The Oncologist®

Head and Neck Cancers

Prospective Head and Neck Cancer Research: A Four-Decade Bibliometric Perspective

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Learning Objectives

Outline trends in the gender and continent of origin of first and corresponding authors of prospective head and neck cancer treatment research.

Identify trends in the presence of pharmacotherapy, radiotherapy, and surgery in prospective head and neck cancer treatment research.

Abstract

Background. It is unknown whether changes in study sponsorship have affected the proportion of prospective research on surgery, radiotherapy, and pharmacotherapy for head and neck squamous cell carcinoma (HNSCC) being published over time.

Patients and Methods. We examined prospective studies from PubMed, Ovid MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1980, 1985, 1990, 1995, 2000, 2005, and 2010. Chi-squared tests were used to identify significant associations between sponsorship and authorship, treatments within study protocols, and presentation of results, whereas time-based trends were analyzed using the Cochran-Armitage test.

Results. Among 309 articles, industry (70, 22.7%) and the U.S. government (65, 21%) were the most common sponsors. There was a significant increase in the proportion of industry-sponsored research (p for trend = .013) and a decline in U.S. government-sponsored research (p for trend = .001) over time. The inclusion of surgery in treatment protocols declined over the past four decades (p for trend = .003). Protocols incorporating pharmacotherapy were more likely to have industry support than those without pharmacotherapy (p = .001), whereas protocols with radiotherapy (p = .003) or surgery (p = .002) were less likely to have industry support.

Conclusion. Industry is the predominant sponsor of prospective HNSCC research, with an emphasis on pharmacotherapy.

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Implications for Practice: This article demonstrates the concurrent growth of industry funding and decline in U.S. government funding for prospective head and neck cancer research from 1980 to 2010. In addition, the study demonstrates a clear association between industry sponsorship and study of pharmacotherapy regimens, as well as a notable decrease in surgical research. Changes in the sponsorship of head and neck cancer research may lead to fundamental changes in the types of therapies being studied and the potential for financial and professional conflicts of interest. The U.S. government has an opportunity to ensure that the future direction of head and neck cancer research reflects the public interest and should re-examine whether funding policies and the Food and Drug Administration 510(k) clearance process may have had an indirect impact on the quantity and quality of surgical and radiotherapeutic research.

Introduction

Head and neck cancer accounted for approximately 633,000 new diagnoses worldwide in 2008, over 90% of which were squamous cell carcinomas (HNSCC) [1, 2]. Currently, surgery, radiotherapy, and pharmacotherapy (including chemotherapy and targeted therapies) constitute the primary modes of treatment for HNSCC. However, there has been controversy among physicians regarding optimal therapeutic regimens, particularly for advanced-stage HNSCC. Specific areas of controversy include the significantly increased use of combined chemotherapy and radiotherapy over the past two to three decades for definitive

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treatment of advanced tumors [3–6], stagnant or declining survival rates for certain types of head and neck cancer [4, 7], and lack of high-quality evidence to guide HNSCC therapy, particularly within the surgical literature [3, 5]. Recent commentary also suggests that in contrast to the dearth of high-quality head and neck surgical oncology evidence, there may be a comparative preponderance of radiotherapy and chemotherapy literature, and that policy-level changes may be necessary to ensure more balanced research output that adequately considers the potential role of each therapeutic modality [3].

Publication trends may reflect both broader changes in cancer research funding and shifts in research priorities by funding sponsors. Industry has taken an increasingly prominent role in supporting biomedical research, providing about 70% of the funding for all biomedical research in the United States in 2008 [8, 9]. Jagsi et al. reported that oncology studies that declared government funding outnumbered those that acknowledged industry sponsorship by 50% versus 17% in 2006 [10]. However, detailed analyses of oncology clinical trials alone have revealed that, with rare exceptions [11], industry sponsorship is now predominant [12–14]. Recently, Sun et al. demonstrated the impact of both industry and government sponsorship on randomized controlled trials (RCTs) for head and neck cancer treatment from 2000 to 2010 [15]. It is conceivable that changes in study sponsorship over time could influence publication trends in the broader head and neck cancer literature.

