The Oncologist®

Health Outcomes and Economics of Cancer Care

Use of High-Cost Cancer Treatments in Academic and Nonacademic Practice

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Abstract

Background. Academic physicians, such as those affiliated with National Cancer Institute (NCI)–designated Comprehensive Cancer Centers, may have different practice patterns regarding the use of high-cost cancer drugs than nonacademic physicians.

Materials and Methods. For this cohort study, we linked cancer registry, administrative, and demographic data for patients with newly diagnosed cancer in North Carolina from 2004 to 2011. We selected cancer types with multiple U.S. Food and Drug Administration–approved, National Comprehensive Cancer Network–recommended treatment options and large differences in reimbursement between higher-priced and lower-priced options (stage IV colorectal, stage IV lung, and stage II–IV head-and-neck cancers). We assessed whether provider's practice setting—NCI-designated Comprehensive Cancer Center ("NCI") versus other location ("non-NCI")—was associated with use of higher-cost treatment options. We used inverse probability of exposure weighting to control for patient characteristics.

Results. Of 800 eligible patients, 79.6% were treated in non-NCI settings. Patients treated in non-NCI settings were more likely to receive high-cost treatment than patients treated in NCI settings (36.0% vs. 23.2%), with an unadjusted prevalence difference of 12.7% (95% confidence interval [CI], 5.1%–20.0%). After controlling for potential confounding factors, non-NCI patients remained more likely to receive high-cost treatment, although the strength of association was attenuated (adjusted prevalence difference, 9.6%; 95% CI −0.1%–18.7%). Exploratory analyses suggested potential heterogeneity across cancer type and insurance status.

Conclusion. Use of higher-cost cancer treatments may be more common in non-NCI than NCI settings. This may reflect differential implementation of clinical evidence, local practice variation, or possibly a response to the reimbursement incentives presented by chemotherapy billing. ***The Oncologist*** 2020;25:46–54

Implications for Practice: Oncology care delivery and practice patterns may vary between care settings. By comparing otherwise similar patients treated in National Cancer Institute (NCI)–designated Comprehensive Cancer Centers with those treated elsewhere, this study suggests that patients may be more likely to receive treatment with certain expensive cancer drugs if treated in the non-NCI setting. These practice differences may result in differences in patient costs and outcomes as a result of where they receive treatment.

Introduction

Health care spending in the U.S. continues to rise; the U.S. spends more on health care than any other country, projected to reach 20% of the gross domestic product by 2025 [1]. Cancer care is a significant contributor to this trend, with overall treatment costs expected to increase from $125 billion in 2010 to $173 billion by 2020 [2]. These trends may have negative consequences for the fiscal sustainability of U.S. safety net health care programs and the unmanageable out-of-pocket costs faced by many patients with cancer.

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Cancer drug prices are a significant contributor to these high overall costs, accounting for approximately 20% of cancer treatment costs in 2014 [3]. In recent years, many cancers have seen the development of biologic drugs as a new therapeutic option, often in combination with traditional cytotoxic agents. These drugs have significantly higher prices than older ones; for example, bevacizumab, indicated for colon and lung cancer, is most commonly billed between $6,812 and $11,291 per infusion [4]. Overall per-patient cancer care spending increased by 36% for Medicare and 62% for privately insured patients from 2004 to 2014, whereas spending on biologic drugs increased 335% and 485%, respectively, during the same time period [3]. Though some biologic drugs have produced substantial improvements in patient outcomes, the benefits from others have been smaller. With high prices and marginal benefits, the cost-effectiveness of many targeted therapies has been questioned [5–7].

Because of the high costs of these drugs, it is important to understand provider factors associated with their use. Academic centers may be faster to implement newer therapies, including many targeted agents [8]; on the other hand, emphasis on providing cost-effective care may be more prominent in the academic setting [9–13]. The high acquisition costs and relative difficulty negotiating discounts may be barriers to the use of expensive drugs in smaller, community practices [14]. Additionally, the profitability of these drugs may also vary significantly across settings, particularly with respect to facility fees and participation in the 340B discount program [14, 15], resulting in different financial incentives to providers. If utilization of biologic drugs were found to be significantly variable across academic and nonacademic practice settings, this would raise questions about both patient access to newer therapies, as well as potentially unnecessary costs. Therefore, the goal of this study was to examine whether provider practice setting was associated with use of high-cost cancer treatments that included biologic drugs.

