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Breast Cancer

Impact of Guideline-Discordant Treatment on Cost and Health Care Utilization in Older Adults with Early-Stage Breast Cancer

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Key Words. Breast cancer • Guidelines • Treatment • Medicare costs • Health care utilization

Abstract

Background. National Comprehensive Cancer Network (NCCN) guideline-based treatment is a marker of high-quality care. The impact of guideline discordance on cost and health care utilization is unclear.

Materials and Methods. This retrospective cohort study of Medicare claims data from 2012 to 2015 included women age ≥65 with stage I–III breast cancer receiving care within the University of Alabama at Birmingham Cancer Community Network. Concordance with NCCN guidelines was assessed for treatment regimens. Costs to Medicare and health care utilization were identified from start of cancer treatment until death or available follow-up. Adjusted monthly cost and utilization rates were estimated using linear mixed effect and generalized linear models.

Results. Of 1,177 patients, 16% received guideline-discordant treatment, which was associated with nonwhite race, estrogen receptor/progesterone receptor negative, human epidermal growth receptor 2 (HER2) positive, and later-stage cancer. Discordant therapy was primarily related to reduced-intensity treatments (single-agent chemotherapy, HER2-targeted therapy without chemotherapy, bevacizumab without chemotherapy, platinum combinations without anthracyclines). In adjusted models, average monthly costs for guideline-discordant patients were $936 higher compared with concordant (95% confidence limits $611, $1,260). For guideline-discordant patients, adjusted rates of emergency department visits and hospitalizations per thousand observations were 25% higher (49.9 vs. 39.9) and 19% higher (24.0 vs. 20.1) per month than concordant patients, respectively.

Conclusion. One in six patients with early-stage breast cancer received guideline-discordant care, predominantly related to undertreatment, which was associated with higher costs and rates of health care utilization. Additional randomized trials are needed to test lower-toxicity regimens and guide clinicians in treatment for older breast cancer patients. ***The Oncologist*** 2019;24:31–37

Implications for Practice: Previous studies lack details about types of deviations from chemotherapy guidelines that occur in older early-stage breast cancer patients. Understanding the patterns of guideline discordance and its impact on patient outcomes will be particularly important for these patients. This study found 16% received guideline-discordant care, predominantly related to reduced intensity treatment and associated with higher costs and rates of health care utilization. Increasing older adult participation in clinical trials should be a priority in order to fill the knowledge gap about how to treat older, less fit patients with breast cancer.

Introduction

Breast cancer is the most prevalent cancer in females, preferentially impacting older women [1]. Treatment is largely driven by nationally recognized, evidence-based guidelines, such as those published by the National Comprehensive Cancer Network (NCCN) [2]. However, the evidence base for guidelines is predominantly derived from clinical trials, in which the population evaluated is often younger and healthier than the general population [3, 4]. Previous literature assessing guidelines in early-stage (I–III) breast cancer suggests that older women may be less likely to receive

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guideline-concordant care [5–8]. These studies considered the presence of any chemotherapy or classes of medications, rather than the specific chemotherapy regimens (single or combination) utilized. In addition, these studies lack details about the types of deviations from chemotherapy guidelines that occur in this population.

Evaluating guideline concordance is particularly relevant because of the focus on delivery of guideline-based care as a strategy to increase value, which is defined as outcomes achieved relative to the cost of care [9]. In early-stage breast cancer, receipt of guideline-based care is associated with improved survival [10–12]. Implementation of pathway programs based on guidelines also decrease variability in care delivery and reduce health care spending [13–15]. These benefits have prompted enthusiasm to include the measurement of guideline-based care within emerging reimbursement models, such as Medicare's Oncology Care Model and the American Society of Clinical Oncology's Patient-Centered Oncology Payment Model [16, 17]. However, experts in the field have cautioned against the expectation of 100% guideline compliance and instead recommended physician engagement in identifying appropriate deviations from pathways [18]. Understanding patterns of guideline concordance and its impact on patient outcomes will be particularly important for older patients.

