summary by Dr. Freudenthal and Mr. Anderson that "On a weight-of-evidence basis, several chemicals used at the plant are more probable candidates as a bladder carcinogen than either aniline or o-toluidine." We do not think that these authors have developed a well-supported case for any of the chemicals mentioned in their letter. We believe that available evidence on the extent of use of various chemicals at the plant, and the toxicologic data on these chemicals, support o-toluidine and aniline as the most likely causes of this bladder cancer excess. The epidemiologic data further support an earlier NIOSH statement (16), based on animal data, that o-toluidine and aniline are potential occupational carcinogens as defined in the Occupational Safety and Health carcinogen policy (29 Code of Federal Regulations, 1990).

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Tamoxifen in Healthy Premenopausal and Postmenopausal Women: Different Risks and Benefits

The discussion of the use of tamoxifen in prevention studies in the editorial by Gray lacks the rigor and detail critical to defining the best way to "go boldly" (1). The central issues ignored in this discussion are that the profile and magnitude of benefits and risks of tamoxifen and the extent of evidence for these are different in premenopausal and postmenopausal women (2). My detailed analysis concludes that, in premenopausal women, the risks are very likely to exceed the benefits. In contrast, a detailed analysis by Bush and Helzlsouer (3) concludes that in the mixed population being currently recruited into the trial, the risks and benefits are approximately equivalent. The references which Gray cites are reviews and opinions. The National Surgical Adjuvant Breast and Bowel Project protocol document analysis is significantly flawed in combining both premenopausal and postmenopausal subjects as well as in ignoring the possibility of serious depression (4) and retinopathy (5), and in omitting likely cases of nonfatal thromboembolism (6).

Good science and better public health can follow from rigorous numerical analyses and well-conceived prevention studies. Contrary to Gray's opinion, I submit that rigorous analyses based on available data suggest that prevention studies which use tamoxifen and include premenopausal or mixed premenopausal and postmenopausal healthy populations do not "have obvious value" and, additionally, such studies are "both scientifically and ethically" undesirable.

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Response

Dr. Love is concerned that the risks of tamoxifen among healthy premenopausal women are "very likely" to exceed the benefits (1). He, and Drs. Bush and Helzlsouer (2), recommend cessation of accrual of premenopausal women to the cancer prevention/tamoxifen study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 tamoxifen prevention study. Although the concerns raised by Dr. Love are legitimate, his analyses can be questioned. In particular, the estimates (1) of the likely "cost" of 10,000 premenopausal women taking tamoxifen for 5 years (50 extra cases of pulmonary emboli, 27 ovarian cancers, 90 mucocutaneous edema, and 100 occurrences of depression) are speculative and not "rigorous analyses." No study has reported statistically significant excesses of pulmonary emboli and no excess risk of thromboembolic disease was found in the Stockholm study (3) despite particular attention being paid to this end point. The excess risk of ovarian cancer is a hypothesis, and it could equally well be argued that tamoxifen may protect against ovarian cancer since it produced a response rate of 18%—comparable to that of paclitaxel (Taxol)—in one advanced disease study (4). The estimates of retinopathy are based largely on one small, nonrandomized, noncontrolled study in Greece (5) that is notable chiefly for its extreme results. The estimate of depression incidence is based on extrapolation from an abstract of a study of adjuvant tamoxifen (6) that does not appear to be placebo controlled nor properly randomized (184 tamoxifen versus 117 controls). Finally, in NSABP P1 the relative risk of breast cancer for the first 3791 women randomized was five times that of the general population (7)—higher than in Dr. Love's analyses.

Nevertheless, his concerns should be addressed seriously, and there are appropriate procedures for doing so. First, the Steering Committees of the various prevention trials should consider—as they do not already have done—whether the evidence cited by Dr. Love and others is sufficiently reliable to mandate cessation of accrual of premenopausal women, or amending the trial procedures in any other way. Second, the independent data monitoring committees of each trial can be alerted to the concerns about these particular risks. They can then monitor the accumulating evidence on these and other end points and advise the steering committees if, in their view, the randomized comparisons provide "proof beyond reasonable doubt" that for all, or for some, types of patients, tamoxifen is clearly indicated or clearly contraindicated. In the meantime, it continues to be scientifically and ethically preferable to randomize high-risk women in tamoxifen prevention studies whenever they and their doctors, in the light of all available evidence, remain substantially uncertain whether or not they will benefit from tamoxifen.

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References


Cost-effectiveness of Home/Hospice Palliative and Supportive Care

I would like to comment on a small aspect of the very interesting article by Smith et al. (1) that appeared recently in the Journal. The following issue was raised by the authors: "Can palliative cancer care be cost-effective?" The comparison noted by the authors, between palliative care utilizing chemotherapy versus care utilizing only support and comfort measures, was interestingly carried out in Canada.

In the Canadian system, most palliative care has been carried out in inpatient palliative care units. In the United States, conversely, the hospice program has grown up dramatically in the last few years, emphasizing home care for these patients and thus allowing them to remain at home during the terminal portion of their illness.

Many studies by the Health Care Financing Administration have demonstrated the cost-effectiveness of the Medicare hospice benefits. Therefore,