

# Frequency, Nature, Effects, and Correlates of Conflicts of Interest in Published Clinical Cancer Research

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**BACKGROUND:** Relationships between clinical researchers and industry are becoming increasingly complex. The frequency and impact of conflicts of interest in the full range of high-impact, published clinical cancer research is unknown. **METHODS:** The authors reviewed cancer research published in 8 journals in 2006 to determine frequency of self-reported conflicts of interest, source of study funding, and other characteristics. They assessed associations between the likelihood of conflicts of interest and other characteristics by using chi-squared testing. They also compared the likelihood of positive outcome in randomized trials with and without conflicts of interest by chi-squared testing. **RESULTS:** The authors identified 1534 original oncology studies; 29% had conflicts of interest (including industrial funding) and 17% declared industrial funding. Conflicts of interest varied by discipline ( $P < .001$ ), continental origin ( $P < .001$ ), and sex ( $P < .001$ ) of the corresponding author and were most likely in articles with corresponding authors from departments of medical oncology (45%), those from North America (33%), and those with male first and senior authors (37%). Frequency of conflicts also varied considerably depending upon disease site studied. Studies with industrial funding were more likely to focus on treatment (62% vs 36%;  $P < .001$ ), and randomized trials that assessed survival were more likely to report positive survival outcomes when a conflict of interest was present ( $P = .04$ ). **CONCLUSIONS:** Conflicts of interest characterize a substantial minority of clinical cancer research published in high-impact journals. Therefore, attempts to disentangle the cancer research effort from industry merit further attention, and journals should embrace both rigorous standards of disclosure and heightened scrutiny when conflicts exist. **Cancer** 2009;115:2783-91. © 2009 American Cancer Society.

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In recent years, relationships between clinical researchers and industry have become increasingly complex. Researchers may not only rely upon industry for study funding<sup>1,2</sup> but may also receive consulting fees, own stock, and hold leadership positions within organizations that profit from selling the very drugs and devices that are the subjects of researchers' investigations.<sup>3,4</sup>

Several studies have suggested that industry-sponsored studies tend to reach conclusions favorable to the sponsor<sup>5-16</sup> and to use study designs more likely to favor the sponsored intervention than studies

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without industrial sponsorship.<sup>8,13,16,17</sup> Studies have also indicated that ties to industry may influence the nature, focus, and dissemination of research undertaken by researchers with those ties.<sup>1,2,18</sup> Concerned by these findings, medical journals have increasingly implemented policies that require researchers to disclose potential conflicts of interest.<sup>19-21</sup>

Although previous studies have sought to define the frequency of conflicts of interest among scientific and medical researchers, many of these estimates are already dated, and few have focused upon cancer research specifically. A recent study found that the majority of clinical trials of systemic anticancer and supportive care drugs reported in the *Journal of Clinical Oncology* in 2005 declared conflicts of interest.<sup>22</sup> Yet the broader epidemiology of conflicts of interest in current, published oncology literature remains unexplored. It is quite possible that studies considering diagnostic tests, technologies, and surgical interventions may differ substantially from trials of pharmacologic agents. Therefore, the impact of the “industrialization of clinical research” upon the field of oncology merits further attention.<sup>23</sup> This is particularly important in light of changes in political priorities that made the competition for scarce federal research funds increasingly intense, potentially fueling an even greater reliance upon private sources in recent years.

Therefore, in this study, we sought to characterize in greater detail the sources of funding for the clinical cancer research recently published in high-impact medical journals, to examine the frequency and nature of conflicts of interest declared, and to consider possible associations between conflicts of interest and investigator characteristics, disease site, study focus, and study outcome.

## MATERIALS AND METHODS

### **Inclusion Criteria**

This study focuses upon research published in 2006 in selected, high-impact, English-language journals. Journals were selected after consideration of journal impact factors, citation half-life, and readership. Only journals that primarily publish original, clinical oncology research were included; journals that focus upon reviews or basic science investigation alone were excluded. Three journals catalogued by the Thomson ISI Journal Citation Index as gen-

eral medical journals were included as follows: the *New England Journal of Medicine*, *JAMA*, the *Journal of the American Medical Association*, and the *Lancet*. Five journals catalogued as oncology journals were included: the *Journal of Clinical Oncology*, the *Journal of the National Cancer Institute*, the *Lancet Oncology*, *Clinical Cancer Research*, and *Cancer*. All articles listed as original investigations were reviewed (in *Clinical Cancer Research*, only articles under the subheading “Cancer Therapy: Clinical” were included); special articles, editorials, and review articles were excluded. Original investigations that were published in the general medical journals were reviewed to determine whether their subjects were oncology.

