Original Article

Treatment-Associated Toxicities Reported by Patients With Early-Stage Invasive Breast Cancer

Christopher R. Friese, PhD[1,2]; Jordan M. Harrison, BSN[1]; Nancy K. Janz, PhD[3]; Reshma Jagsi, MD, DPhil[4]; Monica Morrow, MD[5]; Yun Li, PhD[6]; Ann S. Hamilton, PhD[7]; Kevin C. Ward, PhD[8]; Allison W. Kurian, MD[9,10]; Steven J. Katz, MD[11,12†]; and Timothy P. Hofer, MD[11,13†]

BACKGROUND: Patient-reported toxicities help to appraise the breast cancer treatment experience. Yet extant data come from clinical trials and health care claims, which may be biased. Using patient surveys, the authors sought to quantify the frequency, severity, and burden of treatment-associated toxicities. **METHODS:** Between 2013 and 2014, the iCanCare study surveyed a population-based sample of women residing in Los Angeles County and Georgia with early-stage, invasive breast cancer. The authors assessed the frequency and severity of toxicities; correlated toxicity severity with unscheduled health care use (clinic visits, emergency department visits/hospitalizations) and physical health; and examined patient, tumor, and treatment factors associated with reporting increased toxicity severity. **RESULTS:** The overall survey response rate was 71%. From the analyzed cohort of 1945 women, 866 (45%) reported at least 1 toxicity that was severe/very severe, 9% reported unscheduled clinic visits for toxicity management, and 5% visited an emergency department or hospital. Factors associated with reporting higher toxicity severity included receipt of chemotherapy (odds ratio [OR], 2.2; 95% confidence interval [95% CI], 2.0-2.5), receipt of both chemotherapy and radiotherapy (OR, 1.3; 95% CI, 1.0-1.7), and Latina ethnicity (OR vs whites: 1.3; 95% CI, 1.1-1.5). A nonsignificant increase in at least 1 severe/very severe toxicity report was observed for bilateral mastectomy recipients (OR, 1.2; 95% CI, 1.0-1.4). **CONCLUSIONS:** Women with early-stage invasive breast cancer report substantial treatment-associated toxicities and related burden. Clinicians should collect toxicity data routinely and offer early intervention. Toxicity differences observed by treatment modality may inform decision making. ***Cancer*** **2017;123:1925-34**. © *2017 American Cancer Society.*

KEYWORDS: breast cancer, patient report, treatment-associated toxicities, treatment experience.

INTRODUCTION

Cancer treatments have a narrow therapeutic index. Clinicians constantly weigh the anticipated benefits of anticancer treatments against the risks of treatment-associated toxicities. Toxicities may lead to treatment discontinuation,[1,2] costly health care service use,[3] and premature death.[4] Toxicities place physical, emotional, and financial burdens on patients and families.[5] Toxicity management also consumes clinician and practice resources.[6]

Despite the burdens placed on patients, families, and health care systems, to the best of our knowledge few data sources capture toxicities reliably. Treatment-related toxicity studies generally derive from clinical trials data,[7] health care claims,[8] and single-site patient registries,[9] with notable limitations of generalizability, data quality, and biased reporting. In 2007, a National Cancer Institute-sponsored working group developed a patient-reported version of the Common Terminology Criteria for Adverse Events (CTCAE). The Patient-Reported Outcomes version of the CTCAE

Corresponding author: Christopher R. Friese, PhD, RN, Department of Systems, Populations, and Leadership, University of Michigan School of Nursing, 400 North Ingalls, #4162, Ann Arbor, MI 48109-5482; Fax: (734) 647-2416; cfriese@umich.edu

[1]Department of Systems, Populations, and Leadership, School of Nursing, University of Michigan, Ann Arbor, Michigan; [2]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan; [3]Department of Health Behavior and Health Education, School of Public Health, University of Michigan, Ann Arbor, Michigan; [4]Department of Radiation Oncology, University of Michigan School of Medicine, Ann Arbor, Michigan; [5]Breast Surgical Service, Memorial Sloan Kettering Cancer Center, New York, New York; [6]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; [7]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California; [8]Rollins School of Public Health, Emory University, Atlanta, Georgia; [9]Department of Medicine, Stanford University Medical Center, Stanford, California; [10]Department of Health Research and Policy, Stanford University Medical Center, Stanford, California; [11]Department of Internal Medicine, School of Medicine, University of Michigan, Ann Arbor, Michigan; [12]Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor, Michigan; [13]Veterans Affairs Center for Clinical Management Research, Health Services Research and Development Service Center of Innovation, University of Michigan, Ann Arbor, Michigan

[†]The last 2 authors contributed equally to this article.

We acknowledge our project staff (Mackenzie Crawford and Kiyana Perrino from the Georgia Cancer Registry; Jennifer Zelaya, Pamela Lee, Maria Gaeta, Virginia Parker, and Renee Bickerstaff-Magee from the University of Southern California; and Rebecca Morrison, Rachel Tocco, Alexandra Jeanpierre, Stefanie Goodell, Rose Juhasz, Paul Abrahamse, Kent Griffith, and Irina Bondarenko from the University of Michigan). We acknowledge with gratitude our survey respondents.

