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REVIEW ARTICLE

A Narrative Review of the Association between Pesticides, Organochlorines and Breast Cancer: Current Advances and Research Perspectives

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Abstract

Introduction: Incidence of breast cancer is steadily rising in the US. The role of estrogenic environmental contaminants such as the pesticide 'Dichloro Diphenyl Trichloroethane (DDT)' and the industrial products 'polychlorinated biphenyls (PCBs)' are gaining concern in recent years. Our study tries to draw inference by reviewing published research articles on this association.

Methods: 'Pubmed' database was used for searching relevant articles. Search terms used include 'Pesticide exposure'; 'Breast cancer'; 'Organochlorine compounds'. The results of this search yield 18 research articles which contextually details the concerned concepts.

Discussion: Pesticides may be classified as chemical carcinogens and they operate in a variety of ways. Some are mutagenic which interact with DNA while others like OC pesticides are epigenetic carcinogens. Environmental contaminants (DDT & its metabolites, PCBs) may act alone or in concert simulating the effect of estrogens on breast tissue. Increased concentration of these environmental contaminants may be found in breast tissue of women suffering from malignant breast disease. Some studies have observed that women with high body fat content were observed to carry higher levels of OC as these are environmentally persistent and fat soluble.

Conclusion: This review suggests that exposure to Pesticide compounds increases the risk of breast cancer. Future studies should focus on determining levels of these substances in breast tissue, and not just in the plasma or serum. Some epigenetic process might provide a protective effect among migrants to the US, including activation of biotransformation enzymes.

Keywords

Breast neoplasms, Pesticides, DDT, Chlorinated hydrocarbons

Introduction

Incidence of breast cancer is steadily rising in the United States. As per the CDC report [1], around 250,000 cases of breast cancer are diagnosed among US women each year and about 42,000 die as a result of the same. It is the second leading cause of cancer death among women in US. Multiple explanations have been given for this rise which include an aging population, increased mammographic screening and changes in the prevalence of accepted risk factors associated with prolonged exposure to unopposed estrogen (eg. delayed childbearing and early menarche). The role of estrogenic environmental contaminants such as the pesticide 'Dichloro Diphenyl Trichloroethane (DDT)' and the industrial products 'polychlorinated biphenyls (PCBs)' are gaining concern in recent years. Although widespread use of these compounds ceased in the US during 1970s, their ability to accumulate and persist in adipose tissues has raised fears about their contribution to breast cancer development [2]. They might also modulate the growth of cancer [3]. It is speculated that pesticide exposure transcends the agricultural areas, and has the potential to reach rural workers, urban dwellers, and other individuals of all age groups [4].

The common risk factors for breast cancer do not explain the scenario among young women. In countries such as India, early first childbirth, multiparity and breastfeeding are the social norms, and the use of oral contraceptives and hormone replacement therapy is low. Breast feeding for > 1 year is known to act as a

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protective factor for breast cancer [4]. However, the disease onset among Indian women is at younger age when compared with the western population. This defines a role for environmental factors which needs to be further reviewed.

In the US, the usage of DDT as insecticide was stopped during 1972. However, its usage continued in Third World countries until the 1990s for e.g.: Its usage for agriculture was banned in India during 1989, although it is still used against malaria-bearing mosquitoes. Dichlorodiphenyl dichloroethylene (DDE) is the most prevalent breakdown product of DDT. It persists in the environment, transmitted through the food chain and is stored in fatty tissues of animals and humans. Food items such as poultry, fish, meat, and dairy products serve as sources of exposure for these pesticides through the diet. It is also secreted in cow's milk and human breast milk, and has been detected in household dust and air [5]. OC tend to accumulate in adipose tissue when compared with blood, and breast samples predict the level of OC exposed over time.

The degradation products of OC pesticides include β-hexachlorocyclohexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), polychlorinated biphenyls-28 (PCB28), polychlorinated biphenyls-52 (PCB52), pentachlorothioanisole (PCTA) and pp'-dichlorodiphenyldichloroethane (pp'-DDE, metabolite of pp'-dichlorodiphenyltrichloroethane (DDT)) [6].

Several OC which are identified as 'hormone mimics' are possible risk factors for breast cancer. OC levels and their variability among ethnic groups are attributable to several factors such as diet including fish consumption and other environmental sources including residence in a rural area. The magnitude and the direction (inverse or positive) of relationship between BMI, age and OC levels reflects accumulation and turnover rates, as well as changes over time in exposure (increased or decreased environmental contamination and absorption). The positive association between OCs and age indicates their long term absorption and slow metabolism.

Literature Review

List of the reviewed studies and the salient research process (Table 1).

Table 1: List of the reviewed studies and the salient research process.