Materials and Methods

Patient Population and Physician Assignment

We used state Medicaid and commercial insurance claims data with linked cancer case data from the North Carolina Central Cancer Registry for this study. We focused on adult patients aged 18 to 64 years, with newly diagnosed stage IV colorectal cancer, stage IV lung adenocarcinoma, or stage II–IV head-and-neck cancer. Medicare-eligible patients and those with prior cancers within 5 years of diagnosis were excluded. Patients were also excluded if they did not begin a treatment regimen of interest within 120 days of diagnosis or did not receive all components of a defined treatment regimen within 60 days of starting treatment (supplemental online Appendix 1). We further required patients to have continuous insurance enrollment in either commercial insurance or Medicaid from 180 days prior to starting treatment through 60 days afterward. Patients with missing data for cancer type, insurance, or year of diagnosis were excluded.

Outcome Definition

We studied cancer types for which there were multiple treatment options, one or more of which included a high-cost biologic drug not present in the other treatment options. We included only treatment options that would be considered standard-of-care, as defined by U.S. Food and Drug Administration approval and National Comprehensive Cancer Network recommendation for the given cancer type during the study period.

We identified three such cancer types during our study period. For each cancer, we defined treatment regimens as either "low-cost" or "high-cost." The three cancer types and corresponding treatments, were as follows: stage IV colorectal cancer (low-cost = FOLFOX or FOLFIRI, high-cost = [FOLFOX or FOLFIRI] + [bevacizumab or cetuximab or panitumumab]), stage II–IV head-and-neck cancer (low-cost = cytotoxic chemotherapy, high-cost = cetuximab $\pm$ cytotoxic chemotherapy), and stage IV lung adenocarcinoma (low-cost = [cisplatin or carboplatin] + [paclitaxel, nab-paclitaxel, or pemetrexed], high-cost = [cisplatin or carboplatin] + [paclitaxel, nab-paclitaxel, or pemetrexed] + bevacizumab). A detailed description of cancer types and treatment definitions are provided in supplemental online Appendix 1.

The primary, patient-level outcome was the receipt of a high-cost treatment instead of a low-cost treatment, as defined by agents received within the 60 days after the first observed cancer drug claim. We chose a 60-day period to define treatment received in order to appropriately classify patients who were intended to receive a targeted agent (e.g., bevacizumab) as part of their first line therapy but could not do so immediately because of recent surgery, while avoiding inclusion of potential second-line therapies after cancer progression.

Exposure Definition

The primary, patient-level exposure was the practice setting of the treating provider. First, we used claims to determine the number of "treatment days" (those on which anticancer drugs were billed) during the 60-day outcome period. Patients were then assigned to the provider who billed for drug administration on the plurality of treatment days (and to the provider billing on the first treatment day, in cases of ties), similar to previous approaches [16, 17].

As a proxy for identifying academic versus nonacademic practice, we classified providers as affiliated or not affiliated with the National Cancer Institute (NCI) based on the billing ZIP code in payer claims. First, we used provider network lists from all payers (private insurers and North Carolina Medicaid) to assemble a list of North Carolina ZIP codes that contained one or more oncology practices. Each ZIP code was then categorized as either containing or not containing an NCI-designated Comprehensive Cancer Center, including cases in which "main campus" sites spanned multiple ZIP codes or providers had additional billing ZIP codes; there were eight such ZIP codes. Providers located within an NCI-containing ZIP code were designated as NCI-affiliated or "NCI providers." We categorized providers based on ZIP codes because there was minimal overlap between NCI-designated Comprehensive Cancer Centers and non-NCI oncology practices within North Carolina; of eight NCI-containing ZIP codes,