DOI: 10.1002/cncr.30547, **Received:** October 17, 2016; **Revised:** December 3, 2016; **Accepted:** December 12, 2016, **Published online** January 24, 2017 in Wiley Online Library (wileyonlinelibrary.com)

(PRO-CTCAE) enables patients to report the frequency, severity, and burden of toxicities and addresses well-documented biases observed with clinician-reported toxicity ratings.[10,11]

To the best of our knowledge, few studies to date have solicited the toxicity experience directly from diverse, population-based patient samples. Describing the patterns, correlates, and frequencies of treatment-associated toxicities from a large population-based sample allows clinicians to understand the actual patient treatment experience outside the narrow confines of rigorously conducted clinical trials. Such data could inform targeted, proactive efforts to identify patients at risk of burdensome toxicities, enable earlier intervention, and improve quality of life.

In this context, we analyzed data collected from a population-based survey of women diagnosed with early-stage invasive breast cancer. We examined the frequency and severity of toxicities associated with cancer treatment. We next explored the correlation between toxicity reports and physical health and health care service use. Finally, we examined patient, tumor, and treatment factors associated with toxicities rated as severe or very severe.

MATERIALS AND METHODS

Sampling and Survey Procedures

The iCanCare study is a population-based mailed survey of women with early-stage breast cancer. In partnership with the Los Angeles County and Georgia Surveillance, Epidemiology, and End Results (SEER) programs, the iCanCare study identified 3880 women aged 20 to 79 years who were diagnosed with early-stage breast cancer determined by a definitive breast surgery date between July 1, 2013 and September 31, 2014. Women were sent surveys approximately 2 months after surgery and completed the survey on average approximately 7 months after diagnosis. To enable meaningful analyses across racial and ethnic groups, African American and Latina women were oversampled in Los Angeles County. The following women were excluded from the iCanCare study sampling protocol: those with stage III or IV cancer (because the overall project was focused on patients with early-stage disease), those with Paget disease, or those with tumors measuring >5 cm in size. In Los Angeles County, non-Hispanic white and African American individuals aged <50 years were excluded due to a competing study in these populations.

The study was approved by the Institutional Review Boards of the University of Michigan and partnering institutions. Informed by the methods of Dillman et al,[12] we solicited participation with an incentive of $20 in cash. Study coordinators in respective geographic areas continued to follow up with nonresponders, including up to 9 attempted telephone calls and 2 repeated mailings. Participants received survey materials to their home address with a statement that their answers would not be shared individually with their providers. Study materials were printed in English; women with Spanish surnames received Spanish and English materials.[13]

Of the 3880 women originally identified, 249 were ineligible. Of these 3631 women, 1053 women were not reached or did not return questionnaires, resulting in an overall response rate of 71% (2578 women). After excluding 694 women with ductal carcinoma in situ or bilateral disease, our analytic sample included 1884 observations in the observed data and 1945 observations after multiple imputation. SEER registries linked surveys to standardized tumor registry data.

Measures

Except when indicated, measures were collected from patient questionnaires. The primary outcome was treatment-associated toxicities. Informed by the PRO-CTCAE working group[14] and our pilot work,[15] participants rated the severity of 7 toxicities at their worst during cancer treatment using a 5-point Likert scale (0 indicates none, 1 indicates mild, 2 indicates moderate, 3 indicates severe, and 4 indicates very severe). The toxicities measured were nausea/vomiting, diarrhea, constipation, pain, arm edema, dyspnea, and breast skin irritation. These toxicities were selected after interviews with survivors and analysis of toxicity reports in pilot work.[15]

Because to the best of our knowledge few studies to date have investigated patient-reported, treatment-associated toxicities, we measured toxicities in 3 ways. First, we examined the range of severity ratings across toxicities. Next, we constructed a scale by multiplying the number of toxicities reported by severity. For example, a score of 3 might reflect 1 toxicity that was rated as severe or 3 toxicities rated as mild, and a score of 28 would reflect that a patient reported all 7 toxicities as very severe.

To examine toxicity burden, we examined physical health and health care service use. To measure physical health, we used the 4-item physical function subscale of the Patient Reported Outcomes Measurement Information System (PROMIS) global health measure. The scale is a brief, valid, reliable, precise, and clinically interpretable measure of physical health.[16] Respondents rated each item on a 5-point ordinal scale. The score was standardized and normalized according to the scoring manual;

scores <40 reflected poor physical health.[17] To measure health care service use, we asked patients whether they 1) did not seek help, 2) called/e-mailed their provider, 3) discussed at a routine visit, 4) discussed at an unscheduled visit, or 5) visited the emergency department/hospital. We classified unscheduled care as either an unscheduled clinic visit, emergency department visit, or inpatient hospitalization for toxicity management.

Patients reported their age, race/ethnicity (white, black, Latina, or Asian), education (≤high school, some college, ≥college graduate), and prior comorbidity diagnosis (chronic lung disease, heart disease, diabetes, or stroke) (no diagnosis, 1 condition, or ≥2 conditions). We included 4 separate variables to capture treatment factors: primary breast surgery (lumpectomy, unilateral mastectomy, or bilateral mastectomy), radiotherapy (yes/no), systemic chemotherapy (yes/no), and receipt of both radiotherapy and chemotherapy (yes/no). SEER registries provided tumor information: AJCC summary stage (I or II), grade (1, 2, or 3), and lymph node status (N0 or N1). We calculated the difference between the date of patient survey completion and the cancer diagnosis date.

