residents in the exposed zones in 1976–1991 compared with surrounding districts	No	 RR 0.6 (0.0–3.1) 1 death RR 0.8 (0.4–1.5) 9 deaths RR 0.8 (0.6–1.0) 67 deaths	Analysis limited to those residing in the area at the time of the accident yielded similar RRs. Follow-up remains short.
Warner, 2002 Female incidence 1976–1998	TCDD concentration in the first serum sample collected in 1976 and 1981, later samples back extrapolated to 1977	981 females who were infants to 40 years old in 1976 and resided in one of the most highly TCDD-contaminated zones (A or B) at the time of accident	Yes	Hazard ratio for 10-fold increase in TCDD = 2.1 (95% CI 1.0–4.6) *P* trend = .05, 15 cases	Cohort is young for breast cancer.
Chapaevsk, Russia					
Revich, 2001 Female mortality 1995–1998 Female incidence 1995–1998	Residence where dioxins from a chemical production plant resulted in contamination of air, soil, water, cow's milk, breast milk, blood	Surveillance of Chapaevsk compared to surrounding region	No	SMR 2.1 (1.6–2.7), 58 cases Age-specific incidence for Chapaevsk exceeds regional incidence.	Multiple chemical exposures via multiple pathways are likely.
Hamburg, Germany, herbicide/insecticide worker cohort					
Manz, 1991 Female mortality	Classification of jobs in 1952–1984 for TCDD exposure	399 female workers compared with national mortality	No	SMR 2.15 (0.98–4.09)	Few women (7%) in "high" exposed category. Multiple chemical exposures are likely. Mortality is an insensitive indicator. Reference to general population does not take into account differences between women factory workers and nonfactory and nonworking women.
Flesch-Janys, 1997					Figure 3 shows breast cancer SMR > 2 and CI excludes one. But text says cohort is 1189 males and Flesh-Janys 1998 reports no male breast cancer deaths.
Flesch-Janys, 1998 Male mortality	Cumulative exposure: integrated estimate for every time (area under the curve), combining blood levels with job history	1189 male workers compared to national population and high compared to low exposed workers	No	No deaths expected, none observed	

(*continued*)

TABLE 5
(*continued*)

Author, year Breast cancer outcome Subgroup	Exposure	Study type, population	Confounders considered?	Relative risk (95% CI) deaths/cases	Comment
Flesch-Janys, 1999 Female incidence 1952–1995	Cumulative exposure: integrated estimate for every time (area under the curve), combining blood levels with job history	398 female workers	No	SIR 1.84 (1.17–2.67) 23 cases (with nonrespondents excluded)	SIR 1.55 (0.98–2.32) with nonrespondents treated as noncancer cases, which may understate incidence. Reference to the regional population does not take into account differences between women factory workers and nonfactory and nonworking women.
International worker cohorts					
Saracci, 1991 Male mortality Female mortality	Worked with chlorophenoxy herbicides, chlorophenols, some likely contaminated with dioxins (TCDD)	18,390 workers (1537 females) compared with national populations.	No	SMR 345 (42–1246), 2 deaths SMR 30 (1–166), 1 death	Average follow-up 17 years. Age of workers is not reported. Small number of female deaths.
Kogevinas, 1993 Female incidence Female mortality	Worked with chlorophenoxy herbicides, chlorophenols, some likely contaminated with dioxins (TCDD)	701 female workers exposed <1 to 10+ years (169 probable TCDD exposure) compared with national populations	No	SIR 91 (36–187) 7 cases SMR 30, 1 death	Low statistical power. Likely healthy worker effect.
Kogevinas, 1997 Mortality 1939–1992 Females Males	Worked with phenoxy herbicides, chlorophenols, some likely contaminated with dioxins (TCDD). Exposed to TCDD or higher chlorinated dioxins.	20,851 male and 1012 female exposed workers compared with national populations.	No	SMR 2.16 (0.99–4.10) 9 deaths SMR 2.56 (0.31–9.26) 2 deaths	Serum and adipose testing for a subgroup of males supports job exposure classification, but many workers classified as exposed have levels similar to the comparison population. Breast cancer risk is not elevated in workers from the same cohort who were not exposed to TCDD.
Breast surgery patients					
Hardell, 1996 (Sweden) Incidence	PCDD, PCDF concentration in tumor-free breast tissue	Case-control study of hospital patients operated on for malignant (n = 22) compared with benign (n = 19) female breast condition	Yes	Adjusted OR 1.09 (0.95 – 1.25) per 100 unit (pg/g lipid) increase in OCDD	Low statistical power. Exposure range may be low. Measurement near diagnosis may not represent etiologic period. Controls with benign breast conditions may be at higher breast cancer risk than a general population, reducing ability to detect effects. No significant differences in analysis by receptor status, S-phase, ploidy.
Reynolds, 2005 (US) Incidence	Concentration in breast tissue of 9 individual congeners and two toxic equivalent summary measures	Case-control study of hospital patients operated on for malignant (n = 79) compared with benign (n = 52) female breast condition	Limited to age, race/ethnicity, lactation history	No significant association for toxic equivalent scores or congeners. Many risk estimates are lower than one, with the exception of OCDD Adjusted OR 1.62 (0.64–4.12) for highest compared to lowest tertile.	Low statistical power. Measurement near diagnosis may not represent etiologic period. Controls with benign breast conditions may be at higher breast cancer risk than a general population, reducing ability to detect effects.

SIR indicates standardized incidence ratio; SMR, standardized mortality ratio; TCDD, dioxin; OR, odds ratio; OCDD, octachlorinataed dibenso-p-dioxin; PCDD, polychlorinated dibenzo-p-dioxins and PCDF, polychlorinated dibenzofurans; RR, risk ratio; AJE, American Journal of Epidemiology; bc, breast cancer; 95% CI, 95% confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.
Only the most recent report from a cohort is included unless an earlier report provides information that is not superceded in the later report. All studies controlled for age, gender.

TABLE 6
Association of Serum and Adipose Tissue Levels of DDT and DDE and Breast Cancer Risk in Epidemiologic Studies Published in 2000 to June 2006

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source†	Highest vs lowest exposure category cutpoint‡	Years collected sample	Comments
Nested case-control studies of primary incident breast cancer, serum						
Hoyer, 2000			155/274		1976–1983	Exposure is the average of 2 concentrations taken at 5-year intervals.
Denmark						
DDE	1	(0.5–2.0)		NR		
	0.8	(0.4–1.6)				
	1.4	(0.7–2.8)				
DDT	1.3	(0.4–4.5)		NR		
	2.1	(0.6–7.0)				
	3.6	(1.1–12.2)				
Ward, 2000			150/150		1973–1990	
Norway			Blood bank			
DDE	0.7	NR		NR		
	1.0					
	1.2					
DDT	0.2	NR		NR		
	0.5					
	0.3					
Wolff, 2000			148/295		1985–1991	No evidence of effect modification by menopausal status. Levels of DDE and PCBs were higher in ER– cases than controls, but not different for ER+ cases.
New York						
DDE	0.8	(0.35–1.87)		>1934 ng/g lipid vs <664		
	0.6	(0.26–1.38)				
	1.3	(0.51–3.35)				
Hoyer, 2001			161/318		1976–1978	Similarly decreased risks were seen among ER+ tumors.
Denmark						
DDE (ER–)	0.9	(0.3–2.5)		>1688.9 ng/ml lipid vs <741		
	0.7	(0.2–2.0)				
	0.6	(0.2–1.7)				
Laden, 2001			381/381		1989–1990	No associations when limited to ER+ tumors or postmenopausal women, or within strata of age, age at menarche, age at birth of first child, number of births, BBD history, or family history of breast cancer.
US			Nurses			
DDE	0.95	(0.59–1.53)		>1466 ng/g lipid vs <428		
	0.51	(0.31–0.86)				
	0.91	(0.57–1.47)				
	0.82	(0.49–1.37)				
Hoyer, 2002			162/316		1976–1978	No evidence of increased risk for DDT among p53 mutants, or among DDE for either p53 genotype.
Denmark						
DDT	1.5	(0.81–2.92)		NR		
(Wildtype p53)	0.8	(0.41–1.68)				
	1.3	(0.68–2.59)				

(*continued*)

TABLE 6
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source†	Highest vs lowest Exposure category cutpoint‡	Years collected sample	Comments
Case-control studies of primary incident breast cancer, serum						
Demers, 2000			315/219		1994–1997	Similar results for hospital and population controls.
Canada			Hospital non-BC and population controls			No differences in OC concentrations between ER+ and ER− tumors.
DDE	0.85	(0.45–1.59)		>680 ng/g lipid vs <184.5		
	0.66	(0.37–1.19)				
	1.54	(0.81–2.95)				
	1.36	(0.71–2.63)				
DDT	0.85	(0.47–1.54)		>15 ng/g lipid vs <7		
	1.06	(0.57–1.98)				
	1.07	(0.59–1.94)				
	1.37	(0.73–2.56)				
Millikan, 2000			292/270 African-American		1993–1996	Slightly stronger associations for nulliparous women and those who never breastfed. No differences by menopausal status or ER−status. ORs were higher among African-Americans than whites (1.41 in highest tertile), but not significantly elevated.
North Carolina			456/389 white			
			DMV + Medicare			
DDE	1.05	(0.79–1.40)		>1044 ng/g lipid vs <395		
	1.09	(0.79–1.51)				
Romieu, 2000			120/126		1990–1995	Adjusted for serum DDT level. Risk appears elevated among postmenopausal women. DDT not associated with breast cancer risk.
Mexico						
DDE	1.24	(0.5–3.06)		>3490 ng/g lipid vs < 1170		
	2.31	(0.92–5.86)				
	3.81	(1.14–12.8)				
Wolff, 2000			175/355		1994–1996	No differences were seen when stratifying by race, BMI, age, parity/lactation, or menopausal status. DDE and DDT levels were nonsignificantly elevated in ER+ tumors.
New York			BBD & non-BBD/cancer			
DDE	0.8	(0.49–1.3)		>1040 ng/g lipid vs <450		
	0.93	(0.56–1.5)				
DDT	1.19	(0.73–2.0)		>34 ng/g lipid vs <20.8		
	1.34	(0.82–2.2)				
Zheng, 2000			475/502		1995–1997	No elevated ORs by parity, breast-feeding status, and menopausal status.
Connecticut			Hospital (BBD)+ population			
DDE	1.05	(0.76–1.47)		>660 ng/g lipid vs <296		
	0.96	(0.67–1.36)				
Gammon, 2002			646/429		1996–1997	No increased risk for DDT.
Long Island, NY						No increased risk for DDE in subgroups of parity, breastfeeding, BMI, menopausal status, cancer stage, or ER/PR status.
DDE	0.88	(0.58–1.32)		>1,373 ng/g lipid vs <307		
	0.94	(0.63–1.43)				
	0.92	(0.60–1.42)				
	1.2	(0.76–1.90)				
Pavuk, 2003			24/88		1997–1999	Direction and magnitude of associations did not change in analysis limited to postmenopausal women.
Slovakia			Noncancer population			
DDE	0.53	(0.08–3.27)		>4389 ng/g lipid vs <234		
	3.04	(0.65–14.3)				

(*continued*)

