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Christopher R. Friese, University of Michigan
Jordan M. Harrison, University of Michigan
Nancy K. Janz, University of Michigan
Reshma Jagsi, University of Michigan
Monica Morrow, Memorial Sloan-Kettering Cancer Center
Yun Li, University of Michigan
Ann S. Hamilton, University of Southern California
Kevin C. Ward, Emory University
Allison W. Kurian, Stanford University
Steven J. Katz, University of Michigan

Only first 10 authors above; see publication for full author list.

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Christopher R. Friese, PhD, Jordan M. Harrison, BSN, Nancy K. Janz, PhD, Reshma Jagsi, MD, DPhil, Monica Morrow, MD, Yun Li, PhD, Ann S. Hamilton, PhD, Kevin C. Ward, PhD, Allison W. Kurian, MD, Steven J. Katz, MD, and Timothy P. Hofer, MD

1Department of Systems, Populations, and Leadership, School of Nursing, and Institute for Healthcare Policy and Innovation, University of Michigan
2Department of Health Behavior and Health Education, School of Public Health, University of Michigan
3Department of Radiation Oncology, University of Michigan School of Medicine
4Memorial Sloan-Kettering Cancer Center
5Department of Biostatistics, University of Michigan School of Public Health
6University of Southern California Keck School of Medicine
7Rollins School of Public Health, Emory University
8Departments of Medicine and Health Research and Policy, Stanford University Medical Center
9Departments of Internal Medicine and Health Management and Policy, Schools of Medicine and Public Health, University of Michigan
10Veterans Affairs Center for Clinical Management Research, Health Services Research and Development Service Center of Innovation and Department of Internal Medicine, University of Michigan

# These authors contributed equally to this work.

Abstract
Background—Patient-reported toxicities help to appraise the breast cancer treatment experience. Yet extant data come from clinical trials and healthcare claims, which may be biased. Using patient surveys, we 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. We assessed the frequency and severity of toxicities, correlated toxicity severity with unscheduled healthcare use (clinic visits, emergency department visits/hospitalization) and physical health, and examined patient, tumor, and treatment factors associated with reporting increased toxicity severity.

Results—The overall survey response was 71%. From the analyzed cohort of 1,945 women, 866 (45%) reported at least one 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: chemotherapy receipt (OR 2.2, 95% CI 2.0-2.5), both chemotherapy and radiation therapy receipt (OR 1.3, 95% CI 1.0-1.7), and Latina ethnicity (OR vs whites 1.3, 95% CI 1.1-1.5). A non-significant increase in at least one 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 by treatment modality may inform decision-making.

Keywords
Breast Cancer; treatment experience; treatment-associated toxicities; patient report

INTRODUCTION
Cancer treatments have a narrow therapeutic index. Clinicians constantly weigh anticipated benefits of anti-cancer treatments against risks of treatment-associated toxicities. Toxicities may lead to treatment discontinuation, costly healthcare service use, and premature death. Toxicties place physical, emotional, and financial burdens on patients and families. Toxicity management also consumes clinician and practice resources.

Despite the burdens placed on patients, families, and healthcare systems, few data sources capture toxicities reliably. Treatment-related toxicity studies generally derive from clinical trials data, health care claims, and single-site patient registries, 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 (PRO-CTCAE) enables patients to report the frequency, severity, and burden of toxicities and addresses well-documented biases observed with clinician-reported toxicity ratings.

Few studies have solicited the toxicity experience directly from diverse, population-based patient samples. Describing the patterns, correlates, and frequency 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 for 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 frequency and severity of toxicities associated with cancer treatment. Next, we explored the correlation between toxicity reports and physical health and healthcare service use. Finally, we examined patient, tumor, and treatment factors associated with toxicities rated as severe or very severe.

PATIENTS 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 3,880 women of ages 20 through 79 years who were diagnosed with early-stage breast cancer determined by a definitive breast surgery date between July 1, 2013 and December 31, 2014. Women were sent surveys about 2 months after surgery and completed the survey on average about 7 months after diagnosis. To enable meaningful analyses across racial and ethnic groups, African Americans and Latinas were oversampled in Los Angeles County. The following women were excluded from the iCanCare study sampling protocol: stage III or IV cancer (as the overall project was focused on early-stage patients), Paget’s disease, or tumors > 5cm in size. In Los Angeles County, non-Hispanic whites and African Americans aged <50 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 Dillman’s methods,12 we solicited participation with a $20 cash incentive. Study coordinators in respective geographic areas continued to follow up with non-responders, including up to 9 attempted phone 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 3,880 originally-identified women, 249 were ineligible. From these 3,631 women, 1,053 women were not reached or did not return questionnaires, resulting in an overall response rate of 71% (n=2,578). After excluding 694 women with DCIS or bilateral disease our analytic sample included 1,884 observations in the observed data and 1,945 observations after multiple imputation. SEER registries linked surveys to standardized tumor registry data.