Statistical Analysis

First, we used descriptive statistics to examine patient, disease, and treatment factors in our analytic sample and then examined these factors in the subset of women who rated at least 1 toxicity as severe/very severe, as well as within the subset of women who reported unscheduled care for toxicity management. Next, for each of the 7 toxicities and corresponding severity rating, we calculated the percentage of women who also reported health care service use (telephone call, scheduled visit, unscheduled visit, or emergency department visit/hospitalization) for that toxicity. Using the multiplied scale of the number of toxicities reported by their severity, we next plotted the corresponding PROMIS physical function scores. Using multivariable regression, we examined 2 dependent variables, unscheduled care and PROMIS physical function scores, by toxicity score, controlling for patient, tumor, and treatment factors. Finally, we used multivariable ordinal logistic regression with design weights reflecting the probability of selection and nonresponse to examine the relationship of patient, tumor, and treatment factors with higher levels of toxicity severity.

Unless specified, analyses controlled for geography (Los Angeles County and Georgia) and were weighted to account for differing probabilities of sample selection and nonresponse.[18] We identified small amounts of missing data (range, 0%-3.9% across variables; 93% of observations had complete data). To minimize biased estimates from missing data, we applied a sequential regression multiple imputation framework.[19] We generated 5 independently imputed data sets and computed inferential statistics that combined analyses across data sets.[20] Imputation results were indistinguishable from the complete case analysis. Table 1 is based on complete case analysis (number identified in the table for each variable) and all subsequent figures and regression results are based on multiply imputed data (1945 women).

RESULTS

Table 1 shows patient characteristics, including women who reported any of the 7 measured toxicities as severe/very severe, and those who sought unscheduled care for toxicities via clinic visits, emergency department visits, or hospitalizations.

Frequency and Severity of Patient-Reported Toxicities

Women with early-stage invasive breast cancer reported several toxicities during treatment, many of which were rated as severe or very severe. A total of 132 patients (7%) reported that none of the 7 toxicities occurred during treatment. A total of 1810 women (93%) reported at least 1 toxicity and 866 of the women in the analytic sample (45%) rated at least 1 toxicity as severe/very severe. Among the 7 toxicities, pain was most frequently reported as severe/very severe (23%), followed by constipation (14%) and breast skin irritation (13%).

Toxicities and Health Care Service Use

Figure 1 shows patient reports of health care service use by each toxicity studied and the corresponding severity rating. Across all 7 toxicities, 2% to 4% of patients did not endorse a toxicity rating but discussed the problem during a routine office visit. The majority of patients sought help during an office visit (range, 22%-77% across the 7 toxicities); telephone calls/e-mails and emergency department visits/hospitalizations were less frequently reported. For women who experienced at least 1 toxicity, approximately 9% sought care through a previously unscheduled clinic visit and 5% visited an emergency department or hospital.

Nausea/vomiting and diarrhea were frequent sources of telephone calls/e-mails; 29% of patients with very severe nausea/vomiting and 27% of patients with very severe diarrhea called or e-mailed their provider. Severe arm edema (77%) and very severe skin irritation (71%) were the primary reasons for unscheduled clinic visits. Patients with severe/very severe dyspnea most frequently

TABLE 1. Patient Sample Characteristics by Toxicity Report and Report of Health Care Service Use[a]

Characteristic	No.	Reported ≥1 Toxicities as Severe or Very Severe	Sought Unscheduled Care (Clinic Visit, Emergency Department, or Hospital)
Mean age, y	1884	60	59
Mean time from diagnosis to survey, d	1878	207	218
		%	
Patient factors			
Race/ethnicity			
White	1057	40	11
Black	321	52	16
Latina	315	53	17
Asian	141	48	6
Other/unknown/missing	50	52	17
Education			
<High school	211	57	16
High school graduate	331	37	9
Some college	623	48	12
≥College graduate	698	42	13
No. of comorbidities			
0	1101	41	12
1	527	49	13
≥2	247	52	15
Tumor factors			
AJCC Summary Stage			
I	1264	41	11
II	620	52	16
Positive lymph nodes			
No	1502	42	11
Yes	382	53	18
Treatment factors			
Surgical treatment			
Lumpectomy	1138	39	12
Unilateral mastectomy	393	48	12
Bilateral mastectomy	338	58	16
Radiotherapy			
No/future radiotherapy	975	51	14
Current/past radiotherapy	890	37	11
Adjuvant chemotherapy			
No chemotherapy	1134	35	8
Chemotherapy	736	60	19
Received both chemotherapy and radiotherapy			
No	1667	43	12
Yes	217	59	19
Site			
Georgia	1049	42	12
Los Angeles County	835	47	13

[a] Data are shown as the number (%) or mean (standard deviation) unless otherwise stated. Percentages are based on unweighted data.

visited emergency departments or hospitals for toxicity management (28%), followed by patients with severe/very severe arm edema (27%), severe/very severe diarrhea (18%), and severe/very severe pain (18%).