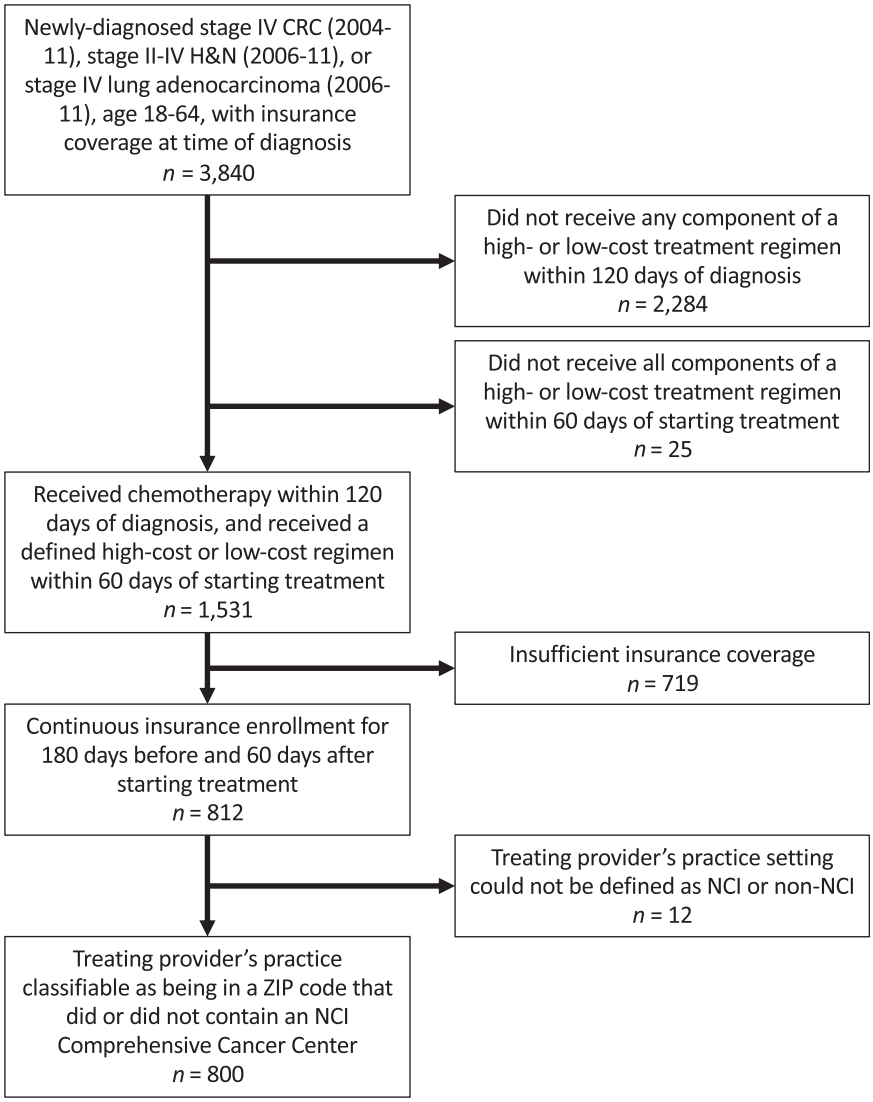

Figure 1. Study population.
Abbreviations: CRC, colorectal cancer; H&N, head-and-neck cancer; NCI, National Cancer Institute–designated Comprehensive Cancer Center.

only one of these also contained a non-NCI oncology practice. Finally, patients were designated as "NCI patients" if their assigned provider was an NCI provider and as "non-NCI patients" if their assigned provider was not an NCI provider.

Potential Confounders

We identified patient characteristics that we hypothesized would be likely to influence a physician's treatment choice. These characteristics included chemotherapy contraindications and frailty indicators. For chemotherapy contraindications, we used diagnosis codes to define common health conditions related to a contraindication or black box warning on the manufacturer label for any of the drugs in our defined treatment regimens. For frailty indicators, we also used a claims-based algorithm to generate a list of conditions associated with frailty (supplemental online Appendix 2) [18, 19]. All characteristics were assessed over the 180-day period prior to the first cancer drug claim and were assessed for balance after weighting (see below).

We also controlled for other potential confounders, including cancer type (colorectal, head-and-neck, lung), treatment billing location (physician office vs. hospital outpatient [20, 21]), and the following demographic factors: gender (female vs. male), race (white vs. nonwhite), age at cancer diagnosis, year of cancer diagnosis, insurance type (Medicaid vs. private), and county-level poverty from U.S. Census data.

Statistical Analysis

To control for potential confounding by the characteristics mentioned above, we used stabilized inverse probability of exposure weights [22, 23]. We assessed covariate balance across NCI versus non-NCI patients by calculating the standardized mean difference for each covariate [24].

