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Original article

Trial sponsorship and self-reported conflicts of interest in breast cancer radiation therapy: An analysis of prospective clinical trials

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ABSTRACT

Purpose: We aim to assess any association between study and self-reported conflict of interest (COI) or trial sponsorship in breast cancer radiation clinical trials.
Materials and methods: We searched PubMed for all clinical trials (CTs) published between 09/2004 and 09/2014 related to breast cancer. We included only radiotherapy CTs with primary clinical endpoints. We classified eligible trials according to the funding source, presence or absence of conflict of interest, study conclusion and impact factor (IF).
Results: 1,603 CTs were retrieved. 72 randomized clinical trials were included for analysis. For-profit (PO), not for profit organization (nPO), none and not reported sponsorship rates were 9/72 (12.5%), 35/72 (48.6%), 1/72 (1.4%), 27/72 (37.5%), respectively. Present, absent or not reported COI were found in 6/72 (8.3%), 43/72 (59.7%) and 23/72 (32%) of the CTs, respectively. Conclusion was positive, neutral and negative in 57/72 (79.1%), 9/72 (12.5%) and 6/72 (8.4%) of the trials, respectively. Positive conclusion was reported in 33/44 (75%) funded trials (PO and nPO) and 5/6 (83.3%) CTs with reported COI. On univariate analysis no association with funding source (P=0.178), COI (P=0.678) or trial region (P=0.567) and trial positive conclusion was found. Sponsored trials (HR 4.50, 95CI-0.1.23-16.53;P=0.0023) and positive trials (HR 4.78, 95CI- 1.16-19.63;P=0.030) were more likely to be published in higher impact factor journals in the multivariate analysis.
Conclusions: nPO funding was reported in almost 50% of the evaluated CTs. No significant association between study conclusion and funding source, COI or trial region was identified. Sponsored trials and positive trials were more likely to be published in higher impact factor journals.

1. Introduction

Breast cancer is a common diagnosis in women, with approximately 230,000 expected cases in 2015 [1]. Adjuvant radiation therapy (RT) is indicated for the majority of women with early stage breast cancer after breast conserving surgery (BCS) to reduce the risk of local recurrence and improve overall survival [2–4]. In addition, post mastectomy RT is indicated in a significant number of women with locally advanced disease to reduce the risk of loco-regional recurrence and improve overall survival [5,6]. The cost of adjuvant RT may range from as little as approximately $5000 for

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accelerated partial breast irradiation (APBI) techniques, to > $13,000 for whole breast RT (WBRT) [7,8].

Private sector funding of biomedical research, particularly in oncology, has increased substantially over the last two decades. Currently, nearly 2/3 of funding is obtained from industry, which was only nearly 1/3 in the early 1980s [9,10]. While industry funding has increased, government funding has fallen, stimulating an increased public-private partnership [11]. Simultaneously, there has been a significant increase in the amount of industry direct-to-consumer (DTC) spending. This includes DTC marketing of prescription medication, medical devices, and genetic testing [12,13]. DTC spending is more likely to increase utilization and increase patient-initiated discussion of treatment [14].

Industry-sponsored studies may be more likely to contain an inferior control arm, but are also published sooner and are more prominently placed at national meetings [15–17]. Both drug and device studies are likely to publish favorable results. Independently of the rigor of a study, physicians are more likely to interpret an industry-sponsored study with negative perception [18]. Radiation oncology is a field generally limited to a small number of major equipment vendors, several of which have been consolidating. Although radiation oncologists may believe themselves to be immune from COI, they are more likely to think their colleagues are not immune [19].

Recognition and reporting of COI is not simply excellent practice, but is now generally required for publication in medical journals [20]. Although COI policies are established and implemented routinely, little is known regarding the impact of COI on research conduct and outcomes, particular in RT. In this study, we aim to report the association between self-reported COI or trial sponsorship and study conclusions in breast cancer irradiation.

2. Materials and methods

A literature search was conducted in the MEDLINE database via PubMed for clinical trials over a 10-year period from September 13th, 2004 through September 10th, 2014. Controlled vocabulary was leveraged in the development of the search strategy below. Only human trials were considered.

