Review

The Undervalued Effects of Polychlorinated Biphenyl Exposure on Breast Cancer

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Abstract

The incidence of breast cancer across the world has been on the rise in recent decades. Because identified risk factors can only explain a relatively small portion of the cases, environmental exposure to organic pollutants is suspected to play a role in breast cancer etiology. Polychlorinated biphenyls (PCBs) are among the most abundant pollutants, and the impact of their exposure on breast cancer risk has been extensively studied in recent decades. However, the results of most epidemiologic studies do not support an association between PCB exposure and breast cancer risk. We hypothesized that the effects of PCBs on breast cancer might have been undervalued for reasons such as insufficient recognition of the confounding effects of several factors and lack of attention on the innate heterogeneity of PCB mixtures or breast cancer. After reviewing the evidence in the existing literature, we concluded that early life exposure, known risk factors of breast cancer, and impact of exposure to other pollutants are the main sources of confounding effects and have potentially masked the associations between PCBs and breast cancer. Because PCBs are mixtures of congeners with varied properties, and because breast cancers of different subtypes are etiologically distinct diseases, the absence of stratified subgroup analysis on individual PCBs and patients with specific biological subtypes and insufficient attention paid to the results of these subgroup analyses may result in an underestimation of the correlations between PCBs and breast cancer. In future studies, these factors must be taken into consideration when exploring the effect of PCB exposure on breast cancer risk.

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Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women in over 100 countries, with 1.7 million cases in 2012 and an estimated 2.1 million newly diagnosed cases in 2018.[1,2] Despite decreases in the use of oral contraceptives and increases in early detection by mammograms, the number of women diagnosed with the disease has continued to rise over the past 50 years. For transitioning countries in South America, Africa, and Asia, this rise have been the most rapid over the last several decades.[1] However, hereditary and genetic factors account for only 5% to 10% of the incidence,[1] which means that nonhereditary factors should explain most of the increased cases. Established factors include those related to lifestyle (smoking, alcohol drinking, obesity), menstruation (early age at menarche, later age at menopause), and reproduction (nulliparity, late age at first birth, and fewer children); however, these are insufficient to explain the continuing increase.[1,3] In the early 1940s, breast cancer incidence rates began to steadily increase in many industrialized countries.[3] During the same period, levels of pesticide and other organochlorine residues in human adipose tissue in the United States showed a parallel increase after their introduction into commerce around the time of World War II.[4] Later in the 1990s, exposure to environmental chemicals such as organochlorine compounds was suggested to play a causal role in the onset of breast cancer through estrogen-related pathways.[3]

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Polychlorinated biphenyls (PCBs), a group of 209 aromatic congeners distinguished by degree and pattern of chlorination, are among the most frequently studied organic pollutants. They were first manufactured in 1929 in the United States and were banned in most countries by the 1980s.[5,6] During this period, PCBs were heavily used in industry as transformers and electrical capacitors because of their good electrical insulating properties and high thermal stability.[5] As a result of their persistence and lipophilicity, PCBs accumulated in biological tissue and concentrated at successively higher levels of the food chain.[7] Currently, after being prohibited for more than 3 decades, PCBs are still ubiquitous in the environment and are abundant in human tissue, blood, and milk.[8]

In 2013, with sufficient evidence on the association of PCBs and melanoma, the International Agency for Research on Cancer classified PCBs as carcinogenic to humans.[6] With regard to breast cancer, although both PCBs and their metabolites were observed to be carcinogenic to breast tissue in in vivo and in vitro experiments,[9-13] conclusions drawn from epidemiologic studies were inconsistent and were considered to provide only limited evidence.[6] Since the early 1990s, of the numerous epidemiologic studies on this issue, a large proportion observed null results.[14-16] Only in a few studies or certain selected subgroups (eg, women who had never lactated, estrogen receptor [ER] positivity or negativity, individual PCB congeners like PCB 138) were direct associations reported between PCBs and breast cancer.[17,18] Some authors paid specific attention to highly controversial conclusions, attributing part of the discrepancies among studies to methodologic differences[19] and insufficient attention paid to the complexity of the chemicals and breast cancer disease.[19-21]

