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The Scientific Impact and Value of Large, NCI-Sponsored Randomized Phase III Cancer Chemoprevention Trials

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Abstract

Background—The cancer research groups of the National Cancer Institute's National Clinical Trials Network have a history of successful conduct of large randomized phase III trials of chemoprevention for cancer. An important question for funding agencies is whether the conduct of large chemoprevention trials provides strong scientific return on investment.

Methods—We evaluated the scientific impact of four large chemoprevention trials – two for breast cancer and two for prostate cancer – using citation analysis, a bibliometric technique. The results were compared to the scientific impact of a series of treatment trials conducted over the same 20-year time period (1991–2010, inclusive). Average annual citation counts were compared using t-tests. Scientific impact was also assessed relative to trial costs.

Results—Twenty-seven treatment trials with 17,208 patients and four chemoprevention trials with 87,550 patients were examined. The mean annual citation rate for primary articles was higher for chemoprevention trials compared to treatment trials (188.1 vs. 40.4, $p < .0001$). For both primary and secondary article publications, mean annual citations for articles associated with chemoprevention trials were also higher (483.9 vs. 69.0, $p < .0001$). Large chemoprevention trials were estimated to provide 50% more total citations from primary and secondary articles on a cost-adjusted basis.

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Conclusion—Based on these criteria, the scientific impact of large phase III cancer chemoprevention trials was very high in absolute terms, and as good as or better than that of treatment trials after accounting for expenditure. For appropriate scientific questions, large chemoprevention trials provide a good scientific return on investment for federal funding agencies.

Keywords

Chemoprevention; clinical trials; scientific impact; citation analysis; bibliometric analysis

1. Introduction

The cancer clinical trial network groups of the National Cancer Institute (NCI) have a history of successful conduct of large randomized phase III trials of chemoprevention for cancer [1–5]. However, such trials are expensive, and only a limited number of research questions have found a consensus around which to conduct such trials. An important research question for federal funding agencies is whether large, randomized phase III chemoprevention trials provide good scientific impact for expenditure, regardless of the trial outcome. To examine this, we compared the scientific impact of four large phase III randomized chemoprevention studies to the impact of a series of randomized phase III treatment trials conducted over the same time period. We used a bibliometric technique, facilitated by the strategic linkage of multiple databases, including citation data and the study and publication databases of multiple NCI network groups.

2. Methods

2.1 Study Sample

We identified four large, randomized phase III chemoprevention trials conducted by the NCI's cancer network groups. Two large prostate cancer chemoprevention studies were conducted by SWOG, an NCI-sponsored National Clinical Trials Network and Community Oncology Research Program (NCORP) group. SWOG's Prostate Cancer Prevention Trial (PCPT) found that daily finasteride use for 7 years reduced the risk of prostate cancer by 25% [2]. However, because an increased risk of high grade prostate cancers was also observed, finasteride is rarely used today to reduce prostate cancer risk [6]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) found that selenium and vitamin E did not prevent prostate cancer, and that vitamin E alone may even increase prostate cancer risk [3,4]. Two breast cancer chemoprevention studies were conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP; now a component of the NRG Oncology Group). The NSABP's Breast Cancer Prevention Trial (P-1) found that tamoxifen decreased the incidence of breast cancer by nearly half in high risk women [1]. The Study of Tamoxifen and Raloxifene (STAR) P-2 trial found that raloxifene provided a similar reduction in risk of invasive breast cancer as tamoxifen, but not non-invasive breast cancer [5].

These four large chemoprevention trials were conducted during the 1990s and 2000s. Chemoprevention and treatment trials comprise the primary intervention approaches within the portfolio of the NCI's trial research programs, and primarily define the different research

programs within the network groups. Therefore to provide context, we compared the scientific impact of these four chemoprevention trials to the scientific impact of a series of treatment trials. Detailed study and publication data were obtained for all SWOG phase III treatment trials conducted over a similar, 20-year period (from 1991–2010, inclusive). We required that treatment trials had been published at least five years prior to 2014 in order to allow trials to accrue at least five years of citation data, consistent with the data obtained from the four chemoprevention trials. Both chemoprevention and treatment trials must have focused on a cancer endpoint; that is, treatment trials were designed to treat existing cancers, and chemoprevention trials to prevent the development of new cancers (rather than an intermediate marker for cancer). Both positive and negative trials were included, since both types of trials have been shown to have similar overall citation counts from their associated publications, and since the sets of chemoprevention and treatment trials we examined both included a mix of positive and negative trials [7].

Each trial examined in this study was previously approved by the Institutional Review Board at each participating institution.

2.2 Publication Data

The “primary” article reported the results of the primary protocol-specified endpoint by randomized treatment arm. A “secondary” article was any other manuscript that relied on trial data, such as tumor biology or biomarker predictors of outcome. Secondary publications that may have been published prior to accrual completion (i.e. design articles) were also included. This report is based on scientific journal articles identifiable in Pubmed [8].

