

BURDEN OF ORGANOCHLORINE SUBSTANCES AS A RISK FACTOR OF BREAST CANCER

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Abstract

Background: Organochlorines are a various group of synthetic chemicals that include polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins/ polychlorinated dibenzofurans (PCDDs/PCDFs or dioxins) and organochlorine pesticides, such as dichlorodiphenyl-trichloroethane (DDT), lindane, aldrin and dieldrin. As many organochlorines and their metabolites have carcinogenic and the weak hormonal (estrogenic and anti-estrogenic) effects, a possible association between breast cancer risk and exposure to organochlorines has been hypothesized. It has been estimated that well established risk factors explain only about 41% of breast cancer cases, with the remainder cases due to unidentified causes. Since known risk factors for breast cancer account only for about half of all cases, there has been continued interest in the role of organochlorines and other environmental pollutants in unexplained breast cancer.

Methods: The literature concerning the association between organochlorines and risk of breast cancer was reviewed. Relevant studies were identified by searching the following databases: the Cochrane Library, Medline, Embase and PubMed. Studies that met the quality criteria included in the review.

Results: Association between organochlorines, such as DDT and PCBs, and breast cancer risk has been reported in a number of epidemiological studies since 1976. The association of PCBs and DDE with breast cancer has been investigated in a series of retrospective case-control studies and in prospective nested case-control studies. In general, the individual epidemiological studies that have been conducted to date and are presented in this review, do not support a positive association between body burdens of single organochlorines and the development of breast cancer. However, the quality of available scientific information is low because the majority of epidemiological studies that have been conducted till now have many limitations and weaknesses.

Conclusion: This review shows that high concentration of single organochlorine compounds are not important predictors for breast cancer. However, a hypothetical association between organochlorine substances and risk of breast cancer cannot be investigated on the basis of single substances levels. The possible synergetic, antagonistic or additive interactions between the substances should be considered. Further research on interactions between organochlorines and other xenoestrogens and natural estrogens is recommended.

Keywords: organochlorines, dioxins, hormones, endocrine disrupters, breast cancer, risk.

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Introduction

Organochlorines are a various group of organic compounds that contain chlorine and include polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins/polychlorinated dibenzofurans (PCDDs/PCDFs or dioxins) and organochlorine pesticides, such as dichlorodiphenyl-trichloroethane (DDT), lindane, aldrin and dieldrin^(1,2). The most abundant of these man-made organochlorine compounds are the PCBs and the pesticide DDT, which were used widely in United States from 1945⁽³⁾. Organochlorine compounds have several properties, such as⁽⁴⁾: a) stability against decomposition or degradation by normal physical or biochemical processes, b) very low solubility in water, c) high solubility in hydrocarbon-like environment (lipophilicity), such as the lipid and fatty tissue. Human exposure to organochlorine substances may occur through air inhalation, ingestion of food and water and skin absorption⁽⁵⁾. Nevertheless, the major route of exposure to these substances is via food (and not drinking water) because of the bioaccumulation of organochlorines in fish and other animal origin food that humans consume⁽⁶⁾. The long term and regular skin absorption of cosmetic products that contain organochlorines or other endocrine disrupters may be another route of exposure^(7,8). The regular application of a variety of cosmetics with estrogenic activity to the underarm and upper breast area may lead to the continuous direct dermal exposure and consequently to the absorption and accumulation in underlying tissues⁽⁷⁾.

Human exposure to organochlorine substances may commence during prenatal and neonatal period. The developing fetus is exposed to organochlorine substances and other persistent organic pollutants through placental transfer because placenta cannot prevent the entrance of organochlorines in the embryonic circulation⁽⁹⁾. Exposure to organochlorine compounds continues postnatally via lactation. Since organochlorines are lipophilic, they are excreted in breast milk and consequently the human breast milk is the major source of

exposure of newborn infants. Given that organochlorine compounds are lipid soluble and degrade slowly is expected to be bioaccumulated in human body and to be found in human adipose tissue, breast milk and blood. In general, the levels of organochlorine substances are about the same at different human tissues (adipose tissue, breast milk, muscle, blood). However, measurements in adipose tissue reflect steady the concentration of lipophilic chemicals while measurements in whole blood, serum and plasma may be influenced by blood lipids, as such, may be biased⁽¹⁰⁾.

