The Role of the Insecticide DDT in Breast Cancer

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Breast cancer is by far the most common cancer among black and white females, with approximately 211,000 new cases expected to be diagnosed in the U.S. in 2004 (1). More importantly, incidence has been increasing. Age-adjusted breast cancer incidence in U.S. females rose from the 88.6 per 100,000 in the early 1970s to 109.8 in the early 1990s (2). This represents a 24 percent increase over that time. This trend is only partially explained by the known risk factors for breast cancer, including advancing age, early menarche, late menopause, late age at first parturition and family history. Therefore, researchers have been searching for additional contributing factors, including environmental exposure to compounds known or suspected to be carcinogenic or estrogenic (estrogenic compounds are recognized as carcinogens, and are considered particularly important in breast cancer). This search has lead to a resurgence of interest in the possible role of the insecticide DDT in breast cancer (3).

Dichlorodiphenyltrichloroethane (DDT) was the first chlorinated insecticide created. Originally prepared in 1873, the compound was found to have mild hormone-like activity but no functional purpose was recognized. It was not until 1939 that Paul Muller of Geigy Pharmaceutical in Switzerland discovered the effectiveness of DDT as an insecticide. DDT immediately came into widespread agricultural and commercial use, with approximately 675,000 tons being applied in the US alone between 1940 and 1972 (4). Beginning in the late 1950s and early 1960s, concerns were raised because of DDT's long half-life, lipid solubility and the subsequent bio-accumulation in higher levels of the food chain. This reached a crescendo in 1962, with the publication of Rachel Carson's book *Silent Spring*. She asserted that widespread use of organic pesticides, and particularly DDT, was causing significant injury to the environment and wildlife. As criticism mounted, many people began to question the validity of early toxicology studies of DDT. However, little new conclusive evidence was developed.

In 1972, the director of the Environmental Protection Agency (EPA), William Ruckelshaus, banned virtually all DDT use in the U.S. In his justification for the ban, Ruckelshaus stated that, “DDT is a potent human carcinogen.” However, some have alleged that the decision was more political than scientific, and the carcinogenic nature had not been established (5). DDT use continued in other parts of the world, and even today a lively debate exists as to whether its benefits exceed its risks. This paper will attempt to review some of the data available about the possible association of DDT with a single type of cancer, breast cancer.

Numerous challenges exist in studying a potential association between DDT and breast cancer. The first is the long latency period that is known to exist for cancer development, even among strong carcinogens. Thus, the majority of studies relating to this topic have been case-control. Others, including arguably the most complete and meaningful studies, have been prospective studies, with nested case control components (6).
Some of the studies have been limited by a small sample size, but many have had large numbers of participants. Finally, review studies have also been done, seeking to increase the power and significance of the various findings by doing meta-analysis (7, 8).

Because the majority of studies have at least some case-control component, much of the discussion will focus on the findings, challenges and shortcomings of this approach. Despite efforts to overcome the deficiencies associated with case-control studies, problems persist, and these make the interpretation of many of the studies difficult. Specific challenges include definition of exposure, selection of controls and potential for confounding factors. The underlying causes for these difficulties, and the various attempts to address them, will be discussed separately in the next several paragraphs. A summary of the conclusions will then be presented, followed by interpretation of current knowledge, and suggestions for future research.

IDENTIFYING EXPOSURE

While defining an exposure is often a problem in case-control studies, it is especially difficult in this subject because people are often unaware of exposure to the compound. An individual may be exposed by using DDT, having it applied to them (this was common in the early period of use, for louse control, among other reasons), working or living in areas where it has been applied or by eating foods that have accumulated DDT residues. Because of these challenges, biological markers have typically been used to assess exposure. These include analysis of serum and other body tissues (typically fat) for presence of DDT and its metabolites (3). Because of the lipophilic nature of these compounds, many studies sought to assess levels in fatty tissue, particularly that of the breast. This would be expected to best reflect the level of exposure at the cells of interest, and provide relevant and meaningful information. However, collection of this material requires an invasive procedure, and thus would not likely be done without a justification greater than research interest. In individuals selected as breast cancer cases, collection was done either at time of biopsy or excision of a malignant mass. Controls were often selected based on the presence of a non-malignant breast mass, and had undergone similar biopsy or excisional procedures (9, 10). Use of such a control group creates a serious challenge in interpretation, because it is conceivable that DDT exposure is a risk factor for non-malignant, as well as malignant, changes in the breast.