TABLE 6
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source†	Highest vs lowest Exposure category cutpoint‡	Years collected sample	Comments
DDT	0.33	(0.06–1.7)		>137 ng/g lipid vs <30		
	1.19	(0.27–5.23)				
Charlier, 2003			159/250		1999–2000	ORs classify exposure as binary (above/below quantification limit). No association for ER status or tumor size.
Belgium			Hospital, noncancer controls			
Total DDT	5.64	(1.81–17.65)		>0.5 ng/g lipid vs <0.5		
Charlier, 2004			231/290		2001–2002	OR is for DDE as above/below quantification limit. Risk was significantly elevated for DDE as a continuous variable. p,p′-DDE level was not associated with ER status, lymph node involvement, bloom stage, or tumor size. No difference in mean DDT level between cases and controls.
Belgium			Hospital, noncancer controls			
DDE	2.21	(1.41–3.48)		>0.5 ng/g lipid vs <0.6		
Raaschou-Nielsen, 2005			409/409		1993–1997	Postmenopausal women only.
Denmark			Noncancer			Most pesticide ORs were higher (although still usually around 1) for ER+ breast cancers than ER–, especially the highest quartile of DDE (1.1 in ER+, 0.1 in ER–)
DDE	1.0	(0.7–1.5)		>904 ng/g lipid vs <16		
	0.9	(0.6–1.4)				
	0.7	(0.5–1.2)				
DDT	0.8	(0.5–1.3)		>31 ng/g lipid vs <15		
	1.4	(0.9–2.3)				
	0.6	(0.3–1.0)				
Case-control studies of primary incident breast cancer, adipose tissue						
Aronson, 2000			217/213		1995–1997	Risk was not modified by menopausal status.
Ontario, Canada			BBD			When HRT users were excluded, the OR for the highest quartile increased to 2.0 (1.0–4.2).
DDE	0.96	(0.55–1.68)		>1390 ng/g vs <369		
	0.92	(0.51–1.67)				OR for DDE was significantly elevated for highest tertile of ER– tumors (2.4, 1.0–5.4), not ER+ . Unstably elevated ORs for PR- (1.5), and for smaller tumors (1.6) (Woolcott et al., 2001).
	1.62	(0.84–3.11)				
DDT	0.82	(0.47–1.43)		>38 ng/g vs <13		
	0.93	(0.53–1.61)				
	1.18	(0.61–2.29)				
Woolcott, 2001			217/213		1995–1997	See Comments in Aronson et al., 2000
Ontario, Canada			BBD			
Rubin, 2006			63/63		1983–1987	
Alaska			Cancer registry,			
DDE	0.57	(0.15–2.19)	Serum bank controls	NR		
	1.43	(0.46–4.47)				
Bagga, 2000			73/73		1995–1996	
California			Reduction mammoplasty patients			
DDE	1.13	(0.79–1.60)		NR		
DDT	1.05	(0.93–1.19)		NR		
Ibarluzea, 2004			198/260		1996–1998	Slightly higher OR among BMI > median (1.46), and among postmenopausal (1.58)
Spain			Noncancer			
DDE	1.04	(0.59–1.84)		>676 ng/g lipid vs <202		
	1.23	(0.69–2.17)				
	1.22	(0.68–2.21)				

(*continued*)

TABLE 6
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source†	Highest vs lowest Exposure category cutpoint‡	Years collected sample	Comments
McCready, 2004			70/69		1995–1997	DDE ORs were higher for *GSTM1* null variants than for wildtypes, and also higher for the *GSTT1* null variants.
Toronta, Canada			Hospital non-BC			
DDE	2.48	(1.08–5.71)		NR		DDT ORs were higher for *GSTM1* null variants than wildtypes, but lower for *GSTT1* null variants than wildtypes.
DDT	2.33	(0.97–5.61)		NR		
Stellman, 2000			232/323		1994–1996	No substantial changes when stratified by ER+/ER–
Long Island, NY			BBD, non-BBD			
DDE	1.14	(0.71–1.81)		>618.81 ng/g vs <212.92		
	0.74	(0.44–1.25)				
Case-case studies of breast cancer recurrence, adipose tissue						
Muscat, 2003			224 cases		1994–1996	
Long Island, NY						
DDE	2.3	(0.9–5.7)		NR		
	1.1	(0.4–3.5)				
DDT	1.2	(0.5–2.9)		NR		
	1.1	(0.4–3.0)				
DDD	2.2	(0.8–6.1)		NR		
	2.3	(0.7–8.0)				
Nested case-case studies of breast cancer survival, serum						
Hoyer, 2000			195 cases		1976–1978	The OR presented is the risk of dying (age adjusted).
Denmark						Exposure is the average of two concentrations taken at 5-year intervals.
DDE	1.24	(0.56–2.77)		>1782.4 ng/g lipid vs <832.0		
	1.74	(0.83–3.66)				
	2.21	(1.07–4.58)				
DDT	0.85	(0.3–2.8)		>169.6 ng/g lipid vs <61.9		
	1.38	(0.5–4.2)				
	1.18	(0.4–3.6)				
Hoyer, 2000			161/318		1976–1978	The OR presented is the risk of dying.
Denmark						No ORs above 1 for ER– tumors.
DDE (ER+)	0.7	(0.3–1.6)		>1688.9 ng/ml lipid vs <741.0		
	1.0	(0.5–2.2)				
	1.0	(0.5–2.1)				
Case-case studies of breast cancer aggressiveness, serum						
Demers, 2000			315		1994–1997	The ORs shown are for lymph-node involvement. The highest exposure OR for tumor size was 1.64 (0.87–3.08) for DDE, and 1.59 (0.84–3.03) for DDT.
Quebec, Canada						
DDE	2.06	(1.02–4.15)		>495.3 ng/g plasma lipid vs <250.0		
	2.91	(1.43–5.91)				
DDT	1.31	(0.68–2.53)				
	1.51	(0.77–2.95)				

NR indicates information not reported; BC, breast cancer; BBD, benign breast disease; DMV, department of motor vehicles; OC, organochlorine; ER, estrogen receptor; 95% CI, 95% confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.

* OR for increasing exposure categories (except reference), adjusted for potential confounding factors.

† Source is population-based unless otherwise specified.

‡ All units are presented in lipid-adjusted ng/g, except ng/mL.

levels and breast cancer aggressiveness,[67] recurrence,[46] or survival.[28] Demers et al.[67] found a dose-related increased risk for DDE and large tumors with lymph node involvement in a hospital-based case control study. Studies of disease progression have the advantage that biological measures taken near diagnosis are more plausibly indicative of exposure during a time relevant to the outcome studied.

Other organochlorine pesticides in serum and adipose tissue

Twenty-one studies published from 2000 to June 2006 reported on 14 organochlorine pesticides other than DDT and DDE, although 5 of the compounds were included in just 1 study during this time period (Table 7). Each has been linked to higher risk in at least 1 study. In a nested case-control study of Danish women that averaged 2 serum measurements of dieldrin from 1976 and 1983, Hoyer et al.[47] reported a dose-related increased risk of ER− tumors (OR = 7.6; 95% CI, 1.3–4.6 for highest quartile), but not ER+ tumors. There also appeared to be an interaction between higher dieldrin levels and a variant of the *p*53 suppressor gene, although the effect did not reach statistical significance.[44] The study found a dose-related increased risk of death with higher dieldrin exposure (OR = 4.6; 95% CI, 1.8–11.5 for highest quartile)[28] and evidence that the elevated mortality was in women with ER+ tumors.[47] In contrast, the Long Island study found no consistently increased risk with dieldrin exposure.[65] Charlier et al.[62,63] reported a 4-fold to 9-fold higher incidence associated with hexachlorobenzene, but Raaschou-Nielsen et al.[34] found a relative risk below 1. Muscat et al.[46] found statistically unstable elevated risk of recurrence associated with hexachlorobenzene, beta-hexachlorohexane, and *trans*-nonachlor. Demers et al.[67] found associations between tumor size and lymph-node involvement for beta-HCH, oxychlordane, and *trans*-nonachlor. It will be informative to see additional reports on these outcomes from the organochlorine studies based on biological measures near the time of diagnosis, although possible effects of differences in treatment must be taken into account.

Pesticides assessed by geographic location, job history, and self-report

A key limitation of the biological markers of organochlorine exposure is that they may not accurately measure or rank exposure during the years when a tumor was initiated or during critical exposure periods in the life cycle when susceptible developing breast tissue was at risk.[6,13] To date, blood and adipose techniques are not useful in assessing exposure to nonpersistent current-use pesticides. The challenge in studies of these compounds is that exposure is usually episodic, so many measurements over a long time would be needed to accurately rank subjects on exposure, and this cannot be done retrospectively because the new pesticides are nonpersistent and no permanent marker of their effect has been identified. Given these limitations, it is essential to explore other exposure assessment tools for the many pesticides (and other compounds) that are hormonally active or shown to be mammary gland carcinogens (Table 8).

Residential location and job histories have been the primary alternatives. Residential location has the advantage that people spend much of their time at home; occupational studies have the advantage of assessing higher exposures than general populations.

Our own research has developed the GIS techniques for assessing historical exposures at the individual level in a case-control study of breast cancer on Cape Cod, Massachusetts. Relative exposure intensity was estimated at each of the women's Cape Cod addresses for each year from 1948 through 1995 based on mapped records of wide-area pesticide application and models of pesticide drift integrated in a GIS.[68,69] The results showed a dose-related, but statistically unstable increase in risk for women who lived near cranberry bogs in which persistent pesticides were applied (OR = 1.8; 95% CI, 0.7–4.5 for highest quantile). Similar results were reported by Aschengrau et al.[70] for earlier diagnosis years in the same region. However, associations were weaker or null across other types of pesticide use for tree pests, mosquito control, and agriculture. The primary limitation of the assessment method is that information is missing regarding earlier exposures for women who moved to Cape Cod from elsewhere. Also, GIS data do not include all town and private spraying and home use. Applying similar GIS methods in a nested case-control study of New York state women, O'Leary et al.[71] found some evidence of increased risk for women living on formerly agricultural land (OR = 1.5; 95% CI, 0.8–2.9), based on 20 cases, and higher risk for women age 26 years and older at the birth of their first child (OR = 6.4; 95% CI, 2.2–18.2, based on 14 cases), suggesting a possible interaction with susceptibility due to late differentiation of the mammary gland, which occurs during the first pregnancy.