The objectives of this study are to evaluate concordance of treatment regimens received (hormone therapy, chemotherapy, and targeted therapies) with NCCN guidelines for older women with early-stage breast cancer; understand categories of discordant treatments; and determine the impact of discordance on health care utilization (hospitalizations and emergency department [ED] visits) and spending.

Materials and Methods

Study Design and Sample Population

This was a retrospective cohort study of Medicare administrative claims data for all adult women age 65 and older with an incident stage I–III breast cancer who received care within the University of Alabama at Birmingham (UAB) Cancer Community Network (CCN) from 2012 to 2015 [19]. The CCN includes 12 cancer centers of varying size and practice structure located in Alabama, Georgia, Florida, Mississippi, and Tennessee [19]. Patients were required to have continuous primary Medicare Part A and B insurance coverage; patients with health maintenance organization coverage were excluded. Data on cancer type, American Joint Committee on Cancer (AJCC) stage (7th edition) [20], hormone receptor (estrogen receptor [ER]/progesterone receptor [PR]) status, human epidermal growth receptor 2 (HER2) status, and date of diagnosis were received from the local cancer registries. Medicare Part A, B, and D claims data from inpatient, outpatient, physician visits (carrier), home health, durable medical equipment, skilled nursing facility, and hospice files from 2012 to 2015 were extracted from the Centers for Medicare & Medicaid Services Chronic Condition Data Warehouse. Patients with claims for metastases were excluded from this analysis. Metastatic disease was identified based on the presence of International Classification of Diseases, Ninth Revision claims on two separate dates for secondary cancer (197.XX–198.XX), excluding breast (198.81, 198.82, 198.2) and lymph nodes (196.XX) [21, 22]. Other exclusion criteria included males, patients with multiple cancers, and patients who did not receive medical treatment (chemotherapy, hormone therapy, or targeted therapy). This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Characterizing Anticancer Drug Treatment Regimens

All treatments (hormonal medications, chemotherapy, and HER2-targeted therapy) including both adjuvant and neoadjuvant medications were identified from Medicare claims using National Drug Codes, Healthcare Common Procedure Coding System, Current Procedural Terminology codes, and generic drug names (supplemental online Table 1). Treatments billed on the same day were considered concurrent. Treatment regimens (single drug, combination, or sequence) were identified as the initial series of treatments after the diagnosis date. If a second medication was added within 120 days of initial treatment, this was considered to be part of the same regimen. Regimen end was defined as a 120-day period without any treatment.

Concordance with NCCN Guidelines

Guideline concordance was defined as treatments (hormonal medications, chemotherapy, and HER2-targeted therapy) listed in NCCN guidelines; dose was not accounted for. To account for NCCN guideline changes over time, concordance status was categorized by the calendar time of first-line treatment matched to the equivalent calendar time version of NCCN Breast Cancer Clinical Practice guidelines. NCCN treatment algorithms separate HER2 positive (HER2+) and HER2 negative breast cancers, so chemotherapy concordance was defined separately for these two groups. Patients with unknown HER2 status were considered as receiving concordant treatment if they received a regimen in either category. Patients receiving first-line, single-agent hormone therapy were categorized as receiving concordant treatment if their ER status was positive or unknown and discordant if their ER status was negative. Patients were also considered as receiving concordant treatment if their initial concordant chemotherapy treatment regimen was followed by hormone therapy. Within the NCCN guidelines, concordant regimens are divided between "preferred" or "other" regimens. All guideline-discordant treatments were reviewed and grouped into discrete categories.