A great increase in the incidence of cancer has been observed the last years, especially for hormonally related cancers, such as breast, prostate and testis cancer⁽¹¹⁾. Hormones play a major role in the etiology of several human cancers, including cancer of the breast, endometrium, ovary, prostate, testis and thyroid. A major area of interest in relation to organochlorines and cancer has concentrated on organochlorines acting as endocrine disrupters and breast cancer. Breast cancer is the most common type of cancer diagnosed in women, both in the developed and developing countries and is the leading cause of cancer death among women 35-54 years old⁽¹²⁾. One out of every ten women in Europe and US will be affected by breast cancer⁽¹¹⁾. The current known risk factors for breast cancer are mainly related to reproductive characteristics of women. In general, prolonged or increased exposure to estrogen is associated with increased risk of breast cancer, whereas reduced exposure is protective⁽¹¹⁾. Therefore, factors that increase the number of menstrual cycles (early menarche, nulliparity, late onset of menopause) are associated with increased risk of breast cancer while factors that decrease the numbers of ovulations (long lactation, high parity) can be protective⁽¹³⁾. Long lactation may be protective not only because decreases the number of ovulations but also because reduces the body burden of women's lipophilic genotoxic chemicals. Other known risk factors are inheritance (e.g. BRCA1 and BRCA2 gene mutations),

exogenous estrogens (oral contraceptives and hormone replacement therapies), radiation, alcohol consumption, obesity and specially postmenopausal obesity and higher educational and socioeconomic status ⁽¹⁴⁾.

However, currently established risk factors of breast cancers explain only a small fraction of the diagnosed cases of breast cancer ⁽¹⁵⁾. Many cases of breast cancer remain unexplained and new risk factors must be sought such as occupational factors, exposure to pesticides and other endocrine disrupters ⁽¹⁶⁾. Approximately 50% of women who develop breast cancer have no identifiable risk factors except increasing age ⁽¹⁷⁾. Madigan et al ⁽¹⁷⁾ have estimated that well established risk factors explain only about 41% of breast cancer cases in U.S., with the remainder cases due to unidentified causes. It is highly likely that this applies to Europe too ⁽¹⁸⁾. Additionally, studies of twin women have shown that more than 60% of breast cancer has an environmental etiology ⁽¹⁹⁾.

Therefore, the purpose of this study was to examine the possible relationship between environmental exposure to organochlorine substances and breast cancer risk.

ROLE OF ORGANOCHLORINES IN BREAST CANCER

As known risk factors for breast cancer account only for about half of all cases, there has been continued interest in the role of organochlorines and other environmental pollutants in unexplained breast cancer ⁽²⁰⁾. Therefore, it is expected and reasonable to investigate whether the chemicals that persist in the environment are potential risk factors for breast cancer and have a plausible biological mechanism of action ⁽²¹⁾. Furthermore, there is a concordance among the rising incidence of breast cancer, the chronological patterns of release of organochlorine compounds in the environment and the attribution of a small fraction of breast cancer cases to known risk factors. Although many organochlorine compounds exist, DDT and PCBs have been the most studied ⁽²²⁾.

The hypothesis that organochlorine compounds increase the risk of breast cancer is based on the carcinogenic and the weak hormonal (estrogenic and anti-estrogenic) effects of many organochlorines and their metabolites ⁽¹⁵⁾. Given that organochlorines may mimic endogenous hormones and alter their metabolism it is expected to increase the risk of breast cancer. Organochlorines, including DDT, PCBs and dioxins may also reduce cell-mediated immune function, which may increase susceptibility to developing breast cancer ⁽²³⁾.

There is much evidence about the possible role of two metabolites of estrogens in the development of breast cancer. Endogenous metabolism of estrogens involves hydroxylation of the steroid to two compounds. Estrogens are metabolized either to the weakly estrogenic 2-hydroxyestrone (2-OHE1), which is known that inhibit cell proliferation, or to the genotoxic 16 α -hydroxyestrone (16 α -OHE1), which is known that enhances breast cell growth and may contribute to the development of breast cancer. Bradlow and co-workers ⁽²⁴⁾ have hypothesized that the 2-hydroxy and 16-hydroxy metabolites of 17 β estradiol and estrone play a role in the development of breast cancer. In a study by Bradlow et al ⁽²⁴⁾ it was found that organochlorine compounds (DDT, DDE, PCBs, lindane and other pesticides) increased the proportion of 16 α -hydroxyestrone and consequently increased the ratio of 16 α -OHE1/2-OHE1 metabolites. Therefore, it could be concluded that organochlorines may increase the risk of breast cancer by affecting estrogen metabolism.