Several studies used the California Department of Pesticide Regulation (DPR) database to assess residential or occupational exposure, based on date, location, and other characteristics of pesticide application. A cohort study among California teachers found no association between breast cancer and exposure estimates based on California pesticide reporting data,[72]

TABLE 7
Association of Tissue Levels of Organochlorine Pesticides (Except DDT/DDE) and Breast Cancer in Epidemiologic Studies Published in 2000 to June 2006

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source¶	Highest vs lowest exposure category cutpoint‡	Year(s) collected sample	Comments
Nested case-control studies of primary incident breast cancer, serum						
Hoyer, 2000 CCC			155/274		1976–1983	Exposure is the average of 2 concentrations taken at 5-year intervals. Dieldrin not analyzed because below LD in many samples.
Denmark						
beta-HCH	1.3	(0.6–2.9)		NR		
	1.2	(0.5–2.9)				
	1.2	(0.5–3.0)				
Ward, 2000			150/150			No elevated ORs for beta-HCH, oxychlordane, trans-nonachlor, HCB, aldrin, dieldrin, mirex, g-HCCH, endrin.
Norway			Blood bank		1973–1990	
Heptachlor epoxide	1.5	NR		NR		
	1.8	NR				
	1.0	NR				
Hoyer 2001			161/318		1976–1978	No ORs above 1.2 for HCB. Little evidence of increased risk among ER+ tumors for dieldrin.
Denmark						
Dieldrin (ER−)	1.2	(0.3–5.4)		>57.1 ng/mL lipid vs < 12.01		
	4.9	(0.9–28.3)				
	7.6	(1.3–46.1)				
Hoyer, 2002			162/316		1976–1978	No increased risk among wildtype-p53.
Denmark						
Dieldrin (p53 mutant)	2.07	(0.48–8.88)		NR		
	4.57	(0.94–22.2)				
	3.53	(0.79–15.8)				
Case-control studies of primary incident breast cancer, serum						
Demers, 2000			315/219		1994–1997	Little evidence of increased risk was similarly seen for oxychlordane and trans-nonachlor. No differences in OC concentrations between ER+ and ER− tumors. Similar results for hospital and population controls.
Quebec, Canada			Hospital non-BC and population			
beta-HCH	0.71	(0.38–1.33)		>22.6 ng/g lipid vs <10.3		
	0.85	(0.44–1.62)				
	0.71	(0.38–1.32)				
	0.83	(0.43–1.61)				
Wolff, 2000			175/355		1994–1996	
New York			BBD and non-BBD			
trans-Nonachlor	0.99	(0.61–1.6)		>50 ng/g lipid vs <26		
	0.73	(0.43–1.2)				
Gammon, 2002			646/429		1996–1997	No elevated risk for chlordane. Nonsignificantly elevated risk for chlordane among nulliparous women. No other elevated risks for dieldrin or oxychlordane in subgroups of parity, breastfeeding, BMI, menopausal status, cancer stage, or ER/PR status.
Long Island, NY						
Dieldrin	1.19	(0.59–2.41)		>33 ng/g lipid vs <15		
	0.91	(0.45–1.84)				
	0.64	(0.3–1.35)				
	1.37	(0.69–2.72)				

(*continued*)

TABLE 7
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source¶	Highest vs lowest exposure category cutpoint‡	Year(s) collected sample	Comments
Lopez-Carillo, 2002			95/95		1994–1996	
Mexico			Non-BBD			
beta-HCH	0.65	(0.28–1.51)		>612.98 ng/g lipid vs <63.0		
	1.05	(0.46–2.4)				
HCB	0.58	(0.24–1.39)		>39.06 ng/g lipid vs <27.69		
	0.46	(0.2–1.07)				
Charlier, 2003			159/250		1999–2000	Exposure classified as above/below the quantification limit. No association between OC level and ER status, or tumor size.
Belgium			Hospital, noncancer			
HCB	9.14	(2.84–29.4)		>0.5 ng/g lipid vs <0.6		
Pavuk, 2003			24/88		1997–1999	Direction and magnitude of associations did not change in analysis limited to postmenopausal women.
Slovakia			Noncancer population			
HCB	0.15	(0.02–1.05)		>2270 ng/g lipid vs <1293		
	0.45	(0.06–3.19)				
Charlier, 2004			231/290		2001–2002	Exposure classified as above/below the quantification limit. Risk is also significantly elevated for exposure as a continuous variable. HCB level was not associated with ER status, lymph node presence, or bloom stage. HCB level was significantly associated with tumor size.
Belgium			Hospital, noncancer			
HCB	4.99	(2.95–8.43)		>0.5 ng/g lipid vs <0.6		
Nested case-control studies of primary incident breast cancer, adipose tissue						
Raaschou-Nielsen, 2005			409/409		1993–1997	Postmenopausal women only.
Denmark			Noncancer			Most pesticide ORs were higher (although still usually around 1) for ER+ breast cancers than ER−. No ORs for dieldrin reached significance. trans-Nonachlor ORs were significantly decreased for the highest quartile of exposure among ER− women. DDE concentrations were higher among less advanced tumors (by size and lymph node involvement).
beta-HCH	0.8	(0.5–1.2)		>92 ng/g lipid vs <56		
	0.6	(0.4–0.9)				
	0.5	(0.3–0.9)				
Oxychlordane	0.6	(0.4–1.0)		>37 ng/g lipid vs <22		
	0.8	(0.5–1.3)				
	0.5	(0.3–0.9)				
cis-Nonachlor	1.6	(0.9–2.9)		>6.8 ng/g lipid vs <3.8		
	0.9	(0.5–1.6)				
	1.5	(0.8–2.7)				
HCB	0.6	(0.4–1.0)		>91 ng/g lipid vs <59		
	0.7	(0.4–1.1)				
	0.5	(0.3–0.9)				
Case-control studies of primary incident breast cancer, adipose tissue						
Aronson, 2000			217/213		1995–1997	No significant association for trans-nonachlor, oxychlordane, HCB, mirex, and beta-HCH (except for the highest quartile for mirex among never-lactating post-menopausal women). No increased risk for cis-nonachlor or trans-nonachlor by ER status. Beta-HCH highest quartile OR for ER−=1.4 (0.6–3.2), but 0.7 for ER+. (Woolcott et al, 2001)
Ontario, Canada			BBD			
cis-Nonachlor	0.81	(0.47–1.39)		>11 ng/g vs <4.4		
	0.48	(0.27–0.86)				
	0.8	(0.41–1.53)				
Stellman, 2000			232/323		1994–1996	Sum of DDE, DDT, DDD, oxychlordane, trans-nonachlor, beta-HCH, and HCB.
Long Island, NY			BBD and non-BBD			
Total OCP	1.29	(0.8–2.08)				
	0.66	(0.38–1.17)				

(*continued*)

TABLE 7
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source[¶]	Highest vs lowest exposure category cutpoint[‡]	Year(s) collected sample	Comments
Zheng, 2000			304/186		1994–1997	
New Haven, CT			BBD controls			
Oxychlordane	0.7	(0.4–1.2)		>47.6 ng/g lipid vs <27		
	0.7	(0.4–1.2)				
	0.7	(0.4–1.3)				
trans-Nonachlor	1.2	(0.7–2.1)		>71.1 ng/g lipid vs <36.5		
	0.7	(0.4–1.3)				
	1.1	(0.6–1.9)				
Woolcott, 2001			217/213		1995–1997	See Comments in Aronson et al, 2000
Ontario, Canada			BBD			
Ibarluzea, 2004			198/260		1996–1998	No significantly higher overall risk for endosulfan-ether, lindane, or TEXB-beta. Risk significantly elevated among postmenopausal women for aldrin and lindane.
Spain			Noncancer			
Aldrin	1.55	(1.0–2.4)		NR		
TEXB-alpha[§]	1.15	(0.64–2.05)		>197.5[†] vs <0.25		Risk is also significantly elevated for TEXB-alpha among women with BMI < median (p-trend = 0.03)
	1.33	(0.76–2.33)				
	1.31	(0.74–2.31)				
McCready, 2004			70/69		1995–1997	No evidence of association for cis-nonachlor, trans-nonachlor, oxychlordane, mirex, and beta-HCH. ORs were notably higher among GSTM1 null variants, especially OCD (2.3), and HCB (2.85).
Toronta, Canada			Hospital excision biopsy patients			
HCB	1.24	(0.53–2.9)		NR		
Cassidy, 2005			17/17		1994–1998	
US			BBD			
Heptachlor epoxide	1.4	NR		15.9 ng/g lipid vs 3.6[‖]		
	2.3	NR				
	3.2	(1.1–9.2)				
Case-case studies of breast cancer recurrence, adipose tissue						
Muscat, 2003			224 cases		1994–1996	RR = 1.4 for highest category of oxychlordane
Long Island, NY						
HCB	3	(1.1–8.4)		NR		
	2.3	(0.7–7.4)				
beta-HCH	1.7	(0.6–5.1)		NR		
	2.7	(0.9–8.3)				
trans-Nonachlor	2.0	(0.7–5.3)		NR		
	2.1	(0.7–6.8)				
Nested case-case studies of breast cancer survival, serum						
Hoyer, 2000 JCE			195 cases		1976–1978	The OR is the risk of dying.
Denmark						Exposure is the average of 2 concentrations taken at 5-year intervals. ORs for beta-HCH, HCB, and dieldrin were higher when exposure was based on two blood concentrations, as opposed to just one. ORs for HCB and beta-HCH were all below 1.65, without linear trends.
Dieldrin	2.6	(1.0–6.7)		>36.0 ng/g lipid vs <6.9		
	3.8	(1.5–9.4)				
	4.6	(1.8–11.5)				

(*continued*)

TABLE 7
(*continued*)

Author, year Place Chemical	Odds ratio*	(95% CI)	Cases/controls Source¶	Highest vs lowest exposure category cutpoint‡	Year(s) collected sample	Comments
Hoyer, 2001			161/318		1976–1978	The OR presented is the risk of dying. ORs for ER– tumors were lower (highest quartile OR = 1.8, 0.3–5.5).HCB ORs were all below 1.1.
Denmark			Random population			
Dieldrin (ER+)	3.4	(1.3–8.7)		>57.1 ng/ml lipid vs <12.0		
	2.6	(1.0–6.3)				
	2.2	(0.9–5.4)				
Case-case studies of breast cancer aggressiveness, serum						
Demers, 2000			315		1994–1997	The ORs shown are for tumor size. ORs for lymph-node involvement increased linearly for each compound, and were significantly elevated for the highest tertile of oxychlordane.
Quebec, Canada						
beta-HCH	0.65	(0.34–1.25)		>18.9 ng/g plasma lipid vs <12.7		
	2.25	(1.12–4.51)				
Oxychlordane	0.99	(0.52–1.89)		>13.7 ng/g plasma lipid vs <10.0		
	1.67	(0.81–3.44)				
trans-Nonachlor	1.52	(0.80–2.89)		>17.9 ng/g plasma lipid vs <12.6		
	2.27	(1.11–4.65)				

NR indicates information not reported; CCC, Cancer Causes and Control; JCE, Journal of Clinical Epidemiology; BMI, body mass index; OR, odds ratio; 95% CI, 95% confidence interval DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.

* OR for increasing exposure categories (except reference), adjusted for potential confounding factors. All analyses age-adjusted. When a study examined more compounds than could reasonably be displayed, ORs and 95% CIs were only shown for the compounds which showed the most substantial elevation or linear dose-response trend.

† picomolar of estradiol equivalent (Eeq)/g of lipid.

‡ all units are presented in lipid-adjusted ng/g, except ng/ml and (Eeq)/g.

§ TEXB: total effective xenoestrogen burden.

‖ For this study only median concentrations were reported for each category.

¶ Source is population-based unless otherwise specified.

