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Shapiro: Exposure to Pesticides and Breast Cancer Revisited
**EXPOSURE TO PESTICIDES AND BREAST CANCER
REVISITED**

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Breast cancer is the most prevalent cancer among women. Although it is clear that the incidence of breast cancer has been on the rise over the last fifty years, the cause of this increase remains unknown. Risk factors for breast cancer are commonly classified into four broad categories: (1) genetic, (2) reproductive/hormonal, (3) lifestyle and (4) environmental (Salehi et al., 2008). Even though there are several established risk factors among these categories, they account for considerably less than half of breast cancer cases in the United States (Falck et al., 1992). It was suggested in the early 1990s that exposure to some environmental chemicals may play a causal role in the etiology of breast cancer through estrogen-related pathways (Salehi et al., 2008). Because many pesticides mimic estrogen, which is a known breast cancer risk factor, they are of interest in etiologic studies of this disease (Brody et al., 2004).

In the last several years there has been an increase in the demand for expanded testing regarding environmental risk factors for breast cancer, specifically exposure to pesticides. Among the prime suspects of the adverse effects of environmental agents is the pesticide DDT, which was banned in 1972. It has received increased attention because once in the human body, DDT and pesticides alike accumulate in body fat and take a long time to eliminate, which poses a huge problem if they are carcinogenic (Harvard, 1994). Although the relationship between pesticide exposure and breast cancer was initially dismissed, it has been revisited due to more recent studies demonstrating that a temporal relationship does in fact exist (Brody et al., 2004).

Pesticide use raises a number of environmental health concerns for the general public as pesticides are commonly used to increase agricultural productivity and control invading insects, weeds, fungi and rodents (Jurewicz et al., 2006). Pesticides have been suspected to present danger to consumers and bystanders, as well as workers during the manufacturing and transporting process of these chemicals. This is a problem of great significance because if pesticides do play a role in the etiologies of breast cancer, many people are put at an increased risk in their daily lives by consuming and inhaling such toxins.

Due to the fact that pesticide exposure is so widespread in the general population and breast cancer is the most common cancer among women, it remains extremely important to determine whether pesticide exposure contributes to an increased risk of breast cancer (Brody et al., 2004). The purpose of this paper is to review scholarly literature on the epidemiologic relationship between exposure to pesticides and the subsequent development of breast cancer.

LITERATURE REVIEW

The association between the possible role of pesticide exposure in the development of breast cancer is of particular interest on Cape Cod, a sandy peninsula on the Massachusetts coast, because of a history of distinctive pesticide use and elevated

incidence of breast cancer (Brody et al., 2004). Brody, et al, conducted an analytic investigation in the form of a population-based case-control study to examine breast cancer risk associated with residential proximity to wide-area pesticide use on Cape Cod. The study was comprised of 1,165 women who were diagnosed with breast cancer according to the Massachusetts Cancer Registry (MCR) in 1988-1995 and 1,016 controls (living and deceased). All subjects were permanent residents of Cape Cod for at least 6 months and the controls were frequency matched to cases on date of birth in decades and vital status in order to address confounders. The investigators used unconditional logistic regression to calculate crude and adjusted ORs and 95% confidence intervals for each source of pesticide exposure and breast cancer.

Both historical records and geographic information systems (GIS) were used for exposure assessment. Exposures were assessed from pesticides applied for tree pests, mosquito control on wetlands, cranberry bogs and other agriculture dating back to 1948 (when DDT was first used there). GIS function as a promising tool for this type of investigation because it has several strengths in comparison to other techniques. For example, it is not prone to error and recall bias like self-reports and is neither as expensive nor limited in the number of agents that can be measured as in biologic or environmental sampling. In addition, GIS can efficiently integrate records of locations where pesticides were used, models of how these compounds travel in the environment, and locations of individuals at the times and places of likely exposures.