### **Coding**

All original oncology articles identified in this manner were then analyzed to determine certain objective attributes: cancer type and/or site, declared source(s) of funding and conflicts of interest, author affiliations, and sex of the primary and senior (final) authors. The sex of the author was determined by inspection of the author’s name; for names in which sex was ambiguous, internet searches were used in an attempt to determine sex, as described elsewhere.<sup>24</sup> The articles were also subjectively coded for study type (prospective clinical vs other) and focus of research (epidemiology, prevention, risk factors for incidence, screening, or diagnostic methods; treatment with curative intent, or treatment with palliative intent).

Data were entered by 2 medical-student coders into a Microsoft Access database (N.S. and S.A.; Microsoft, Redmond, Wash). The senior investigator (R.J.) closely supervised the coding process, including a personal review of 100 articles coded by each of the 2 medical-student coders to improve accuracy and consistency in the coding process. In order further to ensure inter-rater reliability, 10% of the articles, distributed across all included journals, were assessed independently by both coders. All discrepancies in this subset were analyzed further to determine the nature and frequency of coding disagreements for each item. Discrepancies were resolved by the consensus of 2 additional individuals (A.M. and R.J.), and overall error rates for each item were thus determined. For all objective attributes assessed, error rates were less than 5%. For the coding categories on study type and focus, which required subjective assessment on the part of

the coders, we formally assessed the level of interobserver agreement. For classification of the study as a prospective clinical oncology study versus other type of study, the 2 coders were found to agree in 89% of the cases in the overlapped sample. This corresponded to a kappa of 0.74, indicative of good interobserver agreement.<sup>25</sup> For the classification of the major focus of the study as epidemiology, prevention, risk factors for incidence, screening, or diagnostic methods, the 2 coders agreed in 77% of cases, with a kappa of 0.53, indicative of fair interobserver agreement. For the classification of the major focus of the study as treatment with curative intent, the 2 coders agreed in 84% of cases, with a kappa of 0.63, indicative of good interobserver agreement. For the classification of the major focus of the study as treatment with palliative intent, the 2 coders agreed in 99% of cases. Given the infrequency of this classification, kappa is an inappropriate measure of interobserver agreement and was not calculated.

All randomized clinical trials were further examined to assess the authors' subjective interpretation of outcome, and for studies in which overall survival was assessed, to determine an objective measure of outcome based upon the statistical significance of survival impact. The randomized studies identified in the initial coding phase were printed for subsequent blinded coding of outcomes. Sections containing author names and affiliations were blacked out, and all articles were physically cut after the last sentence of the conclusions to blind reviewers as to whether a conflict of interest disclosure was made. All randomized trials were coded for outcomes by 2 blinded coders who had not reviewed the papers in the initial coding phase. Authors' subjective interpretations were graded qualitatively as positive (presenting the intervention arm as preferable to the control arm), neutral, or negative (presenting the control arm as preferable to the intervention arm). Overall survival was assessed quantitatively, with a positive result defined as a significant ( $P < .05$ ) survival difference in favor of the intervention, positive trend ( $P \leq .10$ ) toward significance in favor of the intervention, neutral as no significant difference between the 2 arms, negative trend ( $P \leq .10$ ) toward significance in favor of the control arm, and negative as a significant ( $P < .05$ ) survival difference in favor of the control arm. Discrepancies between the 2 blinded coders were resolved by blinded consensus.