In the crude and weighted data, we fit logistic regression models to estimate the predicted prevalence of high-cost treatment in NCI and non-NCI patients, as well as the prevalence difference between groups. In the weighted analysis, we excluded patients in the nonoverlapping tails of the propensity score distribution [25]. For each estimate, we obtained percentile-based bootstrap 95% confidence intervals (CIs) using 2,000 replicates [26]. To explore potential heterogeneity in the prevalence of

Table 1. Characteristics of patients with cancer during 2004–2011, by treating provider[a] practice location (NCI ZIP code vs. non-NCI ZIP code), in crude data and inverse probability of exposure weighted data (*n* = 800)

	Crude data				Weighted data			
		Treating provider's practice location				Treating provider's practice location		
Characteristics	All patients (*n* = 800), *n* (%)	NCI ZIP code (*n* = 163, 20.4%), *n* (%)	Non-NCI ZIP code (*n* = 637, 79.6%), *n* (%)	SMD	All patients (*n* = 746), *n* (%)	NCI ZIP code (*n* = 155, 20.8%), *n* (%)	Non-NCI ZIP code (*n* = 591, 79.2%), *n* (%)	SMD
Female gender	307 (38.4)	63 (38.6)	244 (38.3)	0.007	301 (40.3)	66 (42.8)	234 (39.7)	0.065
Age, median (IQR), years	54 (49–59)	54 (49–59)	54 (49–59)	0.112	55 (49–59)	55 (49–60)	55 (49–59)	−0.030
Nonwhite race	183 (22.9)	27 (16.6)	156 (24.5)	0.197	142 (19.0)	34 (21.8)	108 (18.3)	−0.088
Poverty prevalence in patient's county, median (IQR), %	14 (12–17)	14 (12–15)	14 (12–17)	0.289	14 (12–16)	14 (13–16)	14 (12–17)	−0.015
Year of diagnosis				−0.394				−0.011
2004–2007	233 (29.1)	26 (16.0)	207 (32.5)		212 (28.4)	44 (28.1)	169 (28.5)	
2008–2011	567 (70.9)	137 (84.0)	430 (67.5)		534 (71.6)	112 (71.9)	422 (71.5)	
Type of insurance				−0.286				−0.055
Medicaid	208 (26.0)	27 (16.6)	181 (28.4)		186 (24.9)	36 (23.1)	150 (25.4)	
Private	592 (74.0)	136 (83.4)	456 (71.6)		560 (75.1)	119 (76.9)	441 (74.6)	
Cancer type				0.199				0.067
Colorectal	255 (31.9)	52 (31.9)	203 (31.9)		249 (33.4)	50 (32.3)	199 (33.7)	
Head-and-neck	310 (38.8)	73 (44.8)	237 (37.2)		280 (37.5)	57 (36.8)	222 (37.7)	
Lung	235 (29.4)	38 (23.3)	197 (30.9)		217 (29.1)	48 (30.9)	169 (28.6)	
Percentage of treatment days occurring in hospital outpatient setting				0.744				0.070
0%	502 (62.8)	61 (37.4)	441 (69.2)		452 (60.7)	97 (62.3)	356 (60.2)	
>0%–50%	94 (11.8)	19 (11.7)	75 (11.8)		89 (11.9)	19 (12.5)	70 (11.8)	
>50%	204 (25.5)	83 (50.9)	121 (19.0)		204 (27.4)	39 (25.2)	165 (28.0)	
Number of drug contraindications[b]				0.066				0.023
0	286 (35.8)	57 (35.0)	229 (35.9)		269 (36.1)	55 (35.4)	214 (36.2)	
1	350 (43.8)	75 (46.0)	275 (43.2)		322 (43.2)	68 (44.0)	254 (43.0)	
≥2	164 (20.5)	31 (19.0)	133 (20.9)		155 (20.8)	32 (20.7)	123 (20.8)	
Selected contraindications								
Recent surgery	353 (44.1)	66 (40.5)	287 (45.1)	0.092	324 (43.5)	68 (43.6)	257 (43.5)	−0.002
Gastrointestinal bleeding or hemoptysis	155 (19.4)	35 (21.5)	120 (18.8)	−0.066	146 (19.6)	33 (21.6)	113 (19.1)	−0.062
Brain metastasis	73 (9.1)	17 (10.4)	56 (8.8)	−0.056	77 (10.3)	19 (12.2)	58 (9.8)	−0.078
Number of frailty indicators present[b]				0.179				0.112
0	531 (66.4)	114 (69.9)	417 (65.5)		513 (68.7)	101 (64.9)	412 (69.7)	
1	150 (18.8)	32 (19.6)	118 (18.5)		134 (18.0)	31 (19.9)	104 (17.5)	
≥2	119 (14.9)	17 (10.4)	102 (16.0)		99 (13.2)	24 (15.2)	75 (12.7)	