This study was extremely thorough and done very well for a number of reasons. First of all, it used a variety of formulas to examine and analyze the data found in order to generate the most accurate results. For example, different algorithms were used to calculate exposures from predominantly aerial- and ground-based applications, which took into account distance from edge of sprayed area, size of sprayed area and direction-dependent constants derived to account for northeast, southeast, northwest and southwest wind directions. Secondly, the researchers matched cases and controls to account for confounders extensively. “The following matched variables and potential confounders were controlled in all adjusted OR analyses based on *a priori* consideration of the research design, well-established breast cancer risk factors, and the completeness of data: age as a continuum term, birth decade (six categories), vital status, year of diagnosis/ reference year, prior breast cancer, age at first birth, family history of breast cancer in a first-degree female relative, education (five categories), and years of residence on Cape Cod during the exposure period” (Brody et al., 2004). If subjects were missing data for the main exposures or other potential confounders listed above, participants were excluded. Fourteen additional confounders were also considered but because none changed the OR by a significant amount, they were not included in the final models.

In 1976, a prospective cohort study was conducted on 121,700 married registered nurses who were enrolled in the Nurses’ Health Study and subsequently followed by questionnaire every two years (Hunter et al., 1997). Information on risk factors for breast cancer was obtained through questionnaires and self-reported diagnoses of breast cancer were confirmed by reviewing medical records. Between 1989 and 1990, 32,826 of the women sent a blood sample and the investigators were then able to assemble their cases for a case-control study. There were a total of 240 eligible case patients, which

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were defined as women who did not have a diagnosis of cancer when they sent in the blood sample and in whom cancer was subsequently diagnosed before June 1, 1992. Hunter, et al, concluded that their data did not support the hypothesis that exposure to organochlorines in pesticides increases the risk of breast cancer.

A strength of this study was the matching of cases to controls in order to control for potential confounding variables. For each case, the investigators matched a control who had not reported a diagnosis of cancer according to year of birth, menopausal status at the time of blood sampling, month in which the blood sample was returned, time of day the blood sample was taken, and for postmenopausal women, postmenopausal hormone use. A limitation in the prospective cohort part of the study was that the investigators reported that women who gave a blood sample were slightly more likely to have a history of either benign breast disease or a family history of breast cancer. These differences could influence the internal validity of comparisons between cases and controls in the subcohort, which is the most important goal of any study. Also, because information on risk factors was obtained via questionnaire, this study is subject to error and recall bias.

A case-control study was conducted to examine whether levels of several pesticide chemical residues, including DDT and PCBs, were higher in mammary adipose tissue from women who had malignant breast cancer compared to those with benign breast disease (Falck et al., 1992). In total, the cases were represented by twenty-three fat samples examined from women who had breast cancer and twenty-seven control samples. The samples were frozen and later forwarded for chemical analysis by one pathologist. Patient height, weight, and smoking histories were collected from medical records or brief telephone interviews.

After chemical analysis, Falck, et al, concluded that mean concentrations of DDT and PCBs were higher in tissues of women who had breast cancer. However, it is important to recognize limitations embedded in the way in which this study was conducted. First, the study population consisted of only fifty subjects, which is a small sample size. In addition, not much of an attempt was made to control potential confounding variables and biases; other than the data collected mentioned above, no additional patient history was available (such as dietary histories). Lastly, all 50 subjects were selected from hospitals, which increases the chance for biased estimates of effect and decreases generalizability of the study results. The difference in the findings could be due to variables not taken into consideration. In order for more accurate results, further investigation of the question of environmental agents and breast cancer with better age matching and attention to other factors known to contribute to breast cancer.

A study examining the relationship between the pesticide DDT and breast cancer was conducted by taking a collection of samples from a prospective cohort study and inserting them into a case-control study (McCarthy, 1993). Archival serum samples were collected from women who were enrolled in the New York University Women's Health Study, a cohort study of hormones, environmental factors and cancer, between 1985 and 1991. In a blinded case-control study, there were 58 cases, which were defined as women who had been diagnosed 1-6 months after joining the study. Concentrations of DDE (a metabolite of the pesticide DDT) in the 58 cases were compared to those

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of 171 matched controls from the same population and relative risk calculations were made.

This study found that there is a strong association between high serum concentrations of DDE (a metabolite of the pesticide DDT) and breast cancer in women. The researchers found that women who had the highest serum concentrations of DDE had four times the relative risk for breast cancer. Although the sample size was small, this leads researchers to believe that organochlorines may in fact act as carcinogens.

“California is the leading agricultural state in the United States, and more than a quarter of all pesticides in the United States are applied there” (Mills & Yang, 2006). Latinas make up a large proportion of the workers in the labor-intensive agricultural field, which puts them at increased risk of exposure to agricultural pesticide chemicals, such as organochlorides. Mills and Yang conducted a population-based regression analysis to examine the possible relation between pesticide exposure to organochlorines and incidence of breast cancer in California Latinas (Mills & Yang, 2006).