Subsequent researchers have sought to use serum levels to assess exposure, and several studies have concluded that serum levels can be expected to be an accurate predictor of residues found in other tissues (11 - 13). However, limitations have been identified, including the need for adjusting for serum lipid content, as opposed to simply reporting on a wet weight basis. Other studies have determined that serum levels are more a reflection of acute or recent exposure to DDT, and do not correlate with levels found in adipose tissue (14). Consequently, there is no consensus as to an appropriate tissue source for residue measurement, but most researchers appear to be moving toward appropriately adjusted serum measurements. Regardless of what tissue source is used, it is important to use caution when comparing residue levels across studies. Considerable variation can result from different analytic techniques and equipment (3).
The debate of exposure assessment also extends to what compounds to measure. There is significant difference in the estrogenic activity of various components and metabolites of commercial DDT. The technical DDT compound that was used for insect control is actually a mixture of multiple isomers. The most common isomer is \( p,p'-\text{DDT} \), but the most hormonally active is \( o,p'-\text{DDT} \). The major metabolites, \( p,p'-\text{DDE} \) and \( o,p'-\text{DDE} \) are less hormonally active than their parent compounds (3). Some have argued that other minor metabolites, such as various hydroxylated constituents, have greater estrogen activity, and are therefore the most likely products to be associated with induction of breast cancer. While the validity of this statement is recognized by others, the reliance on these compounds for epidemiological investigation is greatly hindered by their rapid metabolism and excretion. Therefore, most investigators have relied upon more persistent compounds that would be suggestive of exposure to the parent compound, and presumably, the various metabolites as well. The most persistent and frequently measured compounds are DDT and dichlorodiphenyl-dichloroethylene (DDE). However, the validity of using DDE has been impugned, as well, because humans do not metabolize DDT to DDE very efficiently. Rather, much of the DDE levels found in humans is likely from pre-formed DDE that is consumed in the diet (other animals are more efficient in metabolizing DDT to DDE, and therefore they accumulate DDE in their tissues) (16). This is significant because DDE itself is considered to have a relatively low toxicity compared to the parent compound and other metabolites. Additionally, DDE is not further metabolized by humans, and therefore consumed DDE would end up stored, resulting in no exposure to other compounds. Despite the above stated limitations, most studies have measured \( p,p'-\text{DDT} \) and \( p,p'-\text{DDE} \) residues because of their ease of detection and stability in tissues. These are considered to serve as a proxy for exposure to all related compounds and metabolites. Unfortunately, few if any studies have sought to correlate these bio-markers with self-reported exposures. While self-reported exposure would create a potential for recall bias, it may assist in interpreting measured levels, and could help to differentiate between different chemicals, isomers, metabolites and routes of exposure, which may pose different levels of risk (3).

Another factor with the potential to influence exposure assessment is the analytical techniques employed. There are numerous methods to extract and measure DDE and DDT, with variations including extraction via solvent versus supercritical CO2, and analysis through mass spectrometry versus gas chromatography. A significant variation has been reported as to percent of residues recovered and reported with different techniques, although refinement and validation have reduced the effects of these problems. It is imperative that the investigators identified and followed appropriate quality assurance and quality control efforts before accepting the integrity of the results. Care must once again be used in comparing results from multiple studies, particularly raw data (3).

IDENTIFYING POPULATIONS

After a researcher has determined his/her exposure definition and means of measurement, a study population must be selected for comparison. Cases are almost exclusively chosen based upon histological confirmation of a malignant growth with the breast tissue (10, 17, 18). Controls have been selected from a variety of sources, with nearly
every researcher using slightly different criteria. The criticism of using non-malignant breast patients has already been discussed, but certainly highlights the pitfalls of control selection. Other sources of controls have ranged from women who died accidental deaths, to hospital patients, to seemingly healthy blood donors, to women undergoing elective breast reduction. Studies have also focused on women of different races, socioeconomic status, nationality and residence (9, 19, 20). One meta-analysis found papers from 11 countries (8). This is significant because of the different rates and routes of exposure that could be expected in each of those countries. For example, the use of DDT was stopped decades ago in the U.S. and much of Europe; its use has dropped considerably, but still continues in Mexico and was only recently discontinued in Brazil; and use continues at high levels in Vietnam. Therefore, inter-national comparisons will have a wide discrepancy in rates and methods of exposure.