[a]Based on the plurality definition for identifying the treating provider for a given patient.
[b]Most drug contraindications and frailty indicators are shown in tabulated form, rather than individually, in order to prevent possible reidentification due to cell sizes <11. Among the drug contraindications that have been omitted (hearing loss, acute kidney injury, cirrhosis, viral hepatitis, chronic kidney disease, end-stage renal disease) and the frailty indicators, the average absolute value of the SMD was 0.08 in the crude data and 0.06 in the weighted data.
Abbreviations: IQR, interquartile range; NCI, National Cancer Institute–designated Comprehensive Cancer Center; SMD, standardized mean difference.

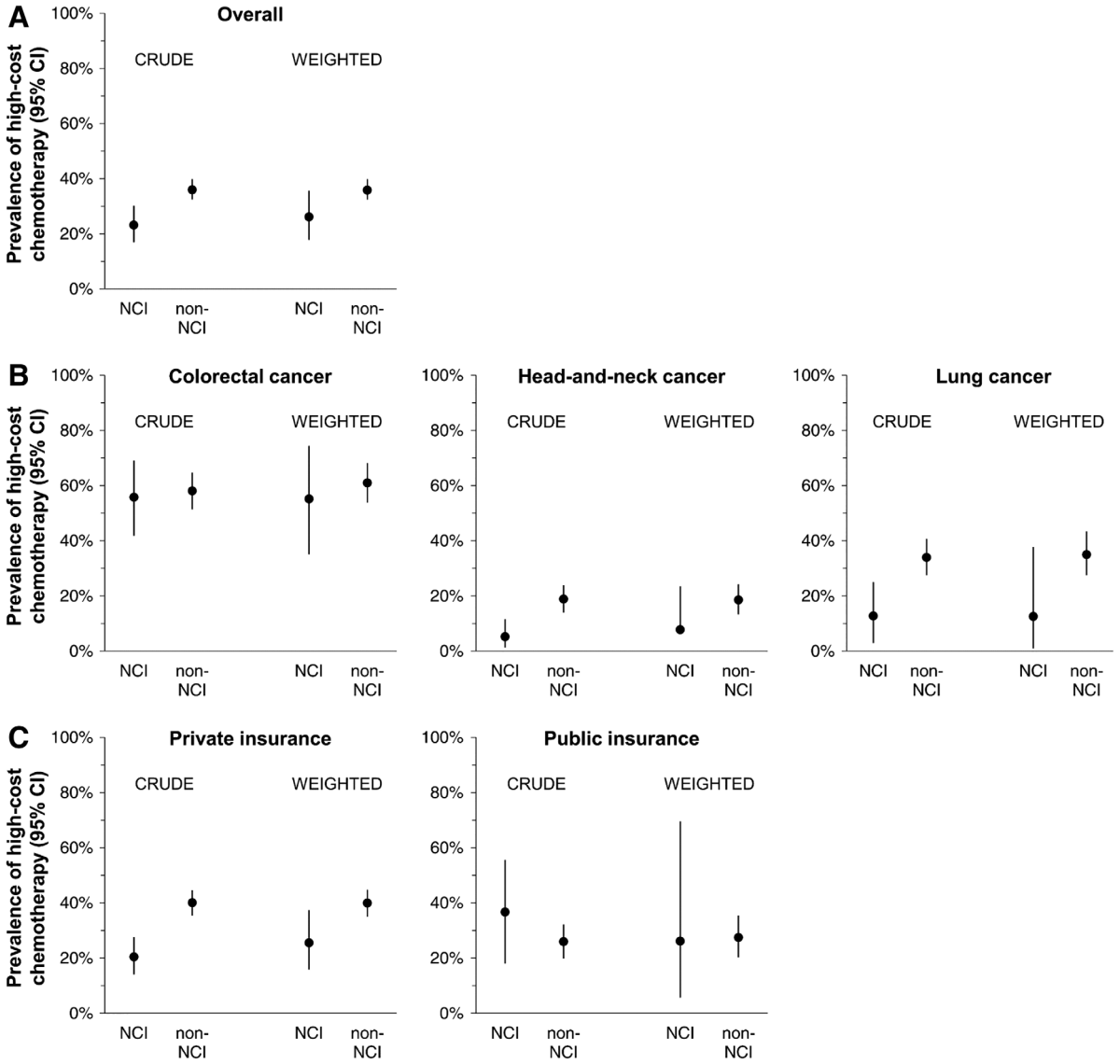

Figure 2. Crude and weighted prevalence of high-cost treatment by NCI classification. **(A):** Overall study population. **(B):** Stratified by cancer type. **(C):** Stratified by insurance type.
Abbreviations: CI, confidence interval; NCI, National Cancer Institute–designated Comprehensive Cancer Center.