Hereditary breast cancer (BRCA1 and BRCA2 gene mutations) accounts for 5%-9% of all breast cancer cases ⁽²⁵⁾. However, mutations of the BRCA1 and BRCA2 genes do not explain the occurrence of all hereditary breast cancer cases ⁽²⁶⁾. A statistically significant association between breast cancer and 13 polymorphisms in 10 genes was found in a systematic review ⁽²⁵⁾. Increased breast cancer risk was found for the polymorphisms in HRAS1, GSTM1, GSTP1,

CYP1A1, CYP1B1, CYP2D6, CYP19 and VDR genes. Some epidemiological studies have particularly suggested a positive relation between breast cancer and CYP1A1 genetic polymorphisms^(27,28). PCBs are strong inducers of CYP1A1 gene. There are a number of studies which suggest that interactions between CYP1A1 polymorphisms and PCBs could be involved in the development of breast cancer^(29,30,31). In other words, the interaction between PCBs and CYP1A1 gene may increase the risk of breast cancer to women that have CYP1A1 gene polymorphisms. These studies showed that increased risk of breast cancer was found in women with CYP1A1 (M2) polymorphism. A greater risk was found in women with higher serum levels of PCBs in combination with the polymorphism as compared to those with lower serum levels of PCBs and the polymorphism. A recent study showed that CYP1A1 (M2) polymorphism was associated with increased risk of breast cancer while DDT exposure increases further the risk of breast cancer among women with CYP1A1 (M2) polymorphism⁽³²⁾. Another polymorphism, CYP1A1 (M1) polymorphism may be a marker of altered estradiol metabolism and of increased susceptibility to breast cancer⁽²⁷⁾.

EVIDENCE OF ASSOCIATION BETWEEN ORGANOCHLORINES AND BREAST CANCER (EPIDEMIOLOGICAL STUDIES)

Association between organochlorines, such as DDT and PCBs, and breast cancer risk has been reported in a number of studies since 1976. Wasserman et al⁽³³⁾ reported that the concentration of total PCBs was about three times higher in women's malignant breast tissue than that in adjacent healthy breast tissue or adipose tissue from the same women, or in normal breast tissue from controls. Until the early 1990s, few epidemiological studies of potential environmental risk factors for breast cancer have been conducted. Since then many population-based studies have been carried out, with a special emphasis on exposure to 'environmental estrogens'.

In 1992, Falck et al⁽³⁴⁾ reported that total PCBs levels were 40% higher in patients with breast cancer than in controls who had benign breast disease. In 1993, a case-control study that conducted in New York found two to four-fold elevations in breast cancer occurrence of women with higher levels of DDE and PCBs compared to women with lower levels⁽³⁵⁾. Since 1993, approximately 35 studies have attempted to replicate the associations observed in the Wolf study and to investigate further the association between breast cancer risk and individual organochlorines. The association of PCBs and DDE with breast cancer has been investigated in a series of retrospective case-control studies and in prospective nested case-control studies.

The potential role of organochlorines in breast cancer has been extensively investigated in many studies^(11,15,36-65) which mainly compared the levels of PCBs and DDT (or DDE and other pesticides) in fatty tissue or serum in women with breast cancer versus controls. Control patients were women either with benign breast disease or women of cancer or any other breast disease. Epidemiological case-control studies measuring serum or plasma levels of organochlorines can be divided into prospective and retrospective studies. In prospective studies blood sample was collected before the diagnosis of breast cancer and in retrospective studies the sample was taken after diagnosis. In retrospective studies the specimen (adipose tissue or blood sample) is taken after diagnosis. The studies that use breast adipose tissue generally enrol women who had undergone a breast surgery. Therefore, control women of these studies have usually benign breast disease.

As illustrated in Table 1.1, results of the majority of prospective studies demonstrate that levels of organochlorines are not significantly higher in women with breast cancer versus women with no breast disease.

Table 1.1 Results of prospective studies regarding the association of serum levels of organochlorines and breast cancer.