A report from the Interagency Breast Cancer and Environmental Research Coordinating Committee identified several gaps in knowledge regarding the relationship between chemical exposure and breast cancer, including the following: (1) the role of the chemicals as cancer enhancers or effect modifiers; (2) the effects of chemical mixtures rather than individual chemicals; (3) assessment of exposures during critical time windows of susceptibility in early life; (4) potential differential effects dependent on breast cancer subtypes; and (5) potential confounding effects of other factors against the effects of environmental toxicants on breast cancer.[20]

Here we explore these gaps in depth on the basis of the existing literature. We hypothesized that these unsolved gaps might have confounded the association between PCB exposure and breast cancer risk, and potentially caused an underestimation of the role of PCB exposure in breast cancer development. Among these gaps, we first address the confounding effects of 3 factors, including impact of early life exposure, influence of known risk factors of breast cancer, and influence of other organic pollutants. Second, we highlight the heterogeneity of PCB mixtures and breast cancer by reviewing the results of stratified subgroup analyses, emphasizing the necessity of grouping as well as the importance of addressing significant findings from subgroup analysis.

Interference of Confounding Factors

Great Influence of Early Life Exposure

In most studies, samples were collected around the time of or after breast cancer diagnosis, which is often in women's middle age. However, it has frequently been pointed out that primary PCB exposure in early life may produce stronger and long-lasting effects on mammary gland (MG) development as well as breast cancer formation.[8,22-25] Late-life sampling may possibly mask the actual associations between PCBs and breast cancer,[25] although the evidence for this is not reliable. It has also been said that the nonsignificant conclusions drawn from numerous studies were largely attributed to the late sampling time, thus adding to the influence of the exposure time window on the relationship between PCBs and breast cancer.[25] On the basis of the existing literature, we evaluated the impact of PCBs on several important time windows through a woman's life, with specific emphasis on PCB concentration alterations over time. We began by exploring whether the hypothesized higher susceptibility in early life plays a causal role in future carcinogenesis. Then, if so, we explored whether samples collected at diagnosis could reflect lifetime PCB exposure, particularly early life exposure. Finally, we investigated the factors correlated with the changes of PCB concentrations through life if late-life sampling was not able to fully represent prior PCB exposure.

Normal female MG development is the first step in understanding breast cancer formation; this process has been thoroughly described in rodents and is similar to that in humans, so a murine model is good for assessing the effect of environmental exposure on MG development. Gestation, puberty, and pregnancy are 3 phases of MG growth during which paramount developmental events occur; for the same reason, these are also considered to be critical time windows during which the MG development may most affected.[22] In humans, MG development begins with budding and branching between 6 and 20 weeks' gestation, and MGs grow at the same rate as the body until before puberty.[22,24] Exponential epithelial growth led by hormones occurs during puberty, until the epithelium is finally filled with a fat pad and forms adult-form glands. Then the MGs stay in this form, with minor changes depending on the menstrual cycle. During pregnancy, the MG will prepare itself for lactation and exhibit obvious differentiation.[22] Interference with these processes will disturb the normal structure and function of MG; for example, interfering with prenatal development during gestation could lead to altered timing of mammary development or formation of the glandular structures, leaving lasting effects on the gland.[22] In both rodent models and humans, the puberty phase, dominated by ductal development, is characterized by the formation of terminal end buds (TEBs), a teardrop-shaped duct end with a diameter of approximately 100 μm in the rat compared to about 70 μm for humans. TEBs are considered to be the most vulnerable MG structure for carcinogen exposure.[26] This unique structure leads the epithelial extension through the fat pad, leaving behind a network of branched ducts.[24] Many endocrine disrupting compounds, including PCBs, have been reported to cause delayed development and reduced differentiation of TEB, resulting in a higher number of TEBs in early adulthood and a longer period during which TEBs are present.[24] Moreover, increased number or longevity of proliferating TEBs may increase susceptibility to other carcinogens.[24] In human studies, prolonged TEB development with measurable PCB exposure in girls has been reported to possibly cause a delay in breast development in puberty, but the lower body mass index (BMI) of the same subgroups should also be mentioned because BMI could also decelerate the