Bibliometrics is a robust methodology that has been used to estimate national and international support for oncology, and thus can provide evidence to guide cancer control policymaking and research funding priorities [16]. The current study is a comprehensive bibliometric analysis of prospective literature on HNSCC therapy, examining authorship, study sponsorship, treatment protocols, and the presentation of results over a four-decade time frame.

Materials and Methods

Four coauthors (G.H.S., J.J.H., N.M.M., and M.P.M.) systematically searched PubMed, Ovid MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for potentially qualified prospective literature describing HNSCC therapeutic regimens. The search strategy is described in the supplemental online data. Databases of conference proceedings and unpublished studies were not reviewed. We included articles published in print during the years 1980, 1985, 1990, 1995, 2000, 2005, and 2010. Potentially qualified articles were then collated into EndNote (Thomson Reuters, New York, NY, http://thomsonreuters.com) and duplicate references were removed.

Inclusion criteria included English-language articles on human subjects with mucosal HNSCC (involving the paranasal sinuses and sinonasal tract, nasopharynx, oral cavity, oropharynx, hypopharynx, and/or larynx); prospective study design (e.g., prospective case series, pilot studies, clinical trials, comparative effectiveness studies, and randomized trials); and evaluation of surgery, radiotherapy, pharmacotherapy (including chemotherapy and targeted therapies), "other" therapy (photodynamic therapy, hyperthermia, viral therapy, and nutritional/dietary therapy), and/or any combination thereof. For a study to qualify as having included a given therapeutic modality, the article was required to mention in the Methods section that the treatment was part of the formal protocol being tested. Any cancer treatments completed prior to the study period and reported in the participants' clinical history were not considered part of the active study protocol. Exclusion criteria included the following: non-English language; animal studies; basic science/experimental research, surveys, reviews, letters, editorials, and any retrospective study design; prognostic and diagnostic studies, cancer surveillance, and studies of symptom alleviation; and articles in which mucosal HNSCC was not the primary disease being studied.

We collected data on first and corresponding authors (sex and nationality); journal impact factor (IF) based on the 2011 Journal Citation Reports (Thomson Reuters); inclusion of distant metastatic disease; RCT study design; inclusion of surgery, radiotherapy, pharmacotherapy, and/or other therapy in the treatment protocol; and presentation of results (positive results favoring experimental therapy, negative results not favoring experimental therapy, or unclear). IF was stratified into high-impact (IF $\geq$ 5) and low-impact (IF $<$ 5) subgroups to facilitate analysis.

The key outcome variable was study sponsorship, classified into six categories: National Institutes of Health (NIH); non-NIH, U.S. government (e.g., Department of Veterans Affairs); foreign government; industry; philanthropic and nonprofit foundations; and none or undeclared. For each government-based category, sponsorship was defined as government-based funding and/or grant support, or employment in a division of any national government. Industry sponsorship was defined as industry-based funding and/or grant support, use of industry-provided drug supplies, employment in industry, honoraria or consulting, or participation in a speakers' bureau or advisory board. Philanthropic and nonprofit sponsorship was defined as funding and/or grant support from private philanthropy or nonprofit foundations, or employment in a philanthropic or nonprofit organization, excluding any academic affiliations. Studies could have more than one sponsor.

Because all variables in this study were categorical, chi-squared tests were used to identify significant associations with study sponsorship. Trends in authorship, treatment type, presentation of results, and sponsorship over time were analyzed using the Cochran-Armitage test. Statistical analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX, http://www.stata.com). All statistical tests were two-sided, and statistical significance was defined as $p < .05$.