The principle consideration in comparing cases and controls is often how best to account for the many various risk factors for breast cancer. Because both breast cancer incidence and DDT and DDE accumulation increase with age, virtually all studies controlled for age of cases and controls. Some studies did this by matching cases and controls by age, while others used statistical correction (18, 21). Most studies also controlled for other known risk for breast cancer, such as familial history, age at menarche, age at menopause, etc. A few also considered hormone replacement therapy, since this often involves estrogen exposure, as well. Many studies sought to control for the effects of breastfeeding; this is because breast feeding is a major route of excretion of DDT residues and would be expected to alter tissue levels (22). After these common factors, the remainder of variables becomes quite large and not consistently applied. Some researchers attempted to control for factors that would affect expected tissue levels, such as fasting status (would alter serum lipid content), Body Mass Index (BMI- an estimation of body fat that would influence the storage ability for DDT and DDE; obesity has also been linked to breast cancer), and as mentioned previously, the lipid content of the serum (23). Dietary variation has quite often been ignored. This presents a two-fold problem; one, breast cancer has been linked with dietary factors such as saturated fat (risk) and fiber (protective) (24); second, diet can influence intake of DDT and its metabolites. Slightly higher levels of DDT and various metabolites were found in meat compared to vegetables and grains, while seafood was significantly higher (25). It has typically been presumed that individuals who consume diets largely from animal origin would be exposed to higher levels of DDT and DDE (due to the bioaccumulation in fat tissue). However, at least one study found this to not be the case; that is, there seemed to be no relation between dietary habits and serum DDT levels (26). Other issues related to diet include the possibility for some compounds in food to potentiate the estrogenic action of DDT (phytoestrogens, for example) and compounds found to inhibit estrogenic actions (isoflavonoids, for example) (23). The wide array of possible interactions of diet with DDT levels and breast cancer make it a particularly complex confounder. While it would be difficult to adequately control for all of the possible effects (particularly since many are not completely understood), it would seem wise to attempt to match cases and controls by dietary habits. Thus far, only a few studies have sought to evaluate dietary effects, and none reviewed matched cases and controls for diet (27 - 29).
DATA ANALYSIS & INTERPRETATION

Similar to the other steps already discussed (defining exposure and identifying the population of interest), an array of methods have been employed to use the data to draw conclusions. Some studies have chosen to compare tissue levels on an arithmetic scale, while others have used a logarithmic one or square root. Further, some studies have looked for a linear relationship (as residues go up, so does breast cancer), while others have sought to elucidate if a threshold phenomenon may occur. This is typically achieved by segmenting the findings into groups (usually quartiles or quintiles) according to tissue levels, then comparing cancer occurrence in the highest exposure group to that of the lowest (3). Comparisons of the extreme quartiles/quintiles would certainly increase sensitivity; however, it would be essential to account for confounders, which are frequently associated with both high exposure to DDT and breast cancer incidence (socioeconomic status, race, etc.). These factors would likely skew results obtained from comparing extremes more than they would affect results based on mean values.

The complexity of appropriately conceiving and executing an effective case-control study for this topic makes it apparent why so many studies have been undertaken, and none have been considered conclusive. As mentioned earlier, researchers have sought to expand their capabilities of discernment through meta-analysis of existing studies or utilizing other study designs. Numerous advantages can be found by incorporating a prospective component (collecting samples, then waiting for development of cancer to assign cases and controls). This not only helps solidify that exposure preceded the disease, but also gives a magnitude of exposure at a distant point in time. In other words, some individuals may have had high levels in the past that have remained steady or declined slightly with time, while others have had steadily increasing levels. Additionally, it helps eliminate some of the selection bias created in matching controls. The two reference populations are more likely to be comparable, at least at time of collection of sample, than if cases were selected from hospitalized and controls from non-hospitalized individuals, for example. While it eliminates some of the drawbacks associated with case-control methods, this approach shares others and creates some of its own. First, matching of cases and controls still needs to be done, and can still lead to introduction of confounders. Second, it largely ignores any events or factors that occur between collection and case selection. This can be both an advantage (if blood is collected prior to initiation of breast feeding, it eliminates the possibility of falsely reducing levels of DDT and DDE), and a disadvantage (if large exposures or other confounders occur after tissue collection, but is not recognized or accounted). Prospective collection of specimens also introduces a selection bias, as samples are more likely to be collected from a “volunteer” population, which may be better educated, of a higher socio-economic status, and non-smokers (30). Several large studies have been done in this fashion, principally through the collection and storage of serum (30-32). The time frames of sample collection varied from one month to 30 years prior to diagnosis of cancer.