high-cost treatment, we conducted stratified analyses by cancer type. Because of differences in reimbursement between insurance types (North Carolina Medicaid reimburses for physician-administered drugs at the federal rate, allowing a modest markup over average sales price [ASP] [27], whereas private insurers reimburse at higher rates [3, 4, 28]), we also stratified by insurance type (private vs. Medicaid).

Data management and statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Sensitivity Analysis

We performed several sensitivity analyses to assess whether the results were affected by our patient-provider assignment method and our approach for controlling patient-level confounding. First, we excluded patients who had drug contraindications or frailty indicators that were infrequent (<2%) in either exposure group or were sparsely distributed with respect to our prespecified subgroups of cancer type and insurance type (acute kidney injury, chronic renal failure, end-stage renal disease); this restriction of the cohort should increase the fundamental comparability between NCI and non-NCI patients with regard to potential confounders (analysis 1). Second, we applied an alternative assignment method in which patients were assigned to the provider who billed on the first treatment day (and to the provider who billed on more treatment days, in cases in which multiple providers billed on the first day) (analysis 2). Finally, the changes described for the two sensitivity analyses above were applied jointly (analysis 3).

Separately, we tabulated patient distribution among unique physicians to assess whether our observations may have been disproportionately affected by a small number of physicians with high patient volume.

Results

After applying our eligibility criteria, 800 patients were included in the study population (Fig. 1). Among these

patients, 31.9% had stage IV colorectal cancer, 38.8% had stage II–IV head-and-neck cancer, and 29.4% had lung cancer. NCI patients made up 20.4% of the total, and the remaining 79.6% were non-NCI patients. Nonwhite race was more common among non-NCI patients (24.5% vs. 16.6%), as was Medicaid insurance (28.4% vs. 16.6%). The receipt of >50% of treatment days in the hospital outpatient setting (as opposed to the office setting) was more common among NCI patients (50.9% vs. 19.0%). Non-NCI patients were more likely to have ≥2 frailty indicators (16.0% vs. 10.4%; Table 1). After weighting, the magnitude of the standardized mean differences of the patient characteristics between exposure groups was significantly reduced, indicating improved confounding control (Table 1).

Within the cohort, a unique physician was identified as the primary treating physician for 607 patients. These patients were assigned to 314 unique physicians; the mean number of patients per physician was 1.9 in both the NCI and non-NCI groups (supplemental online Appendix 3). Only one NCI physician and one non-NCI physician had more than ten assigned patients.

The prevalence of high-cost treatment was 12.7% higher among non-NCI patients versus NCI patients in the crude (unweighted) analysis. After applying inverse probability of exposure weights to balance potential confounders, 26.2% of NCI patients and 35.8% of non-NCI patients received high-cost treatment (prevalence difference 9.6%; 95% CI, −0.1%–18.7%; Fig. 2, Table 2).

In sensitivity analyses, the kappa for agreement between the two exposure classification methods (based on the provider on the plurality of treatment days, or the provider on the first treatment day) was 0.89 (95% CI, 0.85–0.93). The prevalence difference in high-cost treatment for non-NCI versus NCI patients was similar across sensitivity analyses: in analysis 1, the prevalence difference was 12.4% (95% CI, 2.6%–21.6%; supplemental online Appendices 4 and 5); in analysis 2, the prevalence difference was 7.2% (95% CI, −2.7%–16.3%; supplemental online Appendices 4 and 6); and in analysis 3, the prevalence difference was 10.6% (95% CI, 1.2%–19.9%; supplemental online Appendices 4 and 7).

The overall prevalence of high-cost treatment varied across the three cancer types.

