Pesticide Residues and Breast Cancer: The Harvest of a Silent Spring?

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During this century, age-adjusted breast cancer incidence rates have increased in the United States (*1*), and breast cancer incidence has also been associated with international variations in affluence (*2*). The search for the aspects of our 20th-century Western lifestyle that contribute to this increase in breast cancer has identified reproductive and possibly dietary variables as being partially responsible. However, it is unclear how much of the increase in breast cancer incidence these variables explain. Given this incompletely understood secular trend in breast cancer rates and a community climate of concern about the possible carcinogenic hazards of environmental pollution (especially organochlorine pesticides in the food chain), it is somewhat surprising that few investigators have examined the relationship between pesticide exposure and breast cancer.

Although the one ecologic study of this relationship is consistent with the hypothesis that pesticide exposure can indeed lead to breast cancer (*3*), ecologic studies provide weak evidence for causal interpretation. Previous analytic studies are limited to small case–control studies that included only nine case patients (*4*), 20 case patients (*5*), and 44 case patients (*6*). In the largest of these studies (*6*), levels of the organochlorine DDE (bis[4-dichlorophenyl]-1,1-dichloroethene) were equivalent between case patients and control subjects, and case patients had somewhat *reduced* polychlorinated biphenyl (PCB) levels. However, the concentration of a third organochlorine, beta-hexachlorocyclohexane, was significantly higher among case patients than control subjects.

The study by Wolff et al. in this issue of the Journal (*7*) thus represents one of the few sources of data on this matter. In a relatively small prospective study, these authors observed a significant positive association between levels of DDE in stored blood and risk of breast cancer. A positive but nonsignificant association was observed with PCBs. As the authors themselves acknowledge, because of the limited follow-up time in this study, most of the case patients almost certainly had breast cancer at the time of blood sampling. Thus, an effect of occult disease on organochlorine levels cannot be excluded. Nevertheless, although additionally limited by its small size, this study is important because it included adjustment for known risk factors and mutual adjustment for DDE and PCB levels. Further, the authors observed a positive dose–response trend for breast cancer risk at varying DDE concentrations.

Given the sparse human epidemiologic data on the association between organochlorine exposure and breast cancer, is an association biologically plausible? While it is tempting to link these fat-soluble compounds with dietary fat consumption and subsequent risk of breast cancer, current epidemiologic evidence suggests no relation of dietary fat intake and breast cancer in the U.S. (*8*). However, breast cancer is clearly linked to estrogens, and both o,p'DDT and o,p'DDE are weakly estrogenic. At the very small daily doses that some researchers have estimated for human exposure (*9*), however, this source of estrogenic stimulus would appear to be small relative to other endogenous and exogenous sources of estrogens, such as oral contraceptives and postmenopausal hormones.

At the same time, Rogan et al. (*10*) have provided one example of a biologic effect of general population levels of pesticide residues on the breast. In their study, organochlorine levels in the milk of mothers giving birth in North Carolina were correlated with a shorter duration of lactation after controlling for a number of other predictors of lactation duration. Organochlorines are also known to have an extraordinarily complex biologic fate. As Wolff et al. (*7*) point out, DDT and PCBs have been shown to induce cytochrome p450 enzymes in humans exposed to these two agents. The mechanism for this is likely similar to that of dioxins, in that these compounds bind to an Ah-like receptor. This binding initiates the complex process of signal transduction, ultimately resulting in the pleiotropic effects on cellular growth and differentiation associated with these polychlorinated compounds. The prolonged derangements in cellular signal transduction that may occur as these residues persist in sensitive tissues have been suggested as one mechanism responsible for the tumorigenic properties of organochlorines (*11*).

These data, although limited, do suggest the plausibility of an association between organochlorines and increased risk of breast cancer. However, at this stage, these mechanisms are incompletely understood, and they will require considerable additional refinement before becoming truly compelling.

Wolff et al. (*7*) point out that their observations require confirmation in their own and other ongoing prospective studies that have stored blood. This approach will limit the spectrum of organochlorine compounds that can be studied because of the unmeasurably low levels of many metabolites (such as dioxins) in small volumes of blood. In addition, the secular decline in organochlorine residues in the U.S. over the last two decades and geographic differences in residue levels (*12*) suggest that well-performed studies may reach different conclusions depending on when and where they are done. To achieve consensus in these studies, researchers will have to pay careful attention to exposure assessment issues. It would be extremely helpful in this regard if the laboratories conducting organochlorine measurements for these studies instituted a quality control program sufficient

*See "Notes" section following "References."

to minimize interlaboratory measurement differences and ensure that the absolute levels of residues reported from individual studies can be meaningfully interpreted.

What other avenues of epidemiologic inquiry may be useful? At a recent conference on this issue (*13*), it was noted that information is lacking for women workers exposed to organochlorines, and even for women with known or estimable exposure, follow-up for breast cancer is deficient. Existing cohort studies with stored samples will be particularly valuable resources to attempt to confirm the findings of Wolff et al. (*7*) for DDE and total PCB measurements. With available technology, however, measurement of some of the other compounds of interest will require either adipose tissue sampling or drawing at least 100 mL of blood. While this approach is, consequently, not without formidable obstacles, it may be particularly valuable in some of the less developed countries where pesticide exposure is high, breast cancer incidence is rising, and prospective studies may be infeasible. Again, some form of interlaboratory quality control would be extremely helpful in interpreting results from these studies.

Given the state of our current knowledge, what are the "implications for public health intervention worldwide" (*7*) justified by these data? There are presently many good reasons to limit human exposure to organochlorine compounds; at this stage, however, prevention of breast cancer is not yet among them. As Wolff et al. (*7*) state, these compounds are disseminated widely in the environment and the food chain, and their reduction, far less their removal, is a major public policy challenge requiring a variety of risk–benefit calculations impacting areas as diverse as agricultural practice, infectious disease prevention, international relations, occupational health, and nutrition advice. Because the findings of Wolff et al. (*7*) may have extraordinary global implications for the prevention of breast cancer, their study should serve as a wake-up call for further urgent research. However, larger public health interventions aimed at breast cancer prevention would be justified only if the results of additional research confirm these provocative findings.

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Notes

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