Studies	No. of Cases/Controls	Controls	Biological specimen	Statistically significant association between levels of organochlorines and breast Ca
Wolff et al, 1993, USA	58/171	Free of breast cancer	Serum	Positive
Krieger et al, 1994, USA	150/150	Free of breast cancer	Serum	Negative (positive only in black women)
Hunter et al, 1997, USA	236/236	Free of breast cancer	Serum	None
Hoyer et al, 1998, Denmark	240/477	Free of breast cancer	Serum	Negative (positive only in black women)
Dorgan et al, 1999, USA	105/210	Free of breast cancer	Serum	None (positive only for PCB 118 and 138)
Helzlsouer et al, 1999, USA	346/346	Free of breast cancer	Serum	Negative
Hoyer et al, 2000, Denmark	240/477	Free of breast cancer	Serum	None
Ward et al, 2000, Norway	150/150	Free of breast cancer	Serum	None
Wolff et al, 2000a, USA	148/295	Free of breast cancer	Serum	None
Laden et al, 2001b, USA	381/381	Free of breast cancer	Serum	None
Raaschou-Nielsen et al, 2005, Denmark	409/409	Free of breast disease	Stored breast adipose tissue	Negative

It could be concluded that the vast majority of prospective studies failed to confirm the association observed in the Wolff study⁽³⁵⁾. The positive association between the higher body burdens of the organochlorine dieldrin and the increased risk of breast cancer observed in a Danish prospective study by Hoyer et al in 1998 was not observed in a second study⁽⁵⁷⁾ of the same population.

Most of the prospective studies have been conducted in USA to address the possibility that exposure to organochlorines may explain the increased incidence of breast cancer there⁽²¹⁾. The recent study by Raaschou-Nielsen et al⁽¹⁵⁾ is the largest prospective study to date to investigate the association between PCBs and organic chlorinated pesticides and breast cancer risk and is the first prospective study to use stored adipose tissue. The results of this study do not support that higher body level of organochlorine increase the risk of breast cancer. In contrast, this study showed an

inverse association between the risk of breast cancer and levels of specific organochlorine compounds.

As illustrated in Table 1.2, results of the majority of retrospective studies demonstrate that levels of organochlorines are not significantly higher in women with breast cancer versus women with no breast disease.

The largest retrospective case-control study was the study by Gammon et al⁽⁶²⁾ that was conducted in the Long Island - New York City area. The findings of this study, based on the largest sample size to date, do not support the hypothesis that organochlorines (PCBs, DDT/DDE, chlordane, dieldrin) increase the risk of breast cancer. In this study there was no increased risk of breast cancer in women who had specific risk factors (not breastfeed, overweight, hormone receptor-positive tumor).

Table 1.2 Results of retrospective studies regarding the association of serum levels of organochlorines and breast cancer.

Studies	No. of Cases/Controls	Controls	Biological specimen	Statistically significant association between levels of organochlorines and breast Ca
Dewailly et al, 1994, Canada	18/17	Benign breast disease	Breast adipose tissue	Positive
van't Veer et al, 1997, EU	265/341	Free of breast disease	Adipose tissue	None
Lopez-Carrillo et al, 1997, Mexico	141/141	Free of breast disease	Serum	None
Schechter et al, 1997, Vietnam	21/21	Benign breast disease	Serum	None
Moysich et al, 1998, USA	154/192	Free of breast disease	Serum	None (positive only for non lactated women)
Mendonca et al, 1999, Brazil	177/350	Free of breast disease	Serum	None
Dello-Iacovo et al, 1999, Italy	170/190	Free of breast disease	Serum	None
Zheng et al, 1999, USA	304/186	Benign breast disease	Breast adipose tissue	None
Zheng et al, 2000, USA	475/502	Benign breast disease or free of breast disease	Serum	None
Romieu et al, 2000, Mexico	120/126	Free of breast disease	Serum	Positive
Wolff et al, 2000b, USA	175/181	Benign breast disease	Serum	None
Demers et al, 2000, Canada	315/307	Free of breast disease	Serum	None
Aronson et al, 2000, Canada	217/213	Benign breast disease	Breast adipose tissue	None (positive only for PCBs)
Stellman et al, 2000, USA	232/323	Benign breast disease	Adipose tissue	None
Millikan et al, 2000, USA	456/389	Free of breast disease	Serum	None (positive only in black women)
Woolcott et al, 2001, Canada	217/213	Benign breast disease	Breast adipose tissue	None
Gammon et al, 2002, New York	646/429	Free of breast disease	Serum	None
Pavuk et al, 2003, Slovakia	24/88	Free of breast disease	Serum	None (positive only for DDE)
Charlier et al, 2003, Belgium	159/250	Free of breast disease	Serum	Positive
Charlier et al, 2004, Belgium	60/60	Free of breast disease	Serum	Positive
Siddiqui et al, 2004, India	25/25	Benign breast disease	Serum and breast adipose tissue	None
Rusiecki et al, 2004, USA	326/347	Benign breast disease or free of breast disease	Serum and breast adipose tissue	None