development of the breasts.[27,28] During pregnancy, differentiation of terminal structures increases. Interruption of this process can lead to mortality or malnutrition of the offspring in wildlife; in humans, neonates are exposed to PCBs from their mothers' milk.[22]

The main exposures in the 3 time windows are considered to be prenatal exposure from maternal blood, postnatal exposure from breast milk, and later exposure in puberty or pregnancy from daily life.[25,29] The existing evidence does not support the notion that samples collected around the time of disease diagnosis could reflect early life exposure, but it may to some extent reflect differences caused by lactation. The main conclusions were drawn from a lifetime physiologically based pharmacokinetic model that assessed the exposure of persistent organic pollutants, including two PCB congeners, PCB 153 and 180, in the time windows of susceptibility through a given physiologic lifetime history.[25] The model showed a significant difference caused by breastfeeding in childhood, which holds until the child is 5 years old. However, these differences almost completely disappeared by 20 years of age, making it obvious that diagnosis in middle age will not be able to distinguish the difference caused by breastfeeding.[25] In addition, a significant decline in PCB concentrations has been observed in women who lactated, with differences from women who did not lactate still present at 55 years of age even though they were younger than 31 at lactation. Longer lactation duration is believed to lead to lower PCB levels, whereas pregnancy seems to have no impact on women's PCB concentrations.

Finally, consistent with the conclusions from the second questions, prenatal exposure levels, history of being breastfed, exposure during puberty, and lactation all greatly affect the body's PCB burdens and contribute to susceptibility to breast cancer in later life. In addition, body weight changes may also alter PCB concentrations. Conclusions are expected to be more reliable with all these factors taken into account, but data regarding exposure during the prenatal and puberty periods are hardly available. Still, we suggest that other factors that can be obtained from medical history or questionnaire be adjusted in analyses.

In summary, case−control studies are unable to accurately reflect PCB exposure in these women during their own critical breast developmental windows. Absence of exposure information during susceptible times is an important source of underestimation of PCBs. Longitudinal cohorts are the best way to determine early life exposure, even though the investigation process may be painfully slow and costly. If such cohorts are not possible, future studies should at least adjust for the aforementioned important factors.

Confounding Effects of Established Risk Factors of Breast Cancer

Breast cancer is a complex disease. Except for hereditary and genetic factors, a number of risk factors have been confirmed to be related breast cancer, including radiation, aging, menstruation (early age at menarche, later age at menopause), reproduction (nulliparity, late age at first birth, fewer children, no lactation), exogenous hormone intake (oral contraceptive use, hormone replacement therapy), drinking alcohol, smoking, and higher BMI or weight gain during adulthood.[1,2] These risk factors have been becoming more and more prevalent in more countries in recent years and account for a large proportion of the elevated incidence of breast cancer across the world. However, factors like breastfeeding and physical activity have been found to reduce breast cancer risk.[1] Women are exposed to these factors to varying degrees. For women exposed to strong risk factors such as oral contraceptives and hormone replacement therapy, the effect of a low daily dose of PCBs would be too slight in comparison to make a difference in the results.[30,31] People of different residences with a varied lifestyle were exposed differently in regard to these factors. For some groups of breast cancer cases, exposure to certain risk factors might have been the main cause of the disease. Therefore, information related to both risk and protective factors should be collected and assessed in each cohort because it not only helps to assess the confounding effects of these factors but also advances the awareness of breast cancer etiology. Only if the impact of all these factors can be considered may the results be more reliable. Otherwise, ambiguous features of the cases and controls caused by incomplete information in the analysis is likely to dilute the correlations between PCB exposure and breast cancer.