Results

We reviewed 1,165 articles, of which 309 qualified for analysis. There was a steady increase in the total number of prospective therapeutic studies of HNSCC over the study period, from 13 in 1980 to 70 in 2010. Two-hundred sixty (84.1%) of all 309 first authors and 257 (84.6%) of all 305 corresponding authors were male. Of 35 featured countries, the U.S. was the most prolific country of origin for both first (121 out of 309, 39.2%) and corresponding authors (119 out of 305, 39%), followed by Italy (25 authors) and Germany (22 authors). North America produced the highest number of first and corresponding authors (Fig. 1A, 1B). There were no statistically significant changes in first or corresponding authorship by sex or continent of origin over time. However, a higher proportion of studies authored by women

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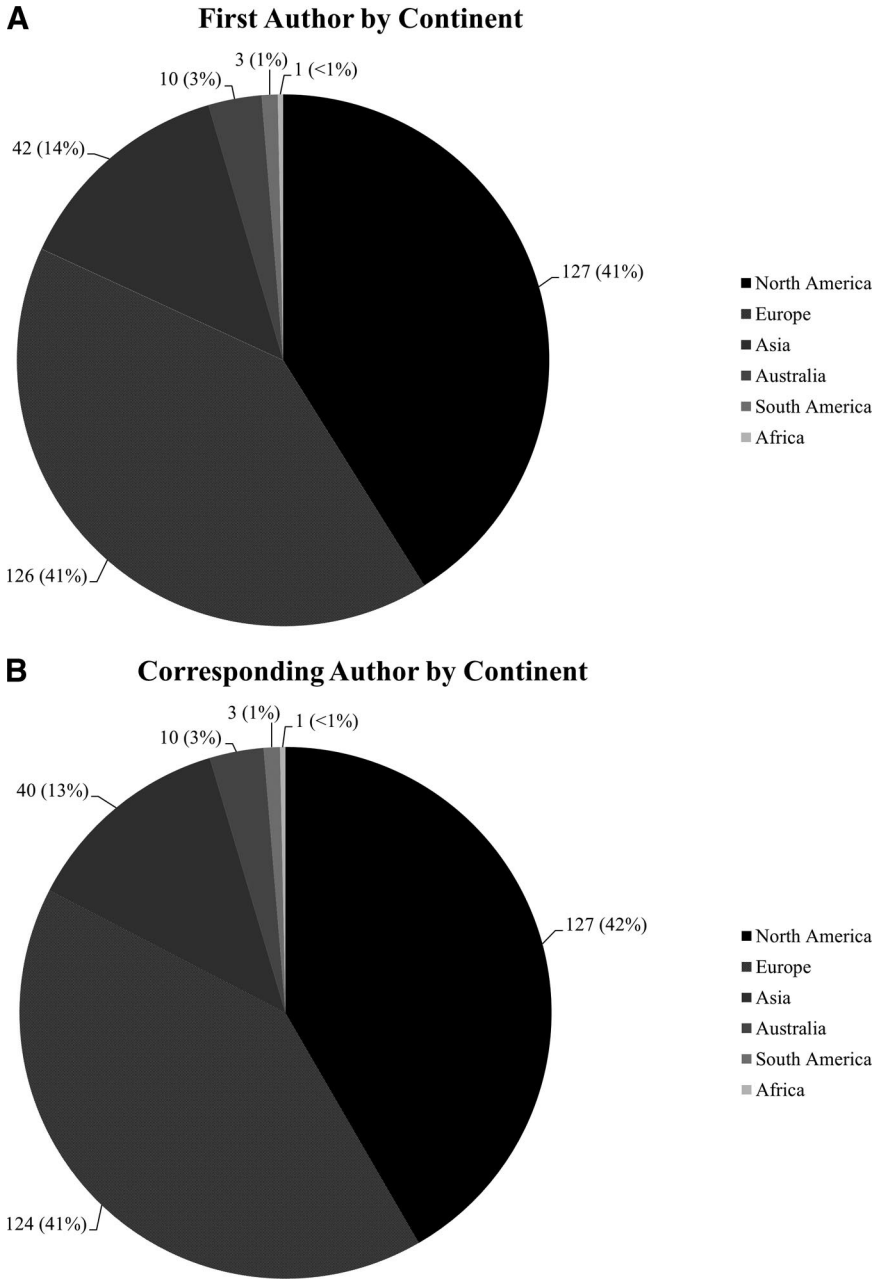