For both NCI and non-NCI patients, high-cost treatment was more common for colorectal cancer than head-and-neck or lung cancer (Fig. 2). The prevalence of high-cost treatment was higher in non-NCI than NCI patients across all three cancer types, although differences were not statistically significant within these subgroups (Table 2). Notably, the prevalence of high-cost treatment was most similar between NCI and non-NCI providers with respect to colorectal cancer, with greater differences for head-and-neck and lung cancer. We also observed variation with respect to patient insurance type; the adjusted prevalence of high-cost treatment was similar between non-NCI and NCI patients with Medicaid (prevalence difference, non-NCI vs. NCI, 1.0% [95% CI, −42.5%–23.6%]), but was greater among non-NCI than NCI patients with private insurance (prevalence difference, non-NCI vs. NCI, 14.4% [95% CI, 1.8%–25.4%]; Table 2).

Table 2. Crude and weighted prevalence and prevalence differences for high- versus low-cost treatment comparing patients treated by NCI versus non-NCI providers

Patient characteristics	*n*	Crude data			Weighted data			
		Prevalence of HC, NCI, %	Prevalence of HC, non-NCI, %	Prevalence difference, non-NCI vs. NCI, % (95% CI)	Sum of weights	Prevalence of HC, NCI, %	Prevalence of HC, non-NCI, %	Prevalence difference, non-NCI vs. NCI, % (95% CI)
Overall	800	23.2	35.9	12.7 (4.9–19.9)	746	26.2	35.8	9.6 (−0.1–18.7)
Cancer type								
Colorectal	255	55.8	57.9	2.1 (−12.7–17.8)	238	55.2	60.8	5.6 (−14.8–26.6)
Head-and-neck	310	5.3	18.8	13.5 (5.8–20.9)	283	7.8	18.3	10.5 (−5.8–20.0)
Lung	235	12.8	33.8	21.0 (7.2–33.2)	221	12.6	34.8	22.2 (−3.5–37.0)
Type of insurance								
Private	592	20.5	40.1	19.6 (11.2–27.8)	575	25.6	40.0	14.4 (1.8–25.4)
Medicaid	208	36.7	26.2	−10.5 (−30.8–8.8)	170	26.2	27.2	1.0 (−42.5–23.6)

Abbreviations: CI, confidence interval; HC, high-cost treatment; NCI, National Cancer Institute–designated Comprehensive Cancer Center.

Discussion

After adjustment for patient characteristics, we observed higher utilization of high-cost treatment in the non-NCI setting compared with the NCI setting, among patients with colorectal, head-and-neck, and lung cancer in North Carolina. This suggests that higher-cost treatment regimens may be used more commonly in nonacademic settings than in academic settings. The magnitude of this association was similar in sensitivity analyses modifying the patient-provider assignment method and/or the patient cohort to achieve better covariate balance.

If the observed association between non-NCI practice setting and more frequent use of high-cost treatment represents a true difference in practice, there are several potential explanations. One possibility is that there are differences between NCI and non-NCI practices with respect to the interpretation and application of clinical evidence. For example, concerns about the limited added benefit from biologic agents may be more common in the NCI setting. Concerns about the high financial cost of these agents, their cost-effectiveness, and their contribution to patient out-of-pocket spending may also be more prevalent in academic settings such as NCI centers, although much of the research and awareness regarding drug costs and financial toxicity has occurred after our study period [5, 29, 30]. Another possibility is that physicians in the non-NCI setting receive relatively more information regarding new drugs through pharmaceutical detailing, which may be more favorable toward the benefits of newer, higher-cost drugs. Another contributing factor may be that the financial incentive to use more lucrative drugs is greater in the non-NCI setting compared with the NCI setting.

The Centers for Medicare and Medicaid Services (CMS) "buy and bill" reimbursement model may contribute to high cancer treatment costs. Under the current "buy and bill" reimbursement model, CMS reimburses providers for physician-administered, "Part B" drugs at the ASP +4.3% (formerly 6% prior to sequestration, applicable to the current study period) [14], with providers keeping the margin between ASP +4.3% and the drug acquisition cost. In North Carolina, Medicaid also follows this formula [27]; private insurers typically reimburse at higher rates [3, 4, 28]. Because reimbursement is therefore tied to drug price, higher-priced drugs are expected to result in greater revenue (though the margin can vary substantially across practices, depending on the prices negotiated with wholesalers) [31]. The relationship between revenue and physician compensation is highly variable across practices and institutions. However, in general, large academic centers tend to compensate physicians on fixed salaries or with formulas to incentivize productivity, whereas physicians in nonacademic practices, particularly those characterized by physician ownership, are more likely to see their personal income affected by practice revenue [32]. Physicians in the non-NCI setting may therefore have a more direct financial incentive to use higher-priced drugs [33].