Some of the risk factors have been reported to affect the metabolism of PCBs and therefore cause fluctuations in human PCB levels. These PCB predictors include age, lactation history and duration, adult weight loss and gain, and BMI, as well as fish consumption and animal fat intake.[25,32-35] Age was found to be positively associated with PCB levels in quite a few studies.[33,34,36,37] This might be explained by the accumulation of long-term dietary intake and lower metabolic potency in elderly women.[33,37] The consumption of seafood and animal fat was related to higher PCB levels.[33,34] As a protective factor, having a history of lactation was related to lower PCB levels, and longer lactation had a greater impact on PCB concentrations.[25,35] People with high BMI had higher PCB levels. Changes in BMI exert statistically significant influences on PCB levels, although the directions were inconsistent. In addition, changes in concentrations of serum and adipose tissues were in the opposite direction due to lipolysis.[25,36,38,39]

As a result of the profound influences these factors have on breast cancer risk and PCB concentrations, the results of previous research might have been affected if the effects of any of these factors were not considered. However, information regarding the above-mentioned factors is rarely available in the majority of studies, thereby resulting in an underestimation of the association between PCBs and breast cancer. To examine the independent effect of PCB exposure, more complete information regarding these factors is needed in future research.

Combined Effects of Chemical Mixtures

An important limitation inherent in epidemiologic studies on the effects of environmental exposure on breast cancer is that humans are not exposed exclusively to the chemical being investigated but instead to a mixture of chemicals, some of which potentially act through common pathways and have interactions.[38,40] Of the huge number of chemicals available on the market, only a small proportion have been tested for health effects, and an even smaller percentage has been evaluated for effects on the MG.[20] Evidence is especially limited regarding the effect of mixtures of chemicals, which decreases the possibility that the influence of specific chemicals can be defined in breast cancer at the population level.

Several environmental pollutants have been found to be linked to increased breast cancer risk in epidemiologic studies, including bisphenyl A (BPA),[41] diethylstilbestrol (DES),[42,43] phthalates,[44]

DDE (a metabolite of dichloro-diphenyl-trichoroethane),[45] polybrominated diphenyl ether (PBDE),[46] and 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD). Moreover, some of them with common estrogenic properties were observed in cell-culture studies to exhibit additive, synergic, and antagonistic effects as a mixture that did not happen when chemicals were assessed singly.[47-49] However, the effects of other pollutants and the interactions between chemicals that were more indicative of environmental exposures were not reflected in the investigations of a single chemical's effect.

Chronic exposure to low-dose chemicals produces great adverse effects on human health. The effect of low-dose exposures, however, is also easy to be confounded by other factors, making it hard to evaluate the effect of single chemicals—and likely to result in an underestimation of their effects.

Future work should examine the combined effects of chemical mixtures rather than single chemicals. Substantial experimental evidence on chemical coexposure and interaction is essential in this process. The contributions of single chemicals can be evaluated through constructing scientific models of coexposure on the basis of findings from future experimental research. Regularly monitoring the concentrations of the emerging environmental contaminants is necessary to control pollution and prevent disease. It would also be helpful in estimating human daily exposure, especially as a combination of coexposure.

Highlights on Results of Subgroup Analysis

PCB Structure-Specific Congener Properties

To date, studies reporting associations between higher total PCBs and increased breast cancer risk are few in number, and most of them reported null results. However, exposure to individual PCB congeners was found to be correlated with breast cancer development in some research.

