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Author Contributions: Drs Klempner and Ali had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Klempner, Bordoni, Ou, Ali.

Acquisition, analysis, or interpretation of data: Klempner, Gowen, Kaplan, Stephens, Ou, Ali.

Drafting of the manuscript: Klempner, Ali.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Gowen.

Administrative, technical, or material support: Kaplan, Ali.

Study supervision: Ali.

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Additional Contributions: We thank the patient for granting permission to publish this information.


**Associations Between Industry Sponsorship and Results of Cost-effectiveness Analyses of Drugs Used in Breast Cancer Treatment**

A 1999 investigation found that industry sponsorship of cost-effectiveness analyses (CEAs) for oncology drugs was associated with lower likelihood of reporting unfavorable conclusions relative to CEAs with other sponsorship. Over the past 15 years, the CEA literature for oncology drugs has expanded dramatically, and oncology now accounts for the largest single pharmaceutical sales area worldwide. We sought to determine whether the association between industry sponsorship and CEA results has persisted.

**Methods** We examined CEAs for breast cancer, the most common target diagnosis among oncology CEAs (36% of studies). We obtained data on all such CEAs published between 1991 and 2012 from the Tufts Cost-Effectiveness Analysis Registry, which was created by searching MEDLINE for all English language CEAs using the key words “QALYs” (quality-adjusted life-years), “cost-utility analysis,” and “breast cancer.” From the registry we extracted study characteristics, results (cost per QALY), and registry-assigned quality ratings (which ranged from 2 to 6).

We considered a study industry-sponsored if a pharmaceutical company provided funding or if one or more study authors was a company employee. Study authors provided sponsorship information for 13 studies with unclear funding information in the publication.

We converted each study’s results to 2013 US dollars using purchasing power parity conversion factors, categorized study results based on 3 thresholds ($50 000, $100 000, and $150 000/QALY), and classified studies as “cost-effective” if all results were equal to or more favorable than the chosen threshold, “not cost-effective” if none were, or “mixed” otherwise (note: each study could contain multiple analyses, with varying assumptions). Using JMP Pro statistical software (version 11.0.0, SAS Institute), we tested bivariate associations between industry sponsorship and study characteristics. We then fitted logistic regressions to estimate independent associations between industry sponsorship and study results, adjusting for drug class, cancer stage targeted, and study quality score.

**Results** Of 105 CEA studies, 65 were industry funded (Table 1). Study quality ratings were nonsignificantly higher among industry-sponsored studies (mean rating, 4.8 vs 4.4 among studies with other sponsorship; P = .09).

Industry-sponsored studies were statistically significantly more likely than other-sponsored studies to report favorable cost-effectiveness results: 75.4% vs 40.0% at $50 000/QALY (P = .004), 80.0% vs 57.5% at $100 000/QALY (P = .03), and 87.7% vs 67.5% at $150 000/QALY (P = .04) (Table 2). Among the subset of CEAs with high quality ratings (≥4.5), industry-sponsored studies were more likely to report favorable findings (75.5% vs 45.5%, P = .04, at the $50 000/QALY threshold).

**Discussion** Our analysis of breast cancer CEAs suggests that pharmaceutical industry-sponsored studies continue to be more likely to report favorable estimates than studies with other sponsorship. These findings have multiple possible explanations.

First, most CEAs have retrospective designs, which can allow investigators to identify and then conduct, based on early looks at clinical and resource profiles, those trials most likely to yield positive outcomes. Second, potential conflicts of interest exist. Pharmaceutical companies can exert influence through grants, educational funds, or manuscript review requirements. Investigators set the values assigned to quality of life, determine the price and duration of interventions, and make other methodological choices that can affect study findings. Making these choices transparently and before results are known could enhance the credibility of CEAs.

Our study has limitations. We examined drugs for breast cancer only. Financial relationships between pharmaceutical companies and researchers were considered, but other less readily detectable factors influencing study findings may exist.