Health Care Utilization and Cost Outcomes

Health care utilization, defined as ED visits or hospitalizations, was identified from the start of cancer treatment until death or censorship. Total costs to Medicare (reimbursements to providers) per patient were summed monthly from the start of cancer treatment until death or censorship and included costs from inpatient, outpatient, physician visit (carrier), home health, hospice, skilled nursing facility, and durable medical equipment files. Part D costs were excluded from this

Table 1. Patient demographics by concordance status (n = 1,177)

Demographics	Guideline concordant (n = 990) Mean (SD) or n (%)	Guideline discordant (n = 187) Mean (SD) or n (%)	p value
Age at time of treatment, years	72.6 (6.7)	73.2 (7.2)	.28
Race, nonwhite	134 (13.5)	36 (19.3)	.04
Treatment center volume, large[a]	727 (73.4)	124 (66.3)	.05
Comorbidity score ≥2[b]	301 (30.4)	58 (31.0)	.87
Breast cancer stage			<.001
I	573 (57.9)	65 (34.8)	
II	341 (34.4)	79 (42.3)	
III	76 (7.7)	43 (23.0)	
ER/PR+[c]	726 (89.5)	92 (66.7)	<.001
HER2+[d]	79 (12.5)	46 (38.7)	<.001
Rate of ED visits per 1,000 subjects	44.5	54.0	.01
Rate of hospitalizations per 1,000 subjects	27.9	28.6	.82
Average monthly cost, upper quartile, $	1,877	3,533	<.001
Average monthly cost, lower quartile, $	362	1,156	<.001

[a]University of Alabama at Birmingham Cancer Community Network treatment center with ≥4,000 cancer patients.
[b]Excluding cancer.
[c]n = 228 unknown.
[d]n = 428 unknown/indeterminate/borderline.
Abbreviations: ED, emergency department; ER/PR+, estrogen receptor/progesterone receptor positive; HER2+, human epidermal growth receptor positive; SD, standard deviation.

analysis because Medicare reimbursements for prescription drugs cannot be determined from Part D event data. Utilization and cost models were adjusted for age at time of treatment, race (white vs. nonwhite), comorbidity score (0–1 vs. 2+), and AJCC cancer stage (I vs. II vs. III). Cancer stage was obtained from the CCN site data, whereas age, race, and comorbidity score were from Medicare claims data. Comorbid conditions were abstracted from the entire CCN period (2012–2015) and classified by the National Cancer Institute Comorbidity Index using a weighted score of 0, 1, 2–3, or 4+ based on the Klabunde-modification for comorbidities [23–26].

Statistical Analysis

Characteristics for all included beneficiaries were described using means and standard deviations for continuous variables and frequencies (percentages) for categorical variables. Demographic differences between guideline-concordant and -discordant patients were assessed using t tests or chi-square tests of independence. Linear mixed effect models were used to evaluate estimates of average monthly costs to Medicare based on concordance status overall and by category of discordance. Unadjusted and adjusted generalized linear models with a negative binomial distribution and log link function were used to estimate utilization rates and their corresponding 95% confidence limits (CL) for ED visits and hospitalizations. The log of total follow-up months was used as an offset. Random effects were added to the cost and utilization models to account for patient clustering within CCN treatment sites. Sensitivity analyses were performed excluding patients with unknown ER/PR or HER2 status, stratifying discordance status by clinical trial participation, excluding HER2+ patients from cost models, and excluding patients with incomplete Part D data. Analyses were performed using the SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Overall Discordance with NCCN Guidelines

Among 1,177 patients with early-stage breast cancer (Fig. 1), 16% received a guideline-discordant, first-line treatment (Table 1). Compared with patients receiving guideline-concordant treatment, patients receiving discordant treatment were more likely to be nonwhite and have a later-stage cancer, ER/PR negative cancer, and HER2 positive cancer (Table 1). Discordance status increased by stage, with 10% of stage I (n = 638), 19% of stage II (n = 420), and 36% of stage III (n = 119) patients receiving a guideline-discordant treatment. In a subset of patients receiving chemotherapy (n = 505/1,177), 37% of patients received guideline-discordant treatment. Less than 1% of patients receiving hormone therapy only (n = 672/1,177) were guideline discordant due to being ER negative. ER/PR or HER2 status was not available in 19% and 36% of patients, respectively. Sensitivity analysis did not reveal any difference in discordance after excluding patients with unknown ER/PR (15% discordant) or HER2 (16% discordant) status.