Figure 1. Categorized by continent of origin. **(A)** First authorship ($n = 309$). Studies may have more than one sponsor. **(B)** Corresponding authorship ($n = 305$). Study protocols may include more than one type of therapy.

were RCTs, as both first (35.7% for women vs. 23.5% for men, $p = .039$) and corresponding authors (38.5% vs. 23.3%, $p = .011$).

The number of RCTs ranged from 4 to 18 annually. There were 51 RCTs analyzing pharmacotherapy, 49 with radiotherapy, 20 with surgery, and 3 with other therapies in the study sample. There were 19 phase III clinical trials: 2 out of 41 (4.9%) studies in 1980 and 1985, 4 out of 93 (4.3%) in 1990 and 1995, and 14 out of 187 (7.5%) in 2000, 2005, and 2010. One-hundred one (32.7%) publications studied distant metastatic disease. Seventy-seven (24.9%) studies were published in high-IF journals.

The largest sponsor of research in this study was industry (70, 22.7%), followed by NIH (57, 18.4%), foreign governments (51, 16.5%), and philanthropic/nonprofit groups (34, 11%). Even when we included support from U.S. governmental sources outside NIH, the proportion of studies with governmental funding (65, 21%) lagged behind industry. Thirty-six (17.2%) studies were sponsored by oncology collaborative groups, and 25 out of 36 (69.4%) were collaborative trials receiving primary National Cancer Institute (NCI) support. One-hundred forty-nine (48.2%) studies lacked a study sponsor or did not report a formal source of support. The yearly number of studies with a given sponsor is depicted in Figure 2. During the 1980–2010 time frame, there was a significant decline in U.S. government-sponsored research as a proportion of all prospective studies (p for trend $= .001$) and an increase in industry-sponsored research (p for trend $= .013$).

The number and proportion of positive studies (232, 75.1%) across all years greatly exceeded negative studies (66, 21.4%) or studies with unclear results (11, 3.6%). There was a

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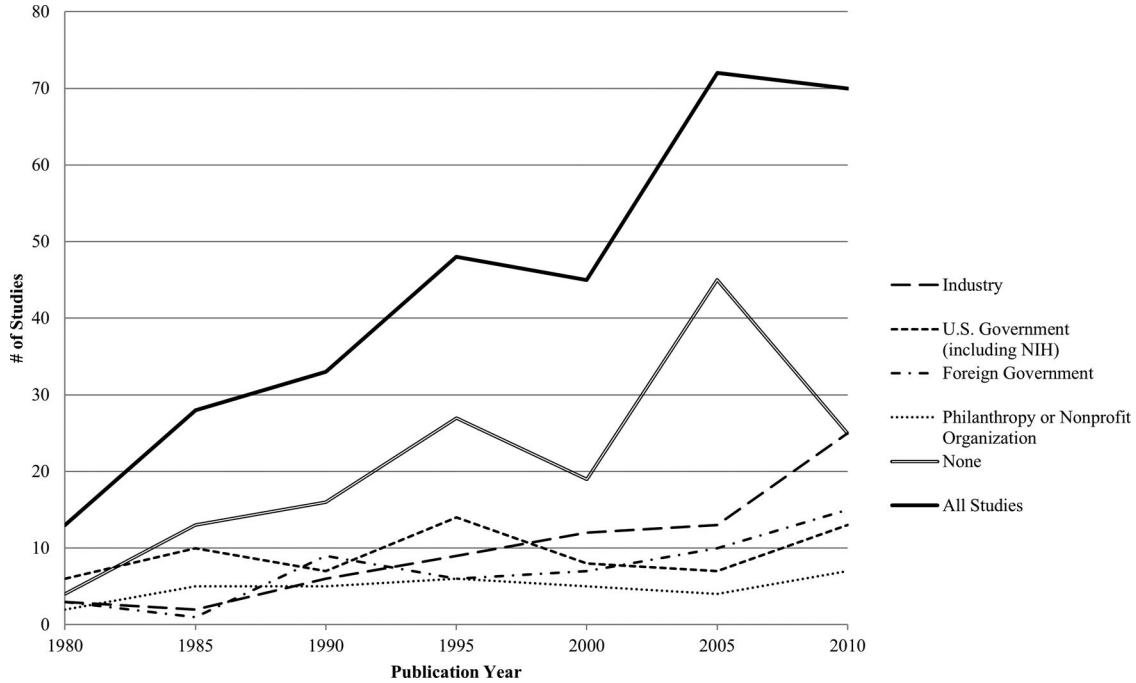

