Exposure to Dichlorodiphenyltrichloroethane and the Risk of Breast Cancer: A Systematic Review and Meta-analysis

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Received: February 5, 2014
Revised: February 13, 2014
Accepted: February 14, 2014

KEYWORDS:
breast cancer, dichlorodiphenyltrichloroethane, meta-analysis, pesticide exposure, systematic review

Abstract
Objectives: This study extended and updated a meta-analysis of the association between exposure to dichlorodiphenyltrichloroethane (DDT) and the risk of breast cancer.
Methods: We reviewed the published literature on exposure to DDE and breast cancer risk to update a meta-analysis from 2004. The total of 35 studies included 16 hospital-based case-control studies, 11 population-based case-control studies, and 10 nested case-control studies identified through keyword searches in the PubMed and EMBASE databases.
Results: The summary odds ratio (OR) for the identified studies was 1.03 (95% confidence interval 0.95-1.12) and the overall heterogeneity in the OR was observed ($I^2 = 40.9\%$; $p = 0.006$). Subgroup meta-analyses indicated no significant association between exposure to DDE and breast cancer risk by the type of design, study years, biological specimen, and geographical region of the study, except from population-based case-control studies with estimated DDE levels in serum published in 1990s.
Conclusion: Existing studies do not support the view that DDE increases the risk of breast cancer in humans. However, further studies incorporating more detailed information on DDT exposure and other potential risk factors for breast cancer are needed.

1. Introduction
Dichlorodiphenyltrichloroethane (DDT) is a synthetic chemical that includes $p,p'$-dichlorodiphenyltrichloroethane ($p,p'$-DDT), $p,p'$-dichlorodiphenyl dichloroethylene ($p,p'$-DDD), and $p,p'$-dichlorodiphenyldichloroethylene ($p,p'$-DDE), and $p,p'$-dichlorodiphenyltrichloroethane ($p,p'$-DDD or $p,p'$-TDE). DDE (dichlorodiphenyldichloroethylene) is the main metabolite of DDT, which is rapidly converted into DDE in biological systems [1]. After identifying its insecticidal function, DDT was widely used...
to prevent malaria and some agricultural pests worldwide. Although the use of DDT was banned in most developed countries in the early 1970s, DDT was still used in some developing countries, such as India, Indonesia, and Mexico, until the 1990s to control the mosquitoes that cause malaria [1,2].

DDT is bioaccumulated in the lipid component of biological systems through the food chain because it is highly lipophilic and is resistant to degradation. Therefore, despite its prohibition in many countries, DDT is still present in the environment and the food chain. DDE in particular has a very long half-life and is of toxicological importance. The half-lives of DDT and DDE in humans have been estimated to be between 6 years and 10 years [3]. The DDT and DDE accumulated in the lipid components, such as adipose tissue, are slowly released into the bloodstream [4]. DDT and its metabolites have been associated with adverse effects including obesity, type 2 diabetes mellitus, and carcinogenicity [5–7]. These chemicals can affect various tissues through mechanisms involving the steroidogenic pathway such as antiandrogenic or estrogenic activity, and receptor-mediated changes in protein synthesis [8–10].

Since DDT and DDE were first reported to be related to breast cancer in 1993 [11], there has been increased attention on the association between exposure to DDT and the risk of breast cancer. Although many epidemiological studies have been conducted to investigate the relationship between DDT exposure and breast cancer risk, there is a large heterogeneity between studies and the findings are not conclusive. Because a meta-analysis study showed no evidence of an association between DDT exposure and breast cancer risk [12], several new epidemiological studies have been published about the relationship between the body burden of DDT and breast cancer risk [13–18].

In the work reported here, we aimed to provide an update of a systematic review and meta-analysis to estimate the association between DDE exposure and the risk of breast cancer based on study characteristics.