Categories of Guideline Discordance

For patients receiving guideline-discordant treatment (n = 187), discrete categories of discordance emerged, including (a) HER2-targeted therapy without chemotherapy, (b) nonapproved platinum-based combinations, (c) single-agent chemotherapy, (d) nonapproved bevacizumab regimens, and

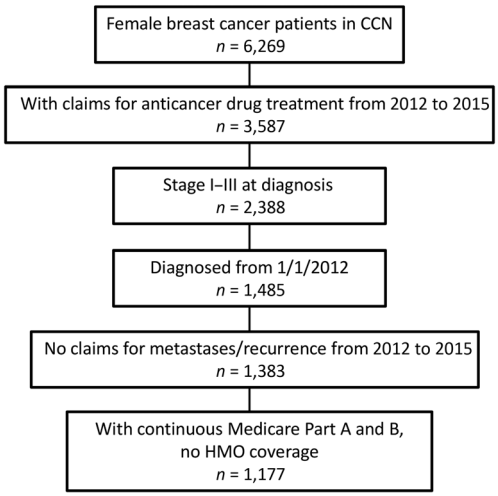

Figure 1. Study population exclusion cascade.
Abbreviations: CCN, Cancer Community Network; HMO, health maintenance organization.

(e) other miscellaneous reasons. Examples of miscellaneous reasons included lower-intensity combinations, receiving hormone therapy before chemotherapy, mismatched chemotherapy and tumor marker status, and therapy schedule nonadherence. The most common reason for discordant treatment was the use of single-agent chemotherapy (19%; Fig. 2). Sensitivity analyses were performed to determine if patients were receiving guideline-discordant treatment due to clinical trial participation. Of all patients included in our analysis, 1.5% were on a clinical trial within 1 month of their initial treatment date, with guideline-discordant patients making up <1% of all patients on a clinical trial.

Costs to Medicare and Health Care Utilization

We observed higher costs to Medicare and rates of health care utilization for patients receiving guideline-discordant treatment compared with guideline-concordant treatment (Table 2). In the adjusted models, average monthly per-patient costs to Medicare after initiation of treatment for guideline-discordant patients were $936 higher when compared with guideline-concordant patients (95% CL $611, $1,260). Differences in costs to Medicare emerged by category of discordance. HER2-targeted therapy without chemotherapy was the highest-costing guideline-discordant category, with $1,941 higher costs per patient per month than patients on concordant treatment (95% CL $1,237, $2,645). However, the costs attributed to this discordance category alone did not drive the difference in costs between guideline-discordant and -concordant patients. In sensitivity analyses excluding HER2+ patients (n = 1,052), guideline-discordant patients had $829 higher costs to Medicare than concordant patients (95% CL $520, $1,138), a difference of $107 from the total sample estimate. For guideline-discordant patients, trends toward increased utilization were also observed (Table 2). Adjusted rates of ED visits per thousand observations were 25% higher at 49.9 per month (95% CL 43.0, 58.0) compared with 39.9 per month (95% CL 32.6, 48.9) for guideline-concordant patients (p = .13). Adjusted rates of hospitalizations per thousand observations

