Patient-reported treatment toxicity and adverse events in Black and White women receiving chemotherapy for early breast cancer

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Abstract

Purpose It is not known whether chemotherapy-related symptom experiences differ between Black and White women with early breast cancer (Stage I–III) receiving current chemotherapy regimens and, in turn, influences dose delay, dose reduction, early treatment discontinuation, or hospitalization.

Methods Patients self-reported their race and provided symptom reports for 17 major side effects throughout chemotherapy. Toxicity and adverse events were analyzed separately for anthracycline and non-anthracycline regimens. Fisher's exact tests and two-sample t-tests compared baseline patient characteristics. Modified Poisson regression estimated relative risks of moderate, severe, or very severe (MSVS) symptom severity, and chemotherapy-related adverse events.

Results In 294 patients accrued between 2014 and 2020, mean age was 58 (SD13) and 23% were Black. For anthracycline-based regimens, the only significant difference in MSVS symptoms was in lymphedema (41% Black vs 20% White, $p = .04$) after controlling for axillary surgery. For non-anthracycline regimens, the only significant difference was MSVS peripheral neuropathy (41% Blacks vs. 23% White) after controlling for taxane type ($p = .05$) and diabetes ($p = .05$). For all other symptoms, severity scores were similar. Dose reduction differed significantly for non-anthracycline regimens (49% Black vs. 25% White, $p = .01$), but not for anthracycline regimens or in dose delay, early treatment discontinuation, or hospitalization for either regimen.

Conclusion Except for lymphedema and peripheral neuropathy, Black and White patients reported similar symptom severity during adjuvant chemotherapy. Dose reductions in Black patients were more common for non-anthracycline regimens. In this sample, there were minimal differences in patient-reported symptoms and other adverse outcomes in Black versus White patients.

Keywords Chemotherapy · Toxicity · Patient-reported · Adverse · Event · Black · White

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Introduction

Breast cancer incidence rates have converged between Black and White women in the USA over the past several decades [1]; however, overall survival rates have diverged dramatically. After being roughly equal in the 1970s [2], mortality rates among women with breast cancer are now 42% higher for Black women compared to White women [2]. This disparity is reflected in breast cancer specific survival rates for hormone receptor positive/HER2 negative (HR + /HER2-) tumors, where mortality rates are 31% higher in Black women with Stage II tumors (HR 1.31, 95% CI 1.03–1.65) and 39% higher with Stage III tumors (HR 1.39, 95% CI 1.10–1.75) compared to White women [3]. In patients with Stage III triple negative breast cancer, breast cancer mortality is 37% higher in Black patients compared to White patients (HR 1.37, 95% CI 1.05–1.55) [3]. Many factors beyond tumor biology disadvantage Black women with breast cancer and contribute to mortality disparity, including structural and socioeconomic factors (unequal access to health insurance and timely healthcare) and comorbidities [4–10].

As an important complement to clinician monitoring of treatment toxicities using CTCAE grades (National Cancer Institute's/NCI Common Terminology Criteria for Adverse Events) [11, 12], patient reports of treatment-related side effects have gained support in clinical trials [13–15] and medical practice [16, 17]. The NCI sponsored Patient-Reported Outcomes version of CTCAE (PRO-CTCAE) [18–20] and the Patient-Reported Symptom Monitoring (PRSM) [21] are examples of patient-reported tools to track a variety of symptoms at multiple time points during cancer treatment [22–24].

In our earlier research using PRSM and PRO-CTCAE, we have reported that chemotherapy regimens commonly used in current clinical practice have widely varying toxicity profiles, with patients on anthracycline-based sequential treatments rating as many as 6 to 7 symptoms as "moderate", "severe", or "very severe" at any given time during chemotherapy [25]. These ratings approximate CTCAE grades 2, 3, and 4 [26]. In the current study, we investigate whether there are differences in symptom experience—symptom "severity" and symptom "interference with daily activities"—between Black and White women receiving (neo)adjuvant chemotherapy for early breast cancer. It would be of clinical concern if greater symptom severity reported by either Black or White patients precipitated a higher rate of change in treatment plans which, in turn, could differentially affect prognosis and survival. We also explore the role of self-reported race in dose delay, dose reduction, early treatment discontinuation, and hospitalization. Lastly, we investigate the association of pre-chemotherapy function and quality of life and how they might affect patient-reported symptoms and adverse events during chemotherapy. Our aim is to gain a better understanding of factors that may contribute to suboptimal chemotherapy completion among Black and White women with early breast cancer.

