Integrative Cancer Therapies
Volume 18: 1–2
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DOI: 10.1177/1534735419859089
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Assessing the Impact of Complementary and Alternative Medicine Trials in Oncology

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Submitted April 7, 2019; revised May 10, 2019; accepted May 27, 2019

We read with interest the work by Zhang et al,[1] who provided a fascinating descriptive analysis of complementary and alternative medicine (CAM) randomized controlled trials (RCTs) in clinical oncology. The authors sampled cancer-related CAM RCTs published in 15 specific journals as the basis for their analysis; they found that few CAM RCTs were published in higher-impact journals over the sampled time period (2006-2015).[1] Furthermore, their results demonstrated lower citation rates for CAM RCTs than the average citation rate for other articles published in these journals.[1] These observations suggest that CAM RCTs in oncology are published in journals of lower impact than non-CAM oncological RCTs. We sought to determine if this was indeed the case and, if so, what reasons could be provided for such a differential.

Two key elements required for such an analysis that were missing from the original article are (1) a comparator group of non-CAM RCTs and (2) a sampling of RCTs beyond 15 preselected journals. To that end, we identified CAM- and non–CAM-related RCTs in clinical oncology through the ClinicalTrials.gov website. ClinicalTrials.gov was queried on November 19, 2017, using the following search parameters: Other terms: "cancer"; Study Type: "All Studies"; Status: excluded "Not yet recruiting"; Phase: Phase III; and Study Results: "With Results." This yielded 1239 trials. Trials were then screened to include only cancer-specific phase III randomized multiarm trials addressing a therapeutic end point (n = 764). Only RCTs with results of the primary end point (PEP) published in the peer-reviewed literature were included (n = 592). Of these, only 19 (3.2%) evaluated a CAM intervention (and therefore represented the CAM RCTs in our analysis). For each trial's publication of the PEP, the impact factor (IF) of the publishing journal was determined through the 2017 Journal Citation Reports.[2]

Comparing the 19 CAM RCTs with the 573 non-CAM RCTs, we found a significantly lower IF of journals publishing the trial PEP results of CAM trials (median IF = 6.5; interquartile range [IQR] = 2.6-26.4) than non-CAM trials (median 26.4, IQR = 13.9-47.7; independent-samples Mann-Whitney U test, $P < .001$). To better understand the basis for this observed difference in IF between CAM and non-CAM studies, we further stratified trials based on the selected end point(s) of each trial. The PEP as well as any secondary end points (SEPs) for each trial were determined; trials were stratified based on whether a disease-related outcome (DRO; eg, overall survival, progression-free survival) was used as either a PEP or a SEP. We hypothesized that publication in higher IF journals may reflect broader scientific and clinical interest in DROs. Only 1 CAM RCT (1/19, 5.3%) included a DRO as an end point,[3] whereas the vast majority of non-CAM RCTs (503/573, 87.8%) included a DRO end point (χ^2 test, $P < .001$). For trials with no DRO end point, the median journal IFs for CAM (6.0, IQR = 2.7-26.4) and non-CAM (6.2, IQR = 3.1-26.4) trials were similar ($P = .30$). Because only 1 CAM trial included a DRO end point, a meaningful statistical comparison with non-CAM trials could not be performed (such an analysis, though, similarly revealed no significant difference in journal IF between the sole CAM DRO end point trial and non-CAM DRO end point studies; $P = .20$).

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Collectively, these results suggest that whereas oncological CAM RCTs are published in journals with lower IFs than non-CAM RCTs, the use or nonuse of a DRO end point may explain at least some of this difference. Stratifying by whether the trial included a DRO end point, IF differences between CAM and non-CAM trials were no longer observed. This interpretation is limited by the inclusion of only a single CAM RCT in which a DRO was an end point; this trial (NCT02311907) evaluated whether glutathione might reduce chemotherapy-induced peripheral neuropathy, where recurrence-free survival was a SEP.[3] However, more robust sampling was seen among trials in which no DRO end point was evaluated, and similar IFs were observed between the 18 CAM and 70 non-CAM RCTs. Our analysis is also limited by use of a single registry (ClinicalTrials.gov) to sample oncological RCTs. As noted by the authors of the original article, rates of CAM RCT participation on trial registries such as ClinicalTrials.gov have been somewhat variable.[1] By using ClinicalTrials.gov, our analysis may have missed relevant RCTs, possibly leading to nonrepresentative or incomplete sampling of CAM trials.[1] On the other hand, a large-scale sampling of all oncological RCTs from a single major registry has the potential to more effectively capture the broader trials landscape than if only a select handful of journals are queried.

Together, we commend Dr. Zhang and colleagues on their work; it is our hope that our analysis above provides some clarity to the question of whether the results of CAM oncological RCTs are published in lower-IF journals than their non-CAM counterparts. We submit that the differential journal IF between CAM and non-CAM RCTs can be explained, at least in part, by the strikingly lower rates of DRO end point use among CAM trials.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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