Primary and secondary articles for the trials included in the analyses were obtained from the available literature. An index of primary and secondary articles was obtained on network group websites [9,10].

2.3 Trial Descriptive Factors

For descriptive purposes, treatment trials were described according to the following baseline characteristics: type of cancer, type of design, type of endpoint, the number of randomized comparisons, type of treatment, and whether the trial was positive according to its primary, protocol-specified endpoint [7].

2.4 Statistical Methods

To examine scientific impact, we calculated the number of primary and secondary articles associated with each trial, and (to account for time) the number of articles divided by the number of years from accrual closure date, through 2014. We also calculated the mean impact factor of the journals in which the primary manuscripts were published, using 2015 scientific journal two-year impact factor levels. Differences were assessed using t-tests. The proportion of primary manuscripts published in high impact general medicine journals (the New England Journal of Medicine, the Journal of the American Medical Association, Lancet), and, separately, high impact general medicine journals or cancer journals (including CA: A Cancer Journal for Clinicians, the Journal of Clinical Oncology, Lancet Oncology)

were compared using Fisher's exact test. The type of secondary articles associated with trials was also assessed; comparisons between chemoprevention and treatment trials were conducted using Chi-square tests.

We also examined scientific impact using citation analysis, a bibliometric technique [11,12]. This approach is premised upon the idea that citation counts are correlated with long-term research impact [13,14]. We created a database of the number of articles in the biomedical literature that cited the trial articles in each year following publication through 2014 using Google Scholar, a web-based scholarly search engine. We also used the Web of Science search engine to conduct a sensitivity analysis for primary article citation counts. The mean annual citation rate for each study was calculated as the ratio of total citations divided by the number of years since publication. The average annual citation rates for chemoprevention and treatment trials were calculated as the simple (unweighted) mean of the study-specific annual citation rates; differences were assessed using t-tests, and, secondarily, non-parametric Wilcoxon ranked sum exact tests to avoid distributional assumptions between the two groups. A sensitivity analysis excluding the estimated number of self-citations was also conducted, in order to assess the extent to which the primary articles were referenced by investigators independent of the original study team. All statistical tests were two-sided.

2.5 Accounting for Expenditure

To account for expenditure, we used published data to derive mean chemoprevention and treatment trial costs. The estimated total cost of the BCPT in 2014 was \$87.6 million, of STAR was \$104.1 million, of PCPT was \$88.5 million, and of SELECT was \$125.4 million [15–18]. The cost of a typical phase III oncology treatment trial in 2014 dollars was \$22.1 million [19]. Typical cost components for trials are shown in Appendix Table 1. We calculated the rate of mean annual citations to mean trial costs (in millions) for chemoprevention and treatment trials using both primary and secondary articles. The ratio of these two rates defined a chemoprevention to treatment trial “citation-cost ratio” (CCR) as follows:

$$CCR = \frac{\text{Mean annual citation rate}_{Prevention} / \text{Mean cost of trial}_{Prevention}}{\text{Mean annual citation rate}_{Treatment} / \text{Mean cost of trial}_{Treatment}}$$

A $CCR > 1.0$ indicates better value for chemoprevention trials on a cost-adjusted basis.

3. RESULTS

3.1 Sample Description

Twenty-seven treatment trials with 17,208 patients were conducted between 1991–2010 (inclusive). Publication and citation data from these studies were compared to the four chemoprevention trials, which together enrolled 87,550 patients. The treatment trials were from a mix of different disease sites, all had superiority designs, and all included systemic drug therapy as part of treatment (Table 1). The chemoprevention trials were designed to identify breast or prostate cancer (respectively), were all superiority designs, and all included systemic chemopreventive agents. Thirty-three percent of the treatment trials were

positive, and 67% were null or negative; the chemoprevention trials had a mix of outcomes as described in the Methods. Mean [standard deviation] accrual time was 4.6 [1.6] years for chemoprevention trials and 4.4 [2.1] years for treatment trials ($p=.87$). There was no difference in the mean time from study completion until 2014 by type of study (13.6 years for chemoprevention trials, 14.3 years for treatment trials, $p=.72$).

3.2 Publication Outcomes

Overall 333 unique articles were published from both types of trials (31 primary articles and 302 secondary articles). The mean (SD) number of publications (47.7 (34.4) vs. 5.3 (5.9), $p<.0001$) and the publication rate per year (3.3 (1.6) vs 0.4 (0.3), $p<.0001$) were much higher for the chemoprevention trials. The mean (SD) two-year impact factor trended higher for chemoprevention trials (31.9 (17.2) vs 19.3 (13.4)), but this difference was not statistically significant ($p=.10$). The primary articles for chemoprevention trials were much more likely to be published in a high impact general medicine journal (75% vs. 11%, $p=.02$), but this difference disappeared when high impact cancer journals were also included (75% vs. 70%, $p=1.0$).