2. Materials and methods

2.1. Study selection

We searched and reviewed the PubMed and EMBASE databases to identify eligible epidemiological studies published in English up to August 2012 using selected common keywords related to DDT exposure and the risk of breast cancer. The reference lists of the identified papers and previous literature reviews were carefully examined for additional studies. The combination of keywords such as DDT, chlorphenotane, dichlorodiphenyldichloroethylene, DDE, p,p'-DDE, 1,1-dichloro-2,2-bis(4 chlorophenyl)ethylene, hydrocarbons, chlorinated, organochlorines, organochlorine pesticides, breast cancer, and breast neoplasm were entered as both medical subject heading (MeSH) terms and text words. The subject of the papers was limited to humans for all databases. We included epidemiological studies that met the following criteria: (1) studies that presented original data from case–control or cohort studies; (2) the outcome of interest was clearly defined as breast cancer; (3) the exposure of interest was DDT or DDT metabolites; and (4) studies that provided measurements with relative risk estimates and 95% confidence intervals (CIs), odds ratios (ORs) and 95% CIs, or values in cells of a 2 × 2 table (e.g., number of cases and controls in exposure categories from which the OR could be calculated). If the data were duplicated or shared in more than one study, only the most recent or more comprehensive study was included in the analysis.

![Database search and selection criteria](image-url)

**Figure 1.** Process used for literature search.
2.2. Data extraction

All studies for which an abstract was present were reviewed and extracted independently by two evaluators (E.S.C. and Y.K.) according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [19]. Disagreements between evaluators about selected studies were resolved by discussion. The following data were extracted from the eligible studies and included in the final analysis: first author’s name, publication year, study years, country, study design, number of participants (cases and controls), type of biological specimen, and OR with 95% CIs for association between the exposure of DDT and breast cancer.

Meta-analytic techniques that weight the logarithm of the OR of each study by a function of its variance were used to calculate a summary estimate. Meta-analyses were performed on the total data set and separately for the type of design (hospital-based case-control, population-based case-control, and nested case-control), study years (2000s, 1990s, 1980s, 1970s, and 1960s), biological specimen (serum, plasma, and adipose tissue), and geographical region of the study (North America, Europe, Asia, and South America). A random effect model was used to estimate pooled ORs regarding the potential heterogeneity of