Author	Location of study and participants	Study design & sample size (n)	Exposure assessment (& method used)	Results	Comments
Demers, et al. [3]	Quebec, Canada Rural and Urban subjects	Case control study (cases = 315, controls = 526)	Concentration of PCG congeners measured in plasma lipids by high resolution gas chromatography	Lymph node invasion among cases increased with p,p'-DDE (OR: 2.54; 95% CI: 1.2-5.35)	Exposure to OC during adulthood is not associated with risk of breast cancer
Silva AMC, et al. [4]	Rondonopolis, Brazil Urban subjects	Case control study (85 cases, 266 controls)	Assessment of environmental exposure to Pesticides through oral questionnaires	Living near cropland with pesticides and women aged > 50 yrs had high risk	Increasing trend of cancer due to diffusion of carcinogenic agents in the environment, including its effect during various stages of organ development
Ting-Ting He, et al. [6]	Qingdao, China Rural and Urban subjects	Hospital based case control study (n = 102)	OC pesticide product accumulation in breast adipose tissue by gas chromatography	High levels of pp'DDE and PCB-52 was found in breast cancer patients	Concentration of pp'DDE and PCB-52 were not related to clinico pathologic parameters of breast cancer
Rodgers K.M [7]	Massachusetts, US	Systematic review of 158 articles	EDCs, PAHs, BPA, Phthalates, PFASs*	Higher risk for exposures during breast development to DDT, air pollution	Chemicals in current consumer use products with potential for cancer causation need to be studied.
Demers, et al. [8]	Quebec, Canada Urban subjects	Case control (cases: 315, controls: 526)	Plasma lipid concentrations of chlorinated pesticides and PCB congeners	Risk for these congeners, OR: 2.02 (1.24-3.28),	Exposure to dioxin like mono-ortho PCB congeners increases risk of breast cancer
Mathur V, et al. [9]	Jaipur, India		Blood samples were collected to evaluate the body burden of OC	OC were significantly high in patients	Rural women had high levels of OC when compared to urban women

Kettles M.K, et al. [10]	Kentucky, US Rural areas	4,859 wells were tested and 1979 survey of amount of pesticide used in each County was examined	Triazine herbicide exposure determined by water contamination data and corn crop production	County level exposure was significant for Medium (OR: 1.14) and High (OR: 1.2) categories	Acres of corn planted serves as a reasonable proxy of triazine use
Rich, et al. [11]	Kentucky, US Rural subjects	Ecologic study, secondary data (1993-97) used to assess atrazine exposure	Public water samples, Acres of corn planted, Pounds of atrazine sold	Null association across all exposure indices	Individual level data are ideal to elucidate the relationship
Guttes, et al. [12]	Hasse, Germany Rural and Urban subjects	Case control study (cases = 45, controls = 20)	Surgically removed breast tissue was examined by capillary gas chromatography	Significantly high pesticide concentration in breast cancer tissues	Surgical procedures did not influence the results
Aronson, et al. [13]	Ontario, Canada Rural and Urban subjects	Case control (cases = 217, controls = 213)	Excision biopsy of breast adipose tissue	Breast cancer risk elevated for PCBs 105 & 118 (OR > 2 in highest category)	Breast tissue biopsy represents cumulative exposure at target site
Wolff, et al. [14]	NewYork city, US Urban subjects	Hospital based Case control study (cases = 175, controls = 355)	OC exposure	OC levels not associated with risk of Breast cancer, nor did it differ with tumor stage or markers	High DDE levels in high BMI individuals, low HPCB among low BMI individuals
Romiew, et al. [15]	Mexico city, Mexico Urban subjects	Subsample of a large breast cancer case control study (cases = 120, controls = 126)	Serum OC levels measured in the original study. Subjects were sampled from them.	Risk increase with high serum DDE levels ($OR_{Q1\text{-}Q4}$ = 3.81, 95% CI: 1.14, 12.8), test of trend, p = 0.02	Longer period of lactation is associated with a slightly decreased risk of breast cancer
Hoyer, et al. [16]	Copenhagen, Denmark Urban subjects	Cohort nested Case control study (cases = 161, controls = 322)	OC (Dieldrin) exposure	Exposure to large levels of OC increase the risk by 7 fold for ERN breast cancer	Adverse effect of OC on prognosis of hormone responsive breast cancer needs to be clarified
Tayour C, et al. [17]	California, US, Rural subjects,	Case control study (cases: 155, controls: 150)	OC & OP (Chlorpyrifos) pesticides were assessed using historic pesticide exposure data and geocoded location histories,	High risk for women exposed to chlorpyrifos	Need to objectively assess exposure to specific pesticides occurring decades before breast cancer diagnosis
Krieger, et al. [18]	San Francisco Bay area, US Urban subjects	Nested case control	Serum levels of DDE and PCBs	Data does not show an association between DDE & PCB exposure	Lack of association was regardless of length of follow-up, case patient's menopausal and estrogen receptor status
Engel L.S, et al. [19]	Iowa and North Carolina, US, Rural subjects	Prospective cohort study (n = 30,454)	Pesticide use assessed by oral questionnaire	Elevated risk for women whose homes were closest to areas of pesticide application	Non-differential exposure misclassification due to recall bias, while self-reporting for exposure assessment
Kaur N, et al. [20]	Delhi, India Urban subjects	Hospital based case control study (42 cases, 42 controls)	Biopsy proven women with carcinoma breast aged ≤ 40 years,	Significant risk was found for heptachlor, DDE, Dieldrin and β-HCH	Exposure to OCPs could increase the incidence of breast cancer among young women in India
Shakeel, et al. [21]	Trivandrum, India	Systematic review of 41 articles	DDT, DDE, PCB, HCB, HCH	DDT is positively associated with breast cancer.	Level of Pesticide exposure is more in developing than developed countries.