The terms and strategy used were based on MEDLINE MeSh terms ("Breast Neoplasms" [Mesh] OR Breast Neoplasm OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Breast Cancer OR Cancer, Breast OR Cancer of Breast OR Mammary Cancer OR Malignant Neoplasm of Breast OR Malignant Tumor of Breast OR Breast Carcinoma 0R Cancer of the Breast) AND (Clinical Trial, Phase II [ptyp] OR Clinical Trial, Phase III [ptyp] OR randomized clinical trial [ptyp]) AND ("2004/09/13" [PDat]: "2014/09/10" [PDat]). The phrase "Breast Neoplasm", "Breast Cancer", and related terms were cross-searched with terms including "Phase II", "Phase III, and "Randomized Clinical Trials." Search terms were limited to the English language and time period specified above.

All retrieved articles published in this period that met our search criteria were then individually screened for eligibility. We included only RT phase II, III clinical trials with primary clinical endpoints.

Two investigators (E.T.T.L. and F.Y.M.) independently selected phase II and III clinical trials with minimum 50 patients as part of the inclusion criteria. Retrieved studies that were not human clinical trials on breast cancer were excluded. We also excluded articles where the main focus was epidemiology, research design, diagnosis, risk assessment, basic science, or clinical guidelines. Editorial, commentaries, reviews, and meta-analyses were also excluded.

Eligible trials were classified according to the funding source: For profit organization (PO), not for profit organization (nPO), no source (NS), and not reported (NR). Additional data recorded included COI (present, absent or not reported), and study conclusion (positive, neutral, and negative). PO represented trials with any kind of pharmaceutical or device company support (i.e. industry support). nPO comprised associations (eg, Radiation Therapy Oncology Group - RTOG), foundations, individuals, universities, government, and community-based organizations. NS comprised the group of trials on which authors stated that there was no PO or nPO source. NR comprised the group of studies which there was no formal statement of funding source at publication. We acknowledge that most trials received at least some departmental funding or staff support at any time during the project execution.

COI were defined as any self-reported financial tie between an author and a pharmaceutical company, such as consulting fees, honoraria, employment, stock ownership, or research grants/travel awards. Positive COI was required to be directly related to the study or if not clear from the same company that funded the study. The study conclusion categorization was based on a modified system proposed by Djulbegovic et al. [21]. Additional information collected included publication impact factor (IF) (IF1 $\geq$ 4.0 and IF2 < 4.0), journal of publication (Journal Name), region where the study was conducted [Americas, Europe, and others (Africa, Asia, Australia)], and period of publication (year). For IF analysis we search the 2014 Journal Citations Reported (Available online at: https://jcr-incites-thomsonreuters.ez67.periodicos.capes.gov.br/JCRJournalHomeAction.action, accessed on October 2014).

Summary statistics were used to describe absolute number and frequency of source of sponsorship/funding source, author COI, and article characteristics. Binary logistic regression using backward likelihood ratio was performed in an effort to identify predictors of trial outcome and the impact factor of the publication. Trial outcome was considered as negative or neutral versus positive, and impact factor considered as <4 versus $\geq$4. Funding (sponsored versus no sponsor or not reported), conflicts of interest (declared versus not declared versus not reported) and region of study (North America versus Europe versus other) were evaluated for their impact on trial outcome and impact factor. Trial outcome and region of study were also evaluated for association with impact factor. Univariate analysis was performed for each of the above variables with the intention that any factor with a p value of <0.1 was included in the final multivariate model. SPSS version 21 (IBM, New York, US) was used for the analysis. A p value of <0.05 was considered statistically significant.

3. Results

We retrieved 1603 clinical trials (CTs) in the initial screen with our search terms. Of these, seventy-six (4.7%) fit our initial inclusion criteria. Each of these studies was then screened via the full-text article and 72 studies (4.4% of all CTs) were eligible for final analysis.

PO, nPO, NS, and NR sponsorship rates were 9/72 (12.5%), 35/72 (48.6%), 1/72 (1.4%), 27/72 (37.5%), respectively. Unfunded trials (NS and NR) represented 28/72 (38.9%). The trial funding source was related to the intervention in 10/72 (13.8%) CTs, not related in 37/72 (51.4%) and not defined in 25/72 (34.8%). Self-reported COI (both present or absent) were reported in 49/72 (68%) CTs. Present COI were reported in 6/72 (8.3%) of CTs and were absent or not reported in 43/72 (59.7%) and 23/72 (32%), respectively. Conclusion was