TABLE 8
Pesticide Exposure Assessed by Geographic Location, Job History, and Self-report, and Breast Cancer

Author, Year Place	Exposure	Comparison	Confounders considered?	Comment
Residence Location				
Aschengrau, 1996 Cape Cod, MA	Living near cranberry bogs	261 cases diagnosed 1983–1986/1371 controls	Extensive	OR, with 15 years latency = 1.3 (0.9 – 2.0)
Cocco, 2000 US	US EPA human monitoring data for average adipose DDE level by state and race for 22 states	State-level mortality 1975–1994	Average per capita income, percent state population living in a metropolitan area, population density, pregnancy rate	DDE and mortality were inversely correlated.
Janssens, 2001 Belgium	Area in crop cultivation and pesticide use	Municipal-level mortality 1985–1994	Population density, degree of urbanization, industrial activity, presence of an incinerator	Potato-growing associated with higher risk.
Brody, 2004 Cape Cod, MA	Exposure in 1948–1995 to wide-area pesticide application on Cape Cod. Individual-level relative exposure assessed by GIS using residential history and historical records reconstruction.	1165 cases diagnosed 1988–1995/1006 controls	Extensive	No consistent pattern was seen across types of use. Statistically unstable, slightly elevated risk for exposure from persistent pesticides on cranberry bogs, tree pests. OR = 1.8 (0.7–4.5) for highest compared to lowest exposure to persistent pesticides on cranberry bogs.
O'Leary, 2004 Long Island, NY	Living on/near agricultural land, within 1 mile of a hazardous waste site where pesticides were disposed, or at a residence served by wells with detectable pesticides	105 cases diagnosed in 1980–1992 /210 controls who NY residents in 1980 and resided at the same address $\geq$ 18 years	Extensive	Living on previously agricultural land OR = 1.5 (0.8–2.9) (20 cases). Women 26+ at first birth who lived on previously agricultural land OR = 6.4 (2.2–18.2) (14 cases)]. No association with water district; unstable association with residence near a pesticide waste site.
Reynolds, 2004 California	Residential history and California Pesticide Use Reporting data for 1993–1995 assessed using GIS.	1552 cases from the California Teachers Study cohort	Extensive	No association for individual or grouped pesticides. Pesticide reporting data are for recent use, and do not correspond to field dimensions. Future refinements may be informative.
Reynolds, 2005 California	Address at diagnosis and average pesticide use per square mile 1990–1997 from California regulatory records	176,302 cases diagnosed 1988–1997 reported to CA Cancer Registry	Ecologic race/ethnicity, SES, urbanicity.	No significant associations with individual pesticide or mixtures in ecologic analysis.
Occupation, Farming				
Cocco, 1998 USA	Job exposure matrix	1986 US deaths, men aged 25–74 years	Indicators of SES	No elevated risk.
Duell, 2000 North Carolina	Self-reported pesticide use and related behavior	862 cases involved in farming/790 controls	Extensive	Overall, farm women do not have higher risk. Women who reported presence in a field during or shortly after pesticide application were at similar risk to women who had never farmed, but risk was elevated when the referent group was farming women who were not exposed; OR = 1.8 (1.1–2.8). Women who reported they did not use exposure protection while applying pesticides had a higher risk when compared to nonpesticide-appliers; OR = 2.0 (1.0 – 4.3).

(*continued*)

TABLE 8
(*continued*)

Author, year Place	Exposure	Comparison	Confounders considered?	Comment
Dolapsakis, 2001 Crete	Organophosphate and ogranocarbamate pesticides used in greenhouses	552 participants in mammographic screening who had extensive work in greenhouses vs 540 with non-agricultural occupation	No	No significant differences in fibrocystic changes, lipoma, malignancy. Significant differences were found for: ductal hyperplasia without atypia OR = 1.87 (1.1–3.13), fibrocystic and ductal hyperplasia OR = 1.85 (1.3–2.6), fibroadenoma OR = 4.86 (1.4–16.7), inflammatory mastitis 2.21 (1.2–4.0), gross cystic disease 1.44 (1.1–2.0). Among exposed women, the rate of malignancy was significantly higher in 40–49-year-old women than older women.
Engel, 2005 UA	Self-reported and husband-reported pesticide use, distance from fields	30,454 wives of men in the Agricultural Health Study (309 cases)	Extensive	Living closest to crops OR = 1.4 (0.9–2.0). Husband's use of all organochlorines OR = 1.3 (0.9–2.0).Husband's use of 2,4,5-TP OR = 2.0 (1.2–3.2). Some evidence of elevated risk for husband's use of dieldrin, captan, 2,4,5-TP. Wives' use of pesticides was not associated with higher risk, but wives who were pesticide applicators were excluded. Additional follow-up will be informative. Validity of self-reports in this study has been investigated and supported.
Mills, 2005 California	Job history combined with California pesticide reporting database	128 cases, 640 controls who were members of farmworker union	County-level fertility, poverty	No clear pattern of statistically significant associations. For women $\leq$ 54 at diagnosis with highest chemical exposure, OR 1.44 (0.55–3.75).
Drinking water				
Kettles, 1997 **Hopenhayn-Rich, 2002** Kentucky	Triazine herbicides, based on well measurements and agricultural use	Incidence in 120 counties	% African-American, % with B.A., median family income, rate of first births to older women	Inconsistent findings do not show higher risk overall. Lack of control for extent of urbanization and residential mobility are problematic.
Other approaches				
McElroy, 2004 Wisconsin	Organochlorine pesticides, PCB, PBDE from self-reported sport-caught fish consumption	1481 cases/1301 controls	Extensive	No elevated risk, overall, but for premenopausal women who ate Great Lakes sport-caught fish: RR = 1.7 (1.16–2.50).

OR indicates odds ratio; 95% confidence interval (CI) follows the OR in parentheses; RR, risk ratio; SES, socioeconomic status.
Only the most recent report from a study is included unless an earlier report provides information that is not superceded in the later report. Adjusted relative risk is shown if it was reported. All studies controlled for age, gender.

but California began detailed recording of pesticide use only recently (1990), so effects with long latency could not be assessed. An ecologic study of cases reported to the California Cancer Registry found no associations[60] and a case-control study of agricultural workers did not find consistent associations, although there was (nonsignificantly) higher risk among younger women with the highest chemical exposures.[73] Currently, use of geographic location to evaluate health risks requires inferences from land use, ecologic-level assessment for large geographic areas, or a great deal of interpolation across time and geography to make use of limited environmental monitoring data (eg, air monitoring stations). These methods could be greatly enhanced by systematic development of national public health and environmental tracking data and modeling techniques.

Given the history of questionnaire-based exposure assessment for diet, tobacco use, physical activity, pharmaceutical hormone use, childbearing, lactation, menstrual history, postmenopausal obesity and weight gain, family history of breast cancer, and other possible breast cancer risk factors, surprisingly little effort has been made to develop these methods for environmental pollutants. The Agricultural Health Study is an important exception, with extensive methods development research to ensure the validity of self-reported pesticide use in this study. The results provide some evidence of higher risk for farm wives living closest to crops (OR = 1.4; 95% CI, 0.9–2.0) and for wives whose husbands reported use of organochlorines (OR = 1.3; 95% CI, 0.9–2.0) or 2,4,5-TP (OR = 2.0; 95% CI, 1.2–3.2).[73] Additional follow-up in this cohort will likely be 1 of the best sources of information on effects of current-use pesticides.

In the Carolina Breast Cancer Study, a population-based case control study, Duell et al.[75] found that farm women did not have higher risk overall. Women who reported their presence in a field during or shortly after pesticide application were at higher risk compared with farming women who were not exposed (OR = 1.8; 95% CI, 1.1–2.8), but their risk was similar to women who had never farmed. Women who reported they did not use exposure protection when applying pesticides had a higher risk when compared with women who said they did not apply pesticides (OR = 2.0; 95% CI, 1.0–4.3), but the study may have been susceptible to recall bias. In a study of women who went for mammograms in Crete,[76] those who worked with organophosphate and organocarbamate pesticides in greenhouses were at significantly higher risk for a variety of nonmalignant breast conditions. Although these conditions are not known to be breast cancer precursors, studies, such as this one, that could identify relevant, environmentally sensitive breast changes would be an important contribution. Among exposed women the rate of malignancy was significantly higher in women ages 40 to 49 years than older women.

In evaluating the sum of literature regarding organochlorine pesticides, an inconsistent and mostly negative picture to date, it is important to remember that widespread exposure of girls and women began in the late 1940s, so women with early-life organochlorine exposure are now in their 50s. Therefore, following this birth-cohort over the next 20 years with methods that attempt to capture developmental exposures is important.

Polycyclic Aromatic Hydrocarbons, Air Pollution, Vehicular Exhaust

PAHs are products of combustion. PAH mixtures and some individual PAH chemicals, such as benzo(a)pyrene, are mammary carcinogens in laboratory animals.[1] The IARC has evaluated soot and other PAH mixtures as known human carcinogens, based primarily on lung and skin cancers, and has identified individual PAHs as probable human carcinogens. Major sources of exposure for general populations are smoking, air pollution, auto exhaust, diesel, and diet.[77] Dietary sources include smoked and grilled foods and foods such as grain that are contaminated by ambient air pollution. Air pollution and vehicular exhaust also contain numerous other chemicals, including some identified as mammary carcinogens or as endocrine disrupting compounds that may affect breast cancer risk.

We identified 3 population-based, 3 hospital-based, and 1 job-registry-based case-control studies of the association between breast cancer risk and environmental exposure to PAHs, including studies that measured air pollution or vehicular exhaust (Table 9). The studies were conducted in Denmark, New York, Poland, and Texas, representing a limited geographic range for air pollution exposures that vary geographically. Other occupational studies that reported on potentially exposed jobs were identified, but we restricted our review to studies that were able to control for at least some breast cancer risk factors. Recent reports from case-control studies consider interactions of PAH exposure with susceptibility due to genetic polymorphisms that affect DNA repair.

The Long Island breast cancer study is a large population-based study of an association between PAHs and breast cancer. Exposure assessment relied on a measure of DNA damage in blood drawn near the time of diagnosis (or reference date). The OR for detectable versus nondetectable adducts was 1.32

TABLE 9
Epidemiologic Studies of Polycyclic Aromatic Hydrocarbons (PAHs), Air Pollution, Vehicular Exhaust, and Breast Cancer Incidence

Author, year Place Subgroup/subanalysis	Exposure measure	Cases/Controls Source	Confounders considered?	Adjusted OR (95% CI)	Comment
Geographic location					
Lewis-Michl, 1996	20-year GIS model of air pollution from	793/966	Yes		No effects for premenopausal women. Risk increased
Long Island, NY	industrial and traffic sources (ever vs never)	Population-based			with exposure from higher number of chemical
Postmenopausal Nassau County:					facilities.
Chemical facility				1.61 (1.06–2.43)	
High density traffic				1.29 (0.77–2.15)	
Suffolk County					
Chemical facility				1.58 (.71–3.51)	
High density traffic				0.89 (.40–1.99)	
Bonner, 2005	Total suspended particulates modeled from air	1166/2105	Yes		*P* trend was nonsignificant unless noted below
Erie, Niagara Co., NY	monitoring since 1960 (>140 vs <84 $\mu g/m^3$	Population-based			
Postmenopausal	TSP)				
Birth address		357/521		2.42 (0.97–6.09)	*P* trend = .01
Menarche address		469/757		1.45 (0.74–2.87)	
First birth address		435/782		1.33 (0.87–2.06)	
Premenopausal					
Birth address		164/283		1.78 (0.62–5.10)	
Menarche address		204/386		0.66 (0.38–1.16)	
First birth address		181/371		0.52 (0.22–1.20)	*P* trend = .04
Occupation					
Petralia, 1999	Job with PAH exposure (ever vs never)	392/371	Yes		Odds ratios for women exposed exclusively to PAH
Erie, Niagara Co., NY		Population-based			are inconsistent, based on very small numbers.
Premenopausal incident breast cancer					Odds ratios are higher for jobs with benzene
Total				1.82 (1.02–3.16)	exposure.
ER positive				2.27 (1.14–4.54)	
ER negative				1.12 (0.47–2.64)	
Hansen, 2000	Job exposed to gasoline and vehicular exhaust	230/12,880	Yes (socioeconomic		
Denmark	(> 3 months in exposed job vs not)	Pension fund registry	status only)		
Male breast cancer deaths					
No lag time					
First exposure < 40 y				2.2 (1.4–3.6)	
First exposure 40–66 y				3.7 (1.7–7.9)	
10 years lag time				1.7 (0.9–3.4)	
First exposure < 40 y				2.5 (1.3–4.5)	
First exposure 40–66 y				5.4 (2.4–11.9)	
				1.2 (0.4–3.3)	
Pah-DNA adducts					
Li, 1996	PAH-DNA adducts, including BP-like adducts,	87/29	No		Total adduct levels were higher in cases than controls
Texas	in breast tissue (adjacent nontumor tissue	Hospital-based: breast			($P < .01$). BP-like adducts were observed in 41% of
	in cases)	cancer vs reduction			cases and no controls. Detection of BP-like adduct
		mammoplasty patients			was unrelated to smoking status. Smoking-related
					adduct detected in smoker who quit 18 years ago.