*PFASs: Per and Polyfluoroalkyl Substances.

Methods

'Pubmed' database was used for searching relevant articles. Search terms used include 'Pesticide exposure'; 'Breast cancer'; 'Organochlorine compounds'. The results of this search yields research articles which contextually detail the relevant concepts. The criterion used for reviewing these articles includes their relevance to the defined review question. This review includes 18 studies which address the determinants of the association between pesticide exposure and the risk of breast cancer.

Discussion

DDT and PCBs both being organochlorine (OC) pesticides are classified as persistent organic pollutants by the Stockholm convention during 2001. These compounds are known for their toxicity, slow rate of degradation and bioaccumulation. The International Agency for Research on Cancer (IARC) has rendered PCBs as definite carcinogens in human beings. The US EPA (Environment Protection Agency) states that PCBs cause cancer in animals and are probable human carcinogens. EPA has set a limit of 0.0005 milligrams of PCBs per liter of drinking water. The FDA (Food and Drug administration) mandates a limit of no more than 0.2-3 parts of PCBs per million parts of food such as dairy product and meat [22].

The Atrazine Ecological Exposure Monitoring Program (AEEMP) in US assesses the atrazine levels in streams and watersheds, which are exposed to atrazine runoff from corn and sorghum production. EPA currently regulates an aquatic plant concentration equivalent level of concern (CE-LOC) of 10 ppb as a 60-day average concentration, which ensures that atrazine levels will not cause significant changes in aquatic plant community structure, function and productivity. Any community water system with a total combined triazine concentration exceeding 2.6 ppb for finished water or 12.5 ppb for raw water over a 90 day rolling average will be inducted into the intensive atrazine monitoring program (AMP) for 5 years [23].

The referenced studies and the biases involved in these studies are discussed herewith. Pesticides may be classified as chemical carcinogens and they operate in a variety of ways.

Process of carcinogenesis

The cancer causing mutations in a cell are a result of damaged genetic material due to exposure to genotoxic agents. Other processes which are involved include inflammation, genomic instability and immune suppression. Carcinogens are likely to damage the mammary cells during their most susceptible stage during adolescence and before pregnancy, when they are rapidly proliferating and not yet fully differentiated. Individuals who are exposed to endocrine disrupting chemicals (EDCs) during early life may be at risk for altered breast development and increased susceptibility of adult breast cancer [7]. The carcinogenic activity of Pesticides is suggested by the xenoestrogen (environmental estrogen) hypothesis where-in these chemicals alter the estrogen metabolism in the body, which produces genotoxic metabolites. Tumor growth is also caused by a genomic response to high estradiol levels, which increases cell proliferation or inhibits apoptosis.

Knazek RA, et al. [24] state that chemicals with estrogenic properties when administered chronically at high levels or when present in unphysiological amounts for long periods, promotes mammary gland carcinogenesis in experimental systems and growth of estrogen responsive human breast cancer. Another biological mechanism apart from estrogenic properties includes aryl hydrocarbon receptor pathway activation which induces the CYP1A, CYP3A and CYP1B1 enzymes in-turn increasing the biotransformation of estradiol to the genotoxic 'catechol estrogens' [8]. Genetic polymorphisms or dietary/lifestyle habits increase the activities of biotransformation enzymes which in-turn could reduce the concentration of the congeners [8].

Genetic association

The risk of breast cancer is associated with polymorphisms in CYP17, CYP19, CYP1B1, CYP1A1, COMT and I1307K [5]. Some are mutagenic which interact with DNA while others like OC pesticides are epigenetic carcinogens. They do not alter DNA but instead act as promoters. These chemicals play a role in the cancer process by a number of non-genotoxic mechanisms such as promotion, peroxisome proliferation, hormone imbalance and cytotoxicity leading to compensatory cell division.

Apart from sequencing the primary genomic changes in cancer, epigenetic changes such as DNA methylation, histone modification and miRNA expression need to be identified. The BCSGI, CAVI, CHD1, CDH3, NAT1, UPAN genes are known to be hypomethylated in breast cancer. The most common histone modifications include acetylation, methylation and phosphorylation. miRNAs are non-coding RNAs which inhibit the translation of targeted mRNAs and cause those mRNAs to be targeted for degradation [25]. Variation in metabolite concentration can change the properties of tumor through epigenetic modifications. Levels of acetyl-CoA, SAM (S adenosylmethionine) and NAD+ (Nicotinamide adenine dinucleotide) can be modulated by environmental factors such as exercise, nutrition and stress levels. These metabolites through the chromatin modifying enzymes can regulate expression of metabolic and growth associated genes [26]. Biotransformation enzymes such as epoxide hydrolase, NAD(P)H: Quinone oxidoreductase and glutathione S-transferases have the potential to detoxify chemicals and influence susceptibility to cancer [27].