## Analysis

For the purposes of analysis, a conflict of interest was defined to be present when a conflict of interest was explicitly declared by the authors, when an author was an employee of industry at the time of publication, or when the study reported industry as the funding source. Statistical analysis was performed by using SPSS version 14.0 software (SPSS, Chicago, Ill). Chi-squared testing was used to determine the significance of associations between industrial funding or conflict of interest and disease site, author characteristics, and study type and focus. Because all applicable articles published in the selected journals during the chosen year were reviewed, the cases in our database constitute the entire universe of applicable data points; therefore, these estimates are exact and contain no statistical uncertainty.

## RESULTS

We identified 2701 original articles published in the selected journals in the year 2006, of which 1534 were oncology studies.

Table 1 details the sources of funding and frequency of conflicts of interest declared in the research articles studied, by journal. Overall, 29% of the papers had conflicts of interest, and 17% declared industrial funding.

As shown in Figure 1, there was a statistically significant difference in the proportion of studies that declared industrial funding ( $P < .001$ ) or that had any conflicts of interest ( $P < .001$ ) by study discipline, as defined by the department of the corresponding author. Studies that had a corresponding author from a medical oncology department or division were most likely to have conflicts (45%), and studies from diagnostic radiology were least likely to have conflicts (4%).

Table 2 presents funding sources and frequency of conflicts of interest by disease type and/or site studied, revealing considerable variability in the frequency of conflicts of interest ( $P = .02$ ) and likelihood of industrial funding ( $P = .001$ ) between different cancer types and/or sites.

There was also a statistically significant association between geography and frequency of industrial funding and conflicts of interest. Of the 965 studies with authors based in North America, 19% declared industrial funding, compared with 17% of the 405 studies from Europe,

**Table 1.** Funding Sources and Conflicts of Interest in Original Cancer Research Publications Appearing in Selected Journals in 2006

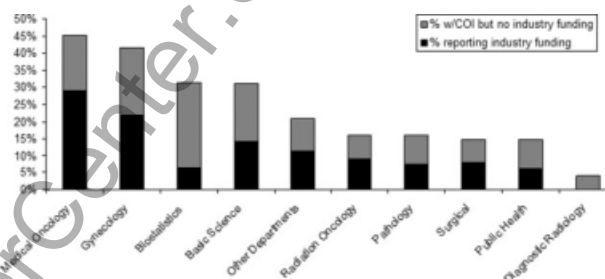
|                            | No. of Oncology Studies | % With Conflict of Interest | % Declaring Industry Funding | % Declaring Government Funding | % Declaring Private Philanthropic Funding |
|----------------------------|-------------------------|-----------------------------|------------------------------|--------------------------------|---|
| Overall                    | 1534                    | 29                          | 17                           | 50                             | 29  |
| <i>Cancer</i>              | 602                     | 16                          | 11                           | 38                             | 27  |
| <i>Clin Cancer Res</i>     | 144                     | 40                          | 25                           | 52                             | 40  |
| <i>JAMA</i>                | 27                      | 44                          | 19                           | 78                             | 22  |
| <i>JCO</i>                 | 565                     | 39                          | 23                           | 50                             | 30  |
| <i>JNCI</i>                | 123                     | 20                          | 6                            | 89                             | 33  |
| <i>The Lancet</i>          | 8                       | 38                          | 25                           | 63                             | 38  |
| <i>The Lancet Oncology</i> | 34                      | 35                          | 18                           | 41                             | 38  |
| <i>NEJM</i>                | 31                      | 61                          | 39                           | 77                             | 10  |

2% of the 117 studies from Asia, and 21% of the 47 studies from elsewhere ( $P < .001$ ). Conflicts of interest were observed in 33% of the North American studies, 27% of the European studies, 5% of the Asian studies, and 40% of the studies from other locations ( $P < .001$ ).

Sex of the first and senior authors was determined in 1505 articles. In these articles, 33% of the first authors and 20% of the senior authors were female. Articles with a woman as first or senior author were less likely to be funded by industry (13% vs 23%;  $P < .001$ ) or to have conflicts of interest (24% vs 37%), but these articles were more likely to have any source of funding declared (76% vs 68%;  $P < .001$ ), when compared with studies in which both first and senior authors were men.

The types of conflicts of interest in the examined articles are described in Figure 2. Most frequent was industrial funding of the study (present in 17% of articles), followed by participation in authorship by an employee of industry (present in 12% of articles).