(*continued*)

TABLE 9
(*continued*)

Author, year Place Subgroup/subanalysis	Exposure measure	Cases/Controls Source	Confounders considered?	Adjusted OR (95% CI)	Comment
Rundle 2000 (*Carcinogenesis*) New York, NY Tumor vs control tissue Non-tumor vs control tissue	PAH DNA adducts in breast tissue(continuous; high vs low)	100/105 Hospital-based: breast cancer vs benign breast disease patients	Yes	 2.56 (1.05–6.24) 1.97 (0.94–4.17)	27% of cases and 13% of controls had "high" adduct levels defined as above the control mean plus one standard deviation. For tumor tissue compared with controls, multivariate OR = 4.43 (1.09–18.01) for each increasing optical density unit.
Rundle, 2000(CEBP) New York	PAH DNA adducts in tumor, nontumor, and benign breast tissue	95/87 Hospital-based breast cancer vs benign breast disease patients	Yes		Null variant of the xenobiotic detoxifying gene *GSTM1* was associated with adduct levels in cases, but not controls. A significant interaction was observed In linear regression, controlled for breast cancer risk factors and PAH exposure, of case-control status and *GSTM1* genotype on adduct levels. Results suggest *GSTM1* plays a role in preventing accumulation of environmental damage in breast tissue.
Motykiewicz, 2001 Poland	PAH DNA adducts in breast tissue	48/30 Hospital-based breast cancer vs benign breast disease patients	No		Higher adducts observed among benign breast disease patients ($P \leq .001$). No significant differences between smokers and non-smokers. No significant effects of genetic polymorphisms. No significant correlation between adduct levels and age; higher levels associated with higher body weight (P –.03).
Gammon, 2002 Long Island, NY	PAH-DNA adducts in blood (>21.9357 per 10^8 nucleotides in quantiles vs nondetect)	576/427 Population-based	Yes	By quantile 1.45 (0.97–2.17) 1.48 (0.99–2.21) 1.01 (0.67–1.52) 1.49 (1.00–2.21)	Detectable vs non-detectable PAH DNA adducts OR = 1.32 (1.00–1.74). OR higher for premenopausal women [1.58 (0.94–2.66)] than postmenopausal [1.19 (0.82–1.72)] and for women under age 65 [1.48 (1.05–2.09)] and elevated for ER+PR+ and ER–PR- but not receptor discordant disease.
Rundle, 2002 New York	PAH-DNA adducts in tumor, non-tumor, and benign breast tissue	104/104 Hospital-based breast cancer vs benign breast disease patients	Yes		Tumor vs benign tissue OR = 4.43 (1.09–18.01) for each increasing optical density unit Non-tumor vs benign tissue OR = 1.97 (0.94–4.17).
Tang, 2002 New York	PAH-DNA adducts in tumor, nontumor, and benign breast tissue	76/79 Hospital-based breast cancer vs benign breast disease patients	Yes		*XPD* alleles related to DNA repair were associated with adduct levels in tumor but not non-tumor or benign tissue. Results do not indicate an association of *XPD* polymorphisms with breast cancer, but the association in tumor tissue suggests a possible role in progression.
Tang, 2003 New York	PAH-DNA adducts in tumor, non-tumor, and benign breast tissue	87/94 Hospital-based breast cancer vs benign breast disease patients	Yes		Results do not support an effect of *SULT1A1* detoxification enzyme polymorphism on PAH-DNA adduct levels

(*continued*)

TABLE 9
(*continued*)

Author, year Place Subgroup/Subanalysis	Exposure Measure	Cases/Controls Source	Confounders considered?	Adjusted OR (95% CI)	Comment
Terry, 2004 Long Island, NY	PAH-DNA adducts in blood	1053/1102 Population-based	Yes		*XPD* is a gene involved in nucleotide excision repair. Gln allele is associated with suboptimal repair. Joint effect of Gln/Gln genotype and adducts > median OR 1.9; 95% CI 1.15–3.15 versus Lys/Lys genotype and nondetectable adducts. Frequency of Glyn allele in controls was 36%.
Shen, 2005 Long Island, NY Never smokers with 399Gln	PAH-DNA adducts in blood	1067/1110 Population-based	Yes	1.92 (1.21–3.07)	Statistically nonsignificant additive interaction between the *XRCC1* 399Gln allele, which plays a role in DNA repair, and PAH-DNA adducts, only among never smokers. No evidence of interaction for codon 194.

BP indicates benzo(a)pyrene; ER, estrogen receptor; GSTM1, glutathione S-transferase M1; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; TSP, total suspended particulates.
Search terms: breast cancer and PAH, polycyclic aromatic hydrocarbon, combustion products, vehicle exhaust, exhaust, traffic, gasoline, benzene, diesel; not tobacco, smoking.

(95% CI, 1.00–1.74).[78] Women with the highest compared with lowest PAH-DNA adducts had an approximately 50% higher breast cancer risk, taking into account an extensive list of breast cancer risk factors. The results did not show a dose-response relation.[79] However, dose may not be well characterized in this study, despite the use of biological measures, because measurements taken after diagnosis may not be representative of the etiologic period, and they do not consider the effects of DNA repair mechanisms. The relative contributions of environmental sources—active and passive smoking, diet, and air pollution—to adduct formation in this study population are unclear.[80,81]

Analysis of possible interactions between PAH exposure, measured by DNA adduct formation, and genetic polymorphisms associated with DNA repair is rapidly evolving. In the Long Island Study, Shen et al.[81] reported a statistically nonsignificant additive interaction between the *XRCC1* 399Gln allele and PAH-DNA adducts, only among never smokers (OR = 1.92; 95% CI, 1.21–3.07 with exposure and mutant genotype), and no evidence of interaction for codon 194. In the same population, Terry et al.[78] reported a joint effect of *XPD* Gln/Gln genotype and adduct levels above the median (OR = 1.9; 95% CI, 1.15–3.15) versus Lys/Lys genotype and adducts below the median. The frequency of Glyn allele in controls was 36%. Tang et al.,[82] in a much smaller study, found *XPD* alleles were associated with adduct levels in tumor but not nontumor or benign tissue, suggesting a possible role in tumor progression. No effect was observed for the *SULT1A1* detoxification enzyme polymorphisms.[83] In the same study, Rundle et al.[84] found the null variant of the detoxifying gene *GSTM1* was associated with adduct levels in cases, but not controls.[85] Results suggest that the *GSTM1* polymorphism plays a role in preventing accumulation of environmental damage in breast tissue. Although these results suggest that molecular epidemiology may reveal the mechanisms for an association between environmental PAH exposure and breast cancer, it will be important to see whether the findings are repeated and extended in other studies.

Two studies relevant to PAHs assessed exposure from residential location together with geographic models of air pollution. Bonner et al.,[86] in a study in Erie and Niagara counties in New York, reported a statistically significant trend (*P*-trend <.05) for higher breast cancer risk among premenopausal and postmenopausal women whose birth address was near a monitoring location with higher levels of total suspended particulates (TSP) measured since the 1960s. Among postmenopausal women, ORs were found to

be elevated but statistically unstable for higher TSP at birth, menarche, and first full-term pregnancy. The lack of an association at menarche and first full-term pregnancy for premenopausal women could be due to lower TSP levels in recent years, shorter lag time, or other factors. Using indicators of industrial density (chemical, metal fabricating, and other specific types of industry) and traffic density over a 20-year period, Lewis-Michl et al.[87] reported higher risk associated with living in areas with air pollution from industrial facilities, with the OR excluding 1 for Nassau County (OR = 1.61; 95% CI, 1.06–2.43), but not Suffolk County on Long Island, NY. Results for living near high-density traffic were inconsistent.

The 2 assessments of occupational exposure to gasoline and vehicular exhaust reported elevated risk of female[88] and male[89] breast cancer. Men who worked for more than 3 months in an exposed job were particularly at risk if their first exposure was before 40 years of age (OR = 3.7; 95% CI, 1.7–7.9 with no lag time; OR = 5.4; 95% CI, 2.4–11.9 with 10 years lag time).

Small hospital-based studies of PAH-DNA adducts in breast tissue found an association between PAH and breast cancer risk in U.S. women,[90,91] but in Poland, Motykiewicz et al.[92] found higher adduct levels in benign breast disease patients than in women with breast cancer. The limitation in studies of this size is illustrated by results in 1 of the studies showing no statistically significant association between case status and family history of breast cancer (OR = 0.87; 95% CI, 0.40–1.89 for cases vs benign breast disease controls; OR = 1.35; 95% CI, 0.68–2.71 for cases vs healthy controls).[84] We excluded studies from review if they relied on reduction mammoplasty controls, because these controls do not arise from the same referral networks as the cases.

Drinking Water Disinfection Byproducts and Other Drinking Water Characteristics

Drinking water disinfection byproducts (DBP) have been the subject of numerous cancer assessments, including a small number of studies that reported on breast cancer[93] (Table 10). The focus of epidemiologic studies of disinfection byproducts has been on bladder, colon, and rectal cancer, but evidence that MX, a major mutagenic constituent of DBP, causes mammary tumors[93] suggests breast cancers should be investigated as well.

Studies of drinking water and breast cancer are limited geographically to China and a few states within the U.S. With the exception of Aschengrau et al.,[22] the study designs suffer from exposure assessment in broad categories based on drinking water supply at diagnosis or death and are poorly controlled for confounding. A meta-analysis of case-control studies yields a relative risk (RR) of 1.18 (95% CI, 0.90-1.54) associated with chlorinated drinking water; the power to detect a RR of 1.20 at $P < .05$ was 0.27.[95] Only 4 of 12 studies in the meta-analysis reported on breast cancer. The availability of water quality records dating to the passage of the Safe Drinking Water Act in 1974 may provide underutilized opportunities to investigate a variety of environmental pollutants and breast cancer at varying geographic scales. For example, the Cape Cod Breast Cancer and Environment Study developed GIS-based drinking water assessment tools.[96] Studies showing higher risk associated with drinking water contaminated by perchloroethylene are reviewed below.