Figure 2. Number of studies with a reported sponsor. Studies may have more than one sponsor. Abbreviation: NIH, National Institutes of Health.

significant increase in the number of positive studies from 61.5% in 1980 to 82.9% in 2010 with a decline in negative studies from 23.1% to 17.1% (p for trend = .002).

The therapeutic modalities we examined were represented as part of the therapeutic protocols of the studies in our sample as follows, in decreasing order: pharmacotherapy (247, 80%), radiotherapy (180, 58.3%), surgery (68, 22%), and other therapy (13, 4.2%). The yearly percentage of studies that included each therapy is depicted in Figure 3. Of these modalities, only surgery demonstrated a significant decline over time as a proportion of treatment protocols (p for trend = .003). All other therapies retained a stable presence in the literature during the study time frame.

About 26.7% of studies that involved pharmacotherapy declared industry support compared with 6.5% of those that did not involve pharmacotherapy ($p = .001$). Pharmacotherapy studies were published more frequently in higher IF journals compared with studies without pharmacotherapy (27.9% vs. 12.9%, $p = .014$). Studies including pharmacotherapy were significantly less likely to have unclear results compared with their nonpharmacotherapy counterparts (2% vs. 9.7%, $p = .014$). Although they were more likely to present both positive (76.1% vs. 71%) and negative results (21.9% vs. 19.3%), neither of these relationships were statistically significant.

Studies that included radiotherapy as part of the therapeutic protocol were less likely to declare industry support (16.7% vs. 31%, $p = .003$). Studies with radiotherapy in the protocol were more likely to be RCTs (36.7% vs. 11.6%, $p < .001$), but were published less frequently in higher IF journals (19.4% vs. 32.6%, $p = .009$). There was no apparent association with either positive or negative presentation of results.

Studies that included surgery as part of the therapeutic protocol were less likely to report industry support compared with those without surgery (8.8% vs. 26.6%, $p = .002$). Studies with surgery in the protocol were published less frequently in higher IF journals (10.3% vs. 29.1%, $p = .002$). As with radiotherapy, studies featuring surgery had no association with presentation of results. Studies with "other" therapeutic modalities were few in number and had no notable associations to report.

We constructed a multivariate logistic regression model to explore potential factors in the predominance of pharmacotherapy in HNSCC research, including study sponsorship, concurrent inclusion of surgery, radiotherapy, and other therapy, metastatic disease within the patient population, year of publication, and IF stratum (Table 1). Research that included pharmacotherapy was again significantly associated with industry sponsorship ($p = .004$). The odds of surgical ($p = .001$) and other therapeutic interventions ($p < .001$) being present within treatment protocols already containing chemotherapy were both significantly lower.

Discussion

In this large-scale bibliometric study of prospective HNSCC therapeutic research, we identified a number of noteworthy trends. First, we observed an overall increase in the number of publications about this field of cancer, but a decline in the proportion of publications incorporating surgery as a component of the treatment protocol. Second, we found an increase in the proportion of studies supported by industry, a trend that has been previously observed [12], as well as an association between industry support and the inclusion of pharmacotherapy in study protocols, suggesting that the availability of funding may influence the distribution of therapeutic modalities investigated in the published literature. Moreover, we noted a decline in the proportion of HNSCC studies sponsored by the U.S. government.