Among the 209 congeners, marked differences exist in their estrogenic activity, biological half-lives, binding affinity to receptors, and cytochrome P450 activity, which results from their varied degrees of chlorination and substitution patterns.[6] For instance, some PCB congeners act as estrogen agonists both in vitro and in vivo, while others show antiestrogenic activity.[50] On the basis of their structural, biological, and pharmacokinetic properties, one study group proposed a classification system and assigned PCB congeners into 3 groups.[51] Group I congeners are weak phenobarbital inducers and are potentially estrogenic; they are composed of nonpersistent congeners in group IA and persistent congeners in group IB. Group IA congeners have one or two unsaturated *para* carbon atoms; their estrogenic activity is expected to be available for only a few months before being eliminated from human bodies.[4] Instead of binding to receptors, the lower-chlorinated congeners act primarily through metabolic activation and the downstream effects of these metabolites.[6] Group II includes non-*ortho* and mono-*ortho* substituted coplanar congeners, which have been shown to be antiestrogenic. The antiestrogenicity is initiated by activation of aryl hydrocarbon receptor in humans, which is thought to best fit their coplanar structure.[6,51] Congeners of this group are more highly chlorinated and more persistent than those of group IA. Further, the antiestrogenic effect in this group is believed to confer protection against breast cancer and could compete with congeners having estrogenic activity. Group III congeners are heavily chlorinated and very persistent compared to the other two groups. They show neither estrogenic nor antiestrogenic activity but phenobarbital-like activity, acting by inducing cytochrome P450 isoenzymes, including CYP1A[52] and CYP2B.[4]

Different congeners have been measured in epidemiologic studies; the numbers of congeners measured were also different because the selection criteria for the target congeners in these studies were different. In the past, epidemiologists have tended to report health effects expressed as the total of individual PCB congener levels or as the concentration relative to a commercial PCB mixture (eg, Aroclor, clophens, phenoclors, fenclors, sovol, PCB_3, PCB_5).[51,53] The components of these products varied. For example, Aroclor was named according to its chlorination degree. The varied use of these technical products in different regions in different years has resulted in a high diversity in percentages of congeners accumulated in the environment or in human tissues.[54] The concentrations of some congeners are believed to be relevant to those of the remaining congeners. Many studies chose these congeners as indicator congeners that represent the remaining congeners. For instance, PCB 153, 138, 118, and 180 have been frequently regarded as the most abundant congeners and were thus selected to be measured in epidemiologic research or investigated in experimental studies.[8,17,18,50,55] However, there were some exceptions. One study selected and measured 19 congeners to be analyzed in their cohort on the basis of the rank of abundance found in the breast milk of Canadian women.[56] Another study measured the PCB concentrations in Mexican women and found the most frequent PCB congeners to be PCB 105, followed by 187, 206, and 195, and the 4 PCB congeners detected at the highest concentrations to be 180, 18, 44, and 126. Obviously, this finding differed from that of other areas, further proving the varied distribution in different regions.[57] Analytical priority is necessary when measuring large numbers of samples. However, no selection criteria were available. It is unclear whether to choose congeners according to the existing literature or according to native monitoring data; whether to choose the most frequently detected congeners or those with the highest concentrations; or whether to measure several certain congeners or all that above a limit of detection. On the basis of the existing literature, and to fully reflect regional differences, we suggest combining the detectable frequency and abundance, and measure as many congeners as possible in the target population.

Although the nonpersistent congeners in group IA are readily metabolized and less detectable in human tissues, their actual estrogenic effect on MG is irreversible and therefore cannot be neglected. Some experimental evidence has indicated that in vivo estrogenic activity is weaker in more highly chlorinated congeners than lower chlorinated ones.[58] However, the effect of these lower chlorinated congeners is barely reflected in the existing literature. A meta-analysis of 25 studies involving 12,866 participants found significant associations between breast cancer risk and group II and III congener exposure, but this was not observed for group I.[59] Another congener-specific meta-analysis including 16 studies showed a significant increase in the risk of breast cancer in individuals with higher PCB 99, 183, and 187 levels; these 3 congeners are persistent, and none belongs to group IA.[50] Exceptionally, 2 small-sample-size studies performed in Spain and

Qingdao, China, offered evidence that PCB 28 and 52 (both of which belong to group IA) are associated with an increased risk for breast cancer.[60,61] The heavy consumption of fish is likely responsible for the strong correlation between breast cancer risk and the less persistent congener found in native populations, although this is not mentioned in either study. In view of this matter, we suggest that not too much attention be paid to the effects of lower chlorinated congeners, because the human exposure level is very low, and although lower chlorinated congeners have stronger estrogenic activity than higher chlorinated ones, their half-lives are much shorter, so it is hard to produce the necessary chronic exposure.

