found to be of minimal benefit in certain subgroups and necessary in others is discussed in our article (1) and its accompanying editorial (2). We find Dr. Atkins’s table showing percent reductions by subgroups potentially misleading because it does not reflect uncertainty in the estimated rates. In addition, it is redundant with the information that we presented in Fig. 4 (1), which shows percent reductions by covariate levels and associated confidence intervals. In the past, strong conclusions drawn from subgroup data have caused considerable confusion among breast cancer clinicians and researchers. An excellent example is the persistent belief, based on early studies and hypotheses concerning endogenous hormone levels, that tamoxifen is not efficacious in younger women (3). Subsequently, findings from individual studies, e.g., NSABP B-14, and results of the Early Breast Cancer Trialists’ Collaborative Group overview strongly supported its use in young women with estrogen receptor (ER)-positive tumors (4, 5).

In regard to variation in mortality by age and the “preliminary nature of these results,” the survival comparisons are mature to the degree that, by design, the number of total events was sufficient to allow for pairwise comparisons between the tamoxifen group and chemotherapy groups with statistical power greater than 80%. As Dr. Atkins indicates, survival comparisons within age subgroups are less reliable. Because there was no statistically significant evidence of an interaction between treatment and age group, we concluded that a benefit exists in both age groups, although the data are suggestive of a greater benefit for younger patients with respect to the other end points, i.e., disease-free survival and distant disease-free survival.

Dr. Atkins suggests that the combined use of chemotherapy and tamoxifen is potentially detrimental to premenopausal patients. Our data provide no evidence of significantly increased mortality due to chemotherapy in younger women; moreover, as Dr. Atkins has stated, the result of the report by the Early Breast Cancer Trialists’ Collaborative Group (an increase of 6% with standard deviation of 23%) was highly variable (5). The earlier NSABP study to which Dr. Atkins alludes addressed the question of adding tamoxifen to chemotherapy in ER-negative and ER-positive patients and is not directly relevant to the question at hand (6).

Finally, with regard to Dr. Atkins’s statement about the B-20 trial confirming “what we already know,” we wish to reiterate that our study is the first prospective, randomized comparison of the addition of chemotherapy to tamoxifen alone in lymph node-negative, ER-positive patients. This treatment approach could not justifiably be adopted without the conduct of such a trial, precisely for the reasons that apparently motivated Dr. Atkins’s letter, i.e., the potential benefits and costs that patients and their physicians must weigh before deciding to choose this treatment regimen.

JAMES DIGNAM
BERNARD FISHER

References


Notes

Affiliations of authors: J. Dignam, NSABP Biostatistical Center, Pittsburgh, PA; B. Fisher, Allegheny University of the Health Sciences, Pittsburgh, PA.

Correspondence to: Bernard Fisher, M.D., Allegheny University of the Health Sciences, Four Allegheny Center, Suite 602, Pittsburgh, PA 15212-5324.

Re: Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China

Hayes et al. (1) reported a nonsignificant relative risk (RR) for non-Hodgkin’s lymphoma (NHL) of 3.0 (95% confidence interval [CI] = 0.9–10.5) among Chinese workers exposed to benzene and other chemicals and stated, “... the possible links with NHL are all provocative new observations.” In their discussion, Hayes et al. cited some of my studies (2–4). Unfortunately, because of the grouping of causes of death in U.S. vital statistics, no separate analysis for NHL was reported in these publications. In the present paper, I will report NHL results that have not been published previously.

Wong (2–4) reported on the mortality of 4602 workers exposed to benzene at seven U.S. chemical plants. The analyses were conducted with the use of the University of Pittsburgh OCMAP Pro- gram (5), which classified NHL (International Classification of Diseases, 8th revision, codes 200 and 202) in two categories according to the usual groupings in U.S. vital statistics: lymphosarcoma and reticulosarcoma (ICD 200) and “cancers of other lymphatic tissues” (ICD 202, 203, and 208), the latter including not only “other lymphomas” but also other cancers such as multiple myeloma. A borderline significant excess of “non-Hodgkin’s lymphopoietic cancer,” which included all types of lymphopoietic cancers, (e.g., NHL, multiple myeloma, and leukemia, ICD 200–209) except Hodgkin’s disease (ICD 201), was reported (2,3). However, no analysis specific to NHL was done at the time. To address the issue of NHL specifically, a separate analysis has been performed. Seven NHL deaths were reported among workers exposed to benzene (some to levels exceeding 50 parts per million [ppm]), compared with 5.12 expected deaths based on the U.S. general population. The standardized mortality ratio (SMR) was 1.37 (95% CI = 0.55–2.82).