Toxicities and Physical Health

The mean physical functioning score on the PROMIS measure was 14.5 (standard deviation, 3), reflecting substantial deficits from the optimal score of 50. Figure 2 shows the relation between the multiplied toxicity rating (number of toxicities and toxicity severity rating) and PROMIS physical scores estimated by a regression model, with corresponding 95% confidence intervals (95% CIs). Higher PROMIS scores reflect better physical functioning and higher toxicity scores reflect more frequent and/or severe toxicity ratings. These scores were averaged across age, comorbid conditions, chemotherapy receipt, employment, marital status, and race/ethnicity. PROMIS physical functioning scores were found to correlate linearly, negatively, and significantly with toxicity ratings ($\beta = -0.2$; 95% CI, -0.3 to -0.2). Patients without toxicity had the highest scores, whereas patients who reported all 7 toxicities as severe reported scores at the lowest possible score of 10 on the scale.

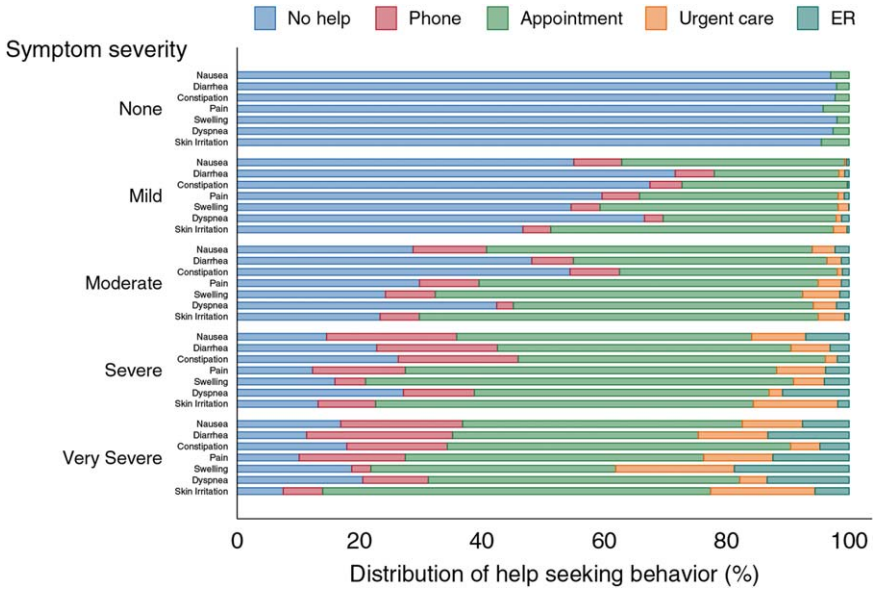

Figure 1. Distribution of patient-reported health care service use by each toxicity and corresponding severity rating. Reported results were based on weighted, imputed data. ER indicates emergency room.

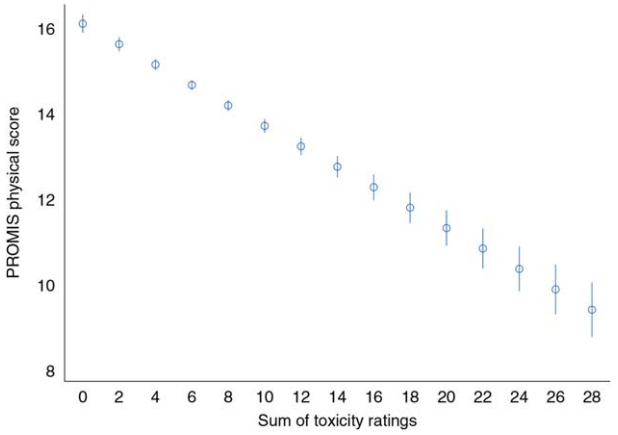

Figure 2. Physical health scores by toxicity severity. Higher physical health scores reflect better physical functioning. Higher toxicity severity scores reflect increased toxicity frequency and/or worse severity. Toxicity scores were found to be inversely proportional to physical health ($\beta = -0.2$; 95% confidence interval, −0.3 to −0.2). Reported results were based on weighted, imputed data. PROMIS indicates Patient-Reported Outcomes Measurement Information System.

Factors Associated With Reporting a Severe or Very Severe Toxicity

Figures 3A to 3C show the unadjusted differences in toxicity reporting by breast cancer treatment. Toxicity severity varied by receipt of chemotherapy (Fig. 3A). For example, 29% of chemotherapy recipients reported severe/very severe pain compared with 19% of women who did not receive chemotherapy. Severe/very severe constipation was reported by 24% of chemotherapy recipients compared with 9% of women who did not receive chemotherapy. Patients who received radiotherapy reported more severe/very severe skin irritation compared with women who did not receive radiotherapy (22% vs 7%), but did not differ with regard to other toxicities (Fig. 3B).

Toxicity severity varied by surgical treatment (Fig. 3C). For 5 of the 7 toxicities studied, women who underwent bilateral mastectomy were more likely to report more severe/severe toxicities (nausea/vomiting, diarrhea, constipation, pain, and shortness of breath). More recipients of bilateral mastectomy (37%) reported severe/very severe pain compared with those undergoing unilateral mastectomy (25%) or lumpectomy (18%).