Tissue accumulation

Mathur, et al. [9] found less pesticide concentration in the body of older women, contrary to the expectation that longer duration of lifetime exposure results in higher concentration of OC. However among females, lactation and menstruation are important means of disposing such compounds from the body. Women having high body fat content were observed to carry higher levels of OC as these are environmentally persistent and fat soluble. Total OC residues in cases were significantly higher when compared to the controls.

MacMohan [28] in his editorial states that DDE is known to be extremely persistent in fat tissue, and women with high exposures even 20 years before the development of breast cancer are likely to have high levels at advanced stages of the disease.

Subjects in many studies have been Caucasian women from US, Canada or Europe. However, black women in US are reported to have higher serum or adipose DDE levels than white women, and in this context we need to assess the risk of breast cancer associated with body burdens of DDE.

Ecological study design and exposure assessment

Kettles, et al. [10] study in the State of Kentucky, used data regarding water contamination, corn crop production and pesticide usage to estimate the exposure to triazine herbicides. Over long periods of use, pesticide residues tend to accumulate and concentrate in the ground water. A variety of chemicals including triazines were tested from 4,859 wells. Triazines were measured by immunoassay and 10% of samples were verified by gas chromatography. The sample readings were averaged to generate a single measure of exposure for each county. Triazines in water samples from the faucets of non-randomly selected homes in counties all over the state were measured by gas chromatography. Acres of corn planted serves as a reasonable proxy of triazine use. A 1979 survey of the amount of pesticide used by applicators in each County was examined. A summary index of triazine herbicide exposure was developed to classify counties into low, medium (OR: 1.14, $p < 0.0001$) or high (OR: 1.2 $p < 0.0001$) exposure levels.

In this study [10], exposure sources were not discrete and had a range of contaminant concentrations. The use of ground and/or surface water may vary within counties. It is difficult to identify discrete sources of exposure for each county as water suppliers cross county lines. However, surrogate exposure data such as crop production and pesticide use were assessed to overcome these limitations.

Group-level exposure estimates from such ecological studies enable negating the recall bias, usually found in case control studies. Bias may result if factors operating at the individual level for eg: Family history of cancer, are not accounted for in the aggregate exposure assessment. Predictor variables may have a high degree of correlation at the group level. Other water contaminants apart from the considered herbicides could act as confounders. Effect of bias was minimized in this study [6] by using narrow exposure data, small units of analysis, weighting of units of analysis by a standardized population and regression to estimate the effect.

Rich, et al. [11] study in the State of Kentucky analyzed various sources of exposure data and validated several exposure metrics used to examine the association of proxy indicators of atrazine exposure and risk of reproductive cancer. Exposure indices to atrazine were derived based on public water measurements, pounds of atrazine sold and acres of corn planted.

Case-control study design and exposure assessment

Demers, et al. study [3,8] at hospitals in Quebec, Canada, assess the concentrations of 14 PCB congeners measured in plasma lipids by high resolution gas chromatography. This study differs from other studies in assessing individual or groups of PCB congener exposure instead of all the congeners at-once. Cases and controls were matched for age (5 year age groups) and region of residence (rural/urban).

Mathur, et al. [9] report a significantly high serum OC (considered for analysis) among breast cancer patients irrespective of age, diet and geographic distribution. Hospital patients recruited for this study had no history of any occupational or accidental exposure to pesticides.

Guttes, et al. [12] examined the possibility of increased concentration of environmental contaminants in surgically removed breast tissue samples from 65 women at Hesse, Germany. The tissue were examined by capillary gas chromatography for p,p'DDT (dichlorodiphenyltrichloroethane), p,p'DDD (dichlorodiphenydichloroethane, p,p'DDE (dichlorodiphenyldichloroethene, Hexachlorobenzene (HCB), Hexachlorocyclohexane (HCH) and Polychlorinated biphenyls (PCB).

Aronson, et al. [13] evaluated the association between the risk of breast cancer and breast adipose tissue concentration of several OC. Exposure to OC was examined in four categories (cutpoints at 85th, 57th & 28th percentile). Since the OC distribution in the adipose tissue was positively skewed, it was log-transformed to improve normality.

Wolff, et al. [14] assessed tumor markers (estrogen and progesterone receptors, p53, erbB-2), as well as blood serum levels of organochlorines (DDE, DDT, trans-nonachlor, higher (HPCB) and lower (LPCB) chlorinated biphenyls). This study [14] reports higher levels of the DDT metabolite DDE among African-americans and Hispanic women. It also reports high DDT and low LPCB

among Hispanics, and high trans-nonachlor and HPCB among African-americans. These relationships could be attributed to the historical patterns of exposure.