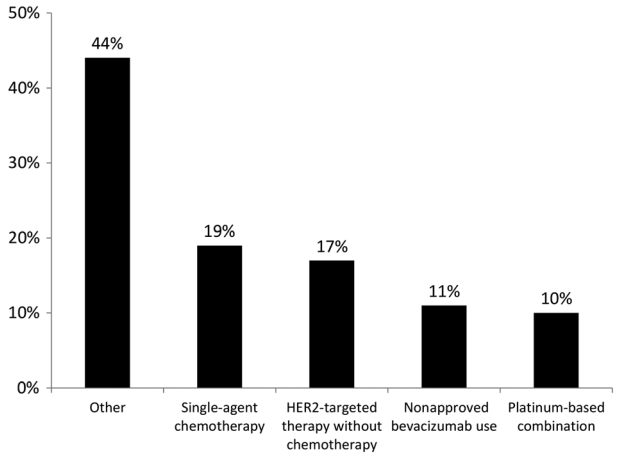

Figure 2. Categories of guideline discordance (n = 187).
Abbreviation: HER2, human epidermal growth receptor 2.

were also 19% higher for guideline-discordant patients at 24.0 per month (95% CL 19.7, 29.2) compared with 20.1 per month (95% CL 15.6, 25.8) for guideline-concordant patients (p = .01). When looking at the category of guideline discordance, patients receiving platinum-based combinations had the highest adjusted rates of ED visits per thousand per month (54.1, 95% CL 31.9, 91.8, p = .39) and single-agent chemotherapy had the highest adjusted rates of hospitalizations per thousand per month (30.4, 95% CL 24.7, 37.3, p < .001; Table 2) when compared with concordant patients. Subgroup analyses by comorbidity score were performed, which showed patients with a comorbidity score ≥2 having higher initial costs to Medicare; however, these higher costs were not due to concordance status. Sensitivity analyses excluding patients without complete Part D data showed no differences in results.

Discussion

Contrary to previous studies that reported guideline concordance of individual chemotherapy, hormone therapy, or HER2-targeted therapy, this study is the first to our knowledge to quantify the rates of *treatment regimen* concordance with NCCN guidelines and to describe the higher costs associated with guideline discordance within a nonclinical trial population of older women with early-stage breast cancer. Although most women receive guideline-concordant breast cancer care, about one in six women do not. Given the lower costs and health care utilization that may be associated with guideline-concordant care, this represents a significant cost to Medicare and to the patients themselves. The increased cost and health care utilization for patients receiving discordant care is consistent with prior studies showing other benefits to patients receiving concordant, guideline-based multimodality care including surgery, radiation, chemotherapy, and endocrine therapy [10–12]. However, these studies characterized chemotherapy concordance using more limited methods. Schwentner et al. and Wockel et al. considered concordance with the St. Gallen 2004 classification, which incorporates selected regimens, and Denu et al. evaluated classes of chemotherapy, such as anthracycline- or taxane-based regimens [10–12]. In contrast, this study includes full characterization of chemotherapy

Table 2. Results of regression analyses on cost and health care utilization for stage I–III patients overall and by category of guideline discordance (n = 1,177)

Outcomes overall and by category of guideline discordance	Unadjusted models			Adjusted models[b]		
	β[a]	CL	*p* value	β[a]	CL	*p* value
Average monthly cost, $	1,262	919, 1,605	<.001	936	611, 1,260	<.001
HER2-targeted therapy without chemotherapy	2,034	1,272, 2,796	<.001	1,941	1,237, 2,645	<.001
Nonapproved bevacizumab use	500	−460, 1,460	.31	−121	−1,013, 772	.79
Platinum-based combination	181	−833, 1,196	.73	−18	−953, 918	.97
Single-agent chemotherapy	348	−382, 1,077	.35	−61	−734, 612	.86
	On-guideline rate/1,000 (CL)	**Off-guideline rate/1,000 (CL)**	***p* value**	**On-guideline rate/1,000 (CL)**	**Off-guideline rate/1,000 (CL)**	***p* value**
ED visits	47.3 (41.0, 54.5)	62.4 (46.3, 84.3)	.08	39.9 (32.6, 48.9)	49.9 (43.0, 58.0)	.13
HER2-targeted therapy without chemotherapy		50.3 (26.9, 94.0)	.87		49.4 (30.2, 80.9)	.52
Nonapproved bevacizumab use		116.9 (85.3, 160.0)	<.001		45.9 (31.0, 68.1)	.48
Platinum-based combination		43.2 (23.2, 80.5)	.80		54.1 (31.9, 91.8)	.39
Single-agent chemotherapy		84.8 (38.4, 187.5)	.11		43.9 (34.3, 56.1)	.51
Hospitalizations	25.9 (20.4, 32.9)	33.3 (28.9, 38.4)	.06	20.1 (15.6, 25.8)	24.0 (19.7, 29.2)	.01
HER2-targeted therapy without chemotherapy		27.6 (18.2, 42.0)	.83		28.4 (16.3, 49.4)	.22
Nonapproved bevacizumab use		64.2 (48.7, 84.5)	<.001		22.5 (13.7, 36.9)	.58
Platinum-based combination		16.6 (6.8, 40.7)	.32		16.9 (9.7, 29.5)	.63
Single-agent chemotherapy		55.3 (36.3, 84.2)	<.001		30.4 (24.7, 37.3)	<.001