Among the 261 industry-funded studies, 62% had a major focus upon treatment with curative intent. This was significantly higher than the proportion among studies not funded by industry (36%;  $P < .001$ ). Few studies, funded by industry or not, had a major focus upon treatment with palliative intent, but the proportion of industry-funded studies with this focus was higher than the proportion of studies not reporting industrial funding (5% vs 2%;  $P = .002$ ). Industry-funded studies were less likely than those not declaring industrial funding to focus upon epidemiology, prevention, risk factors for incidence, screening, or diagnostic methods (20% vs 47%;  $P < .001$ ).



**FIGURE 1.** This figure depicts the frequency of conflicts of interest (including industrial funding) declared by articles with corresponding authors from different departmental and divisional affiliations.

Of the 661 prospective clinical studies identified in our dataset, 211 (32%) were industry-funded, and 312 (47%) had a conflict of interest. The majority (81%) of the industry-funded studies were prospective clinical studies, whereas only 35% of studies that did not declare industrial funding were prospective clinical studies ( $P < .001$ ).

Table 3 presents the results of the blinded outcomes analysis of the 124 randomized trials identified in the sample. Among studies that reported overall survival, those studies with conflicts of interest were more likely to have positive findings ( $P = .04$ ). There was no observed difference in the likelihood that the author interpretation was positive nor in the likelihood that the author interpretation was more positive than the objective assessment of effect on overall survival. No significant differences were observed between studies reporting industrial funding

**Table 2.** Funding Sources and Conflicts of Interest by Cancer Type and/or Site

|                         | No. of Oncology Studies* | % With Conflict of Interest | % Declaring Industry Funding | % Declaring Government Funding | % Declaring Private Philanthropic Funding |
|-------------------------|--------------------------|-----------------------------|------------------------------|--------------------------------|---|
| Overall                 | 1534                     | 24                          | 17                           | 50                             | 29  |
| Breast                  | 263                      | 29                          | 16                           | 55                             | 35  |
| Hematologic             | 211                      | 35                          | 21                           | 40                             | 29  |
| Gastrointestinal        | 214                      | 29                          | 16                           | 54                             | 30  |
| Urinary                 | 66                       | 27                          | 18                           | 35                             | 18  |
| Prostate, testis, penis | 128                      | 35                          | 23                           | 58                             | 30  |
| Lung                    | 137                      | 32                          | 21                           | 49                             | 20  |
| Nervous system          | 67                       | 3                           | 4                            | 45                             | 34  |
| Gynecologic             | 83                       | 20                          | 6                            | 61                             | 28  |
| Head and neck           | 72                       | 18                          | 11                           | 47                             | 33  |
| Skin                    | 60                       | 33                          | 18                           | 58                             | 28  |
| Sarcoma                 | 61                       | 16                          | 8                            | 38                             | 36  |

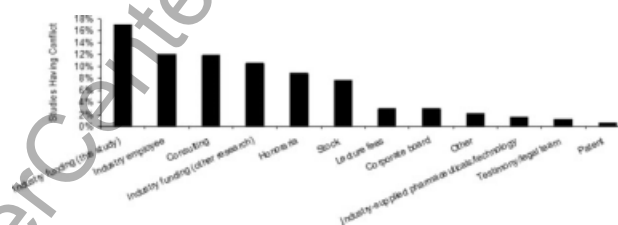
\* Studies that considered several cancer types and/or sites are included in each major type and/or site category, that these studies considered.

and those not reporting industrial funding for any of the blinded outcomes assessed.

## DISCUSSION

In this study, we have found that conflicts of interest characterize a substantial minority of the clinically oriented cancer research published in high-impact medical journals. Conflicts of interest were most likely in articles with corresponding authors from departments of medical oncology, those from North America, and those with male first and senior authors, and the frequency of conflicts varied considerably depending upon disease site studied. Articles that reported industrial funding were more likely to have a focus on treatment than were studies that did not report such funding, and randomized trials with a conflict of interest were more likely to report positive survival outcomes.