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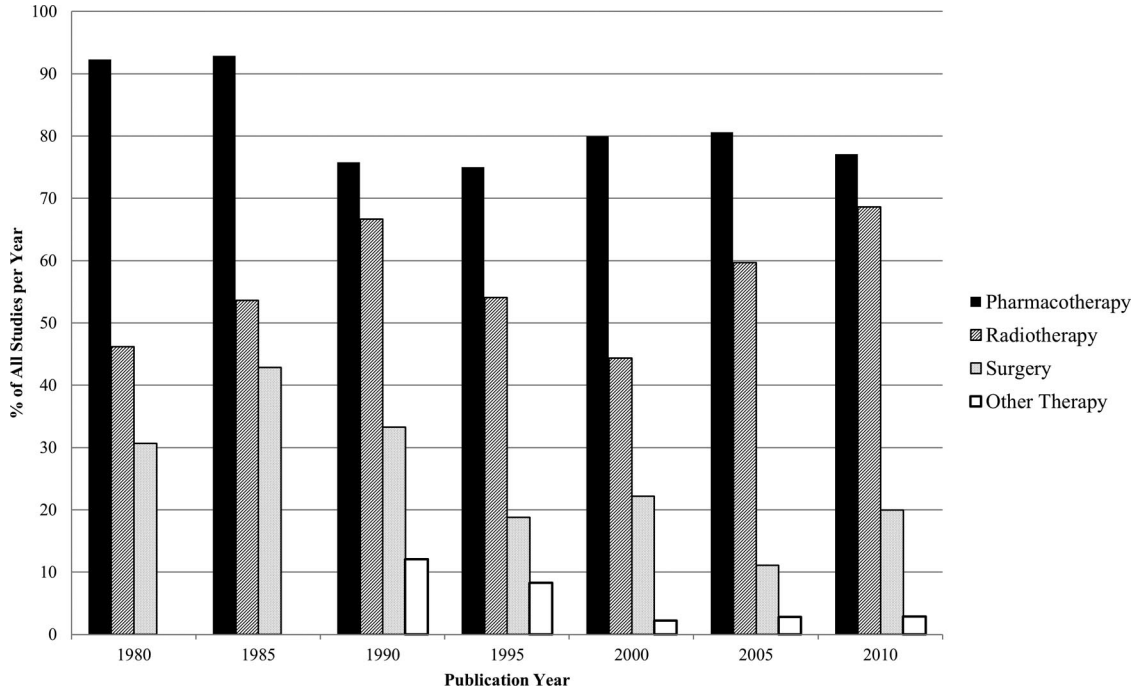

Figure 3. Percentage of studies incorporating a given therapy within study protocols. Study protocols may include more than one type of therapy.

Three major issues related to these findings warrant discussion. First, the decline of both surgical research and U.S. government-sponsored research may reflect ongoing global research trends. A recent bibliometric analysis of 49,111 oncology articles determined that surgical research comprised less than 9% of the sample, global cancer surgery research is poorly cited relative to other aspects of oncology, and only 5% of annual global expenditures into cancer research are directed toward surgery [17]. Study sponsorship trends are more worrisome. The U.S. federal government has traditionally been the largest government-based sponsor of biomedical research worldwide, but starting in the past decade, private industry has overtaken it as the predominant source of funding [9, 18]. For now, the majority of HNSCC randomized trials are led by U.S. government sponsors [15], and the growth of industry funding certainly benefits laboratories strapped for funding and continues to energize the innovation process. However, with increased industry funding, increased industry input on research objectives and longstanding concerns about financial conflict of interest and irregularities in study conduct follow. This confluence of issues directly poses a challenge for the core missions of NCI, and ongoing U.S. federal budget concerns threaten to exacerbate this situation further. Researchers and policymakers urgently need to strategize on how to, at the very least, maintain federal funding to ensure that the direction of cancer research reflects the public interest.