Additional studies are needed to determine whether similar associations between industry sponsorship and results ex-
Table 1. Characteristics of Published Cost-effectiveness Studies of Drugs for Breast Cancer Treatment With Industry and Other Sponsorship

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Pharmaceutical Company-Sponsored (n = 65)</th>
<th>Other Sponsorship (n = 40)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>30 (46.2)</td>
<td>12 (30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>1 (3.3)</td>
<td>8 (66.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>6 (20.0)</td>
<td>1 (3.3)</td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>21 (70.0)</td>
<td>3 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>2 (6.7)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>20 (30.8)</td>
<td>17 (42.5)</td>
<td></td>
<td>.22</td>
</tr>
<tr>
<td>First line</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>9 (45.0)</td>
<td>15 (37.5)</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Second line</td>
<td>8 (40.0)</td>
<td>1 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate*</td>
<td>8 (12.3)</td>
<td>1 (2.5)</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Hematopoietic growth factor</td>
<td>6 (9.2)</td>
<td>2 (5.0)</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Targeted therapy*</td>
<td>6 (9.2)</td>
<td>10 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer stage targeted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive</td>
<td>1 (1.5)</td>
<td>8 (20.0)</td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>Early (stage IIIA or below)</td>
<td>37 (56.9)</td>
<td>26 (65.0)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Advanced</td>
<td>26 (40.0)</td>
<td>5 (12.5)</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Both early and advanced</td>
<td>1 (1.5)</td>
<td>1 (2.5)</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Average quality rating of paper, mean (SD)†</td>
<td>4.8 (0.8)</td>
<td>4.4 (1.0)</td>
<td></td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviation: QALYs, quality-adjusted life-years.

* Adjusted odds ratio, 95% CIs, and P values are from logistic regressions predicting cost-effectiveness results as a function of industry sponsorship, with adjustment for the variables presented in Table 1: drug class (hormonal, chemotherapy, or other), cancer stage, and study quality score.

† Values are from logistic regressions predicting cost-effectiveness results as a function of industry sponsorship, with adjustment for the variables presented in Table 1: drug class (hormonal, chemotherapy, or other), cancer stage, and study quality score.

‡ Includes trastuzumab and lapatinib.

Table 2. Relationship Between Results and Sponsorship of Cost-effectiveness Studies of Drugs for Breast Cancer

<table>
<thead>
<tr>
<th>Cost-effectiveness Threshold, QALY, $</th>
<th>Sponsored Studies Reporting Cost-effective Results, No. (%)</th>
<th>Reporting Cost-effective Results, Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>C Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 000</td>
<td>49/65 (75.4)</td>
<td>16/40 (40.0)</td>
<td>4.01 (1.55-10.92)</td>
<td>.004</td>
</tr>
<tr>
<td>100 000</td>
<td>52/65 (80.0)</td>
<td>23/40 (57.5)</td>
<td>3.14 (1.14-9.08)</td>
<td>.03</td>
</tr>
<tr>
<td>150 000</td>
<td>57/65 (87.7)</td>
<td>27/40 (67.5)</td>
<td>3.27 (1.05-11.08)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviation: QALYs, quality-adjusted life-years.

* Data are from Center for the Evaluation of Value and Risk in Health (CEVR)יום and Thorat et al.6

† P values for categorical variables (drug class, cancer stage) are from fisher exact tests; P value for the continuous variable (average quality rating) is from a Wilcoxon rank sum test.

‡ Includes denosumab.

§ Tufts registry reviewers assigned each study a quality score from 1 (lowest quality) to 7 (highest quality) using the following criteria: whether the authors correctly computed the incremental cost-effectiveness ratios, performed a sensitivity analysis, correctly used and specified the health economic assumptions used in the study, and appropriately and explicitly estimated the utility weights.

ist for CEAs of drugs treating other cancers. Registering CEAs and their methods at inception could help address the conflicts of interest that might underlie these associations.

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Author Contributions: Dr Lane had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis. Study concept and design: All authors. Acquisition, analysis, or interpretation of data: Lane, Friedberg. Drafting of the manuscript: Lane. Critical revision of the manuscript for important intellectual content: Friedberg, Bennett. Statistical analysis: Lane, Friedberg. Administrative, technical, or material support: Bennett. Supervision: Friedberg, Bennett.