Organic Solvents and Other Occupational Exposures

A number of organic solvents, including common chlorinated solvents, such as methylene chloride, have been identified as mammary gland carcinogens.[1] Exposure is common in the workplace and at lower levels from air, drinking water, and consumer products. Detection of organic solvents in breast milk confirms their availability to breast tissue. Labreche and Goldberg[97] hypothesize that organic solvents or their metabolites initiate or promote breast carcinogenesis through genotoxic or related mechanisms.

In the only population-based study we identified of an organic solvent and breast cancer, Aschengrau et al.[22] reported higher risks in a case-control study of women who were accidentally exposed to perchloroethylene leaching from improperly prepared drinking water distribution pipes, although the increase in risk was not monotonic (adjusted OR = 1.6; 95% CI, 1.1–2.4 for exposure >75th percentile). Some misclassification within the exposed group is likely because the assessment is based on a model of the water distribution system; however, participants classified as unexposed were unlikely to be exposed from other water sources, a strength in this study that is uncommon in studies of environmental pollutants. Possible confounders were extensively evaluated.

Because to our knowledge there have been no other studies of organic solvents and breast cancer in general populations, we reviewed a hypothesis-generating ecologic study of Toxics Release Inventory data and breast cancer in Texas counties as an example of methods that may identify directions for future research. The study found significantly higher incidence associated with 10 of 12 pollutants.[23] In multiple regression models, styrene releases were significantly associated with county-level breast cancer rates for women and men, women, and women

TABLE 10
Disinfection Byproducts, Other Drinking Water Characteristics, and Breast Cancer Incidence and Mortality

Author, year Place Breast cancer outcome	Exposure	Exposure measure	Study population	Confounders considered?	Relative risk (95% CI)*	Comment
Individual level						
Aschengrau, 2003 Cape Cod, MA Incidence	Perchloroethylene from improperly prepared pipes	Residence location and model of drinking water distribution system; self-reported bathing, bottled water, and filter use	672 cases, 616 controls from affected region	Extensive	> 75th %ile OR 1.6 (1.1–2.4) > 90th %ile OR 1.3 (0.7–2.6)	Unexposed group is likely not exposed at home. Misclassification among the exposed is likely, due to limitations of the water distribution model and limited information about personal behaviors (volume of tap water used at home).
Young, 1981 Wisconsin Mortality 1972–1977	Trihalomethanes	Death address categorized by high, medium, low chlorination 20 years prior	8029 cases, noncancer controls	Urbanicity, marital status, occupation	High vs no chlorine OR 1.36 (0.84–1.87)	No information on length of residence at the assessed address.
Gottlieb, 1982 (AJE) Louisiana Mortality	Organic pollutants, chlorination	Death, birth addresses categorized by surface vs groundwater, chlorinated vs non-chlorinated	974 cases, noncancer controls	Race, death year, county industrialization	Surface vs groundwater at death: OR 1.21 (1.00–1.46) (chi-square $p < .05$); lifetime water source: OR 1.30 (1.00–1.69) (chi-square $p < .05$). Chlorinated vs nonchlorinated: OR 1.51 (1.16–1.95) (chi-square $p < 0.01$)	
Gottlieb, 1982 (EHP) Louisiana Mortality	Chlorination	Death address categorized by high, low chlorination vs non-chlorinated	862 cases, 847 noncancer controls	Race, year, parish of death	High chlorine OR 1.58 (1.09–2.29) Low chlorine OR 1.61 (1.13–2.30) No effect in urban parishes.	Protective rural lifestyle may be associated with nonchlorinated (groundwater) supplies.
Zierler 1986 Massachusetts Mortality 1969–1983	Chlorination	Death address categorized by chlorination vs chloramination	8018 cases	Population density, surface vs groundwater, % below poverty	OR .89 (0.85–0.93) (all controls) OR 0.97 (0.89–1.05) (lymphoma controls)	Inadequate control for socioeconomic status. Other drinking water contaminants may affect cardiovascular deaths among controls.
Ecologic						
Yang, 2000 Taiwan, China Mortality	Calcium, magnesium	1990 annual mean	252 municipalities	Fertility rate, urbanicity	Highest vs lowest tertile calcium RR 0.87 (0.81–0.93); magnesium RR 0.85 (0.79–0.90)	Authors characterize population and exposure parameters as stable over many years.

(*continued*)

TABLE 10
(*continued*)

Author, year Place Breast cancer outcome	Exposure	Exposure measure	Study population	Confounders considered?	Relative risk (95% CI)*	Comment
Marcus, 1998 North Carolina Incidence	Trihalomethanes	1993–1994 average of quarterly levels in municipal supplies	71 water districts	Income, education, urbanicity, race	Highest vs lowest RR 1.1 (0.9–1.2)	When restricted to supplies where 75% of the population is in the same house or county as in 1985: whites 1.1(0.9–1.3), blacks 1.2 (0.8–1.8)
Kettles, 1997 Kentucky Incidence	Triazine herbicide	Address at diagnosis and herbicide measured in nonrandom samples of well water, tap water; acres of corn; pesticide applicator survey; index of these measures	120 counties	Race, education, income, rate of first births to older women	Summary index: high vs low 1991–1992 adjusted OR = 1.07 (1.01–1.14); 1993–1994 1.20 (1.13–1.28)	Urbanicity not controlled. No information on length of residence at the assessed address.
Page, 1976 Louisiana Mortality	Multiple contaminants	% of population drinking water from the Mississippi River and tributaries		Urbanicity, income, occupation		
Meta-analysis						
Morris, 1992 US	Chlorination, chlorination by-products	Various: residential location and surface vs groundwater; chlorination level; measured by-products	4 studies: Young, Gottlieb (AJE), Zierler, Wilkins	(See individual studies)	Relative risk 1.18 (0.90, 1.54)	Only 4 of 12 studies report breast cancer risk. Power to detect specified relative risk at alpha = .05 1.20 1.40 1.60 .27 .69 .93

95% CI indicates 95% confidence interval; OR, odds ratio; AJE, American Journal of Epidemiology, EHP, Environmental Health Perspectives; RR, relative risk.

Only the most recent report from a cohort is included unless an earlier report provides information that is not superceded in the later report. All studies werer controlled for age, gender.

* Adjusted relative risk is shown if it was reported.

age older than 50 years, explaining 9% to 14% of variance. Analyses were controlled for age, race, and Hispanic ethnicity, but it would be useful to know whether variation in TRI exposures among Texas counties is strongly correlated with income, education, and reproductive patterns. Styrene is used in the synthetic rubber industry, plastics manufacturing (including production of polystyrene food packaging), and is in resins, coatings, paints, tobacco smoke, food, building materials, and consumer products. It showed increased mammary tumors in 1 study but not in several others. Texas ranks first among states in TRI-reported styrene releases. Cantor et al.[97] reported elevated breast cancer mortality associated with occupational exposure to styrene based on death certificate data.

Occupational studies

The remaining studies of breast cancer and organic solvents investigate workplace exposures, although the occupational literature also remains woefully inadequate to evaluate the association between organic solvents and breast cancer. Historically, fewer women than men have been employed long-term in industrial jobs characterized by relatively well-defined chemical exposures, and occupational studies have focused on men, thus providing little information regarding breast cancer risks. The *Environmental Health Perspectives* 1996 monograph[99] from a conference on benzene, which is a mammary carcinogen in animals, contained no reference that we could find to breast cancer in 9 articles describing several major epidemiologic studies, signaling a major gap.

Occupational studies since 1995 of breast cancer and organic solvents and miscellaneous chemical exposures are summarized in Table 11. In 1 of what we consider to be the best-designed studies, Hansen[100] found an elevated risk of breast cancer diagnosis in a population of young women (age <55 years) for all jobs with extensive exposure to solvents, and more elevated risk was associated with longer duration of employment and longer lag times, as would be expected for a causal relation. Risk was approximately doubled for women with more than 10 years in an exposed job and 15 years lag time (OR = 1.97; 95% CI, 1.39–2.79). Band et al.[101], in a registry-based case control study of Canadian women, found elevated incidence among pre- and postmenopausal women in the food industry (OR = 3.86; 95% CI, 1.06–14.1) and dry cleaning (OR = 5.25; 95% CI, 1.41–19.5). Perchloroethylene is a common dry cleaning solvent, so elevated risk among these workers is consistent with the Aschengrau et al.[22] drinking water study. Lamba et al.[102] found slightly higher mortality among black (OR = 1.15; 95% CI, 0.98–1.30) and white (OR = 1.10; 95% CI, 1.03–1.17) women hairdressers in the U.S., and Pollan and Gustavsson[103] found higher risk among Swedish women who were hairdressers in both 1960 and 1970 (RR = 1.27; 95% CI, 1.11–1.47). Gardner et al.[104] found elevated incidence associated with potential exposure to solvents in leather and fur processing (OR = 3.25; 95% CI, 1.11–9.53) and to solvents and dioxin in glass manufacturing, in which risk was found to be more elevated among premenopausal women (OR = 2.70; 95% CI, 1.20–6.05). Blair et al.[105] found elevated risk among women who worked with solvents in aircraft maintenance (RR = 1.6; 95% CI, 0.9–2.8), and risk was higher for jobs in which workers were exposed to freon, solder flux, isopropyl alcohol, Trichloroethane, toluene, methyl ethyl ketone, and methylene chloride. Many of the specific solvents were correlated with each other, reducing ability to attribute risk to particular compounds. In a retrospective cohort study, Rennix et al.[106] found higher risk among U.S. Army enlisted women in jobs with likely medium or high solvent exposure (IRR = 1.48; 95% CI, 1.01–2.07). Chang et al.[107–109] reported higher incidence in a large cohort of electronics factory workers in Taiwan. We excluded these reports from Table 11, however, because most of the women had been employed less than 1 year and 40% had been employed for less than 1 month, but this cohort may yield more useful information in the future.

Several studies have assessed risks in nursing and health and science laboratories, which involve exposures to solvents, therapeutic agents, and the sterilant, ethylene oxide, which is a mammary gland carcinogen in animals. In reports from the last 10 years, Band et al.[101] found elevated risk for nurses in British Columbia (OR = 1.54; 95% CI, 1.05,–2.28). Gunnarsdottir and Rafnsson[110] found similarly elevated risk among Icelandic nurses (SIR = 1.52; 95% CI, 0.96–2.28 for nurses with 20 years experience) and higher risk with lag times of 30 years and longer (SIR = 3.30; 95% CI, 1.12–7.18 for 50 years of lag time). They report that nurses were similar to the national comparison population in number of children and age at first birth. We are continuing to seek studies of nurses in which findings for chemical exposures are unlikely to be confounded by established breast cancer risk factors. In a study specific to ethylene oxide, Norman et al.[111] found an approximately 2-fold increased risk (standardized morbidity ratio) in women who worked in a plant with documented exposure. In a previous review, Goldberg and Labreche[112] found limited evidence of higher risk among women in the pharmaceutical industry and beautician trades and little support for increased risk in textile workers or dry cleaning.