Second, specific barriers may particularly affect surgeon-scientists attempting to conduct high-quality research, including modest surgical presence on NIH peer-review grant committees, inconsistent biomedical research training, increasing administrative burdens, and difficulties in overcoming various methodological, ethical, and economic barriers to conducting randomized trials and other high-quality surgical research [17, 19–22]. Some authors have suggested that the rise of translational research in the 1990s may have facilitated the transference of molecular compounds from laboratory to clinic, but not surgical translational work [23, 24]. The relatively modest contribution by philanthropic and nonprofit groups to HNSCC research and declining U.S. government investment might be a result of less vigorous advocacy by patient support groups. Greater public awareness of head and neck cancer may be helpful to promote increased funding, as it has for breast cancer [25]. Stagnation in national budgets for medical research is also pressuring researchers to pursue commercialization of their scientific discoveries to remain fiscally solvent, a process that is conducive to drug and other product-based research but not necessarily to research on surgical procedures. It is also possible that resources are being shifted away from surgery simply to address unmet research needs in other treatment modalities.

Finally, the preponderance of pharmacotherapy trials relative to surgery and radiotherapy studies may relate to the U.S. Food and Drug Administration (FDA) regulatory process. Unlike drugs, certain medical devices (i.e., FDA class I and II products) can circumvent full premarket assessment via the 510(k) clearance process, which allows manufacturers to market devices if they are found to be substantially equivalent or similar to either a previously 510(k)-cleared device or a device approved prior to the passage of the Medical Device Amendments of 1976. The 510(k) process does not require that the manufacturer demonstrate safety, effectiveness, or innovation [26]. Most radiotherapy delivery devices and surgical robots today fall into the class II category, which would potentially qualify for the 510(k) process. Because 90% of 510(k) submissions for class I and II devices are ultimately approved [27], the barriers to market entry using the 510(k) process are substantially less burdensome for manufacturers

Table 1. Multivariate logistic regression model of prospective head and neck squamous cell carcinoma research that included pharmacotherapy in the treatment protocol

Study characteristics	Odds ratio (95% CI)
Industry sponsorship	
Yes	6.2 (1.8–21.6)
No	Reference
U.S. Government sponsorship	
Yes	0.8 (0.4–2.0)
No	Reference
Foreign government sponsorship	
Yes	1.7 (0.6–4.8)
No	Reference
Other sponsorship	
Yes	0.3 (0.09–0.9)
No	Reference
Surgery in treatment protocol	
Yes	0.3 (0.1–0.6)
No	Reference
Radiotherapy in treatment protocol	
Yes	0.6 (0.3–1.2)
No	Reference
Other therapy in treatment protocol	
Yes	0.05 (0.01–0.2)
No	Reference
Focus on metastatic disease	
Yes	2.3 (0.9–5.6)
No	Reference
Year of publication	
2010	0.2 (0.02–1.7)
2005	0.2 (0.02–2.0)
2000	0.2 (0.02–2.3)
1995	0.2 (0.02–2.2)
1990	0.3 (0.03–3.6)
1985	1.6 (0.1–23.2)
1980	Reference
Impact factor of publishing journal	
High impact factor	1.6 (0.6–4.5)
Low impact factor	Reference

Abbreviation: CI, confidence interval.

[26]. Consequently, there is less incentive for industry to fund expensive clinical trials and other high-quality research for surgery and radiotherapy devices when such research simply may not be necessary for product clearance. Given that the Institute of Medicine has now expressed concerns about the 510(k) process, it may be worth investigating whether implementation of this policy has contributed to a decline in both surgical and radiotherapeutic research across all oncologic subspecialties.