Another method to mitigate some of the complications associated with case-control studies is through combining multiple studies into a single discussion or analysis. This approach not only increases the power of the study to detect associations (by increasing number of participants); it also serves to reduce the impact of confounding factors. Only
one self-described meta-analysis was located for this topic, but another publication combined and analyzed the data from five independent studies. The meta-analysis initially examined 35 studies, and eventually compiled and analyzed the results and conclusions from 22 of these. The conclusive values (odds ratios, confidence interval) of the various studies were analyzed for comparison. Additionally, the researchers made an attempt to standardize the raw data across a portion of the studies for comparison and integration. In an effort to make comparisons accurate and legitimate, separate analyses were done to account for the variety of confounding factors found in each study. For example, studies that controlled for breastfeeding were compared separate from those that did not (23). Unfortunately, the variations in study design, chemical analysis and data interpretation limited the ability of the meta-analysis to truly examine the information as a single group.

Many of the difficulties encountered in the meta-analysis were overcome in the combined analysis of five studies. While great differences still existed amongst the studies, they were, as a whole, much more homogenous than the studies contained in the meta-analysis. Characteristics that improve the comparability include the fact that all specimens examined were serum (although methods of reporting varied, and had to be standardized); and many of the same confounders were controlled for in each study, reducing the amount of statistical manipulation necessary. The power of the comparison was increased by the fact that cases and controls were chosen from a variety of sources, but were from limited geographical regions; the large number of participants examined (1400 cases and 1462 controls); and the fact that studies used a combination of retrospective and prospective collection (7).

Several reviews have also been done to attempt to integrate and interpret the numerous studies available. These provide a rapid synopsis of many studies, and are particularly beneficial in assessing potential flaws, biases or confounders for each. However, the conclusions expressed are based upon the interpretation of data provided by others, with no new information being developed. This fact introduces potential for bias in what material is drawn from the studies for discussion and how it may be interpreted out of context. These limitations certainly preclude reviews being the final authority on this topic.

CONCLUSIONS

Even though the assertion that DDT is a carcinogen is not new, the earliest studies to actually attempt to discern a link with breast cancer were quite limited and crude. In 1980, Unger et al. found increased DDT in case specimens in a study containing 11 cases and 22 controls (33). However, a small follow-up study did not detect a relationship (34). Although these studies were equivocal, they suggested the subject deserved further investigation. It was not until the late 1980s and early 1990s that large, well-controlled studies were performed (including using serum collected throughout the previous two decades). These studies continued to provide conflicting conclusions. Wolff et al. found a significant difference between cancer rates experienced in the highest quintile of DDT and DDE residues versus the lowest quintile (35). This was a well-designed and controlled study that was initially considered to almost be definitive. However, a similarly designed and executed study by Krieger (that included Wolff) was completed a year later,
which found no association (36). Confusion continued to reign, as two studies from Mexico yielded conflicting results (37, 38). Some studies even found a lowered odds ratio, although rarely statistically significant (32, 39). Subsequent studies have begun to yield more consistent findings, with five major nested case-control studies finding no association between breast cancer and residues of DDT and DDE (3). The stated goal of the combined analysis of five studies was to increase the power of the individual studies. This was done because none of the original studies had detected a significant association, but suggestions of effects in specific subgroups were observed. Even though all of the studies are considered to be large, they had limited power to perform these subgroup analyses. Therefore, the combined analysis undertook to reanalyze the primary data by use of a standardized approach to control for confounding and to assess effect modification. The final combined data did not substantiate the existence of any association, either as a whole or within the suspect subgroups, even when comparing women with highest levels of residues to those with lowest levels (7). The meta-analysis also found no statistical support for an association, even though several of the studies included had originally concluded a link existed (8). Unfortunately, the authors of the meta-analysis were not able to offer an explanation for the discrepancy in the results of the studies they used, as correction for specific confounders could not be shown to make all results comparable. They did suggest that the different conclusions reached by the studies did not result from differences in exposure levels among the populations. In other words, it is not because the population used in one study had dramatically different exposure levels than the population of another study. This was based upon the observation that results were consistently negative among the studies that had the highest mean residue levels, as well as the studies that had the widest variation for residue levels. This would also seem to argue against a threshold effect, although that was not explicitly discounted.