Romieu, et al. [15] analyzed the relation between lactation history, OC serum levels and the risk of breast cancer within a subsample from a larger breast cancer case control study. Participants in this study were a subsample from another study which assessed the association between diet and reproductive factors, and risk of breast cancer among residents of Mexico city.

Hoyer, et al. [16] conducted a cohort nested case control study to investigate the influence of OC on risk of breast cancer, and survival according to the receptor status (Estrogen receptor positive - ERP or negative - ERN). The receptor status which determines the dependence of breast cancer growth on estrogen will have implications for assessing the potential estrogenic OCs influence on risk of breast cancer and survival. For assessment, OC concentration was categorized in four levels of exposure using quartiles as cut-points.

Tayour C, et al. [17] study evaluated the risk of postmenopausal breast cancer associated with historic pesticide exposure in California's central valley, which is an agriculturally productive region in the US. Exposure assessment was done from the GIS-based method which combines state-reported pesticide use data, land use surveys, and geocoded address for providing estimates of pesticide exposure within a 500 meter buffer around the residential and occupational locations. In this region, the drift of pesticides poses a source of non-occupational exposure.

Assessment of risk and limitations therewith

The Food Quality Protection Act of 1996 required the US EPA to conduct a new type of risk assessment for pesticides which were found to have a common mechanism of toxicity. This cumulative risk assessment is designed to evaluate the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals which share a common mechanism of toxicity [29].

In Kettles, et al. study [10], exposure to triazine herbicides was associated with increased risk of breast cancer in the range of 1.1-2.0. Larger quantity of corn planting and pesticide use were found to have a protective effect against breast cancer, as farmers from such plantations are likely to be more skilled at the application process. This leads to decreased pesticide run-off and less contamination of water. A dose response relationship might be expected when comparing outcome with medium and high triazine exposure levels. This effect may have been minimized due to underreporting of breast cancer cases.

A possible limitation of Kettles study [10] includes misclassification of individuals as per the county of exposure. Given the long latency period for cancer, migration into and out of the counties should have been assessed. All stages of the disease were combined together in this study. It would have been ideal to analyze stage specific incidence of breast cancer.

Rich, et al. [11] study found a null association for breast cancer across all exposure indices both by county and area development districts (ADD). This study found a weak correlation between levels of atrazine in water with corn production and sales of atrazine. This possibly could be explained by the premise that:

- Atrazine may be used for other purposes not routinely reported,
- Shorter half life of atrazine (< 60 days) due to the acidic soil in Kentucky,
- Atrazine may be purchased in one area but used in another.

Demers, et al. study [8] report a significantly higher PCB concentration among cases when compared with controls (6.4, se: 0.2 vs. 5.8, se: 0.2) ng of TEQ/kg of lipids (TEQ: toxic equivalents); p = 0.005, adjusting for age, geography, body mass index, duration of breastfeeding and history of benign breast disease. These results suggest that exposure to dioxin like mono-ortho PCB congeners increases the risk of breast cancer. Alternatively, plasma lipid levels of PCB congeners may not be causally related to the disease but may be an indicator of women metabolically predisposed to breast cancer (Table 2).

Guttes, et al. [12] report that after adjusting for age, higher concentration of p,p'-DDT, p,p'-DDE, HCB as well as few PCB congeners were detected in tissue from cases (breast cancer) than from controls (benign breast disease). The comparison shows significance for mean concentration of p,p'-DDE (p = 0.017) and PCB 118 (p = 0.042). A tendency toward higher concentration of PCB 153 and 180 was also evident. This provides evidence that chlorinated hydrocarbons can act as potential cancer promoters. The study found that the surgical procedure did not influence the results, as there was consid-

Table 2: Risk estimate of PCB concentration among cases in Demers, et al. study [8].

Pesticide compound	OR	95% CI (fourth vs. first quartile)
PCB 118	1.6	1.01, 2.53
PCB 156	1.8	1.11, 2.94
Mono-ortho congeners (PCB 105, 118, 156 expressed in TEQ*)	2.02	1.24, 3.28

*: 2,3,7,8-tetrachlorodibenzo-p-dioxin toxic equivalents (ng/kg).

erable variation in the average concentration of chlorinated hydrocarbons and minimal variation in the tumor and surrounding breast tissue. With regard to p,p'DDE and PCB - 153, the concentration in human blood serum could be correlated with the concentration in breast tissue. This correlation does not apply for majority of other chlorinated hydrocarbons.

Wassermann, et al. [30] study found that the concentrations of p,p'DDT and total PCB were significantly higher in tumor tissue than in the surrounding breast and fat tissue. Aronson, et al. [13] demonstrated a clear association for some PCBs measured in the breast adipose tissue with the risk of breast cancer. The risk is > 2 in the highest concentration categories of PCBs 105 and 118, and the ORs increase linearly across categories (Ps for trend ≤ 0.013). While adjusting for age, menopausal status and other factors, OR > 1 was found for almost all OCs.