Figure 4 shows the results of a multivariable logistic regression model that demonstrated significant associations between the toxicity category plus patient and treatment factors associated with the toxicity severity. We also included a variable to reflect patient receipt of both chemotherapy and radiotherapy. Three toxicities were found to be more frequently associated with more severe ratings: pain (odds ratio [OR], 4.7; 95% CI, 4.2-5.3), skin irritation (OR, 2.1; 95% CI, 1.8-2.5), and constipation (OR, 1.5; 95% CI, 1.4-1.7). Women who received systemic adjuvant chemotherapy were more likely to report more severe toxicity (OR, 2.0; 95% CI, 1.7-2.4). Patients who received both chemotherapy and radiotherapy had an

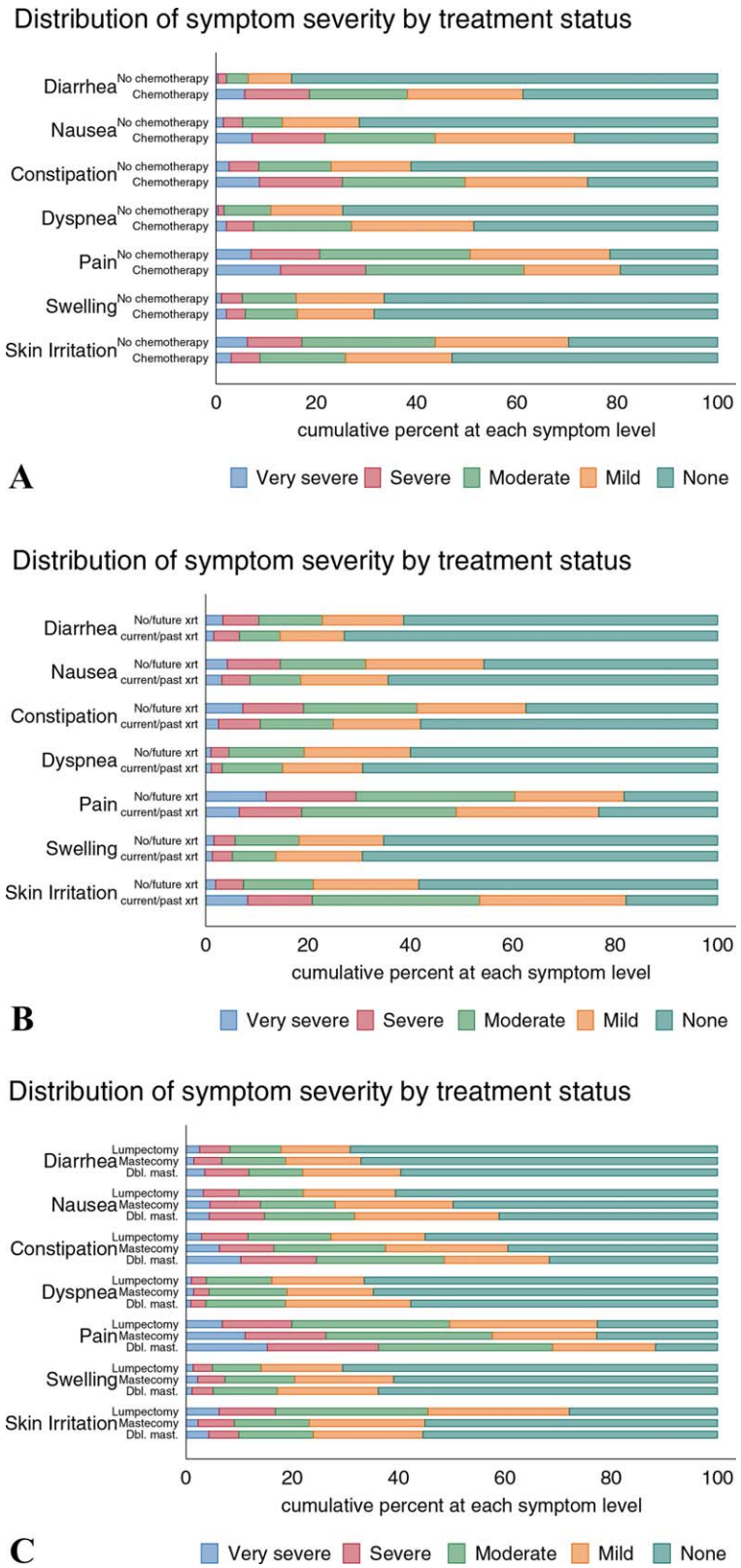

Figure 3. Toxicity severity by breast cancer treatment. (A) Differences in toxicity severity by receipt of chemotherapy (1945 patients). (B) Differences in toxicity severity by receipt of radiotherapy (xrt) (1945 patients). (C) Differences in toxicity severity by receipt of breast cancer surgery (1945 patients). Dbl. mast. indicates bilateral mastectomy. Reported results were based on weighted, imputed data.