No clear consensus has been reached in how to interpret current information. Most published reviews concur with the conclusions of the combined analysis of five studies and the meta-analysis: There is no significant evidence to suggest a direct link between exposure to DDT and breast cancer (3, 40 - 42). This is not a universal assessment, as others have cited the positive findings of some studies as being adequate to justify at least a weak association (43, 44). Regardless, it is unlikely that there could be any means to bring all of the varying results into a single interpretation. There are clearly too many variables, confounders and biases to clear the confusing body of evidence that has been compiled.

**SUGGESTIONS FOR FUTURE RESEARCH**

It should be apparent that, since no consensus has been reached about how to interpret current information, there is not a clear direction for the future. However, there do seem to be trends that suggest a shift in the expectations and pursuits of researchers and clinicians. It seems that most investigators have conceded that it is unlikely any additional broad-based studies of the general population will produce a "smoking gun" conclusion. Instead, previous research will serve as a guide in suggesting specific variables to be investigated, with the predominant suggestion being that future studies should be nuanced toward looking at new and unique aspects of the problem. Are there specific
populations that are more susceptible? These could include genetic and racial sensitivities, since there are heritable and racial links that have already been established for breast cancer. Could sensitivity to DDT or other hormonally active compounds be a part of that? Is there a difference in how different types of tumors would be affected by DDT, since some malignancies are more responsive to hormones than others? Does menopausal status influence the body’s sensitivity to DDT and its metabolites? Some researchers are also pursuing more precise measurements of specific DDT compounds and isomers. The goal of this investigation is to ascertain whether an association has been obscured by high residues of p,p’-DDE, which appears less toxic but more prevalent than other metabolites. Obviously, much more time and research will be needed before a conclusion can be made about such possibilities.

Generally, concerns about the threat posed by DDT are also tempered by the recognition that use of the pesticide is declining almost worldwide, and the exposure and accumulation of residues (and whatever risks, if any, these may present) should abate accordingly. Indeed, levels of residues in breast milk have dropped significantly in recent decades (45). Similarly, the meta-analysis noted a trend of tissue residues decreasing with time, consistent throughout all but one study. This is, of course, in contrast to the breast cancer incidence, which has been increasing markedly during the same timeframe. Even if the latency period is quite long, a downward trend could be expect in breast cancer in the near future, if DDT is a significant contributing factor.

The potential association of DDT exposure and breast cancer is an enormous and complex issue. It can often be anticipated that, if enough studies are done, potentially conflicting results may be found. But it is generally expected that additional research will bring clarity, and eventually a preponderance of evidence will make a final resolution possible. Arguably, this has not occurred with this topic. However, careful consideration of the various studies has led me to conclude that no substantial support exists to claim a blanket association. Many of the studies that found an association had methodological issues that limit their validity. These issues range from small sample size, to poor selection of controls, to failure to adjust for significant confounders. The two most credible sources that concluded an association existed were Wolff and Romieu (35, 37). However, the association found in Wolff’s study was barely significant (OR 3.68, CI 1.01 to 13.50, p<0.035), and he and collaborators were unable to replicate those findings in later studies. In the case of the Romieu study, the conclusions were more statistically significant (OR 3.81, OR 1.14 to 12.80, p<0.02); but a similar study conducted at approximately the same time in the same geographical area (Mexico City) obtained very different results (OR 0.76, CI 0.41 to 1.42) (38). In contrast, many well-designed and well-executed studies have failed to prove an association. This is not to say that additional research is not warranted; rather, what research is done would be best directed at some very specific questions, as outlined in the section titled “Suggestions for Future Research.” The allocation of resources available for breast cancer research may prove more beneficial in other areas. It would seem apparent that, even under the most cautious of interpretations, DDT could only be considered a minor factor in the increase in breast cancer incidence, and whatever its effects, they will be diminishing with time. While pursuit of the truth should guide all research choices, a pragmatic recognition that
the truth may not be discernable is sometimes warranted. This may be the case for the association DDT and breast cancer.

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