MEASURES

Except where indicated, measures were collected from patient questionnaires. The primary outcome was treatment-associated toxicities. Informed by the PRO-CTCAE working group14 and our pilot work,15 participants rated the severity of seven toxicities – at their
worst during cancer treatment – using a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = 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

As few studies have investigated patient-reported, treatment-associated toxicities, we measured toxicities in three 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 one toxicity rated as severe or three toxicities rated as mild, and a score of 28 would reflect that a patient reported all seven toxicities as very severe.

To examine toxicity burden, we examined physical health and healthcare service use. To measure physical health, we used the 4-item physical function subscale of the Patient Reported Outcome 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 below 40 reflected poor physical health.17 To measure healthcare service use, we asked patients whether they 1) did not seek help, 2) called/emailed 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, Asian), education (high school or less, some college, college graduate or more), and prior comorbidity diagnosis – chronic lung disease, heart disease, diabetes, or stroke – (no diagnosis, one condition, two or more conditions). We included four separate variables to capture treatment factors: primary breast surgery (lumpectomy, unilateral mastectomy, bilateral mastectomy), radiation therapy (yes/no), systemic chemotherapy (yes/no), and receipt of both radiation and chemotherapy (yes/no). SEER registries provided tumor information: 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.

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 one toxicity as severe/very severe, as well as in the subset of women who reported unscheduled care for toxicity management. Next, for each of the seven toxicities and corresponding severity rating, we calculated the proportion of women who also reported healthcare service use (phone call, scheduled visit, unscheduled visit, emergency department visit/hospitalization) for that toxicity. Using the multiplied scale of number of toxicities reported by their severity, we next plotted the corresponding PROMIS physical function scores. Using multivariable regression, we examined two 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 non-response to examine the relationship of patient, tumor, and treatment factors to 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 non-response.\textsuperscript{18} We identified small amounts of missing data (range of 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.\textsuperscript{19} We generated five independently-imputed data sets and computed inferential statistics that combined analyses across datasets.\textsuperscript{20} Imputation results were indistinguishable from the complete case analysis. Table 1 is based on complete case analysis (N identified in table for each variable) and all subsequent figures and regression results are based on multiply-imputed data (N=1,945).

\section*{RESULTS}

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

\subsection*{Frequency and Severity of Patient-Reported Toxicities}

Women with early-stage invasive breast cancer reported a number of toxicities during treatment, many of which were rated as severe or very severe. 132 patients (7\%) reported that none of the seven toxicities occurred during treatment. 1,810 women (93\%) reported at least one toxicity and 866 of the women in the analytic sample (45\%) rated at least one toxicity as severe/very severe. Among the seven toxicities, pain was most frequently reported as severe/very severe (23\%), followed by constipation (14\%), and breast skin irritation (13\%).

\subsection*{Toxicities and Healthcare Service Use}

Figure 1 shows patient reports of healthcare service use by each toxicity studied and the corresponding severity rating. Across all seven toxicities, 2-4\% of patients did not endorse a toxicity rating, but discussed the problem during a routine office visit. Most patients sought help during an office visit (range between 22\% and 77\% across the seven toxicities); telephone calls/emails and emergency department visits/hospitalizations were less frequently reported. For women who experienced at least one toxicity, 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/emails; 29\% of patients with very severe nausea/vomiting and 27\% of patients with very severe diarrhea called or emailed 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 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 (SD) physical functioning score on the PROMIS measure was 14.5 (3), reflecting substantial deficits from the optimal score of 50. Figure 2 shows the relationship 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. 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 correlated linearly, negatively, and significantly with toxicity ratings ($\beta = -0.2$, 95% CI $-0.3$ - $-0.2$). Patients without toxicity had the highest scores, whereas patients who reported all seven toxicities as severe reported scores at the lowest possible score of 10 on the scale.

Factors Associated with Reporting at Severe or Very Severe Toxicity

Figures 3A-C show the unadjusted differences in toxicity reporting by breast cancer treatment. Toxicity severity varied by chemotherapy receipt (Figure 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 rates of 9% for women who did not receive chemotherapy. Radiation therapy recipients reported more severe/very severe skin irritation than women who did not receive radiation (22% versus 7%), but did not differ on other toxicities (Figure 3B).

Toxicity severity varied by surgical treatment (Figure 3C). For five of seven toxicities studied, women who received bilateral mastectomy were more likely to report more severe/severe toxicities (nausea/vomiting, diarrhea, constipation, pain, and shortness of breath). More bilateral mastectomy recipients (37%) reported severe/very severe pain than those receiving unilateral mastectomy (25%) or lumpectomy (18%).