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**COMMENT & RESPONSE**

**Differing Perspectives on Breast Cancer Chemoprevention**

**To the Editor** The Viewpoint by Narod⁴ creates a moment of pause concerning current views of chemoprevention, using any agents in high-risk populations of women. The successful use of tamoxifen citrate for the adjuvant treatment of breast cancer has saved perhaps millions of lives and continues to do so. Tamoxifen in the title is a convenient hook. The chemoprevention strategy, by identifying populations, was destined to die eventually because few individuals benefit but nearly everyone experiences adverse effects or worries about them. In 1990 tamoxifen was the only drug to move forward into chemoprevention trials using large, correctly powered populations but only at risk for breast cancer and very low incidence. The translational research that identified the small risk of endometrial cancer with tamoxifen use² served to protect women from a serious adverse effect. However, this created a justifiable concern for women without disease. Additionally, the description of rat liver carcinogenesis with tamoxifen³,⁴ in 1992 was not reassuring to women. Despite the fact that the US Food and Drug Administration approved tamoxifen for risk reduction in 1998, few women chose this option because of adverse effects. Furthermore, adherence dwindles in the treatment setting, when there is certainty of death on recurrence. Adherence is an issue in chemoprevention. Nevertheless, progress has been made that should not be discounted. In 1990, before the initiation of chemoprevention trials, an alternate strategy using selective estrogen receptor modulators (SERMs) was stated: “Important clues have been garnered about the effects of tamoxifen on bones and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis... [These] may significantly retard the development of breast cancer. The targeted population would be postmenopausal women in general, thereby avoiding the requirement to select a high-risk group to prevent breast cancer.”⁵ The result was raloxifene hydrochloride, which reduces the incidence of breast cancer during the treatment and prevention of osteoporosis but without the worry of endometrial and rat liver cancer.⁶ Better SERMs are on the way to target multiple diseases. Specifically, the extended use of SERMs to treat and prevent osteoporosis and, perhaps, coronary heart disease makes this strategy of value to prevent the morbidity following the diagnosis of tens of thousands of breast cancers. This is a bonus to medicine and health care management.⁷ The failure of past chemoprevention clinical strategies, focusing on populations rather than delivering precision medicine, can no longer be justified.

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**To the Editor** Despite its continued ability to prevent a substantial proportion of breast cancer cases for at least 15 years after cessation of treatment, Narod⁴ argues that breast cancer prevention with tamoxifen is dead. We dispute this contention. While aromatase inhibitors show evidence of greater effectiveness, they are only for postmenopausal women, and an important time to offer preventive therapy is during the late premenopausal period, in which tamoxifen is the only proven agent. There have now been 4 large tamoxifen prevention trials, and the clear evidence for substantial reductions in breast cancer incidence has been summarized in Cuzick et al.² However, despite the long follow-up in 2 of them, it is still too early to evaluate its effect on breast cancer mortality. This was not the primary end point for any of these trials and breast cancer incidence still exceeds mortality by more than 10-fold, so the number of events needed to see a mortality effect is still inadequate. For example, in IBIS-I, after a 16-year median follow-up, there have been 503 invasive breast cancers but only 57 breast cancer deaths. As cancer occurred at a constant rate in IBIS-I, median follow-up after cancer is only 8 years, which again is inadequate to evaluate mortality. Women entered this trial at a median age of 49.9 years and more than 95% (6806 of 7154) were still alive at the last report, so they still have much life to be lived. We are in the process of analyzing metastatic spread in cases, which will give an earlier indication of the likely effect on mortality, but even this will take more time. In addition, because tamoxifen therapy only prevents the less fatal estrogen receptor-positive breast cancer, an 18% mortality reduction is projected.³ To demonstrate a mortality reduction with even 50% power, 216 breast cancer deaths would be needed and to date only 92 have been reported in all of these trials.²⁴