| Author (year)          | Study years | Country   | Design       | n (cases/controls) | Biological specimen | OR (95% CI)   |
|------------------------|-------------|-----------|--------------|--------------------|---------------------|--------------|
| Aronson (2000)         | 1995–1997   | Canada    | Hospital CC  | 217/213            | Adipose tissue      | 1.10 (0.78–1.55) |
| Charlier (2004)        | 2001–2002   | Belgium   | Population CC| 231/290            | Serum               | 2.21 (1.41–3.48) |
| Cohn (2007)            | 1959–1967   | USA       | Hospital CC  | 129/129            | Serum               | 1.29 (0.85–1.96) |
| Dello Lacovo (1999)    | 1997–1998   | Italy     | Population CC| 170/195            | Serum               | 1.02 (0.68–1.54) |
| Demers (2000)          | 1994–1997   | Canada    | Population CC| 315/307            | Plasma              | 0.91 (0.70–1.17) |
| Demers (2000)          | 1994–1997   | Canada    | Hospital CC  | 315/219            | Plasma              | 1.01 (0.74–1.39) |
| Dorgan (1999)          | 1977–1987   | USA       | Nested CC    | 105/207            | Serum               | 0.70 (0.47–0.99) |
| Gammon (2002)          | 1996–1997   | USA       | Population CC| 643/427            | Serum               | 1.20 (0.76–1.90) |
| Gatto (2007)           | 1995–1998   | USA       | Population CC| 355/327            | Serum               | 1.05 (0.82–1.35) |
| Helzlsouer (1999)      | 1974        | USA       | Nested CC    | 235/235            | Serum               | 0.94 (0.71–1.25) |
| Helzlsouer (1999)      | 1989        | USA       | Nested CC    | 105/105            | Serum               | 0.88 (0.56–1.38) |
| Hoyer (1998)           | 1976        | Denmark   | Nested CC    | 237/469            | Serum               | 0.88 (0.56–1.37) |
| Hoyer (2000)           | 1976–1978/  | Denmark   | Nested CC    | 240/477            | Serum               | 1.04 (0.70–1.55) |
|                         | 1981–1983   |           |              |                    |                     |              |
| Ibarluzea (2004)       | 1996–1998   | Spain     | Hospital CC  | 198/260            | Adipose tissue      | 1.16 (0.83–1.62) |
| Itoh (2009)            | 2001–2005   | Japan     | Population CC| 349/349            | Serum               | 0.74 (0.48–1.13) |
| Iwasaki (2008)         | 1990–1995   | Japan     | Nested CC    | 139/278            | Plasma              | 1.23 (0.80–1.90) |
| Krieger (1994)         | 1964–1969   | USA       | Nested CC    | 150/150            | Serum               | 1.31 (0.82–2.09) |
| Laden (2001)           | 1989–1990   | USA       | Nested CC    | 372/372            | Plasma              | 0.79 (0.61–1.01) |
| Liljegren (1998)       | 1993–1995   | Sweden    | Hospital CC  | 43/35              | Adipose tissue      | 0.40 (0.10–1.20) |
| Lopez-Carrillo (1997)  | 1994–1996   | Mexico    | Hospital CC  | 141/141            | Serum               | 0.68 (0.43–1.07) |
| McCready (2004)        | 1995–1997   | Canada    | Hospital CC  | 68/52              | Adipose tissue      | 2.48 (1.08–5.71) |
| Mendonca (1999)        | 1995–1996   | Brazil    | Hospital CC  | 162/331            | Serum               | 1.05 (0.75–1.46) |
| Millikan (2000)        | 1993–1996   | USA       | Population CC| 748/659            | Plasma              | 1.07 (0.86–1.32) |
| Moysich (1998)         | 1986–1991   | USA       | Population CC| 154/192            | Serum               | 1.15 (0.74–1.79) |
| Olaya-Contreras        | 1995–1996   | Colombia  | Hospital CC  | 153/153            | Serum               | 1.56 (1.02–2.39) |
| Pavuk (2003)           | 1997–1999   | USA       | Hospital CC  | 24/85              | Serum               | 1.49 (0.45–4.87) |
| Raaschou-Nielsen (2005)| 1993–1997   | Denmark   | Nested CC    | 363/363            | Adipose tissue      | 0.87 (0.69–1.10) |
| Romieu (2000)          | 1990–1995   | Mexico    | Population CC| 120/126            | Serum               | 2.02 (1.14–3.57) |
| Rubin (2005)           | 1981–1987   | USA       | Population CC| 63/63              | Serum               | 0.97 (0.41–2.32) |
| Schecter (1997)        | 1994        | Vietnam   | Hospital CC  | 21/21              | Serum               | 0.69 (0.23–2.07) |
| Stellman (2000)        | 1994–1996   | USA       | Hospital CC  | 232/323            | Adipose tissue      | 0.94 (0.66–1.33) |
| van’t Veer (1997)      | 1991–1992   | Five European countries | Hospital CC | 265/341 | Adipose tissue | 0.75 (0.52–1.08) |
| Wolff (1993)           | 1985–1991   | USA       | Population CC| 58/171             | Serum               | 2.30 (1.31–4.04) |
| Wolff (2000)           | 1994–1996   | USA       | Hospital CC  | 151/317            | Serum               | 0.86 (0.61–1.22) |
| Wolff (2000)           | 1987–1992   | USA       | Nested CC    | 110/213            | Serum               | 0.83 (0.50–1.37) |
| Zheng (1999)           | 1994–1997   | USA       | Hospital CC  | 304/304            | Adipose tissue      | 1.02 (0.73–1.41) |
| Zheng (2000)           | 1995–1997   | USA       | Hospital CC  | 475/502            | Serum               | 1.01 (0.79–1.28) |

CC = case-control study; CI = confidence interval; OR = odds ratio.
the study populations. Statistical heterogeneity between studies was assessed with the \(Q\)-statistics and quantified by \(I^2\), which measured the percentage of total variation in included studies [20]. Significant heterogeneity was defined as the \(Q\)-statistics test \(p < 0.1\) or \(I^2\) greater than 50%. We assessed potential publication bias by examining funnel plots and using Egger’s test. All the statistical analyses were performed using the Stata 12.0 software (StataCorp, College Station, TX, USA).