It has been controversial whether the concentrations of total PCBs, or whether grouped or individual congeners actually reflect their effect on breast cancer formation. Several reasons support the former notion. For instance, because PCBs present as complex mixtures, potential interactions, including additive, antagonistic, and synergistic effects, might exist among different congeners; their biological effects might thus be expected to represent an integrated response of individual components in the mixtures.[4] In addition, PCBs are broad-acting toxins; grouped or individual congeners represent only a limited spectrum of toxicities.[58] Therefore, some authors believe that total PCBs rather than individual PCBs should be used in analysis.[14] However, for the same reason, marked differences in persistence and estrogenic responses within groups determine that the total effects are more than additive; combining all PCBs would mask the underlying interactions.[6,50,62] As a result, some research uses individual or grouped congeners rather than total PCBs in analysis.[63,64] We support congener-specific study for the following reasons. (1) Although all congeners were named PCBs, their properties were almost totally unrelated to each other, and they therefore can be treated as concentration-related-only different chemicals. (2) Although congeners in group IA showed strong estrogenic potential in experiments, their lack of persistence and exposure levels around the limit of detection make it less necessary to consider their antagonistic activity toward the more persistent and abundant congeners in groups II and III. (3) People are exposed to numerous chemicals, so additive, antagonistic, and synergistic effects might exist not only among PCB congeners but also among all other chemicals; the effects of congeners with higher persistence and abundance were believed to be less confounded than those of other chemicals.

To sum up, as a result of the varied definitions of total PCBs among studies and the high diversity of congeners' properties, the evaluation of individual PCBs may result in more comparable and less confounding effects. However, we suggest a full evaluation of the chemicals' effects on human health using both total PCBs and individual PCBs.

Subgroup Analysis Stratified by Hormone Receptor Status

The growth and development of MG is regulated by estrogen and progesterone, which mainly act through the ER and progesterone receptor (PR). The normal reproductive hormone estrogen, however, is also linked to an increase in breast cancer risk.[65,66] Among all breast cancer patients, about 60% to 85% have disease that expresses ER and/or PR in the cancer tissue.[67-70] On the basis of the expression of ER and PR, disease may be classified as hormone receptor (HR) positive or negative. Disease with positive ER and/or PR expression is sensitive to endocrine therapy, and a good prognosis is predicted.[71] In contrast, HR^- tumors are not influenced by estrogen and do not respond to endocrine therapy treatment.[72,73] One study wondered whether the etiology of HR-defined breast cancers was heterogeneous and thus reviewed 31 studies to find an association between reproductive-related exposures and increased risk of ER^+ but not ER^- tumors.[74]

PCBs were first studied as potential carcinogens for their estrogenic or antiestrogenic activities.[51,75] The metabolites of PCBs have similar structures with estrogens and can act as estrogen agonists or antagonists.[6] Experimental research observed a high proliferation of ERα-positive breast carcinomas in postmenopausal women when organochlorine levels in the surrounding adipose tissue reached a certain level.[76] Therefore, it was hypothesized that the hormones might act in different pathways in HR^+ and HR^- disease; also, HR^- disease may respond to PCB exposure differently than HR^+ disease, which may further cause diversity in the metabolism of PCBs and PCB concentrations in human bodies. Accordingly, it is particularly important to stratify patients according to HR status in analysis.