TABLE 11
Solvents, Related Occupational Exposures, and Breast Cancer Incidence and Mortality Identified by "Breast Cancer" Search Strategy

Author, year Place	Exposure	Comparison	Confounders considered?	Relative risk (95% CI)*	Comment
Population-based case—control study					
Aschengrau, 2003 Cape Cod, MA	Perchloroethylene from improperly prepared drinking water pipes assessed from residence location and model of distribution system; self-reported bathing, bottled water, and filter use	672 cases, 616 controls from affected region	Extensive	>75th %ile OR 1.6 (1.1–2.4) >90th %ile OR 1.3 (0.7–2.6)	Unexposed group is likely not exposed via drinking water at home. Misclassification among the exposed is likely, due to limitations of the water distribution model and limited information about personal behaviors (volume of tap water used at home).
Occupational case—control studies					
Cantor, 1995 USA	Usual occupation on death certificate classified by probability and level of exposure	33509 deaths in 24 states, homemakers excluded, vs noncancer deaths	No		
Cocco, 1998 USA	Longest-held job	Men 24–74 who died of breast cancer in 1986 vs non-breast cancer deaths	Socio-economic status, BMI, tobacco, alcohol	Motor vehicles and motor vehicle equipment OR 3.1 (1.2–8.2) No pattern of elevated risk is observed for categories of exposure to pesticides, PAHs, organic solvents	Number of cases in each occupation is small; the number with "high" exposures smaller. Exposures are broadly categorized with little information about probability, intensity, or duration of exposure.
Hansen, 1999 Denmark	Job with extensive solvent use: fabricated metal products, wood and furniture industry, printing and publishing, chemical industry, textile and clothing industry	7802 women born 1934–1969 with primary breast cancer diagnosed 1970–1989 Vs living, cancer-free women employed before the date of diagnosis of the case	Socio-economic status based on job category, gravidity, age at first birth	Odds ratios elevated for all exposed job categories. Most confidence intervals exclude one. All ORs higher with lag time. Employed in an exposed job >1 year No lag time OR 1.27 (1.13–1.43); 15 years lag time OR 1.43 (1.24–1.67) Employed in an exposed job >10 year No lag time OR 1.31 (1.01–1.75); 15 years lag time OR 1.97 (1.39–2.79)	
Aschengrau, 1998 Cape Cod MA	Complete job history classified by probability of exposure to 33 estrogenic substances	261 women diagnosed 1983–1986 vs 753 population-based controls	Extensive	No elevated risk associated with exposure to one or more xenoestrogens. PCB exposure OR 3.2 (0.8–12.2) 4-octylphenol OR 2.9 (0.8–10.8)	Small numbers result in unstable estimates. Numbers were too small to consider duration of exposure.
Band, 2000 British Columbia	Usual job from complete job history	995 women diagnosed 1988–1989 vs 1020 population-based controls	Extensive	Pre and postmenopausal Laundering and dry cleaning OR 5.24 (1.41–19.5); food, beverage processing OR 3.86 (1.06–14.1) Premenopausal: Food industry OR 6.78 (1.70–27.1) 9 cases; Transportation OR 5.13 (1.31–20.1 Postmenopausal: Nurses OR 1.54 (1.05–2.28); Laundering and dry cleaning OR 4.85 (1.26–18.7)	Small numbers in each occupation result in unstable estimates. Multiple comparisons increase risk of associations occurring by chance.

(*continued*)

TABLE 11
(*continued*)

Author, year Place	Exposure	Comparison	Confounders considered?	Relative risk (95% CI)*	Comment
Lamba, 2001 USA	Usual job reported on death certificate	1180 hairdressers vs noncancer deaths	No	White women MOR 1.10 (1.03–1.17) Black women MOR 1.15 (0.98–1.30)	
Gardner, 2002 Shanghai	Complete job history	1458 women diagnosed 1996–1998 vs population-based controls	Extensive	Breast cancer risk was not significantly elevated for broad employment categories: medical and public health, teacher, clerical, farmer, rubber & plastic. Elevated risk was seen for some subgroups with likely chemical exposures: Farmer > 10 years OR 2.08 (1.15–3.74) 34 cases, 20 controls. Leather and fur processor OR 3.25 (1.11–9.53) 12 cases, 5 controls. Glass manufacturing workers OR 2.08 (1.14–3.82) 30 cases, 18 controls; higher risk among premenopausal women OR 2.70 (1.20–6.05); significant dose-response. Additional elevated odds ratios were statistically unstable.	Study participants' average duration of employment was 24 years. Authors suggest possible dioxin and solvent exposure in glass manufacturing; solvent exposure in leather and fur processing.
Thompson, 2005 US	Metalworking fluids assessed by detailed industrial hygiene analysis and job history	99 cases , 626 controls nested in cohort of autoworkers employed between 1941–1985, followed to 1994	No	No overall association. Exposures to soluble metalworking fluids within 10 years of diagnosis OR 1.18 (1.02–1.35) per mg/m^3-year	Some evidence that association is limited to women diagnosed before age 51. No control for breast cancer risk factors.
Occupational cohorts					
Shannon, 1988 Toronto/Ontario	Worked in lamp factory some time during 1960–1975 in coiling and wire drawing department where methylene chloride, trichloroethylene, other compounds were used	1044 women (203 exposed) followed 1964–1982 vs to Ontario population	No	SMbR = 204 (88, 402) (8 cases); At least 5 years of coil/wire work and at least 15 years since first exposure SMbR = 300 (129–590)	
Gunnarsdottir, 1995 Iceland	Employed as a nurse	2159 women who were nurses during 1920–1979 followed 1955–1989 vs national population	No	20 years lag time SIR 1.53 (1.06–2.16) 30 years lag time SIR 1.70 (1.05–2.59) 40 years lag time SIR 1.97 (1.02–3.44) 50 years lag time SIR 3.30 (1.12–7.18) at least 20 years employment SIR 1.52 (0.96–2.28)	Nurses are similar to the national average in number of children and age at first birth. Risk is nonsignificantly elevated for shorter lag time.
Norman, 1995 New York state	Regular employees in a plant where ethylene oxide exposure was documented	342 women followed 1982–1987 vs with national rates	No	1985 SMbR 2.55 (1.31–4.98) 8 cancers 1986 SMbR 2.09 (1.10–3.95) 9 cancers 1987 SMbR 1.88 (0.99–3.58) 9 cancers	Median duration of employment about 2 years. Lag time ≤ 11 years.
Aronson, 1998 Canada	Employed > 1 year in specified occupation	Women employed 1965–1971 followed to 1991; exposed occupation vs blue collar workers	No	Metal fitters and assemblers RR 2.15 (1.12–4.15)	Multiple comparisons were assessed, increasing the likelihood of observing elevated risk by chance. Duration and intensity of exposure unknown.

(*continued*)

TABLE 11
(*continued*)

Author, year Place	Exposure	Comparison	Confounders considered?	Relative risk (95% CI)*	Comment
Blair, 1998 Utah	Worked with solvents in aircraft maintenance in 1952–1956	3138 women followed 1952–1990; Exposed vs unexposed workers	No	Mortality rate ratios Any solvent RR 1.6 (0.9–2.8) 28 cases; Freon RR 3.8 (1.7–8.8) Solder flux RR 3.7 (1.6–8.4) Isopropyl alcohol 3.7 (1.6–8.9) Trichloroethane 3.3 (1.0–11.2) Toluene RR 2.0 (0.9–4.2) Methyl ethyl ketone RR 2.1 (0.9–4.7) Methylene chloride 3.0 (1.0–8.8)	Half of cohort exposed to trichloroethylene. The fraction unexposed to solvents is not reported. Exposures to many specific solvents are correlated, reducing ability to attribute risk to a specific compound. Lower and non-significantly elevated relative risks were reported for other compounds in addition to those shown here. There was a deficit in breast cancer in the cohort compared with Utah population, suggesting that elevated risk due to confounding by a social factor would have to be exposure-specific within the workforce.
Petralia, 1998 Shanghai	Occupation at time of diagnosis or retirement scored for probability and level of exposure (none, low, medium, high).	Employed women diagnosed in 1980–1984 vs Shanghai population	No	Rubber and plastics products makers SIR = 1.8 (1.4–2.3) Benzene: high probability of exposure SIR 1.3 (1.0–1.7), high level of exposure SIR 1.3 (1.0–1.7) Pesticides: high probability of exposure SIR 1.3 (0.6–1.5), high level of exposure SIR 1.3 (0.6–2.5) Solvents: high probability × high level SIR 1.4 (1.1–1.8)	Reference population may not be comparable to exposed women workers in reproductive history and other breast cancer risk factors. Sensitive workers may leave exposed employment.
Pollan, 1999 Sweden	Occupation in 1970	Others in major job category	Geographic area, town size	Hairdresser RR1.21 (1.08–1.37) Hairdresser in both 1960 and 1970: RR 1.27 (1.11–1.47) Metal plater, coater RR 2.14 (1.21–3.77) Pharmacist RR 1.34 (1.07–1.64)	
Weiderpass, 1999 Finland	1970 occupation classified by job exposure matrix	23,683 women with breast cancers diagnosed in 1971–1995 compared with economically active women	Ecologic control for social class, mean number of children, mean age at first birth, job turnover rate	Among postmenopausal women with medium/high exposure: Aromatic hydrocarbons SIR 1.14 (1.00–1.30) Textile dust SIR 1.14 (1.06–1.23) No elevated risk: formaldehyde, other organic solvents, gasoline, metals, engine exhaust, pesticides Unstable risk estimated for premenopausal women.	Authors cite studies showing cross-sectional job classification is equivalent to full job history, but does this apply to women?

(*continued*)

TABLE 11
(*continued*)

Author, year Place	Exposure	Comparison	Confounders considered?	Relative risk (95% CI)*	Comment
Wennborg, 2001 Sweden	Work in research laboratories, excluding departments such as biochemistry and physics, with other occupational exposures	1173 women laboratory workers followed 1970–1994 vs Swedish population and 721 non-laboratory workers	No	Non-laboratory workers: SIR 0.66 (0.26–1.35) 7 cases Work with solvents: SIR 1.13 (0.66–1.81) 17 cases Work with radioisotopes (known breast carcinogen): SIR 0.95 (0.43–1.79) 8 cases	The deficit in breast cancers among non-laboratory workers suggests selection of healthier women into these workplaces. Swedish regulations may result in low exposures even in laboratories that handle chemicals. Workers were relatively young and many had short duration of employment. Failure to find elevated risk for radioisotopes, which are known breast carcinogens [SIR 0.95 (0.43–1.79) 9 cases].
Blair, 2003 St. Louis	Work in specific activities in dry cleaning	2566 white and 1483 black women who were members for at least one year before 1978 in the dry cleaning union vs US population	No	SMR 1.0 (0.8–1.3) Black women SMR 1.4 (0.90–2.0) Medium/high exposure SMR 1.2 (0.8–1.7)	
Rennix, 2005 US	Work in job with medium or high exposure to VOCs, solvents	274,596 US Army women on active duty at least one year in 1980–1996 (184 cases)	Race, diagnosis year	IRR 1.48 (1.03–2.12)	Cases limited to women diagnosed on active duty.
Ecologic epidemiology					
Coyle, 2005 Texas	Annual county TRI-reported releases of 12 toxicants	61 counties with TRI releases vs 193 without	Race, ethnicity	TRI releases were associated with higher breast cancer incidence ($P < 0.04$) for 10 of 12 toxicants. Styrene was significantly associated with county breast cancer rate for women and men (R^2 9%), women (R^2 8%), and women > 50 (R^2 14%).	Address at diagnosis does not provide information about duration of exposure. County TRI may be correlated with reproductive patterns or other breast cancer risk factors, resulting in confounding.

