Estrogens May Link Pesticides, Breast Cancer

A controversial hypothesis suggests that pesticides' impact on estrogen metabolism can trigger cancer.

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Since chlorinated pesticides were put into widespread use in the 1940s and caused concerns about reproductive failures and deaths in wildlife, researchers have tried to link exposure to them with increased risk of cancer in people. These studies have had conflicting or inconclusive results. But over the past five years, a better understanding of estrogen and its metabolites, coupled to findings on the estrogen-like nature of many pesticides, has led researchers at Cornell University to suggest a hypothesis for how chlorinated pesticides might cause breast cancer. This hypothesis, which is based on both biochemical and epidemiological findings, is that chlorinated pesticides can trigger breast cancer by adversely affecting the metabolism of estrogen.

The hypothesis has had mixed reviews in the research community. Some breast cancer researchers, such as Louis Kuller of the University of Pittsburgh, claim the Cornell researchers have "done an outstanding job" and, if their hypothesis is correct, "it will have major implications in the prevention and etiology of breast cancer." Others, such as Barry Goldin of Tufts University, oppose the hypothesis because it conflicts with other findings.

Although their chemical structures do not closely resemble those of steroid hormones such as estrogen, progesterone, or testosterone, a number of chlorinated pesticides strongly mimic estrogen in the body, studies show. Like estrogen, DDT, methoxychlor, and chlordecone (kepone) promoted the implantation of embryos in rats and maintained their pregnancies. Kepone, heptachlor, and chlordane also prompted proliferation of breast tumor cells, as does estrogen (*1*).

The estrogen-like nature of these compounds has fostered concern in the medical community because there is also evidence that breast cancer risk in humans is linked to cumulative exposure to estrogen. Women who start menstruating at an earlier age and enter menopause at a late age, for example, are more prone to breast cancer than women who are menstrual for relatively shorter periods of time. Reduction of estrogen by frequent and long-term breast feeding or by removal of ovaries can lower cancer risk (*2*).

These findings have led researchers to scrutinize the potential of chlorinated pesticides to foster breast cancer, the incidence of which has steadily risen worldwide since 1940.

Several studies have shown that women with breast cancer have greater concentrations of DDT or its metabolites in their breast fat or blood samples than control groups of women without the cancer. These studies found exposure to DDT was linked to a 2- to 10-fold increase in breast cancer risk (*3*). Animal studies show, in addition, that injections of some pesticides can stimulate the development of breast cancers in male mice normally resistant to breast cancer (*1*).

"Good" and "bad" estrogens

Laboratory studies by Cornell researchers Jack Fishman and H. Leon Bradlow suggest how pesticides might foster breast cancer. Estradiol, the main type of estrogen generated by women, is primarily converted in the body to 16-α-hydroxyestrone (C16) or to 2-hydroxyestrone. Although these compounds differ only in the placement of an OH group, they have markedly different effects in the body. The "good estrogen," 2-hydroxyestrone, interacts weakly with the estrogen receptor without triggering the growth-promoting genes, the Cornell researchers found. In contrast, C16, the "bad estrogen," strongly activates the estrogen receptor, prompting breast cell proliferation (*1*). Studies have also linked the bad estrogen to DNA damage.

Animal and human studies have shown that high levels of the bad estrogen are tied to an increased risk of breast cancer. Cornell's Bradlow discovered, for example, that human breast cancer cells had levels of the bad estrogen that were more than four times

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higher than those of normal breast cells (*4*). This and other findings led Bradlow and Devra Lee Davis, both of Cornell and the World Resources Institute, to postulate that certain pesticides might foster breast cancer by altering the ratio of bad and good estrogen in breast tissue.