Demers, et al. [3] study reports that OC exposure among cases influences the growth or aggressiveness of the disease rather than initiating breast cancer. The mean plasma concentration of chlorinated pesticides was not statistically different among cases when compared with controls. After adjusting for confounders, the RR of having large tumor (≥ 2 cms) increased significantly for β-HCH (OR: 2.25, 95% CI: 1.12-4.51) and trans-nonachlor (OR: 2.27, 95% CI: 1.11-4.65), comparing the highest to the lowest tertiles. The RR of axillary lymph node involvement was statistically significant for p,p'DDE (OR: 2.91, 95% CI: 1.43-5.91), oxychlordane (OR: 2.34, 95% CI: 1.10-4.97), and PCB-153 (OR: 2.12, 95% CI: 1.05-4.3) (third vs. first tertile).

In Romieu, et al. [15] study, serum DDE levels were higher among cases (mean = 3.84 µg/g lipids, sd = 5.98) than among controls (mean = 2.51 µg/g lipids, sd = 1.97). Following adjustment for age, age at menarche, duration of lactation, Quetelet index and serum DDT levels, a positive relation was found for serum DDE levels with the risk of breast cancer (Table 3).

But serum DDT level was not related to the risk of breast cancer. Among post menopausal women, an increased risk was associated with high serum DDE levels (Q1-Q4, OR: 5.26, 95% CI: 0.8-34.3, p = 0.03). Independent of serum DDE levels, a longer period of lactation was associated with slightly decreased risk of breast cancer (OR: 0.91, 95% CI*: 0.85-0.99), *change in risk per 10 months of lactation. We could infer that lactation decreases the cumulative exposure to estrogens.

Table 3: Risk estimate of DDE levels among cases in Romieu, et al. [15] study.

Quartiles	OR	95% CI
Q1 - Q2	1.24	0.5 - 3.06
Q1 - Q3	2.31	0.92 - 5.86
Q1 - Q4	3.81	1.14 - 12.8

Test of trend, p value = 0.02.

Equivocal association

Some studies may not report an association between blood or adipose tissue levels of DDE and the risk of breast cancer. The major route of exposure to human beings is not through the more estrogenic o,p'-DDT found in technical DDT but through the less estrogenic p,p'-DDE found in the diet. It could be hypothesized that among lactating women, these lipophilic OC could be potentially excreted in breast milk.

The matched analysis in Krieger, et al. [18] study found no difference in the serum levels of DDE (mean difference = 0.2 ppb; 95% CI: -6.7, 7.2) or PCBs (mean difference = -0.4 ppb; 95% CI: -0.8, 0.1) among case patients and control subjects. The lack of association was present regardless of year of diagnosis, length of follow-up, or case patient's menopausal and estrogen-receptor status. Notable limitations of the study includes its small sample size, uncertain value of serum organochlorine (OC) levels as a surrogate marker for tissue levels and the unanswered question of the appropriate interval between serum or tissue sampling and breast cancer development.

MacMohan [28] states that the available epidemiological evidence does not infer any association between exposure to DDT and increased risk of breast cancer. In Wolff, et al. [14] study, OC levels were significantly higher among minority than Caucasian women. However regardless of ethnicity, OC exposure was not associated with increased risk of breast cancer in the study [14].

Demers, et al. [3] study did not find a relationship between the risk of breast cancer and OC exposure. A dose related increased risk for p,p'-DDE exposure was found to be associated with lymph node invasion (OR: 2.54, 95% CI: 1.2-5.35), and both lymph node involvement and large tumor (OR: 2.33, 95% CI: 0.94-5.77). The possibility of OC like p,p'-DDE increasing the aggressiveness of breast cancer needs to be further researched.

Hoyer, et al. [16] study reports that environmental OC exposure does not lead to development of an ERP breast cancer. Larger serum levels of dieldrin led to larger ERN tumors (OR: 7.6, 95% CI: 1.4-46.1, p value: 0.01), which were most often disseminated at the time of diagnosis than ERP tumors. No association could be observed for the ERP tumors. The risk of dying for the remaining evaluated compounds was higher among patients with ERP breast cancer when compared with ERN. For PCBs, RR was 2.5 (95% CI: 1.1, 5.7). At the highest dieldrin quartile exposure group, the frequency of large tumors (size > 50 mm) was 27.3% (average size, 37 mm) and 8.7% (average size, 27 mm) for ERN and ERP tumors, respectively. The corresponding proportion for disease spread was 61.5% and 45.8%.

Tayour C, et al. [17] study did not find an association

between breast cancer and exposure to a select group of OC pesticides. However the outcome was significantly likely among women exposed to chlorpyrifos, after adjusting for exposure to other pesticides (OR = 3.22, 95% CI = 1.38, 7.53).