[a]Guideline-discordant versus guideline-concordant treatment.
[b]Models adjusted for age, race, comorbidities, cancer stage.
Abbreviations: CL, 95% confidence limit; ED, emergency department; HER2, human epidermal growth receptor 2.

concordance with NCCN guidelines, including differentiation of "preferred" and "other" listed regimens.

The characterization of guideline-discordant treatments is the most striking aspect of this analysis, as it illustrates an important practice pattern in breast cancer care delivery—the reduction in chemotherapy intensity. All commonly observed categories observed within this study could be considered within this framework: HER2-targeted therapy without chemotherapy, bevacizumab without chemotherapy, single-agent chemotherapy, and anthracycline-sparing platinum regimens. We hypothesize that underutilization and use of alternate, lower-intensity approaches may be due to concerns about toxicity in older patients. Previous studies by Griggs et al. showed higher likelihood of chemotherapy intensity reductions in patients who were obese, black, or less educated [27–30]. However, these studies predominantly included younger (<65 years of age) breast cancer patients and did not consider effects of reduced-intensity treatment in older women, who may have much different toxicity concerns than younger patients undergoing treatment. Older patients receiving chemotherapy are more likely to be hospitalized [31, 32], with nontrivial rates as high as 24% for the TAC regimen (docetaxel, doxorubicin, cyclophosphamide) [32]. Older women who receive anthracyclines are 25% more likely to develop congestive heart failure than women who do not receive anthracyclines [33]. These complications can result in declines in quality of life and functional status for older patients [34]. However, toxicity concerns should be assessed using validated approaches and must be balanced with potential benefits of treatment [35]. Adjuvant therapy provides similar benefit to healthy, older patients as for younger patients [36, 37]. A large study testing a reduced-intensity approach of adjuvant capecitabine alone compared with standard chemotherapy found that risk of death was near double for older women receiving capecitabine only [38]. Additionally, although the hazard of death for older, frail breast cancer patients has been shown to be 3.1 times higher than robust patients, this effect was not due to treatment differences [39]. Therefore, it is critical to consider the functional age of a patient when making treatment decisions [34].

The focus on reduced-intensity treatment in the early-stage setting contrasts with our prior study of discordance in the metastatic setting, where we observed both reduced-

