We heartily agree with the insight and perspective concerning the tamoxifen–endometrial cancer dilemma provided by the highly informative correspondence by Gal et al. The authors’ explanation for why endometrial cancers associated with tamoxifen administration should be low grade is consonant with our findings in this regard (see our response to the letter from Dr. Carcangi). We agree that some of the examples portrayed in our article might be only remotely, if at all, related to tamoxifen. However, it appeared to be most prudent to describe all such events as fully as possible in order to avoid understating this relationship. This approach has already provoked the attention of investigators such as Dr. Gal and his associates.

It is hoped that they, as well as others, will provide further information that might help resolve this important issue.

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Re: Breast Cancer and Serum Organochlorines: a Prospective Study Among White, Black, and Asian Women

The recent article by Krieger et al. (1) is the second to appear in the Journal regarding organochlorine compounds and breast cancer. The study was well designed, carefully conducted, and properly analyzed and yielded evidence that clearly supports an association between DDE and breast cancer. Having read media reports, including the authors’ own interpretation of their study as “negative,” our review of the data in the article lead to a strikingly different conclusion.

One decision is whether to focus on differences in mean values between case patients and control subjects versus an analysis of exposure in categories. The continuous measure has greater statistical power if the entire distribution is shifted in one group relative to the other. Their data do not suggest such a shift, except perhaps for black women. However, a categorical analysis has the advantage of making no assumptions about the pattern of differences or about the allowance for thresholds, ceilings, or other irregularities; the main disadvantage is that boundaries were chosen arbitrarily. The choice of tertiles made by the authors is a reasonable one.

A second judgment concerns the need to conduct analyses separated by ethnicity, which is justified by the markedly different patterns of neighborhood location, history of migration, breast cancer risk factors, and, ultimately, different patterns of results for analysis of DDE. Thus, the relatively large study became a series of three small studies, with 50 case patients in each.

Given the stratification by race, analysis in categories, and adjustment for confounders, none of which seems particularly unusual or arbitrary, the following patterns were found for tertiles of DDE [Table 3 (1)]. Odds ratios for white women were 1.0 (referent), 1.9 (95% CI = 0.6-6.0), and 2.4 (95% CI = 0.5-10.6); for black women, they were 1.0 (referent), 2.3 (95% CI = 0.6-8.4), and 3.9 (95% CI = 0.9-16.1). Asian women showed a small decrease in risk with increasing exposure. Based on the magnitude of odds ratios and exposure–response gradients, these are strikingly positive results from a very small study—entirely consistent with the previous study by Wolff et al. (2). Only by rigidly adhering to the criterion of statistical significance, which is of dubious value in general in epidemiology (3,4)—particularly in studies of such limited statistical power, could Krieger et al. or other reviewers conclude that “our results do not support the hypothesis that DDE and polychlorinated biphenyls (PCBs) are a risk factor for breast cancer.” The recent study (1) greatly reduces the possibility that metabolic changes associated with cancer might explain the case–control differences found previously (2), countering the single greatest challenge to the previous study. Thus, the still small literature on this topic is more strongly suggestive than ever.

Krieger et al. were helpful in providing sufficient data for the reader to come to an independent and contrary conclusion, but they did a disservice to the casual reviewer and the public by compartmentalizing their study as “negative.” MacMahon (5) effectively describes the dilemma of trying to disseminate potentially fallible results to the scientific community while minimizing public overreaction. The problem he describes is genuine, but the solution is not to provide reassuring conclusions that contradict the data.

References


(4) Greenland S: Randomization, statistics, and causal inference [see comment citation in Medline]. Epidemiology 1:421-429, 1990

(5) MacMahon B: Pesticide residues and breast cancer! [editorial] [see comment citation in Medline]. J Natl Cancer Inst 86:572-573, 1994

Response

We are glad to respond to the issues raised in Dr. Savitz’s thoughtful correspondence. We entirely agree that our study (I) does not definitively disprove the hypothesis that exposure to DDE and to PCBs is related to risk of breast cancer. His conclusion that our research