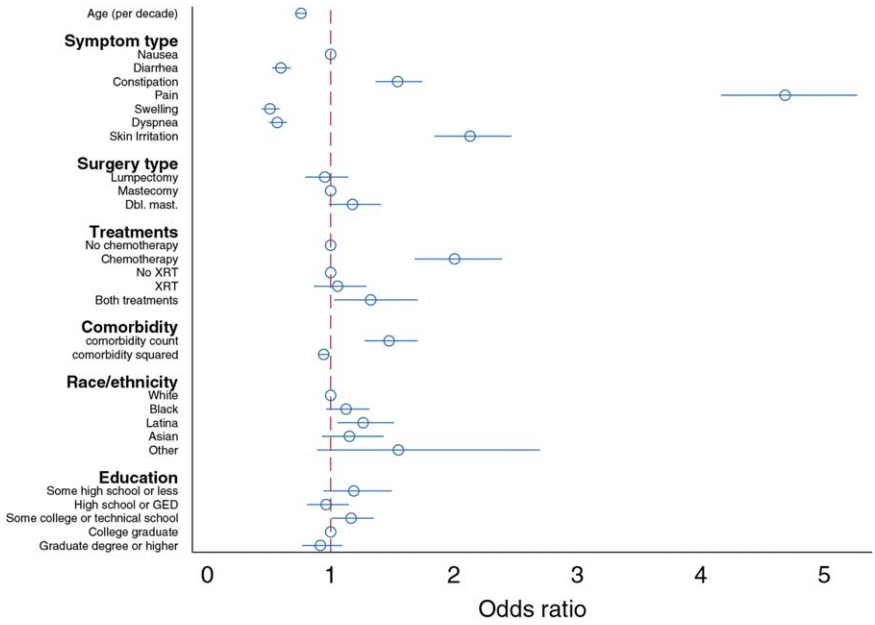

Figure 4. Factors associated with reporting more severe toxicities. Reported results were based on weighted, imputed data. Note that the odds ratio represents the odds of being in a higher versus a lower level of toxicity severity. GED, General Educational Development; Dbl. mast., bilateral mastectomy; XRT, radiotherapy.

additional 30% higher odds of more severe toxicity (OR, 1.3; 95% CI, 1.0-1.7) compared with those receiving only chemotherapy. Patients who underwent bilateral mastectomy were more likely to report higher toxicity (OR, 1.2; 95% CI, 1.0-1.4) than unilateral mastectomy recipients, but the difference did not reach statistical significance.

Older patients were significantly less likely to report higher toxicity (OR, 0.8; 95% CI, 0.7-0.8). Patients with more comorbidities were more likely to report higher toxicity (OR, 1.4; 95% CI, 1.3-1.5 for the first comorbidity). Latina women were more likely than white women to report higher toxicity (OR, 1.3; 95% CI, 1.1-1.5). Compared with college graduates, women with some college education were more likely to report higher toxicity (OR, 1.2; 95% CI, 1.0-1.3).

DISCUSSION

In this population-based sample of women with early-stage, invasive breast cancer, a substantial number of patients reported clinically burdensome toxicities during treatment. A scaled measure that captured the number and severity of toxicities was associated with poorer physical health and increased health care service use, including unscheduled clinic visits, emergency department visits, and inpatient admissions. Compared with those without severe toxicities, women who reported at least 1 severe toxicity differed with regard to age, comorbidity history, race/ethnicity, and breast cancer treatment. These novel data solicited directly from patients highlight opportunities to improve supportive care through targeted toxicity management and data-informed patient-provider communication.

High rates of burdensome toxicities reported by women with early-stage breast cancer support recent assertions that many women with curable disease experience "collateral damage" from breast cancer treatment.[21] Nearly 25% of chemotherapy recipients in the current study endorsed severe/very severe nausea/vomiting during their cancer treatment. This finding likely reflects the inconsistent adoption of chemotherapy-induced nausea and vomiting guidelines across diverse chemotherapy settings.[22] It is unclear whether patients receive standardized education regarding toxicities expected during treatment. Targeting toxicities that occur frequently and are reported as severe or very severe is one important clinical intervention with which to improve outcomes for women with early-stage breast cancer.

Importantly, toxicity severity correlates with clinically significant physical health deficits. Breast cancer survivorship guidelines stress the importance of optimal physical health for survivors of breast cancer.[23] The data from the current study suggest burdensome toxicities occur in patients who do not receive chemotherapy and interfere with physical health, which may threaten long-

term outcomes. Supportive care programs that extend beyond chemotherapy recipients are needed to reduce toxicity severity, maintain health, and enhance the survivorship period. For example, routine toxicity assessments across chemotherapy, surgery, and radiotherapy clinics would identify high-priority areas for interventions.

The findings of the current study are congruent with a prospective study of Italian women recently diagnosed with breast cancer and treated with adjuvant systemic therapy who completed similar patient-reported toxicity measures.[24] High rates of gastrointestinal symptoms were reported. Compared with the current study, lower rates of pain were reported. In a small, longitudinal study of women receiving doxorubicin-based chemotherapy for early-stage breast cancer, the most frequent, severe, and distressing physical symptoms reported included pain.[25] The differences observed may be due to the different survey time points or survey prompts; on average, participants in the iCanCare study completed surveys 7 months after undergoing definitive breast surgery. In the survey, women rated the severity of their toxicities at their worst during treatment. Although prior work has suggested that patient recall of toxicities is valid and reliable,[26] we cannot exclude the possibility of recall bias.

The current study finding of higher toxicity burdens for nonwhite patients may explain prior findings of lingering quality of life deficits for Latinas with breast cancer[27]; culturally sensitive toxicity management interventions may be warranted. Women may perceive that bilateral mastectomy is associated with improved survival and minimal differences in other outcomes.[28] The data from the current study suggest that recipients of bilateral mastectomy experience more toxicity severity compared with other surgical options; pain reports are nearly double those compared with women who undergo lumpectomy. Decision aids for women that present patient-reported outcome rates across surgical modalities may bridge knowledge gaps. If women are aware of the pain differences reported by procedure, their treatment preferences may differ. Given the differential effects of chemotherapy and radiotherapy, it is not surprising that women who received both of these treatments reported higher toxicity severity than patients who received unimodal treatment; targeted interventions may be warranted in women who receive multimodal treatment.