Secondary articles associated with chemoprevention trial articles more often pertained to methods, design, or recruitment (21% vs. 7%, $p=.0004$), biomarker predictors of outcomes (29% vs. 16%, $p=.009$), and dietary or epidemiological examinations (4% vs. 0%, $p=.01$), and less likely pertained to investigations of tumor biological characteristics alone (2% vs. 15%, $p<.001$). Chemoprevention and treatment trial secondary articles were about equally likely to focus on clinical, treatment, or demographic predictors of outcomes (21% vs. 20%, $p=.74$). Chemoprevention trial articles were more often published in non-oncology journals (51% vs. 39%, $p=.03$).

3.3 Citation Analysis

For primary articles, for the four chemoprevention trials, there were 9,262 citations; for the 27 treatment trials, there were 12,062 citations (Figures 1A and 1B, respectively). The mean (SD) number of citations per year was much higher for chemoprevention trials (188.1 (69.6) vs 40.4 (53.1); t-test, $p<.0001$; Wilcoxon test, $p=.001$; Figure 2). Using the Web of Science search engine, the difference between chemoprevention and treatment trial primary article citations was similar (126.6 (48.4) vs. 24.6 (33.5); t-test, $p=.02$; Wilcoxon test, $p=.0008$). The mean (SD) two-year impact factor was more than twice as high (42.4 (17.0) vs 19.6 (13.5), $p=.03$) for the chemoprevention trials.

The mean (SD) number of citations per year for all secondary article citations was 295.8 (167.2) for chemoprevention trials and 28.6 (43.8) for treatment trials (t-test, $p<.0001$; Wilcoxon test, $p=.0002$). The mean total number of citations per secondary publication was similar for chemoprevention and treatment trials (68.5 vs. 71.6, $p=.87$).

For the combination of primary and secondary articles, for the chemoprevention trials, there were 23,311 citations, and for the treatment trials, there were 21,187 citations (Figure 1C and 1D, respectively). The mean (SD) number of citations per year was much higher for chemoprevention trials than treatment trials overall (483.9 (201.8) vs. 69.0 (78.3); t-test, $p<.0001$; Wilcoxon test, $p=.0003$; Figure 2C).

For chemoprevention trial primary articles, the mean rate of self-citation was 9.5%, and for treatment trial primary articles, the mean rate was 8.1%. This difference was not statistically significant ($p=.60$). Excluding self-citations, the mean number of citations per year for primary articles was 172.5 for chemoprevention trials and 37.9 for treatment trials (t-test, $p<.0001$; Wilcoxon test, $p=.002$).

3.4 Citation Rates per Expenditure

The mean trial costs for the four chemoprevention trials was \$101.4 million. Based on primary articles only, the ratio of mean annual citation rates per expenditure (in millions) was 1.86 for chemoprevention trials ($188.1/101.4$) and 1.83 for treatment trials, for a CCR of 1.02, indicating approximately equal scientific value according to citation counts. In contrast, based on the combination of primary and secondary articles, the ratio of mean annual citation rates per expenditure was 4.77 for chemoprevention trials and 3.12 for treatment trials, or about 50% higher ($CCR=4.77/3.12=1.53$) for chemoprevention trials.

4. Discussion

The citation rate for large, NCI-sponsored phase III cancer chemoprevention trials was more than seven times that of treatment trials when both primary and secondary article citations were considered. Large chemoprevention trials were also estimated to provide as good as or greater scientific impact than treatment trials on a cost-adjusted basis. Thus despite their sizeable budgets, large chemoprevention trials provide good scientific impact according to citation analysis.

The secondary science derived from the four chemoprevention trials was much greater than for most of the treatment trials we examined. Moreover, articles from chemoprevention trials were more often published in non-oncology journals, suggesting that chemoprevention trial findings have a wider scientific impact than oncology alone. Because large chemoprevention trials are rare, individual chemoprevention trials may be more likely to be utilized for secondary examination [20]. After the PCPT results were published, the study was transitioned into a separately funded translational science resource, to allow internal and external investigators to access study samples and correlative data to examine biomarker, risk, and cancer etiology research questions [21]. The SELECT trial was transitioned into an observational cohort, maintains a large biorepository available to researchers, and has multiple embedded ancillary protocols [22]. In both instances, targeted funding allowed investigators to maximize the value of the data and identify new research questions to be examined.