The second study consisted of 1165 men exposed to relatively high levels of benzene (up to several hundred ppm) at...
two rubber hydrochloride plants in Ohio. NHL mortality in this cohort has not been reported previously (4). Based on the updated data with mortality observed through 1987, an analysis for NHL has been performed. There were three NHL deaths in the Pliofilm study, compared with 3.28 expected (SMR = 0.91; 95% CI = 0.19–2.66).

Hayes et al. also cited a Canadian study of petroleum distribution workers (6). Distribution workers are responsible for transporting gasoline (2% to 3% benzene) in tank trucks, ocean tankers, or barges and are potentially exposed to benzene. Wong et al. (7) have conducted a similar study of 18,135 gasoline distribution workers in the United States. They found no increased risk for NHL (SMR = 0.42; 19 observed deaths; 95% CI = 0.25–0.65).

Further supporting evidence that there is no association between benzene exposure and NHL comes from case–control studies (summarized in Table 1). The risk ratios reported in these case–control studies of NHL and benzene ranged from 0.49 to 1.2. Therefore, these case–control studies support the results of cohort studies of workers exposed to benzene. Thus, the NHL results from the Chinese study are inconsistent with those of other (cohort or case–control) studies, and the NHL results reported by Hayes et al. are indeed “provocative new observations” and should be viewed with caution.

**OTTO WONG**

### Table 1. Case–control studies of non-Hodgkin’s lymphoma and benzene exposure

<table>
<thead>
<tr>
<th>Authors (year)*</th>
<th>Location</th>
<th>No. of cases</th>
<th>Exposure</th>
<th>Relative risk (confidence interval [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schumacher and Delzell (1988)</td>
<td>North Carolina</td>
<td>501</td>
<td>Benzene</td>
<td>0.77 (95% CI = 0.56–1.07) for whites; 0.94 (95% CI = 0.47–1.87) for blacks; 1.0 (95% CI not reported)</td>
</tr>
<tr>
<td>Ott et al. (1989)</td>
<td>West Virginia (nested within a cohort of chemical workers)</td>
<td>52</td>
<td>Benzene</td>
<td>0.54 (95% CI = 0.25–1.00)</td>
</tr>
<tr>
<td>Scherr et al. (1992)</td>
<td>Boston</td>
<td>303</td>
<td>Benzene</td>
<td>0.54 (95% CI = 0.25–1.09)</td>
</tr>
<tr>
<td>Blair et al. (1993)</td>
<td>Iowa and Minnesota</td>
<td>622</td>
<td>Benzene</td>
<td>1.0 (95% CI not reported)</td>
</tr>
<tr>
<td>Siemiatycki (1991)</td>
<td>Montreal, Canada</td>
<td>215</td>
<td>Benzene</td>
<td>0.8 (95% CI = 0.4–1.6)</td>
</tr>
<tr>
<td>Franceschi et al. (1989)</td>
<td>Northeast Italy</td>
<td>208</td>
<td>Benzene and solvents</td>
<td>1.14 (95% CI = 0.57–2.28)</td>
</tr>
<tr>
<td>Cartwright et al. (1988) and Bernard et al. (1984)</td>
<td>Yorkshire, U.K.</td>
<td>158</td>
<td>Benzene</td>
<td>0.49 (95% CI = 0.21–2.00)</td>
</tr>
</tbody>
</table>


### References


### Notes

**Editor’s note:** The study described in (2,3) was sponsored by the Chemical Manufacturers Association; the study described in (7) was sponsored by the American Petroleum Institute. In addition, Dr. Wong has served as a paid consultant to the petroleum and chemical industry.

**Correspondence to:** Otto Wong, Sc.D., Applied Health Sciences, 181 Second Ave., Suite 628, San Mateo, CA 94401. E-mail: ottowong@aol.com.