Response

Wertheimer and Leeper question my assertion (1) that the collective epidemiologic evidence of exposure to magnetic or electric fields increases breast cancer risk (3). I stand by this statement: The odds ratios (ORs) presented by Vena et al. (3) in their summary were 0.89, 0.97, 0.64, 1.31, and 1.25, depending on the definition of exposure; none of these estimates were significantly different from the null value, and none were interpreted as such. It is certainly possible to generate higher or lower point estimates of the OR in this or, indeed, in any other dataset; however, most researchers would consider this exercise to be inappropriate.

Wertheimer and Leeper point out an earlier study (4) they conducted that has indicated increased breast cancer risk among women living near “high power-line configurations.” This study has not been referenced by either Loomis et al. (2) or myself (1); it presents detailed, cancer type-specific analyses of data that have been collected in the mid-1970s and have been previously reported in aggregated form (3). The conclusion of the investigators that magnetic or electric fields exercise a generalized “promoting” effect on virtually all types of cancer (4,5) has not been supported by the results of recent, methodologically strong epidemiologic investigations of all cancer types [Table 3 in reference (6)].

I agree with Wertheimer and Leeper that one should question negative results from studies with a real or presumed high degree of nondifferential exposure misclassification. But one should also question positive results generated from databases with a demonstrable potential for built-in selection bias. The Centers for Disease Control and Prevention have reported that mortality from breast cancer is higher among blacks than among whites by 19% (7); yet the database utilized in the report by Loomis et al. (2) provides the misleading impression that mortality is higher among whites than among blacks by 44% (P<10⁻⁶).

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References

(1) Trichopoulos D. Are electromagnetic fields a risk or protective factor for breast cancer in women? [editorial; see comment citations in Medline]. J Natl Cancer Inst 86:885-886, 1994

Re: Dangers of Using “Optimal” Cutpoints in the Evaluation of Prognostic Factors

Altman et al. (1) are to be commended for their thoughtful commentary on the (mis)use of cut points in the evaluation of prognostic factors. In particular, their bringing the adjustment formula to the attention of a wider audience is appreciated.

It should be pointed out, however, that any search for an “optimal” cut point that divides patients into high-risk groups versus low-risk groups and that is based on a value of a continuous variable should not be undertaken at all unless that continuous variable has first been found to be prognostic, perhaps by Cox regression. This precaution alone, without any consideration of P-value correction, would avoid the problem illustrated by Table 2 in their commentary. In addition, it should be made clear that the (uncorrected) P values associated with cutoff determined through a search procedure are biased. They serve only as a guide to cutoff selection and not as a true type I error rate. Indeed, subdivision by effect size (hazard ratio) is probably a superior strategy.

Finally, since prognostic factors are usually initially found in studies looking at several potentially prognostic factors, there are severe multiple testing problems in all such investigations. Initial reports of prognostic factors require confirmation on independent datasets. If the dataset is sufficiently large, half the data can be used for legitimate exploratory model building, and the remainder can be used for verification. This approach was taken by Shuster et al. (2), Trueworthy et al. (3), and Harris et al. (4).

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Response

We thank Cantor and Shuster for their helpful remarks. We agree with most of their comments. In particular, their suggestion that prognostic factors should be demonstrated to be significant in Cox regression (i.e., without grouping) before considering the creation of categories echoes the remarks in our final paragraph. It should, however, be taken into account that this requires an almost correct specification of the time regression function, which might not be linear.

There are important multiple comparison problems in many prognostic factor studies. Data splitting is certainly a valuable technique, but as Cantor and Shuster note, one needs a large dataset for this to be viable. The three studies (1-3) they cite had sample sizes of 668, 1535, and 1021, which are much larger than in most such studies. Not only do larger studies allow a sensible analysis of only one half the data, they are also much less likely than small studies to include uninformative variables in their prognostic models simply by chance variation. However, standard errors of estimated regression coefficients are larger when data splitting is used. Other problems are discussed by Hirsch (4).

Resampling and cross-validation techniques should therefore be considered as serious and possibly better alternatives (5-7).

We note that the three studies (1-3) the authors cite all used recursive partitioning to derive prognostic models, which inherently requires cut points for all continuous variables. While we agree that a cutoff selection based on P values is not desirable, the issue of how best to handle continuous variables in this procedure remains controversial.

Concerning the general problem of studying several potentially prognostic factors, we think that standard models that are based on established factors with predefined functional shape and/or cut points should be agreed on. These standard models should be used as a starting point and as a reference when evaluating new factors. The additional prognostic effect of the new factor can then be estimated in a simple way without the well-known problems associated with variable selection procedures and the interpretation of a derived final model.

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Toxicity of Isotretinoin in a Chemoprevention Trial to Prevent Second Primary Tumors Following Head and Neck Cancer

The synthetic retinoid isotretinoin, 13-cis-retinoic acid (cRA), is currently being studied as a chemopreventive agent for lung and upper aerodigestive tract cancer. Given orally, the drug has reversed oral premalignancy and prevented second primary tumors following head and neck cancer (1-4).

There is evidence from these studies of a chemopreventive effect across a wide range of doses, from the dose of 50-100 mg/m² per day used in the adjuvant study following head and neck cancer (2) to the lower dose of 0.5 mg/kg per day used in the maintenance phase of the oral premalignancy trial (3). In these trials, the side effects associated with isotretinoin have been greater than those seen with administration of placebo or beta carotene. The side effects most commonly associated with isotretinoin include the following: dry skin, cheilitis, conjunctivitis, hypertriglyceridemia, and arthralgias. All of these side effects clearly become more severe and more common as the dose of isotretinoin is increased.

Study participants in chemoprevention trials have varied considerably in their risk of developing cancer. The acceptable side effects of a chemoprevention agent are also variable, based on both the actual risk of developing cancer and the participant’s perceived risk. Randomized, placebo-controlled trials are now being performed with patients at high risk for the development of second primary tumors based on their history of a previous head and neck cancer or non–small-cell lung cancer. These second primary tumors occur predominantly in the upper aerodigestive tract and lungs and consequently pose a great threat to these patients (5-8).

The trial to prevent second primary tumors following treatment of a stage I or II squamous cell cancer of the head and neck is being performed through The University of Texas M. D. Anderson Cancer Center, its Community Clinical Oncology Program (CCOP), and the