Only four retrospective case-control studies found higher levels of total PCBs or individual congeners and other organochlorines in women with breast cancer (cases) than control women. Dewailly et al ⁽³⁶⁾ measured the levels of PCBs and 10 individual congeners in breast adipose tissue of 17 women with benign breast disease (controls), of 9 women with breast cancer with estrogen receptor positive (ERP) and of 9 women with breast cancer with ER negative (18 cases). Women with ER positive breast cancer had higher levels of organochlorines than controls. Furthermore, results of more recent retrospective studies have shown that high concentration of organochlorines may increase the risk of breast cancer ^(11, 65). In a study by Romieu et al ⁽⁵⁵⁾ that was conducted in Mexico, the levels of DDT and DDE were measured in 120 cases and 126 controls and it was found that high levels of DDE may increase the risk of breast cancer. However, a previous study that was conducted in Mexico City ⁽⁴¹⁾ didn't find an association between levels of DDE and breast cancer. Several studies that have been conducted in countries where DDT is still in use or was used until lately, didn't find an association between levels of DDT or DDE and breast cancer ^(40, 47, 64). A recent study that has been conducted in Slovakia showed that higher serum levels of PCBs were inversely associated with breast cancer risk, while higher serum levels of DDE were positively associated with risk of breast cancer ⁽⁶⁶⁾. Another recent study that was conducted in USA didn't find an association between environmental exposure to PCBs and breast cancer ⁽⁶³⁾

Several studies performed sub-group analyses, either according to some characteristics of the women (history of breastfeeding, parity, menopausal status, race), or according to the characteristics of tumours (size, stage, receptor status). Although these studies were considered to be large, they had limited power to perform subgroup analysis ⁽⁶¹⁾. No consistent subgroup findings have emerged. Studies by Krieger et al ⁽³⁷⁾, by Millikan et al ⁽⁵⁶⁾ and by Hoyer et al ⁽⁴³⁾ found a statistically significant association between high levels

of organochlorines and breast cancer only in African-American women but not in Caucasian women. However, a fourth study didn't support differences by race ⁽⁵¹⁾. Furthermore, individual studies have suggested that high levels of organochlorines may increase the risk of breast cancer only in non lactated women ^(42, 56). In addition, many studies have presented analysis for individual or groups of PCB congeners. Although many studies have suggested an association between increased risk of breast cancer and PCB congeners 118 and 138 ^(57, 59, 60) there are several studies that have drawn opposite conclusions ^(46, 53, 62). Women with breast cancer are usually grouped by tumor size and grade, and by estrogen receptor status (positive or negative). Many studies have investigated the association between the levels of organochlorines and particular tumor type (estrogen receptor status) or tumor aggressiveness. Although, Dewailly et al ⁽³⁶⁾ observed that women with breast cancer and estrogen receptor positive had higher levels of organochlorine burden than controls or women with estrogen receptor negative, more recent studies ^(63, 67) have not confirmed the observation made by Dewailly. However, study by Wollcott et al ⁽⁶⁷⁾ found that PCBs concentrations were strongly positively associated with tumours of "poor prognosis" (higher grade).

The evidence to date concerning the association between the risk of breast cancer and levels of organochlorines is not entirely consistent and there is accumulative evidence from the individual studies that high concentrations of organochlorine compounds are not important predictors for breast cancer. In general, the individual epidemiological studies that have conducted to date do not support a positive association between body burdens of organochlorines, mostly DDT and PCBs, and the development of breast cancer. Many recent studies have conducted in order to reanalyze the primary data by using a standardised approach.