Engel L.S, et al. [19] conducted the agricultural health study during the period 1993-97 at Iowa and North Carolina, US. In this prospective study, they found no clear association for risk of breast cancer among wives of farmers, with farm size or washing of clothes worn during pesticide application. However, the risk was modestly elevated among women whose homes exist closer to the areas of pesticide application. In this study, exposure assessment was based on self-reporting, covering the subject's use over their lifetime. Recall bias could introduce non-differential exposure misclassification which could undermine the risk estimate.

Ting-Ting He, et al. [6] demonstrated that OC pesticides pp'-DDE and PCB52 are risk factors for breast cancer, with a detection rate of > 90% in cases. However, the concentration in breast adipose tissue is not related with the clinicopathologic parameters of breast cancer, such as menopause, age, residence, pathologic diagnosis, histologic grade, status such as ER (estrogen receptor), PR (progesterone receptor), HER2 (human epidermal growth factor) and KI-67 index. The authors thus opine that ER related signaling may not be involved with OC pesticide induced breast cancer development.

Risk factors

In Kettles, et al. study [10], the data from the Kentucky statewide cancer registry shows that a high incidence of breast cancer was associated with higher education and non-black race. In Rich, et al. [18] study, the attribute 'race' does not show the expected protective effect at the ecological level that it shows for individual level in other studies.

Demers, et al. study [8] evaluated confounders such as body mass index (weight (kg)/height (m^2)), total energy consumed, alcohol consumption, age at smoking first cigarette, number of reproductive years, age at first child, total breast-feeding duration, use of oral contraceptives, use of hormone therapy, first degree family history of breast cancer and history of benign breast disease. The authors discuss the mechanisms of causal relationship is through the induction of bio-transformation enzymes which may in-turn affect the estradiol metabolism. The authors opine that higher the activities of biotransformation enzymes in a person (due to genetic polymorphisms or dietary/lifestyle habits), the lower is the concentration of these congeners (PCB 118).

In Krieger, et al. [18] study, serum DDE levels were higher among black case patients compared with black controls (mean difference = 5.7 ppb; 95% CI: 3.3, 14.8), and PCB levels were lower among white case patients compared with white controls (mean difference = -0.6 ppb; 95% CI: -1.2, -0.1). When compared with white women, OC levels were significantly higher among black and Asian women. The mean difference for DDE was 11 ppb for black women (95% CI: 4.3, 17.6) and 12.6 ppb for Asian women (95% CI: 6.0, 19.2), and for PCBs was 0.8 ppb for black women (95% CI: 0.2, 1.4) and 1.4 ppb for Asian women (95% CI: 0.8, 1.9).

Mathur, et al. [9] study reports that rural women had higher levels of OC when compared with urban females as it is adsorbed as a consequence of routine, unintentional or accidental contact with pesticides or their byproducts. Major route of exposure among urban population is through the ingestion of contaminated processed food such as fatty meat and poultry. The urban women can afford the same when compared with the less prosperous farmers (who themselves produce raw meat from their fields). Subjects consuming non-vegetarian diet had higher levels of OC than those consuming vegetarian diet.

Wolff, et al. [14] examined the relationship between race and DDE levels. Race is also an indicator of the socioeconomic status. Lower rates in certain racial/ethnic groups were attributed to differences in their reproductive factors. Hispanic and Asian women experience earlier childbirth, higher parity and longer lactation. Although the incidence of breast cancer is similar among african-american and caucasian women, the affected age group among african-american women is much younger. These women have poor prognosis regardless of age at diagnosis as the disease is diagnosed at a more advanced stage and due to other antecedent factors.

This study [14] reports that tumors among minority women were of slightly higher stage than among Caucasians, but tumor markers were similar across the racial/ethnic groups. Higher DDE levels were associated with increasing body mass index (BMI), decreasing level of education, nulliparity and family history of breast cancer. HPCB levels decreased with BMI and were not correlated with the risk factors for breast cancer. These relationships can be attributed to metabolic differences in OCs related to BMI. African-American women with higher OC levels have poorer survival than Caucasian women, even among postmenopausal women. This pattern is neither explained by medical care nor their socioeconomic status. Environmental factors may play a role in these differences. The slow turnover among obese women explains the positive association of DDE levels with BMI. Minority women had higher BMI on average. This may have contributed to their higher current levels of certain OC compounds. Innate metabolism may also differ among racial/ethnic groups, which can affect long-term disposition of OCs as well as the risk of breast cancer.

Rodgers K.M, et al. [7] systematic review during 2006-2016 highlights evidence suggesting higher risk for breast cancer when exposure to chemicals happen

during breast development (in utero, adolescence, pregnancy). Some of these chemicals include DDT, dioxins, perfluorooctane sulfonamide (PFOSA), and air pollution (risk estimate range: 2.14 to 5.0). Also, for occupational exposure to solvents and gasoline components the risk estimate was in the range of 1.42 to 3.31. The Long Island breast cancer study reports higher risk for exposure to polycyclic aromatic hydrocarbons (PAH) among women with genetic variations, especially in the DNA repair genes.