Patients and providers seek to boost the value of cancer care services. Despite excellent survival rates, cancer treatment often leads to costly toxicity management, including emergency department visits and hospitalizations,[29] and unscheduled clinic visits that strain busy clinicians. The value of cancer care may improve if toxicities can be managed proactively, before they worsen. Researchers have examined the efficacy of routine toxicity assessments coupled with notification of aberrant results to providers, with mixed results.[29,30] The results of the current study underscore the need for further research that examines novel strategies with which to reduce preventable treatment toxicities.

Strengths of the current study include an excellent response rate, a diverse patient sample, and patient-centered measures of toxicity and health care service use. Unlike chart review and claims-based approaches, our use of patient-reported measures may overcome documented concerns for clinician reporting of toxicities[31] and measurement challenges in health care claims.[8] However, several aspects of the current study merit comment. First, the current study data were cross-sectional and causal relationships could not be assumed. We did not have access to medical records to ascertain regimens, dosages, and timing of chemotherapy and radiation, nor did we have clinician reports of toxicities and health care service use, which could address concerns for patient recall. The survey timing should be considered when interpreting toxicity reports and health care service use. Although our work was informed by the National Cancer Institute's PRO-CTCAE working group,[14] the study measures are not identical in terms of the timing of administration and rating categories. Although the regions studied are diverse, the results may not be generalizable to other settings. Given the overall project goal of understanding treatment patterns in patients with early-stage breast cancer, the results of the current study are germane to patients with early-stage disease; similar investigations in patients with advanced disease would identify toxicity frequency and intensity within the setting of more frequent multimodal treatments.

Nearly one-half of women with early-stage, invasive breast cancer experience toxicities they perceive as severe or very severe, including women who do not receive adjuvant systemic chemotherapy. These findings have important clinical implications. The toxicity burden faced by patients may be greater than acknowledged by clinicians, and warrants routine assessment during and between clinic visits. Differential toxicity patterns identified in this diverse, population-based sample of women may help clinicians when they review the risks and benefits of breast cancer treatment options. Data-driven patient education and communication tools that compare patient-reported outcomes from breast cancer treatments could inform decision making and prepare women for the treatment

experience. Pain control is challenging for many women across diverse treatment plans. Gastrointestinal toxicities plague chemotherapy recipients despite available practice guidelines. Additional studies must help clinicians to distinguish the duration of treatment-associated toxicities and their impact on therapy completion. Finally, the data from the current study speak to the need for culturally tailored interventions coupled with management protocols to improve quality of life for patients at risk of burdensome toxicities.

FUNDING SUPPORT

Supported by the National Cancer Institute (NCI) (grant P01CA163233 to Steven J. Katz). Cancer incidence data collection was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; the Centers for Disease Control and Prevention (CDC)'s National Program of Cancer Registries under cooperative agreement 5NU58DP003862-04/DP003862; and the NCI's Surveillance, Epidemiology, and End Results Program under contract HHSN 261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute. Cancer incidence data collection in Georgia was supported by contract HHSN2612013000015I, Task Order HHSN26100006 from the NCI, and cooperative agreement 5NU58DP003875-04-00 from the CDC. The ideas and opinions expressed herein are those of the authors. The State of California, Department of Public Health, the NCI, and the CDC and their Contractors and Subcontractors had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article.

CONFLICT OF INTEREST DISCLOSURES

Reshma Jagsi has acted as a paid consultant and member of the medical advisory board for eviti Inc; has received grants and/or has grants pending from the National Institutes of Health (R01 and P01), the American Cancer Society, the National Comprehensive Cancer Network Foundation, and the Translational Breast Cancer Research Consortium; and has received support from AbbVie Pharmaceuticals for a drug only for a phase 1 trial for work performed outside of the current study. Allison W. Kurian has received research funding from Myriad Genetics, Invitae, Ambry Genetics, GenDx, and Genomic Health for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

Christopher R. Friese: Conceptualization, methodology, investigation, writing-original draft, writing-review and editing, and visualization. **Jordan M. Harrison**: Investigation, writing-original draft, and writing-review and editing. **Nancy K. Janz**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Reshma Jagsi**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Monica Morrow**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Yun Li**: Methodology, investigation, software, formal analysis, writing-original draft, and writing-review and editing. **Ann S. Hamilton**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Kevin C. Ward**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Allison W. Kurian**: Conceptualization, methodology, investigation, writing-original draft, and writing-review and editing. **Steven J. Katz**: Conceptualization, methodology, investigation, writing-original draft, writing-review and editing, and visualization. **Timothy P. Hofer**: Methodology, investigation, software, formal analysis, writing-original draft, and writing-review and editing.