Figure 4 shows the results of a multivariable logistic regression model, which shows significant associations between the category of toxicity, plus patient and treatment factors associated with the severity toxicity. We also included a variable to reflect patient receipt of both chemotherapy and radiation therapy. Three toxicities were more frequently associated with more severe ratings; pain (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 radiation therapy had an additional 30% higher odds of more severe toxicity (OR 1.3, 95% CI 1.0-1.7) over those receiving only chemotherapy. Patients who had 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). Latinas 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 healthcare service use, including unscheduled clinic
visits, emergency department visits, and inpatient admissions. Compared to those without
severe toxicities, women who reported at least one severe toxicity differed in 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 suffer “collateral damage”
from breast cancer treatment. Nearly one quarter of chemotherapy recipients in our study
endorsed severe/very severe nausea/vomiting during their cancer treatment. This finding
likely reflects inconsistent adoption of chemotherapy-induced nausea and vomiting
guidelines across diverse chemotherapy settings. It is unclear whether patients receive
standardized education about toxicities expected during treatment. Targeting toxicities that
occur frequently and are reported as severe or very severe is one important clinical
intervention 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
breast cancer survivors. Our data 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 radiation therapy
clinics would identify high-priority areas for interventions.

Our findings 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. 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. 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 definitive
breast surgery. In the survey, women rated the severity of their toxicities at their worst during
treatment. While prior work suggests patient recall of toxicities is valid and reliable, we
cannot exclude the possibility of recall bias.
Our finding of higher toxicity burdens for non-white patients may explain prior findings of lingering quality of life deficits for Latinas with breast cancer; centrally sensitive toxicity management interventions may be warranted. Women may perceive that bilateral mastectomy is associated with improved survival and minimal difference in other outcomes. Our data suggest that bilateral mastectomy recipients experience more toxicity severity relative to other surgical options; pain reports are nearly double those compared with women who receive lumpectomy. Decision aids for women that present patient-reported outcome rates across surgical modalities may bridge knowledge gaps. If women were aware of the pain differences reported by procedure, their treatment preferences may differ. Given the differential effects of chemotherapy and radiation therapy, it is not surprising that women who received both of these treatments reported higher toxicity severity than uni-modal treatment; targeted interventions may be warranted in women who receive multi-modal 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, and unscheduled clinic visits that strain busy clinicians. Cancer care value 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. Our results underscore the need for further research that examine novel strategies to reduce preventable treatment toxicities.

Strengths of our study include an excellent response rate, a diverse patient sample, and patient-centered measures of toxicity and healthcare service use. Unlike chart review and claims-based approaches, our use of patient-reported measures may overcome documented concerns for clinician reporting of toxicities and measurement challenges in healthcare claims. However, several aspects of our study merit comment. First, our data are cross-sectional and causal relationships cannot be assumed. We did not have access to medical records to ascertain regimens, dosages, and timing of chemotherapy and radiation, nor do 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 healthcare service use. While our work was informed by the NCI’s PRO-CTCAE working group, the study measures are not identical in terms of timing of administration and rating categories. While the regions studied are diverse, results may not be generalizable to other settings. Given the overall project goal of understanding treatment patterns in early-stage breast cancer, our results are germane to patients with early-stage disease; similar investigations in patients with advanced disease, would identify toxicity frequency and intensity in the setting of more frequent multi-modal treatments.

Nearly 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 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 distinguish the duration of treatment-associated toxicities and their impact on therapy completion. Finally, our data speak to the need for culturally-tailored interventions coupled with management protocols to improve quality of life for patients at risk for burdensome toxicities.

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Cancer incidence data collection in Georgia was supported by contract HHSN261201300151, 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 manuscript.
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REFERENCES


Figure 1. Distribution of Patient-Reported Healthcare Service use by Each Toxicity and Rated Severity
ER=Emergency Room. Results reported are based on weighted, imputed data.
Figure 2. Physical Health Scores by Toxicity Severity

PROMIS=Patient-Reported Outcomes Measurement Information System. Higher physical health scores reflect better physical functioning. Higher toxicity severity scores reflect increased toxicity frequency and/or worse severity. Toxicity scores were inversely proportional to physical health ($\beta = -0.2$, 95% CI $-0.3$ to $-0.2$). Results reported are based on weighted, imputed data.
Figures 3A-C. Toxicity Severity by Breast Cancer Treatment
3A: Differences in toxicity severity by chemotherapy receipt. N=1,945
3B: Differences in toxicity severity by radiation therapy receipt. N=1,945
3C: Differences in toxicity severity by breast cancer surgery. N=1,945
Results reported are based on weighted, imputed data.
Figure 4. Factors Associated with Reporting More Severe Toxicities
GED=Graduate equivalent diploma. Dbl. mast=Bilateral mastectomy. Results reported are based on weighted, imputed data. Note: the odds ratio represents the odds of being in a higher vs. a lower level of toxicity severity.
Table 1
Patient Sample Characteristics by Toxicity Report and Report of Healthcare Service Use

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*Cancer. Author manuscript; available in PMC 2018 June 01.*
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Data are n (%), mean (SD), unless otherwise stated. Percentages are based on unweighted data.