Figure 2. (A) Odds ratios (ORs) for DDT exposure and breast cancer. (B) Funnel plot of all included studies.
3. Results

The PubMed and EMBASE search yielded 530 papers and 44 papers remained after screening based on the inclusion criteria. On reviewing of the full text of the remaining 44 papers, we identified 35 papers on the exposure to DDE and the risk of breast cancer. Two papers each consisted of two subpopulations and we treated the data of each subgroup as a separate study (Figure 1).

Table 1 gives the details of the 35 studies that were included in the meta-analysis. All were case–control studies and of these 10 were prospective (nested case–control) and 16 were hospital based case–control studies, and 11 were population based case–control studies, which consist of 8160 cases and 9280 controls. Five studies indicated a significant positive association with the risk of breast cancer, whereas no significant association was observed in 32 studies. Twenty-two studies conducted in the USA and Canada, eight in Europe, three in Asia, and four in South America. In most studies, the level of DDE was measured in serum samples.

Overall, there was no significant association between the exposure to DDE and the risk of breast cancer in the meta-analysis of all case–control studies (OR 1.03, 95% CI 0.95 to 1.12; Figure 2A) and there was some evidence for heterogeneity (p = 0.006, $I^2 = 40.9$). However, no significant publication bias was observed in the selected studies (Begg’s funnel plot was symmetric; Egger’s test, p for bias = 0.145; Figure 2B).

To resolve the heterogeneity, we performed subgroup meta-analyses by the type of study design, study years, type of biological specimen, and country (Table 2). We found a borderline statistically significant summary OR for population-based case–control studies with 1.19 (95% CI 0.99–1.44), although there was a considerable heterogeneity based on the 11 studies ($I^2 = 61.3$). However, there was no significant association in other subgroup meta-analysis.

Figure 3 shows the subgroup meta-analysis for population-based case-control studies with estimated DDE levels in serum published in 1990s. The OR for this subgroup indicated 1.28 (95% CI 1.00–1.65; Figure 3A), although there was a high heterogeneity (Figure 3B). In other stratified meta-analyses, there was no significant association between exposure to DDE and the risk of breast cancer (data not shown).

4. Discussion

We found that there was no significant evidence of an association between the risk of breast cancer and exposure to DDE with recent published literature. Subgroup meta-analyses by the type of design, study years, biological specimen, and geographical region of study also do not support a relationship between exposure to DDE and the risk of breast cancer. However, population-based case–control studies with estimated DDE levels in serum and published in the 1990s showed marginally significant findings, which need further investigation.