A systematic review of epidemiological studies concluded that there is no direct association between exposure to PCBs in adulthood in general population and risk of

breast cancer ⁽⁶⁸⁾. Additionally, it was concluded that the possibility that individual congeners may increase the breast cancer risk for some subgroups of women cannot be ruled out. Recently a pooled analysis of five U.S. epidemiological studies has investigated the association between DDE and PCBs and risk of breast cancer ⁽⁶⁹⁾. The pooled analysis that reanalyzed the data of these five studies in order to increase precision and maximise statistical power, consisted of 1400 case patients with breast cancer and 1642 controls. Laden et al ⁽⁶⁹⁾ have concluded that “there is no association between plasma or serum concentrations of DDE and PCBs and an increased risk of breast cancer”. It was also concluded that exposure to these compounds is unlikely to explain the high rates of breast cancer in the north-eastern United States”. In a recent meta-analysis by Lopez-Cervantes et al ⁽⁷⁰⁾ 22 studies were included and the relationship between DDT exposure and breast cancer risk was investigated. The pooled analysis by Lopez-Cervantes et al concluded that there is strong evidence to discard the putative relationship between DDT and breast cancer risk. However, the pooled analysis had limited statistical power and failed to demonstrate statistically significant results (OR 0.91, 95%CI 0.71-1.12).

LIMITATIONS OF EPIDEMIOLOGICAL STUDIES

The strengths of the epidemiological evidence are the consistency of findings across several studies and the fact that the studies were based on the measured levels of organochlorines rather than on reported exposure.

However, many limitations have been noted in epidemiological studies. Many studies had small sample size and consequently had limited statistical power. The largest retrospective case-control study that was conducted by Gammon et al ⁽⁶²⁾ relied on only 646 cases (women with breast cancer) and 429 controls. Furthermore, the pooled analysis conducted by Lopez-Cervantes et al relied on only 1857 cases and 2644 controls. In contrary, the sample of the study that investigated the relationship between

hormone relationship therapy and breast cancer risk consisted of more than 150.000 women (cases and controls) ⁽⁷¹⁾. Another limitation was that many studies didn't control confounding variables, such as known risk factors of breast cancer. History of breast-feeding was not considered in many studies. Additionally many studies have used different control subjects (women with benign breast disease and women free of benign breast disease). Use of women with breast benign disease as controls might be a great confounding factor since there is some evidence that suggest that women with a previous history of benign breast disease have higher risk of breast cancer ⁽⁷²⁾. If the effect of organochlorines on breast diseases is similar of the effect on breast cancer then many studies have been biased and they have underestimated the effect of organochlorines ⁽⁷³⁾. Additionally, biological specimens (serum, breast adipose tissue or adipose tissue of different origin), measurement methods, types of organochlorines and specifically number of PCB congeners varied among studies. Many studies used serum as a biological specimen while others used breast adipose tissue or adipose tissue of other origin. Although it has been found that measurements of persistent, lipid-soluble chemicals in breast and abdominal adipose tissue are correlated ⁽²⁾, serum levels can be very sensitive to short term changes in diet ⁽⁷³⁾. Another potential limitation of these studies is that the critical age of exposure to organochlorines was not assessed and thus the association between period of exposure and breast cancer risk was not illustrated. It has been established that undifferentiated breast cells are more vulnerable to carcinogenic exposure and that tumor initiation is more likely to occur during early breast development ⁽⁷⁴⁾. Thus, it could be concluded that concentration of organochlorines is not the only risk factor of breast cancer. Timing of exposure to high levels of organochlorines is another major determinant which should be considered. One of the most major limitations of the conducted studies (individual epidemiological studies and pooled analysis) was that they didn't consider the

combination effect between the organochlorines and the endogenous sex hormones⁽¹⁸⁾.

Conclusion

In conclusion, the evidence to date concerning the association between the organochlorines and risk of breast cancer is not entirely consistent and suggests that organochlorine compounds are not important predictors for breast cancer. However, the quality of available scientific information is low because the majority of epidemiological studies that have been conducted till now have many limitations and weaknesses. Further research on interactions between organochlorines and other xenoestrogens and natural estrogens is recommended. It appears urgent that research programmes should focus on the potential effects of organochlorines and other endocrine disrupters to breast cancer and other hormone-related cancers. Current studies investigate breast cancer and other hormone related cancers without considering the potential effects of these harmful chemical substances. The identification of the effects and role of organochlorines may help explain some cases of breast cancer.

The role of health care professionals should be focused on the education of the public in order to minimize their exposure to organochlorines and other harmful substances. Information and education are important public health tools that are relatively low cost and can have major impact on reducing environmental and health effects⁽⁷⁵⁾. Information and education are critical to public empowerment. Health care professionals should inform people about risks, options for preventing risks, actions for reducing them and possible alternatives. Information can also discourage behaviours that lead to risks and make people to demand safer environmental conditions. Information and education will enable people to identify products that contain potentially hazardous substances, or that are environmentally friendly and have been produced by using organic methods.

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