Our work complements other studies that have sought to illuminate the frequency, nature, and effects of conflicts of interest in modern clinical oncology research. Hampson and colleagues recently examined the conflict of interest disclosure forms submitted by authors of abstracts presented at the 2004 and 2005 annual meetings of the American Society of Clinical Oncology.<sup>26</sup> They found that 23.8% of the abstracts in 2004 and 17.0% in 2005 disclosed research funding, and 23% of the abstracts in those 2 years had at least 1 author who disclosed a personal financial interest. They also found that almost 20% of abstracts had at least 1 author who was employed by or played a leadership role in a commercial entity. Our find-



**FIGURE 2.** This figure depicts the frequency of different types of conflict of interest declared in the articles analyzed.

ings provide a complementary perspective on these important issues. After all, although certain abstracts—particularly those presented in plenary sessions—may be quite influential, abstracts are primarily intended to present preliminary findings and do not always result in peer-reviewed publications, which are the primary means by which research findings influence practice.<sup>27</sup> Therefore, it is useful also to consider the sources of funding and nature of conflicts disclosed in the clinical studies that have achieved publication in high-impact journals.<sup>28</sup> Our findings that 12% of articles had authors who were employees of industry and that 17% were funded by industry provide a useful complement to the insights yielded by the work of Hampson et al.

Other researchers have previously examined the published cancer-research literature for conflicts of interest and funding sources. Tuech and colleagues<sup>29</sup> characterized the sources of sponsorship and competing financial interests disclosed in 655 cancer randomized trials published from 1999-2003 in 12 international



**Table 3.** Outcomes of Randomized Trials

|  | <b>Studies With No Conflict of Interest, n=52</b> | <b>Studies With Conflict of Interest, n=72</b> | <b>P</b> |
|--|---|--|----------|
| No. (%) with positive author interpretation of outcomes  | 29 (56)   | 48 (67)  | .22      |
| No. (%) in which overall survival was assessed   | 36 (69)   | 51 (71)  | .85      |
| <b>Overall survival outcomes*</b>  |   |  | .04      |
| <b>Positive (significantly favoring intervention)</b>  | 5 (14)  | 15 (29)  |          |
| <b>Positive trend</b>  | 1 (3)   | 4 (8)  |          |
| <b>Neutral</b>   | 26 (72)   | 31 (61)  |          |
| <b>Negative trend</b>  | 2 (6)   | 1 (1)  |          |
| <b>Negative (significantly favoring control)</b>   | 2 (6)   | 0  |          |
| No. (%) in which author interpretation was more positive than supported by analysis of overall survival outcome alone† | 15 (50)   | 16 (50)  | 1.00     |

\* Positive defined as a significant ( $p < .05$ ) survival difference in favor of the intervention; positive trend defined as a trend ( $p \leq .10$ ) toward significance in favor of the intervention; neutral defined as no significant difference between the 2 arms; negative trend defined as a trend ( $p \leq .10$ ) toward significance in favor of the control arm; negative defined as a significant survival difference in favor of the control arm.

† Author interpretation was deemed to be more positive than supported by analysis of overall survival alone when author interpretation was coded as positive but overall survival outcome was neutral, negative trend, or negative, as well as when author interpretation was neutral and overall survival outcome was negative trend or negative. Percentage is calculated from the total number of neutral, negative trend, and negative studies.

journals and found that 227 trials disclosed industrial funding. Riechelmann and colleagues examined conflicts of interests disclosed in 289 clinical trials and 43 editorials that considered systemic anticancer agents and supportive-care drugs published in the *Journal of Clinical Oncology* in 2005 and found conflicts in 69% of the trials.<sup>22</sup> The higher rates of conflicts observed in those studies are consistent with the observation in the current study that prospective studies and studies conducted by medical oncologists are more likely to have conflicts of interest. Our study, thus, complements those studies by considering a larger selection of study types in more detailed fashion (including a differentiation between governmental and private philanthropic funders) in a more recent year, as well as by analyzing the distribution of funding sources by disease site and author sex.