95% CI indicates 95% confidence interval; OR, odds ratio; BMI, body mass index; PAHs, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyls; MOR, mortality odds ratio; SMbR, standardized morbidity ratio; SIR, standardized incidence ratio; RR, relative risk; SMR, standardized mortality ratio; IRR; Ind. H *Industrial Health*; AEP *Annals of Epidemiology*; PCMR, proportionate cancer morbidity ratio; TRI, Toxics Release Inventory.

* Adjusted relative risk is shown if it was reported.

Only the most recent report from a cohort is included unless an earlier report provides information that is not superceded in the later report. All studies were controlled for age and gender.

Most occupational studies we reviewed have important methodological weaknesses. Many have follow-up periods that are short for a cancer with long latency and include women who are young for breast cancer diagnosis. Records-based studies are particularly likely to be problematic. Many rely on mortality, which is an insensitive disease indicator given substantial breast cancer survival. In addition, use of employment records or death certificates rather than more detailed lifetime job histories may misclassify women's exposure; because their length of employment in a 'usual' job may be short, and job exposure matrices have not been designed specifically to assess women's experiences, which may typically differ from men in the same job category. Studies that rely on comparisons with breast cancer incidence and mortality rates in general populations may suffer from confounding by physical activity, reproductive history, and other breast cancer risk factors that differ between blue-collar women, other employed women, and women who are not employed. Stronger studies use comparison groups that are similar to the exposed women for these variables. In addition to confounding specific to breast cancer, studies of occupational exposures may understate risk because of 'healthy worker effects' or because workers with sensitivity to the exposure leave due to acute or short-term illness (eg, skin rashes or respiratory distress), so that cancers are not observed. Studies that compare factory workers to the host community may understate the contrast if the factory is a source of regional pollution resulting in exposure to the comparison group. In studies that analyze dozens of occupations from large databases, it is difficult to link job categories to specific exposures, interpret inconsistencies across jobs with overlapping exposures, and evaluate the role of chance.

In addition, it is difficult to assess consistency in the occupational studies—for example, to answer the question of what fraction of reasonably well-designed studies that investigated a particular exposure found an association. Interpretation is further complicated because job classifications are not comparable from one study to another, and many workplace chemical exposures are correlated with each other, so the putative exposure may not be the important one.

Conclusions and Recommendations

Existing epidemiologic evidence is inadequate to evaluate possible links between breast cancer and hundreds of environmental pollutants identified as mammary gland carcinogens in animals or as hormonally active compounds, specifically estrogen mimics. Studies primarily of DDT/DDE and PCBs, recent attention to PAHs, and limited study of dioxin, organic solvents, drinking water disinfection byproducts, and various pesticides leave an enormous balance of chemicals suggested by toxicologic research that have not been investigated seriously or at all in epidemiologic studies.

Despite this large remaining gap, research in the last 5 years has strengthened the human evidence that environmental pollutants play a role in breast cancer risk.

Limitations

This review is the broadest assessment to date of evidence on a range of environmental pollutants included in breast cancer epidemiologic studies. However, our ability to draw conclusions is limited by factors that affect the identification of research for review and by weaknesses in the underlying studies.

We made efforts to inclusively identify articles, and we are confident that we have found articles indexed by "breast cancer," but we likely have missed occupational studies that report on many diseases and are not indexed by terms encompassed by the MeSH term "breast neoplasm."[113] In addition, publication bias—the greater tendency for studies showing statistically significant associations to be published—may result in the underidentification of negative results.[114] Our review is also limited by the definition of boundaries that did not include studies of environmental chemical exposures via diet or smoking. The recent State of California review of breast cancer and tobacco smoke is consistent with an association between tobacco smoke, which contains PAHs and other chemicals of interest, and breast cancer in younger women.[115] To our knowledge, studies of diet and breast cancer have not addressed food contaminants.[116]

We introduced this review with an analysis of methodologic challenges to provide background for our evaluations of individual studies. Returning to those issues, we see that challenges remain unresolved in this field.

In particular, exposure assessment methods limit interpretation, especially for negative results, because misclassification that nondifferentially affects both cases and controls is likely to bias results to the null.[21] Exposures often are poorly quantified, the range of measured exposures may be narrow (with few or no unexposed or highly exposed), and the timing of measurement may not be etiologically relevant. In addition, chemicals occur in unspecified mixtures. For example, pesticides may be identified as the exposure of interest, but they occur in combination with unidentified surfactants, synergists, and preservatives

that may be relevant to breast cancer, and there would be variation across the study population in exposure to specific active and inactive ingredients. Most important, practical exposure measures are lacking for many chemicals of interest.

Limitations in the analysis of confounders, multiple breast cancer outcomes, and susceptibility are other problem areas. Recent population-based case-control studies measure confounders extensively, but many occupational studies do not, and this limits the opportunities to take advantage of higher exposure settings. In addition, new questions are emerging concerning whether some confounders may fall along the causal pathway. For example, controlling for age at menarche may obscure effects of environmental chemicals that influence breast cancer by influencing this variable. In another problem with the specification of causal models, few studies have separated different types of breast cancers with possibly different etiologies (eg, premenopausal vs postmenopausal or ER-positive vs ER-negative disease). Similarly, genetic susceptibilities remain to be discovered. Studies that combine subdiseases with different etiologies and subpopulations with different susceptibility may obscure associations.

The studies we rely on in our assessment of the strength of evidence are those that have best measured exposures, potentially confounding variables, and susceptibility.

Strength of epidemiologic evidence

Based on a relatively small number of studies, the evidence to date generally supports an association between breast cancer and PAH exposures in conjunction with genetic polymorphisms that lead to suboptimal DNA repair. Given that exposure to PAHs is widespread and can be reduced, both further study and policies to reduce exposure should be public health priorities.

The strength of evidence also supports an association between PCBs, which are banned, and breast cancer risk in the 10% to 15% of women who carry certain genetic variants.

A few strong studies and numerous records-based occupational assessments provide evidence of an association between breast cancer and organic solvents. Because many of these compounds are identified as mammary carcinogens and exposure is common, organic solvents should be a high priority for future breast cancer study, including efforts to gain access to exposed workers for thorough investigation of breast cancer incidence rather than mortality, and controlling for confounding by physical activity and other work-related variables. Future study also must identify exposures from everyday activities, such as pumping gas, and from building materials and consumer products.

Lack of evidence for an association between organochlorine pesticides and breast cancer may be due to a true lack of association or to shared methodological weakness across a large number of studies. Because these chemicals are banned in many countries and restricted worldwide, further research is valuable primarily as a model for effects of other chemical exposures for which there is ongoing exposure. It should be a priority only when researchers have access to novel data that resolves earlier methodological problems.

The evidence regarding dioxin and breast cancer is thus far inconclusive. The only study that to our knowledge controlled for confounding[51] reported an increased breast cancer risk for younger women exposed from the Seveso accident, but other findings are mixed. Continued follow-up with the Seveso cohort is critical.

Research needs

The primary barrier to progress is a lack of adequate methods to assess relevant exposures for a disease that develops over decades and is affected by exposure in utero and perhaps early life as well as closer to diagnosis. Multiple strategies must be integrated in the breast cancer research agenda:

- Development of new methods and laboratory capacity to assess biological markers and personal environmental samples, particularly for nonpersistent contaminants. Personal environmental samples have the advantage of clearly defining exposure sources, although prospective measurements or development of models that allow estimates of earlier exposure are needed to make etiologic inferences. Methods are needed both for intensive local study and for large-scale, geographically dispersed studies, such as the Sister Study, a study of women ages 35 to 74 years whose sisters had breast cancer.[117] Studies that link biological markers with major sources of exposure are needed to translate findings into risk reduction.
- New epidemiologic investigations of previously unstudied and understudied endocrine disruptors and mammary carcinogens to which women are commonly exposed, especially chlorinated solvents, diesel exhaust, dibutyl phthalate, ethylene oxide, perfluorooctanoic acid, bisphenol A, and others identified by Rudel et al.[1]
- Identification of preclinical biological markers of disease to provide an alternative to decades-long follow-ups.

- Continued investigation of gene–environment interactions, carefully designed and targeted so that investments in genetics do not drain resources from the more immediately modifiable environmental side of the equation.
- Development of sophisticated health and environmental tracking systems that can provide better exposure assessment based on geographic location.
- Identification and ongoing study of uniquely exposed populations, such as the Seveso cohort and the Agricultural Health Study.
- Inclusion of women in occupational studies, developing adaptations for women who move in and out of small, dispersed workplaces, such as in nail salons or house cleaning.
- Expansion of research in African-American and U.S. immigrant populations, and in developing nations to extend the diversity of study populations, capitalize on research opportunities that arise from changing exposure scenarios, and address the disparities in age at diagnosis and aggressiveness of disease in African-Americans and the rapidly rising incidence among immigrants.
- Support for a portfolio of studies that cover the lifespan. Future research must pursue models of early life effects of chemicals, including dioxin and bisphenol A, for which we have evidence of prenatal effects on mammary gland development, and it must pursue late-acting effects, following the model of risk associated with hormone replacement therapy, oral contraceptives, and pregnancy in the 5 years before diagnosis.

Patterns of increasing breast cancer incidence in the U.S. over several decades and rapidly rising risk in previously low-risk populations provide evidence that risk reduction is a realistic goal, and the relatively poor prediction of individual risk suggests opportunities for discovery of additional risk factors. Currently, however, weaknesses in the epidemiologic literature argue for greater reliance on animal and mechanistic studies as a basis for national chemicals policies that reduce exposure to chemicals that may cause breast cancer.

A formal assessment of the fraction of breast cancers that may be due to environmental pollutants is premature because we lack estimates of parameters that contribute to this calculation. We lack estimates of relative risk because so many relevant chemicals have never been studied, and we have limited information regarding the prevalence in the population of relevant levels of exposure. Considering the examples of 2 exposures (PAHs and PCBs), for which we now have meaningful evidence of an association with breast cancer, we do know that the patterns of exposure and the estimates of relative risk suggest substantial public health impact. Exposure to PAHs is ubiquitous from air pollution, tobacco smoke, and cooked food,[118,119] and the observed relative risks are similar in range to the 20-fold to 2-fold increased risks typically associated with many risk factors that have received attention for breast cancer, including nulliparity, age at first full-term pregnancy, age at menarche, age at menopause, body weight, hormone replacement therapy, and physical inactivity.[4,120,121] Exposure to PCBs is high for subgroups of U.S. women, such as those eating a lot of fish,[118] and the 2-fold to 3-fold increased risk observed in susceptible women is higher than for many breast cancer risk factors. Because environmental pollutant exposures are both common and avoidable, reducing them should be a public health priority. Given that the American Cancer Society estimates more than 200,000 new breast cancer diagnoses a year in the U.S., if even a small percentage is due to preventable environmental factors, modifying these factors would spare thousands of women.

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