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 just 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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Note

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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...
Radiation Therapy Oncology Group (RTOG). The study was approved by each institution's investigational review board, and informed consent was obtained from all study participants. The trial has accrued 580 patients from 77 participating institutions, of which 268 patients were assessed for toxic reactions. Patients were enrolled who had no current evidence of malignancy and had undergone definitive local treatment of their initial head and neck cancer between 16 weeks and 3 years earlier than their enrollment in the trial. The initial treatment period was an 8-week run-in phase; only those patients who took more than 75% of the study medication and remained free of cancer continued in the study. Patients were randomly assigned to receive treatment with 30 mg/d isotretinoin or placebo throughout the 3-year study period. Study participants were seen every 3 months during their first year in the study.

Each patient's toxic reactions were assessed at each visit by a physician and graded using the National Cancer Institute's Common Toxicity Criteria. A supplemental toxicity scale was also used to assess the dermatologic toxic effects associated with retinoids. Cervical spine x-rays were used to assess skeletal changes. Patients found to have toxic reactions that could be attributed to the study drug and that were associated with a more than grade 2 toxicity were given a reduced dose. The end points for the analysis were the frequency and severity of toxic effects reported for each randomly assigned patient.

The trial started in December 1991, and this analysis was done using all the data received as of December 28, 1993. Of the 366 patients randomly selected by the cutoff date, there were 268 patients with follow-up data for analysis. Of these 268 patients, 64% and 26% were followed for at least 6 and 12 months, respectively.

Dose reductions were prescribed for 36 of 135 (27%) patients in arm A and 3 of 133 patients (2%) in arm B of the study (P = .0001). Dermatologic toxic reactions, cheilitis, and conjunctivitis were all observed more commonly in arm A than arm B (Table 1). The majority of toxic effects reported were mild and did not require dose reductions.

Twelve patients refused to take the drug any longer and were classified as noncompliant. Another 14 patients had their treatment discontinued: some patients after developing a second primary tumor (n = 4), some who died without developing one (n = 5), and some for other reasons (n = 5). The remaining 243 patients continued on the drug.

The preliminary toxicity data from this multicenter study is consistent with the findings of a single institution study (1) that used a comparable dose of isotretinoin in patients with oral premalignancy. Side effects were observed in patients who were administered a dose of 30 mg/d isotretinoin, but, for this group of previously treated cancer patients with a very high risk for developing second primary tumors, the side effects were acceptable to a majority of the patients and physicians treating them.

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References

Table 1. Toxic effects reported in a second primary tumor prevention trial

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Skin</th>
<th>Cheilitis</th>
<th>Conjunctivitis</th>
<th>Elevated triglycerides</th>
<th>Arthralgias</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>1 I 21</td>
<td>1 I 25</td>
<td>1 I 36</td>
<td>9 I 4</td>
<td>3 I 3</td>
<td>17 I 9</td>
</tr>
<tr>
<td>Arm B</td>
<td>3 I 35</td>
<td>2 I 31</td>
<td>0 I 13</td>
<td>0 I 0</td>
<td>1 I 0</td>
<td>6 I 1</td>
</tr>
</tbody>
</table>

*Grade I
- Skin reaction: Mild dryness of skin/mucous membranes, ± redness, ± pruritis, controlled with emollients, mild peeling of palms and soles.
- Cheilitis: Chapped lips ± mild fissures.
- Conjunctivitis: Mild discomfort, minimal redness.

*Grade II
- Skin reaction: Moderate dryness of skin/mucous membranes, with redness, not controlled with emollients, moderate peeling of palms and soles; causes functional disability.
- Cheilitis: Moderate fissures with crusts and exudates.
- Conjunctivitis: Mild discomfort with redness, needs artificial tears.

*Grade III
- Skin reaction: Moderate dryness of skin/mucous membranes covering one third of the body, not controlled with emollients, may have vesicles, severe peeling of palms and soles, causes functional disability.
- Cheilitis: Severe, marked with swelling, and hemorrhagic.
- Conjunctivitis: Not relieved by artificial tears.
†Glossitis at prior brachytherapy site.


Notes

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Re: Breast Cancer Mortality Among Female Electrical Workers in the United States

In their report, Loomis et al. (1) described an excess of female breast cancer among certain "electrical" occupations that they postulate was due to extremely low frequency electromagnetic field exposure. The greatest excess risk was found in telephone installers, repairers, and line workers who, as a group, had an adjusted odds ratio of 2.17 for mortality for breast cancer relative to other employed women. We suggest problems exist in studies that do not investigate the presence of confounding exposures and that use job titles as surrogates for worker exposures.

Loomis et al. discount the existence of ionizing radiation exposure in these groups of workers. We have recently completed a study (2) of a telephone central office facility where workers install and maintain lines and switches for the telephone company. We found that the cross-bar switching machinery, historically used in the central office facility, contained vacuum tubes having at least 1 μCi of radium bromide and were located in racks holding 60 tubes per rack. While these cross-bar switches have been replaced by modern equipment that do not utilize radium bromide tubes, they were still in use in at least one central office facility as late as 1992. Of importance to the issue of breast cancer was the finding that central office facility workers, who may be included in the category "installers, repairers, and line workers," may have carried these tubes in their shirt pockets. The telephone company estimated the dose rate from these tubes to be about 4 mR/h at the point of bodily contact (3). The role of this potential exposure to a well-established carcinogenic agent in the development of male and female breast cancer among central office facility workers has not yet been evaluated; however, it is not unrealistic to assume that it may be far greater than whatever cancer-inducing effect is postulated by the inhibition of melatonin from exposure to electromagnetic fields. If the category of telephone installers, repairers, and line personnel (as used by Loomis et al.) includes central office facility workers, then our findings suggest the presence of a major confounder—ionizing radiation.

For telephone pole workers, exposures to extremely low frequency electromagnetic fields may not be different from those in other occupations. Means of limited exposure levels to extremely low frequency electromagnetic fields among telephone installers, repairers, and line (pole) personnel measured by the National Institute for Occupational Safety and Health (NIOSH) investigators ranged from 1.3 to 14.8 mG. The highest value was obtained from a worker who was using a gasoline-powered drill for 2-minute intervals, with levels of exposure up to 718 mG that could not be attributed to exposure to either telephone wires (carrying 48-V DC current) or overhead 60-Hz power lines. Because the workers in prior years used hand drills, the use of the gas drill is relatively new. With the exception of the use of the drill, no mean measurement of worker exposure exceeded 4.5 mG; these values are supported by a study conducted by telecommunications industry research (4). In this study, the extremely low frequency electromagnetic field exposure levels were measured in the same group of workers cited by Loomis et al. These values approximate those that NIOSH investigators have found in office settings, where sporadic exposure to electrical devices such as pencil sharpeners, computers, fans, and other equipment similarly skew the mean values upward (5,6). The overall exposure to extremely low frequency electromagnetic fields of telephone installers, repairers, and line workers may not be any higher than that of many other occupational groups of workers.

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