Pesticide Residues and Breast Cancer?

Brian MacMahon*

As if we needed it, the Journal brings another reminder of the caution with which the results of a single epidemiologic study, or even a handful of them, should be regarded. Hard on the heels of the largest epidemiologic study, until now, showing a positive relationship between breast cancer risk and serum levels of DDE (the major metabolite of DDT), and published last year in the Journal (1), comes the even larger study reported in this issue in which no relationship was found (2). An editorial (3) also accompanied the 1993 report, clearly stressing the need for further research to confirm the provocative finding before considering its “far-reaching implications for public health intervention worldwide” (1).

The two studies are similar in a number of respects. Both are case-control studies nested in cohort studies—the 1993 study in the prospective New York University Women’s Health Study (1) and the 1994 study in the Kaiser Foundation multiphasic health examination cohort in the San Francisco Bay Area (2). Both studies, the sera were drawn prior to the diagnosis of breast cancer. In the New York study, as the authors did recognize, breast cancer was probably present at the time the blood was drawn, since it was diagnosed within 6 months of the draw.

However, the Kaiser study has a number of features that favor its conclusions over those of the New York report. Although the largest up to that time, the New York study had only 58 breast cancer cases; the new study has 150. The New York study had slightly more control women (171) than did the new study (150), but there was careful matching of controls to cases in both studies, and the greater number of cases in the new study is a substantial strength. Moreover, because of the much larger numbers of potential cases available, the Kaiser investigators were able to select three groups of equal size from each of three major racial groups; in New York, 80% of the cohort were Caucasian and it is not indicated that race was matched in the other hypotheses linking exposure to particular temporal phases in the development of breast cancer, but to no avail. Clearly, we shall hear more on this topic, but, for the moment, we must conclude that the available epidemiological evidence overall is not supportive of an association between exposure to DDT and increased risk of breast cancer.

I suspect that I was asked to write this editorial not simply to recapitulate the observations and conclusions that can be derived from the accompanying report, but to ponder on why the conclusion from the perfectly respectable study of Wolff et al. (1), and of a few previous, less powerful studies appear, at this point, to have been incorrect. The spectrum of man’s diseases is complex, and his environment labyrinthine. Their interaction forms a thicket that is made only more dense by the addition of biochemical and other laboratory markers of exposure and/or disease. The imaginative investigator looks for patterns in this thicket, as others look for pictures in clouds. Investigators’ own ambitions, as well as the demands of the systems in which we work, have led to widespread belief that on perceiving a pattern in the thicket it is better to report it, even if it turns out to be only a bunch of leaves, than to fail to report a pattern that someone else later discovers to be a pheasant. Many investigators, including the writer of this editorial, have proceeded on the basis of this belief (4).

If science operated in a vacuum, the tendency to over-report suspicious patterns would not necessarily be a bad one—it gives...
other investigators, as well as the original observer, the opportunity to follow possible leads. However, it has two implications. First, under this system, we must expect many tentative positive findings not to be confirmed. Second, we do not operate in a vacuum and, however cautiously the investigator may report his or her conclusions and stress the need for further evaluation, much of the press will pay little heed to such cautions. Even when it does, by the time the information reaches the public mind via print or screen, the tentative suggestion is likely to be interpreted as a fact. There seems little that investigators can do to mitigate this problem; in the case of a report published by myself and colleagues (4), a less provocative title and the selection of a journal less likely to catch the eye of the press might have been wise, but both title and journal seem to be appropriate selections for the studies now under discussion.

With respect to levels of PCB in serum, the New York and Kaiser studies are in agreement, with each other and with the majority of the small previous literature on the subject, in finding no evidence of association between residual PCB serum levels and breast cancer risk. The finding is reassuring not only for its substance but for its implication to epidemiology—well-designed studies of the same issue sometimes do come to similar conclusions. It is heartening when they do. When they do not, as in the case of DDE, this difference in conclusions should not be seen as a cause to doubt the utility of the whole enterprise but as a rather good example of the scientific method in progress—the statement of a hypothesis and an attempt to evaluate it published quickly in the same journal. With repeated iterations, we will eventually come to a conclusion in which we can have much confidence.

References


Note

Manuscript received March 1, 1994, accepted March 1, 1994

Epidemiology and Biostatistics Program of the National Cancer Institute

Mitchell H. Gail, Jacques Benichou*

Two studies in this issue of the Journal (1,2) test predictions of breast cancer risk based on the model in Gail et al. (3). Before discussing these results, we shall briefly review the purposes and features of the Gail et al. model.

One widely used measure of risk is relative risk, which is the ratio of risk in a woman with specified risk factors compared with the risk in a woman with no risk factors. For example, according to the Gail et al. model, a 40-year-old nulliparous woman who had menarche at the age of 14 years, who has had no breast biopsies, and who has one first-degree relative (mother or sister) with breast cancer has a relative risk of 2.76 compared with a 40-year-old woman with no risk factors (age at menarche ≥14 years, no biopsies, no affected first-degree relatives, and age of first live birth younger than 20 years old).

The Gail et al. model goes beyond relative risk by computing individualized absolute risk (i.e., the chance that a woman with specific risk factors at a given age will develop breast cancer in a specified future time period). For example, using the Gail et al. model (3) and methods to compute confidence intervals [CIs] (4,5), we estimate that the first woman described above would have a chance of 11.6% (95% CI = 10.2%-13.2%) of developing breast cancer between the ages of 40 and 70 years. The Gail et al. model calculates such absolute risks by first computing a relative risk based on the woman's age and individual risk factors and by then combining this information with an estimate of the base-line hazard rate for a woman with no risk factors. For the Gail et al. model to be correct, both the relative risk model and the base-line hazard estimates must be correct.

The concept of individualized absolute risk, as opposed to relative risk, has two uses. The statistical power of prevention trials, such as the Breast Cancer Prevention Trial to study tamoxifen (6), depends primarily on the number of breast cancers expected to develop during the trial, which in turn reflects the individualized absolute risks of trial participants. Thus, absolute risk is useful for planning such studies. In the Breast Cancer Prevention Trial, a modification of the Gail et al. model was also used to decide which younger women were at an absolute risk that was high enough to be eligible for the study. The primary purpose for developing the Gail et al. model, however, was to give women a realistic and individualized estimate of the chance of developing cancer over various time horizons. Many women with a family history of breast cancer seriously overestimate their risks and are reassured by empirically based estimates from the Gail et al. model. Harris (7) describes how the

*Affiliation of authors Division of Cancer Etiology, National Cancer Institute, Bethesda, Md

Correspondence to Mitchell H Gail, M D, Ph D, National Cancer Institute, Division of Cancer Etiology, Executive Plaza North, Rm 403, 6120 Executive Blvd., Rockville, MD 20892

See "Notes" section following "References "

Journal of the National Cancer Institute, Vol. 86, No. 8, April 20, 1994