That financial incentives may influence cancer treatment decisions would not be a new finding [34–38]. However, few studies have analyzed the use of cancer drugs with respect to the financial incentives in place since the significant changes made by the Medicare Modernization Act during 2005 and 2006. Recent work has identified significant differences in practice with respect to usage of high-price drugs between the physician office and hospital outpatient settings [9]. Our results suggest that similar differences may be present between academic cancer centers and nonacademic practice. The high-cost drugs we studied appear to be more prevalent in non-NCI settings, and reimbursement policies for these drugs may be a contributing factor. Our finding of effect measure modification by patient insurance type (e.g., privately insured patients, but not Medicaid patients, were more likely to receive high-cost treatment in the non-NCI setting) may suggest an additional source of variation in the use of high-cost drugs, warranting further study.

This study should be interpreted with respect to several limitations. We studied an adult, nonelderly population in a single state, and our results may not be generalizable to other geographic regions or to older patients. Our results are unlikely to be driven by the practice patterns of a small number of oncologists, given the large number of physicians involved in the treatment of our patient sample; however, it is possible that our results reflect institutional practice patterns, given the relatively small number (three) of NCI-designated Comprehensive Cancer Centers in North Carolina. The eligibility requirement of continuous insurance enrollment removed a significant number of patients, particularly Medicaid patients, and therefore our sample may not fully reflect the population of patients with cancer across the socioeconomic spectrum. We used treatment outside of NCI-designated Comprehensive Cancer Centers as our proxy for nonacademic practice; however, this categorization groups together many different practice types—including tertiary care hospitals, group practices, and solo practices—with different drug purchasing and physician compensation arrangements. We categorized providers as NCI or non-NCI on the basis of practice ZIP code, rather than direct records of employment or institutional affiliation. Resulting misclassification should be minimal, however, because of minimal presence of non-NCI providers within ZIP codes containing NCI-designated Comprehensive Cancer Centers within North Carolina. If NCI patients received our high-cost–defining agents (bevacizumab, cetuximab, and panitumumab), or other high-cost experimental agents, through clinical trials, then it is possible that only the cytotoxic components of the treatment regimen would appear in claims; this could result in differential misclassification of high-cost patients as low-cost patients, which would bias results away from the null. If molecular diagnostic testing was differentially available in the NCI versus non-NCI setting, this may have affected the portion of patients judged to be candidates for treatment with a biologic drug. As with all nonrandomized studies, confounding by unmeasured variables—such as patient-level income or distance to care—remains possible.

Conclusion

These findings may have implications for patient care and for reimbursement policy. The biologic agents that we classified

as belonging to "high-cost" treatments in this study are all supported by randomized, phase III clinical trials demonstrating improvement in overall survival for certain patients with colorectal, head-and-neck, and lung cancer [39–45]. From this perspective, increased utilization of these high-cost treatments, which we observed in the non-NCI setting, may indicate the delivery of higher-quality care. However, there are also concerns regarding the costs of these drugs with respect to the magnitude of clinical benefit compared with lower-cost alternatives. Bevacizumab is not cost-effective for colorectal cancer within the U.S. health care system [5], and cetuximab or panitumumab are unlikely to be as well [29]. Cetuximab in combination with radiotherapy has not been compared with cisplatin-based chemoradiotherapy for head-and-neck cancer [46] and may be inferior [47] if given to patients who could tolerate cisplatin-based chemoradiotherapy. The Dana Farber Cancer Center recently removed bevacizumab from its treatment pathway for stage IV non-small cell lung cancer, leading to significant cost savings without an appreciable decrement in patient survival [48]. The "high-cost" treatment regimens examined in this study may offer clinical benefit over lower-cost alternatives, but because of their high prices their *value* (defined as benefit per unit cost) may still be low. From this perspective, lower use of these agents in NCI-approved Comprehensive Cancer Centers may also be appropriate and consistent with a prioritization of high-value care. To the extent that the revenue-generating capability of these drugs contributes to their use, our findings indicate an opportunity to reduce unnecessary spending by decoupling provider reimbursement from drug price.

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Disclosures

Aaron P. Mitchell: Conquer Cancer Foundation (H); **Hanna K. Sanoff:** Bayer, Merck (RF); **Jennifer L. Lund:** GlaxoSmithKline (E—spouse). The other authors indicated no financial relationships.

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