The enormous scientific impact from secondary science associated with chemoprevention trials suggests greater potential use of treatment trials as data resources. Randomized phase III treatment trials include large samples of uniformly staged and treated patients, prospective data collection on tumor characteristics and baseline clinical prognostic factors, long term follow-up, biologic sample collection and, increasingly, common quality of life instruments [23]. The linkage of trial data to external data resources (i.e. Medicare claims) provides the opportunity to examine treatment utilization, comorbid conditions and late effects of treatment [24,25]. In both chemoprevention and treatment trial settings, the use of

trial repositories and databases as resources for secondary science promises to contribute to a virtuous cycle, in which new research questions are generated, then examined in future trials, which again become new resources for secondary science.

No other study in the literature has previously examined differences in scientific impact between chemoprevention and treatment trials. Our analytic approach was facilitated by the strategic linkage of multiple databases, including citation data from Google Scholar and the study and publication databases of a large NCI network group. However, the study had limitations. Treatment trials from only a single network group were used. This enabled thorough examination of the secondary science associated with trials through use of a comprehensive publication database, but also allowed for the potential for selection bias if the relationships we identified are not generalizable to other networks. Additionally, the inclusion of breast and prostate cancer chemoprevention trials only could generate more citations than trials for less common cancers. Citation data provide an empirical metric to assess scientific impact whose magnitude can be reliably and independently ascertained. However, the ultimate goal of clinical research is to change practice for the better, and citation counts do not explicitly represent clinical impact of the intervention. A different approach would be to examine a trial's effect on clinical practice guidelines, though this approach could be limited, since clinical practice guidelines often do not adequately represent the available scientific evidence [26–30]. An approach to calculating value in clinical trials that uses quality-adjusted survival if a practice change occurred would be a useful and complementary alternative in this setting.[31] The use of citation data is also limited by the fact that any particular citation does not represent a uniform level of impact, and citation analysis may not fully represent the scientific impact of a given trial. Also, a fair comparison of trial costs for chemoprevention versus treatment trials is complicated by the different nature of the two research settings with respect to types of patients, interventions, and funding sources. In particular, although chemoprevention trials have much larger sample sizes, the interventions, testing, and monitoring are less expensive, and toxicities and hospitalizations are limited.

Large, randomized cancer chemoprevention trials have the potential to positively impact large segments of the population, both in relation to their primary endpoints and in the secondary hypotheses that can be tested from the trial databases. Our findings indicate that the scientific impact is very large in absolute terms, and as good as or better than that of treatment trials after accounting for expenditure. Therefore given a pertinent and timely cancer chemoprevention research question, the conduct of a large, randomized phase III chemoprevention trial will provide a good scientific return on investment to funding agencies.

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Appendix

Table 1:
Standard Cost Components for Cancer Clinical Trials *

Component	Category
<i>Per study costs</i>	
	Data collection
	Data management
	Data analysis
	Institution review board
	Study amendments
	Data verification
<i>Per site costs</i>	
	Site recruitment
	Site retention
	Administration
	Monitoring
<i>Per patient costs</i>	
	Patient recruitment
	Patient retention
	Staff requirements: Clinical research associate
	Staff requirements: Physician
	Clinical procedures
	Central laboratories

* Derived from: Sertkaya A, Birkenbach A, Berlind A, Eyraud J. Examination of clinical trial costs and barriers for drug development. Report, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Washington, DC, July 2014.

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Figure 1: Number of citations by calendar year. Citations are shown separately for each study, ordered according to the total study-specific citation counts. Each color represents citation counts for a different study over calendar year. Figures are truncated at the year 2000 for presentation purposes.

Average Annual Citation Rates for Treatment and Chemoprevention Trials

Figure 2:
Average annual citation rates for treatment and chemoprevention trials.

Table 1:

Treatment Trial Characteristics

Study Descriptive Factor	N=27
Cancer type	
Breast	2 (7%)
Gastrointestinal	5 (19%)
Genitourinary	2 (7%)
Gynecologic	1 (4%)
Leukemia	4 (15%)
Lung	6 (22%)
Lymphoma	2 (7%)
Melanoma	1 (4%)
Myeloma	3 (11%)
Sarcoma	1 (4%)
Design Type	
Equivalence or non-inferiority	0 (0%)
Superiority	27 (100%)
Endpoint type	
Survival (overall)	13 (48%)
Other time to event (e.g. progression-free survival) ^a	5 (19%)
Tumor response	1 (4%)
Multiple endpoints	8 (30%)
Number of randomized comparisons	
1	25 (93%)
2	3 (12%)
Intervention included...^b	
Systemic therapy	27 (100%)
Biologic therapy	4 (15%)
Surgery	2 (7%)
Radiation therapy	6 (22%)
Transplant	3 (11%)
Trial outcome^c	
Positive	9 (33%)
Null or Negative	18 (67%)

^aIncluding progression-free survival, disease-free survival, event-free survival, time to treatment failure, time to metastasis, or relapse-free survival.

^bIntervention may include more than one of the types listed.

^cDefined according to the trial's primary, protocol-specified endpoint.