In today's increasingly cost-conscious health care paradigm, research on innovative surgical techniques and comparative effectiveness studies with other treatment modalities are both more important than ever. Escalating health care costs in cancer treatment are being driven by a variety of issues: the sheer volume of oncologic surgical cases, the use of promising but costly technologies in surgery such as robotics, and the high costs of chemotherapeutic agents [17, 28]. Yet, based on our findings, head and neck surgical researchers today face withering support from both the U.S. government and industry. Surgeons today are not only pursuing fewer NIH grants as a group but also successfully winning these grants in significantly lower proportions [29], ultimately reducing the overall impact of surgery on oncologic research discourse. This is evident in our study in which there was a relative decrease in NIH sponsorship for studies involving surgical interventions, as well as an overall decline in U.S. government sponsorship over time.

Furthermore, our study identified just five publications with both industry funding and a surgical component in the 7 years analyzed, with no more than a single publication in any given year. It has been theorized that industry invests in drugs and not new surgical techniques because of differences in commercial exploitability, and because pharmacologic research is perceived to be more exciting by popular media than research on surgery or radiotherapy [16]. This may be reflected in part by the consistently high prevalence of pharmacotherapy studies, along with their positive association with industry funding, in our study. Given that low research investment in cancer may be correlated with poorer health outcomes [17], it is imperative to reconsider policies that encourage insightful investigations in all aspects of oncologic therapy.

There are several limitations to this study. First, as a bibliometric analysis, we evaluated only every fifth year for logistical reasons, exchanging a longer time frame of study for fewer inclusive years. Because we were interested in long-term trends, we did not consider this a detrimental issue. Our definition of study sponsorship was necessarily expansive to account for any potential noteworthy relationship between the study sponsor and the authors. We note that our methods of analyzing years of data at specific intervals and defining sponsorship have been published in previous bibliometric studies [15, 30]. A prior finding that U.S. government-sponsored head and neck cancer randomized trials was associated with positive reporting of results [15] was not replicated in this analysis, which we speculate is because of the inclusion of articles other than RCTs and a longer time frame of study. We relied on disclosures provided within each article, which have been known to be incomplete in the reporting of industry affiliations [31, 32]. We also acknowledge the possibility that, over time, the rate of industry disclosures may have increased as a result of greater investigator and editorial awareness of the influence of industry sponsorship on research.

Next, we noted that even after limiting our study sample to prospective research, nearly half of the studies did not list a study sponsor or explicitly denied having external support. In many cases, these projects may have been funded by the investigators or their institutions. Whether the lack of listed funding sources in some of these papers is a result of failure to report funding, conflict of interest, or other pertinent information on the part of the authors or the journals remains unclear. We did not contact corresponding authors or journals to obtain missing information, so it is conceivable that the prev-

alence of each type of study sponsor is higher than what was observed herein.

Finally, we excluded all retrospective studies to focus primarily on original articles that generally would be considered "high-level" research within the evidence-based medicine community. Surgery has long been dominated by retrospective research, particularly case series, and this is indirectly reflected in our analysis. Although prospectively designed research is not guaranteed to be higher quality, there are many valid prospective study designs, other than the RCT, that are suitable for answering surgical questions [33]. These methodologies were not excluded in our analysis. Furthermore, prospective studies require significantly more planning, coordination, and resources for primary data collection, and theoretically would require at least nominal funding or support from external sponsors. Most retrospective studies, reviews, and meta-analyses simply are not as resource-intensive as a long-term prospective study.

Conclusion

Though the U.S. government historically has been a prominent sponsor of prospective HNSCC research, over the past four decades, its involvement has declined precipitously. Industry is now the predominant sponsor, primarily supporting studies with pharmacotherapy in the treatment protocol. Of the primary therapeutic modalities, only the presence of surgery has declined over time. Ensuring that sufficient high-quality prospective research explores the role of surgery in HNSCC management will require long-term strategies to strengthen interest, training, and funding in surgical research. Health care stakeholders should carefully consider the ramifications of industry funding being the predominant influence on the future of cancer research, as well as the potential impact of the FDA 510(k) clearance process on the quantity and quality of oncologic research in both surgery and radiotherapy.

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Disclosures

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