The analysis utilized 1988-2000 data from the California Cancer Registry, the population-based cancer registry that monitors cancer incidence and mortality within the state, and pesticide use data from 1970-1988 from the California Department of Pesticide Regulation. A total of 23,513 Latinas were diagnosed with breast cancer in California between 1988-2000. The researchers used negative binomial regression models in order to control age, socioeconomic status and fertility rates. Mills and Yang found that breast cancer was positively associated with organochlorine exposure.

This study had both strengths and limitations that are important to consider when interpreting the results. A strength in the study design was that is used a 19- year exposure period (1970-1988) that predated the identification of newly diagnosed cases of breast cancer (1988-1999). This extended period allows sufficient latency for potential exposure and disease association to become manifest. Also, this study focused on a population with a tradition of agricultural employment and consisted of a large sample size. Lastly, the use of the CCR, into which more than 95 percent of all cancers are annually assessed, provided a large number of breast cancer cases for analysis. The limitations include the ecological nature of the exposure assessment.

Annette Hoyer and her colleagues conducted a retrospective cohort study to further investigate the proposed relationship between the chlorinated compounds found in some pesticides and breast cancer (Feeny, 1999). Together they studied blood samples taken from 720 Danish women that had been previously collected for a heart study, before cancer had appeared in any of the subjects. However, since that study 240 of the participants developed breast cancer.

The study found an association between exposure to certain chemicals in pesticides and incidence of breast cancer. Dieldrin, which is a pesticide that has been banned in the United States, appeared to pose the greatest risk. Women whose blood had the highest concentration of dieldrin were more than twice as likely to develop breast cancer compared to those with very low concentrations of this chemical. Also, a component of the pesticide lindane appeared to increase one's chance of developing breast cancer but to a lesser degree than dieldrin.

SUMMARY AND CONCLUSIONS

When collectively reviewing the studies discussed above, it is imperative to keep in mind several issues that arise out of the nature of epidemiological studies. First, the majority of the studies examining the possible relationship between the exposure to pesticides and subsequent development of breast cancer are in the form of case-control studies. This type of study is affected by bias more than any other study design, which results in the need for critical analysis when interpreting results. Because of ethical issues, studies that are less prone to such errors are more difficult to conduct. Another major concern in conducting case-control studies is that the majority of the information regarding previous exposures is collected directly from the subjects under study. Since cases and controls are selected based on disease status, and the history of exposures is then assessed based on personal experience/memory, problems of recall bias and limitations in recall of exposures are introduced. A third issue to keep in mind when conducting this type of study is that cases and controls may differ in characteristics or exposures other than the ones that have been identified for study. Although there are approaches to deal with these types of problems, such as matching, in doing so a different set of practical and conceptual problems become an issue (Gordis, p. 161-172).

Although the prevalence of breast cancer's history is extremely long, our knowledge of the various agents that cause breast cancer has followed much more slowly. It is important to understand that cancer-producing chemicals in our environment, such as pesticides, are uncontrolled and they are multiple. Although it would be rare for one single exposure to such agents to manifest breast cancer in someone, an individual can have multiple exposures to the single agent or be exposed to small amounts of a number of different pesticides. "It is quite possible that no one of these single exposures alone would be significant to precipitate malignancy- yet any single supposedly 'safe dose' may be enough to tip the scales that are already loaded with other 'safe doses'" (Carson, p. 237).

By analyzing the results of the studies previously discussed, it is clear to see that there are differing beliefs as to whether or not pesticides play a role in the etiology of breast cancer, and if so, to what extent. Although the majority of the studies do not give conclusive evidence that pesticides act as a causative agent, any scientifically proved correlation between the exposure to pesticides and such a prevalent disease is enough to show that the two are related and demonstrates the need for further investigation, especially when a dose-dependent relationship has been shown. As mentioned before, breast cancer is the most frequently diagnosed cancer among women and the known risk factors account for less than half of the cases. Because so much of the etiology of breast cancer remains unknown, any evidence that demonstrates a relationship between the proposed risk factor and disease is enough to prove that a temporal relationship does in fact exist and should serve as a wake up call for further research.

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