and higher-intensity therapy [40]. Although HER2-targeted therapy without chemotherapy was seen in both studies, categories of discordance in metastatic breast cancer also included bevacizumab in nonapproved chemotherapy combinations (instead of as a single agent) and nonapproved combination chemotherapy. This difference is likely due to the availability of well-tolerated single agents within the guidelines for metastatic disease, which contrasts with the exclusive use of combination chemotherapy for patients with early-stage disease. The pattern of reduced-intensity treatment is supported by differences observed by cancer stage in this study. For patients with stage I cancer, the concordance was 90%, likely due to the recommended treatment for this population being hormone therapy alone, a well-tolerated option. For patients with stage III cancer, for whom chemotherapy would be recommended and a low-toxicity regimen is not available, concordance was 64%. Thus, the guideline-discordant treatment patterns observed in this study, in which the average age was 73 years, likely represent a gap in available data for how to treat older early-stage breast cancer patients. The choice to prescribe reduced-intensity treatment may reflect a perception that specific patients would not tolerate guideline-based combination chemotherapy, due to an unmeasured factor such as functional status or frailty. Provision of reduced-intensity treatment may provide a false sense that these patients are unlikely to experience complications from treatment. The higher rates of ED use and hospitalization observed during this timeframe would suggest this approach should be reconsidered and further studied. Few clinical trials include patients >70 years of age, much less focus specifically on this older population to provide clinicians with guidance on optimal treatment strategies [3, 4]. Because of strict eligibility criteria, clinical trial populations are rarely representative of the general cancer population, thereby limiting the generalizability of study results [41, 42]. Furthermore, clinical practice guidelines in cancer and elsewhere are single disease focused with challenging limitations in older multimorbid adults [43]. Increasing the participation of older adults on clinical trials and designing trials specifically for frail and multimorbid older adults with cancer should be a priority in order to fill these important gaps [41].

Given the increased costs and health care utilization associated with guideline discordance in this study, concordance is not only an important consideration for individual patient care, but should also be considered a larger public health concern. Considering the ~250,000 U.S. breast cancer cases estimated for 2017, with about 45% of those cases age 65 or older [1], as many as 18,750 (1 in 6) may not be receiving standard-of-care treatment. At an estimated increase in cost of ~$950 per month, this may contribute to higher than necessary costs of breast cancer care. Additionally, the cost differential between guideline-discordant and -concordant treatments could be further increased by later costs associated with potential future recurrences, as discordance was largely related to reduced-intensity treatment [22]. This large population is a target for the emerging pathway programs, such as those established by Blue Cross Blue Shield and Anthem [13, 14, 44], as even modest reductions in cost may result in profound savings to payers.

The use of administrative claims data in evaluating guideline concordance has several limitations. Although we are able to observe what treatment the patient received, this may not reflect what was recommended by the physician. We are unable to evaluate patients who did not get any medical treatment for their breast cancer. Also, this data source does not allow for consideration of patient or physician preferences in decision-making. There may be other unmeasured confounders that we are unable to capture with administrative claims data, such as patient prognosis, functional status, frailty, comorbidity severity, symptoms, quality of life, or true out-of-pocket costs, that may influence physician's choice of reduced-intensity treatment versus no treatment. We are also unable to assess any differences in discordance due to physician characteristics. Finally, patients were those with continuous Medicare Part A and B coverage receiving care in the UAB CCN and may not represent all breast cancer patients in the U.S. or in the southeastern U.S.

We recognize that the emphasis on combination chemotherapy results in an "all or nothing" approach, which may not be palatable for clinicians caring for frail, older patients with multiple comorbidities. Although we believe that this study demonstrates a natural response to the lack of available data on lower-toxicity regimens for older patients, efforts must be made to expand inclusion criteria to increase participation of older patients in clinical trials to fill this growing gap in knowledge about optimal patient care for older patients.

Conclusion

About one in six early-stage breast cancer patients received guideline-discordant care, which is associated with higher costs and rates of health care utilization. Discordance is predominantly related to reduced-intensity treatment. Additional randomized clinical trials are needed to test lower-toxicity regimens and ultimately guide clinicians in treatment for older, less fit patients with breast cancer.

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Disclosures

Supriya K. Yagnik: Genentech, Inc. (E, OI); **Andres Forero:** Pfizer, Novartis, Seattle Genetics, Incyte, Syndax, Tracon, Gilead (RF [Institution]); **Gabrielle B. Rocque:** Pfizer, Genentech, Pack Health, Carevive (RF), Pfizer, Genentech (C/A). The other authors indicated no financial relationships.

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