Finally, the current study adds to the literature that has explored correlations between industrial funding and positive study outcome. Several previous studies have examined the relation between funding sources and outcomes of published clinical trials. These prior studies include a seminal analysis of 107 controlled clinical trials, which found that a substantially higher proportion of studies favoring new therapies were funded by industry than the proportion of studies favoring traditional therapies that were funded by industry.<sup>6</sup> Since then, several other studies have explored this issue in greater detail,<sup>5,7,8,16,30-34</sup> including several that have focused

upon specific medical specialties, such as cardiology,<sup>35</sup> psychiatry,<sup>36,37</sup> gastroenterology,<sup>38</sup> and orthopedics.<sup>13,39-41</sup>

In general, these studies have also found that industry-funded studies are more likely to have positive study outcomes than those conducted without industrial funding, although some have failed to identify a relation between funding source and trial outcome.<sup>42</sup> Relatively little work of this nature has explored the oncology literature. A small but influential study examined 44 cost-effectiveness studies of new drugs in oncology, documenting that industry-sponsored studies were less likely to report unfavorable qualitative conclusions concerning the cost or cost effectiveness of the drugs than nonprofit-sponsored studies.<sup>11,43</sup> More recently, another study examined 150 health-economics studies within the field of oncology and found that industry-sponsored studies were more likely to be cost-minimization studies and more likely to draw positive qualitative conclusions about costs than those supported by nonprofit organizations.<sup>44</sup> Another recent study of breast-cancer clinical trials found that of 56 studies published in the year 2003, those that reported an involvement with a pharmaceutical corporation were more likely to report positive conclusions.<sup>45</sup>

Similarly, we find among the randomized trials that assessed survival in our sample, those studies with conflicts of interest were more likely to report positive outcomes. However, because we did not find a higher rate of discordantly positive author interpretations of outcome in the

studies with conflicts of interest, we do not believe that the reason underlying this observed difference is simply interpretation or a tendency for studies with conflicts of interest to focus upon outcomes other than overall survival. Another potential mechanism is publication bias<sup>46</sup>; author groups with conflicts of interest may be even more likely to publish positive results (or less likely to publish negative results) than others. These findings are also consistent with the suggestion that studies supported by industry are more likely to use study designs that are more likely to yield positive results (such as trials with a placebo rather than active controls).<sup>8,47</sup>

The primary limitation of this study is that our data rely upon self-reports by authors of any relevant funding sources and potential conflicts of interest. We did not validate these self-reports by obtaining personal financial information from the authors or by querying corporate board membership or employee lists. Recent news reports reveal that authors may not always openly disclose relevant conflicts. Furthermore, we are able only to ascertain the prevalence of those conflicts that were published, and it is possible that some journals might not have published all conflicts that were reported. This is most likely to lead to some degree of underestimation of the prevalence of these conflicts, although it is also possible that some authors may over-report potential conflicts where none exist. Some of the associations observed in the current study may result from systematic differences in the likelihood of disclosing conflicts of interest rather than differences in rates of actually existing conflicts, particularly in the face of differing journal policies<sup>48-54</sup> and differing cultural norms. Another potential limitation arises from the focus upon 8 high-impact journals, most of which are published in the United States. Journals published in other countries may differ meaningfully, and future studies should seek to characterize the frequency, nature, and associations of conflicts of interest as reported in those journals. Nevertheless, we believe this study to present 1 of the most complete and updated analyses of the frequency, nature, and effects of conflicts of interest in clinical cancer research in existing literature.

In summary, the current study suggests that a substantial minority of the broad range of modern, high-impact, published, clinical cancer research is open to the influence of conflicts of interest. Certain study characteristics, including discipline, national origin, and author

sex, are correlated with the likelihood of conflict. The frequency of conflicts varies by cancer site and/or type studied, and studies with conflicts of interest are more likely to focus upon treatment rather than diagnosis and prevention. Most disturbingly, it appears that cancer research studies in which conflicts of interest are present are indeed more likely to report positive outcomes. In light of these findings, attempts to disentangle the cancer-research effort from industry ties merit further attention, and medical journals should be supported in embracing both rigorous standards of disclosure and heightened scrutiny when conflicts exist.

### Conflict of Interest Disclosures

The authors hereby certify that this is an original, unpublished work that is not under consideration elsewhere. We have no conflicts of interest to disclose.

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