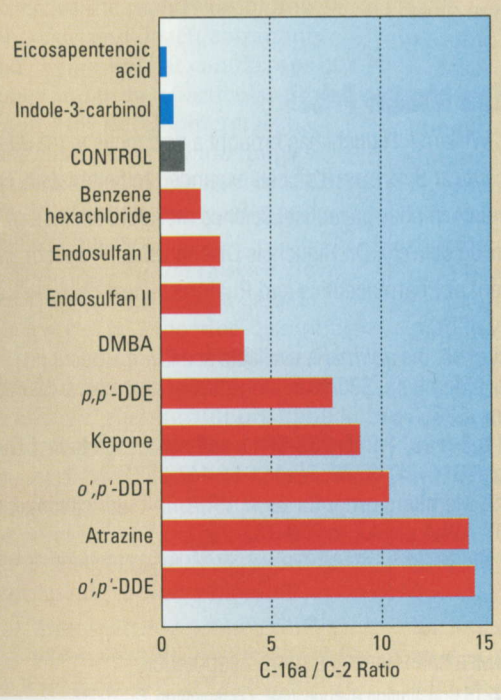
To test this hypothesis, the Cornell researchers added to cultured breast cancer cells the pesticides atrazine, DDT, kepone, endosulfans, or benzene hexachloride. All of these pesticides significantly boosted the ratio of bad to good estrogen in the treated cells in comparison to untreated control cultures. The pesticides tripled or quadrupled the amount of the bad estrogen, and several of them caused a higher bad estrogen–good estrogen ratio than did the known carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA) when it was added to the breast cancer cells (*5*).

The researchers also measured the estrogen ratio in breast cancer cell cultures that were incubated with compounds thought to prevent cancer. These included indole-3-carbinol, which is found in broccoli, and eicosapentenoic acid, which is found in fish oil. These compounds fostered a drop in the estrogen ratio to one-third of that seen in unexposed control cells.

"There's good news and bad news coming out of this research," said Davis. "The good news is that broccoli and fish oil might be beneficial in preventing breast cancer. The bad news is that some commonly used organochlorine pesticides can boost production of a hormonal metabolite that appears to be a marker for breast cancer risk."

Pesticides alter estrogen metabolism

Recent research has demonstrated the ability of pesticides to influence the ratio of "bad" to "good" estrogen in cultured breast cancer cells (*5*). Pesticides and pesticide metabolites increased the ratio (red bars); two food compounds found in broccoli or fish oil lowered the ratio (blue bars). "Bad" estrogen (α-hydroxyestrone) strongly activates the estrogen receptor, prompting breast cell proliferation.



Assay for breast cancer risk?

The Cornell researchers pointed out that assays of the ratio of bad to good estrogen, which can be efficiently measured in urine, may prove useful to scientists trying to assess the breast cancer risk posed by environmental compounds. But the usefulness of this urine assay rests on the assumption that the estrogen ratio is an accurate predictor of cancer risk.

"We're talking hypothesis here rather than fact based on adequate testing in human populations," said Regina Ziegler of the National Cancer Institute. Even the assumption that estrogen in general plays a major role in causing breast cancer is still a hypothesis and not proven, she added. "What impresses me about endogenous hormones and breast cancer is how little we know—how many hypotheses there are that have not been adequately tested."

Goldin of Tufts University also questions whether C16 is as bad as the Cornell researchers contend it is. His study, which compared Asian women with Caucasian women, found no differences in the urine levels of the estrogen metabolite, even though Asian women have a lower risk of breast cancer than Caucasian women (*6*). "I don't believe the C16 estrogen metabolite is some evil component," Goldin said.

Davis conceded that more studies need to be done not only to confirm the findings that have been made so far but to present a fuller picture of how pesticides might cause breast cancer. "I'm sure there will be other hormonal factors that turn out to be important," Davis said, "but it looks at this point that C16 does play a functional role in breast cancer, and we're moving ahead to investigate this."

Davis is currently collaborating with researchers in Mexico to assess blood levels of DDT and urine levels of good and bad estrogen in women who live in areas where exposure to chlorinated pesticides is high. The investigators, funded by the National Cancer Institute, hope to evaluate whether pesticide exposure is linked to increased breast cancer risk and a high bad-to-good estrogen ratio.

The Cornell researchers are also conducting laboratory studies to elucidate the effects the bad estrogen has on the estrogen receptor and cellular DNA. In addition, Bradlow is exploring potential links between a high bad-to-good estrogen ratio and other hormonally mediated diseases such as cervical cancer and lupus. "This ratio may turn out to be far more useful than for just breast cancer," Davis said.

But more work is needed to corroborate the link between breast cancer, pesticides, and estrogen metabolites. As Davis's Cornell colleague Nitin Telang pointed out, "What we have are observations leading toward the truth. We still have a long way to go."

References

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