| Table 2. Meta-analysis of the effect of the exposure to DDT on the risk of breast cancer according to subgroup |
|----------------------------------------------------------------------------------------------------------------|
| **Studios included** | **No. of Studies** | **OR** | **95% CI** | **Heterogeneity** | **Egger’s test** |
| | | | | **p-value** | **$I^2$ (%)** | **(p for bias)** |
| **Type of study design** | | | | | |
| Hospital CC | 16 | 1.02 | 0.91 to 1.15 | 0.183 | 24.0 | 0.780 |
| Population CC | 11 | 1.19 | 0.99 to 1.44 | 0.004 | 61.3 | 0.212 |
| Nested CC | 10 | 0.90 | 0.81 to 1.01 | 0.554 | 0.0 | 0.274 |
| **Study years** | | | | | |
| 2000s | 2 | 1.28 | 0.44 to 3.71 | 0.001 | 91.5 | — |
| 1990s | 27 | 1.03 | 0.94 to 1.24 | 0.034 | 35.9 | 0.169 |
| 1980s | 4 | 0.87 | 0.69 to 1.09 | 0.575 | 0.0 | 0.908 |
| 1970s | 2 | 0.92 | 0.73 to 1.17 | 0.808 | 0.0 | — |
| 1960s | 2 | 1.30 | 0.95 to 1.77 | 0.962 | 0.0 | — |
| **Type of biologic specimen** | | | | | |
| Serum | 24 | 1.07 | 0.93 to 1.11 | 0.006 | 47.0 | 0.365 |
| Plasma | 5 | 0.97 | 0.85 to 1.11 | 0.325 | 14.1 | 0.910 |
| Adipose tissue | 8 | 0.98 | 0.83 to 1.16 | 0.141 | 36.0 | 0.228 |
| **Country** | | | | | |
| North America | 22 | 1.01 | 0.92 to 1.10 | 0.185 | 21.0 | 0.524 |
| Europe | 8 | 1.02 | 0.81 to 1.29 | 0.010 | 62.0 | 0.246 |
| Asia | 3 | 0.92 | 0.63 to 1.36 | 0.226 | 32.8 | 0.900 |
| South America | 4 | 1.20 | 0.78 to 1.83 | 0.012 | 72.8 | 0.707 |

CC = case–control study; CI = confidence interval; OR = odds ratio.
Many studies did not report an increased risk, despite the first publication reporting an excess of breast cancer associated with exposure to DDE [11]. Five studies [11, 14, 18, 21, 22] among the 35 pooled studies included in our meta-analysis found a positive association between exposure to DDE and the risk of breast cancer. There was moderate heterogeneity among the pooled studies. The inconsistency and heterogeneity of the studies could be explained by potential confounders or modifiers that might affect the relationship between DDE and the risk of breast cancer. One potential explanation for the huge differences in the risk of breast cancer and the moderate heterogeneity among pooled studies is that there is a delayed time between exposure and diagnosis. As DDT can remain in the body for a long period, there is a limitation to identifying accurately the exposure period and levels of exposure.

As DDT crosses the placenta to the fetus and is secreted in breast milk [23], human exposure begins during the early prenatal period and continues during the breastfeeding neonatal period. Evidence for DDE release from fat storage tissue in humans has been provided by breastfeeding studies, which have been found to decrease the risk of breast cancer [24, 25]. Exposure during the prenatal and neonatal periods may reduce the distinction between the exposed and unexposed groups and make it harder for such studies to show a true causal association. The age at exposure to chemicals such as DDE is also an important modifier in explaining the relationship between exposure and the risk of disease. Cohn et al [27] reported that DDT was associated with breast cancer only for women potentially exposed at a young age (prior to 14 years of age). Thus the relationship between age at exposure to DDT
and breast cancer represents an important area in need of further research.

The other limitation is combined exposure with other chemicals in the natural environment. Many persistent organic pollutants, including DDT, are known or suspected to be endocrine disruptors. However, these chemicals do not all have the same effect; some chemicals have an agonistic role in estrogenic effects, but others have an antagonistic role. Thus current estimations may rule out the possibility that there is a particular hazard from these mixtures or one chemical, whereas exposure to several different chemicals may have a pronounced effect due to their combination.

In summary, our meta-analysis found no evidence that there is an association between exposure to DDE and the risk of breast cancer. Although our results indicate no relationship, there are still several limitations to this study, such as the delay time between exposure and diagnosis, age of exposure, the effect of susceptible populations, and combined exposure with other potential carcinogens. It is particularly important to recommend studying the relationship between DDT and breast cancer based on age of exposure and combined exposure to a number of potential carcinogens.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

This research was supported by a grant (12161MFDS767) from Ministry of Food and Drug Safety, Osong, Korea in 2012.

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