REFERENCES

1. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. *J Clin Oncol.* 2004;22:4302-4311.
2. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol.* 2003;21:4524-4531.
3. Vandyk AD, Harrison MB, Macartney G, Ross-White A, Stacey D. Emergency department visits for symptoms experienced by oncology patients: a systematic review. *Support Care Cancer.* 2012;20:1589-1599.
4. Klepin BH, Pitcher BN, Ballman KV, et al. Comorbidity, chemotherapy toxicity, and outcomes among older women receiving adjuvant chemotherapy for breast cancer on a clinical trial: CALGB 49907 and CALGB 361004 (alliance). *J Oncol Pract.* 2014;10:e285-e292.
5. Martinez KA, Friese CR, Kershaw T, Given CW, Fendrick M, Northouse L. Effect of a nurse-led psychoeducational intervention on healthcare service utilization among adults with advanced cancer. *Oncol Nurs Forum.* 2015;42:E310-E318.
6. Paessens BJ, von Schilling C, Berger K, et al. Health resource consumption and costs attributable to chemotherapy-induced toxicity in German routine hospital care in lymphoproliferative disorder and NSCLC patients. *Ann Oncol.* 2011;22:2310-2319.
7. Lamont EB, Herndon JE 2nd, Weeks JC, et al; Cancer and Leukemia Group B. Measuring clinically significant chemotherapy-related toxicities using Medicare claims from Cancer and Leukemia Group B (CALGB) trial participants. *Med Care.* 2008;46:303-308.
8. Barcenas CH, Niu J, Zhang N, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. *J Clin Oncol.* 2014;32:2010-2017.
9. Hassett MJ, Rao SR, Brozovic S, et al. Chemotherapy-related hospitalization among community cancer center patients. *Oncologist.* 2011;16:378-387.
10. Dueck AC, Mendoza TR, Mitchell S, et al; National Cancer Institute PRO-CTCAE Study Group. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol.* 2015;1:1051-1059.
11. Atkinson TM, Li Y, Coffey CW, et al. Reliability of adverse symptom event reporting by clinicians. *Qual Life Res.* 2012;21:1159-1164.
12. Dillman DA, Smyth JD, Christian LM. Internet, Phone, Mail, and Mixed-Mode Surveys: The Tailored Design Method. 4th ed. Hoboken, NJ: John Wiley & Sons Inc; 2014.
13. Hamilton AS, Hofer TP, Hawley ST, et al. Latinas and breast cancer outcomes: population-based sampling, ethnic identity, and acculturation assessment. *Cancer Epidemiol Biomarkers Prev.* 2009;18:2022-2029.
14. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst.* 2014;106(9).
15. Harrison JM, Stella PJ, LaVasseur B, et al. Toxicity-related factors associated with use of services among community oncology patients. *J Oncol Pract.* 2016;12:e818-e827.

16. Schalet BD, Hays RD, Jensen SE, Beaumont JL, Fries JF, Cella D. Validity of PROMIS physical function measured in diverse clinical samples. *J Clin Epidemiol.* 2016;73:112-118.
17. Patient-Reported Outcomes Measurement Information System. PROMIS Physical Function Scoring Manual. https://www.assessmentcenter.net/documents/PROMIS Physical Function Scoring Manual.pdf. Accessed May 31, 2016.
18. Groves RM, Fowler FJ Jr, Couper MP, Lepkowski JM, Singer E, Tourangeau R. Survey Methodology. Hoboken, NJ: John Wiley & Sons Inc; 2011.
19. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. http://www.statcan.gc.ca/pub/12-001-x/index-eng.htm. *Surv Methodol.* 2001;27:85-95.
20. Rubin DB, ed. Multiple Imputation for Nonresponse in Surveys. Hoboken, NJ: John Wiley & Sons Inc; 1987.
21. Helwick C. Dr. Susan Love: time to address "collateral damage" of breast cancer treatment. http://www.ascopost.com/issues/may-25-2016/dr-susan-love-time-to-address-collateral-damage-of-breast-cancer-treatment/. Accessed December 28, 2016.
22. Gilmore JW, Peacock NW, Gu A, et al. Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE Study. *J Oncol Pract.* 2014;10:68-74.
23. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *CA Cancer J Clin.* 2016;66:43-73.
24. Montemurro F, Mittica G, Cagnazzo C, et al. Self-evaluation of adjuvant chemotherapy-related adverse effects by patients with breast cancer. *JAMA Oncol.* 2016;2:445-452.
25. Byar KL, Berger AM, Bakken SL, Cetak MA. Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life. *Oncol Nurs Forum.* 2006;33:E18-E26.
26. Harrison JM, Stella PJ, LaVasseur B, et al. Toxicity-related factors associated with use of services among community oncology patients. *J Clin Oncol.* 2016;12:e818-e827.
27. Janz NK, Friese CR, Li Y, Graff JJ, Hamilton AS, Hawley ST. Emotional well-being years post-treatment for breast cancer: prospective, multi-ethnic, and population-based analysis. *J Cancer Surviv.* 2014;8:131-142.
28. Hamelinck VC, Bastiaannet E, Pieterse AH, et al. Patients' preferences for surgical and adjuvant systemic treatment in early breast cancer: a systematic review. *Cancer Treat Rev.* 2014;40:1005-1018.
29. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol.* 2016;34:557-565.
30. Mooney KH, Beck SL, Friedman RH, Farzanfar R, Wong B. Automated monitoring of symptoms during ambulatory chemotherapy and oncology providers' use of the information: a randomized controlled clinical trial. *Support Care Cancer.* 2014;22:2343-2350.
31. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. *Nat Rev Clin Oncol.* 2016;13:319-325.