Some researchers have evaluated the effects of PCBs by ER status, PR status, or combined ER and PR status after evaluation in breast cancer of all subtypes, although many of them obtained no significant findings regardless of HR status.[17,39,77-85] Some did observe statistically significant results in certain subgroups, especially ER^- patients. One study observed higher concentrations of PCB 99, 138, 153, and 180 and total PCBs in ER^- than in ER^+ cases.[86] A nested case–control study found no association between higher organochlorine burden in the body and risk of breast cancer, but observed a pattern of substantially lower risk of ER^- breast cancer in association with higher levels of PCBs.[87] In line with the high levels of PCBs among ER^- women, pesticides were also found to be statistically higher in ER^-/PR^- than in ER^+/PR^+ cases[17] or higher in ER^- than in ER^+ cases.[84] As a result of the positive associations between PCB concentrations and age, and the negative associations between age and risk of HR^- breast cancer, the significant results were less likely to be chance findings. In contrast, some PCB congeners were reported to positively associated with ER or PR expression.[19,88,89]

Several explanations have been suggested regarding these significant findings. One study described lower levels of estrogens in ER^+ cases and higher levels in ER^- cases, which was explained by the ER^+ tumors' growth-dependent uptake of estrogen.[40,84] The tendency of higher levels of PCBs and other pesticides in ER^- cases observed in some research was consistent with that of the human hormone estrogen.[17,84,86,87] An experimental study reported that PCB 138, 153, and 180 can compete with the binding of ER and androgen receptor, and interfere with sexual hormone–regulated processes.[90] Accordingly, absence of ERs might induce the accumulation of PCBs in ER^- patients.

In addition to ER and PR, a set of other tumor prognostic markers in breast cancer, including HER2, adhesion molecule E-cadherin, proliferation index Ki-67, and p53 (tumor suppressor), have also been investigated in the associations between breast cancer and PCBs for cancer formation or for predicting prognosis.[19,73,84] However, evidence of such associations is quite limited. In the future, research on more biomarkers in relation to concentrations of organic chemicals is recommended to advance breast cancer prevention.

ER and PR are the most widely studied markers in breast cancer. Patients with different HR status vary in therapy and prognosis, but

increasing evidence also indicates distinctions in their etiology. In some cases, a factor can act in opposite directions in developing different subtypes of breast cancer. Given the high percentage of HR^- breast cancer patients, the absence of stratification according to HR expression might result in counteractions between subtypes and lead to misleading results. Considering that many studies do not include HR status in their analyses, the inability to evaluate the important impact of HR expression in these studies is another source of underestimations of the effects of PCBs on breast cancer.

Further research is needed to explore the interactions between xenoestrogens and HRs. In future epidemiologic studies on the effect of organic pollutants on breast cancer development, cases need to be regularly stratified according to HR status. Because of the distinct biological features of different disease subtypes, more attention must be paid to the significant findings from these subgroups.

Conclusion

Early life exposure to PCBs greatly influences lifetime breast cancer risk, but exposure assessment is mostly conducted at about the time of breast cancer diagnosis, which means it is not possible to accurately study exposure to PCBs during the time windows of susceptibility. Factors known to be related to breast cancer risk are not considered or well controlled in the previous research; indeed, the impact of these unmeasured features is a source of confounding effects. Instead of single chemicals, people are exposed to chemical mixtures, but exposure to other chemicals is not only hard to measure but also difficult to control in assessing the effect of single PCBs. These 3 limitations were widely encountered in the epidemiologic research and affected the evaluation of associations between PCB exposure and breast cancer risk. PCBs are a group of congeners with varied properties, and breast cancers of different biological subtypes are etiologically distinct diseases. Stratification is vital, and the results of subgroup analysis deserve particular attention.

For the abovementioned reasons, the effect of PCBs on breast cancer may be undervalued. Because most of these reasons are modifiable, in future studies that consider all these factors in their study design, conclusions on the association between PCB exposure and breast cancer may be a little different—and more reliable.

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