Silva A.M.C, et al. [4] report a 2.08 times increased risk of breast cancer among women 50 years of age and older who reported early menarche. This shows that the increasing trend of cancer may be attributed not just with increasing lifespan but also due to the diffusion of carcinogenic agents in the environment. Also, chronic exposure to low doses of pesticide during various stages of organ development produces an increase in the carcinogenic process. This study also shows that women living near plantation areas with pesticide application are 2.37 times at risk of breast cancer.

Kaur N, et al. [20] report significantly higher blood levels of α-, β-, γ-HCH, heptachlor, DDE, endosulfan 1 & 2, and dieldrin isomer levels among breast cancer patients when compared with controls. Young women with breast cancer were found to have significantly higher serum levels of all the OC compounds except aldrin, p,p'DDT and methoxychlor.

Developed vs. developing countries

Shakeel, et al. [21] investigated the effect of DDT, DDE, PCB, HCB and HCH on the development of breast cancer between the developed and developing Countries. The study reports that the level of pesticide exposure is higher in developing countries, than the developed world. Although pesticides are used in large amounts in developing Countries, there is lack of research addressing their relation with breast cancer. However, research results from the developed countries cannot be generalized to developing countries. This review [21] also found a positive association for DDT with the risk of breast cancer. The results for other pesticides were equivocal. It was found that industrialized countries use more of PCBs and the developing countries use HCH, DDT and its derivatives. The chemical property of DDT used in developed countries post-1970 has changed from the more estrogenic o,p'-DDT to the lesser estrogenic p,p'-DDE. Although the pesticide usage is 100 fold more in India, there is no proportionate increase in the tissue levels of these pesticides or of cancers. Some epigenetic process might provide a protective effect in such scenarios, including activation of biotransformation enzymes. This presumption arises when we analyze the breast cancer incidence among migrant Asian women in US and Europe, where-in the morbidity is lesser than the natives. We need to factor the synergistic effect of these Pesticides also.

Future area of research

The contradictory results from various studies could be attributed to various factors including geographic variation, divergent study designs, biological matrices used for OC pesticide exposure assessment including historic exposure, various age groups, race and dietary patterns.

We need to use ecological proxies of individual level covariates (race, education, income) with caution in ecological studies, as these variables could be inter-related (distribution of race in the population is associated with other socio-economic indicators such as poverty, access to screening, smoking pattern etc). These variables could in-turn have an interactive effect on the incidence of cancer.

Data from studies done at the individual level are recommended for elucidating the relationship between estrogenic environmental exposures and female reproductive cancers. A population based case control study would enable the analysis of multiple risk factors as well as the stage specific incidence of breast cancer.

Research should focus on determining levels of carcinogenic substances in breast tissue, and not just in the plasma or serum, as this represents cumulative internal exposure at the target site. We need to explore the estrogen receptor (ER) status of breast cancer, which may merely represent various stages in disease progression. Although usage of DDT and PCBs have been phased out and blood levels are thus reducing, available evidence suggests that past exposures during early stages of life contributes to the risk of breast cancer in the later stages. This suggests precautionary use of other chemicals which disrupt mammary gland development, as evidenced from toxicological studies.

Phytochemicals and other bioactive dietary compounds can modulate epigenetic events. Therapeutic research should target reversible epigenetic modifications.

Conclusion

Wide variations exist for risk of breast cancer among different racial, ethnic, geographic and migrant groups. The variable geographical pattern of breast cancer across the Country is due to the differences in known risk factors such as parity, age at menarche, menopause and alcohol consumption. Estimating the risk of adult breast cancer with previous cumulative exposure requires accurate measurements over many years, which presents methodological challenges. Many studies either do not specify the timing of exposure or assess exposure during a biologically relevant window (during various stages of breast development).

The effects of OC are mediated at least in part through pathways other than the estrogen receptor pathway. We need to determine the interactive effect

of a mixture of OCs in the pathogenic pathway. Xenobiotic combinations may have additive, synergistic or antagonistic effects. Extensive analysis of such dose response relationships is required. Environmental contaminants (DDT & its metabolites, PCBs) may act alone or in concert simulating the effect of estrogens in breast tissues. Research process should delineate the estrogen receptor and non-estrogen receptor mediated pathway as well as explore the effect of xenoestrogens on signal transduction and growth regulatory pathways. Future research should focus on the metabolic pathways involved in the biotransformation of chemical carcinogens, including the various cytochrome P450 enzymes involved in their metabolism.

We need to clarify the possible adverse effect of environmental OC exposure on the prognosis of hormone responsive breast cancer. It is difficult to obtain epidemiological evidence for evaluating the life-long risk to humans from these chemicals given the long duration of study. Alternatively, toxicological evidence should enable the public health decisions. Further studies should assess the tissue levels of p.p'-DDE and their influence on the stage of breast cancer, metastatic potential or lymph node involvement.

Further research should focus on chemical-specific associations and examine different levels of exposure and dose-response relations. This will enable the planning of public health interventions, more so for people unknowingly exposed to these chemicals in the air.

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Conflicts of Interest

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