Methods

Study participants

This study is an ancillary data analysis of women with Stage I–III breast cancer enrolled in one of three studies investigating the impact of moderate exercise during chemotherapy. It is an exploratory analysis that was not specifically powered to investigate differences between Black and White patients. Chemotherapy regimens were at the discretion of the treating oncologists and their patients, depending on breast cancer stage [27] and phenotype. The daily clinic schedule was reviewed to identify all women who were scheduled for adjuvant or neoadjuvant chemotherapy. The enrollment period for the three studies was February 2014 through February 2020. The protocols were identical with the exception of age criteria at diagnosis: women age 21–64 years (NCT02167932), women age 65 or older (NCT02328313), and women age 21 or older (NCT03761706). NCT02328313 was a multi-site study that included the University of North Carolina at Chapel Hill (UNC) N.C. Cancer Hospital, UNC Rex Healthcare, Duke University Medical Center, MD Anderson Cancer Center, and Ohio State University Comprehensive Cancer Center. The other two studies were conducted at the N.C. Cancer Hospital only. The studies were approved by the UNC Lineberger Comprehensive Cancer Center (LCCC) Protocol Review Committee and the Institutional Review Boards (IRB) of participating sites. Further details regarding study protocols have been published previously [25, 28, 29].

Measures

Assessments and patient-reported outcomes (PRO) measures

Prior to start of chemotherapy, study participants completed a brief battery of assessments and questionnaires. Research staff conducted three assessments: Short Physical Performance Battery (SPPB) [30], Timed Up and Go (TUG) [31, 32], and Blessed Orientation Memory Concentration test (BOMC) [33, 34]. Study participants completed questionnaires pertaining to Instrumental Activities of Daily Living (IADL) [35], Mental Health (Mental Health Index/MHI) [36] (subscales Depression and Anxiety), Physical Function

[37], Social Activities [38], Social Support (subscales Emotional and Tangible) [39], Quality of Life (Functional Assessment of Cancer-General/FACT-G) [40], and Fatigue (Functional Assessment of Chronic Illness Therapy/FACIT-Fatigue) [41]. Participants also self-reported their age, race, education, marital status, and alcohol consumption.

Chemotherapy regimens

The chemotherapy regimens of study participants were determined by treating oncologists in consultation with their patients depending on tumor stage [27] and phenotype. The most common regimens were (a) doxorubicin/cyclophosphamide before/after paclitaxel (AC-T), (b) docetaxel/cyclophosphamide plus/minus anti-HER-2 therapy (TC), (c) docetaxel/carboplatin plus anti-HER-2 therapy (TCH), and (d) doxorubicin/cyclophosphamide before/after paclitaxel/carboplatin (AC-TC), and comprised 81 percent of all regimens. Growth factors (pegfilgrastim) were used for docetaxel/cyclophosphamide and docetaxel/carboplatin regimens, and for doxorubicin/cyclophosphamide when administrated every 2 weeks (dose dense). In our previous research [25], we have reported significant differences in the toxicity profiles of these four regimens, and especially with regard to anthracycline-based versus non-anthracycline-based regimens.

Patient-reported toxicity

Patient-reported symptom scores were recorded for 17 commonly occurring side effects of (neo)adjuvant chemotherapy: fatigue, insomnia, anxiety, depression, dyspnea, peripheral neuropathy, joint pain/arthralgia, muscle pain/myalgia, abdominal pain, general pain, lymphedema/edema of the extremities, constipation, diarrhea, nausea, vomiting, mucositis, and hot flashes. At infusion visits throughout chemotherapy treatment, patients were asked to rate these symptoms (using paper or electronic tablet). Symptom reports were collected at every infusion visit for patients receiving chemotherapy every 2 or 3 weeks, and every other week for patients receiving weekly infusions. For two studies (NCT02167932 andNCT02328313), the reporting format was the patient-validated Patient-Reported Symptom Monitoring (PRSM) (Online Appendix 1) [24]. For the most recent study (NCT03761706), the NCI's PRO-CTCAE was used, when it became publicly available in April 2016 (Online Appendix 2) [19, 42]. The two instruments are similar in format and include 7-day recall questions regarding symptom "severity" (intensity/frequency) and symptom "interference with daily activities" using a 5-point Likert-type scale. Previous studies have similarly combined results collected from both instruments [25, 28, 29].

Electronic medical record (EMR)

Research staff extracted the following data from the EMR: height and weight for Body Mass Index (BMI), comorbidities at diagnosis, breast cancer diagnosis and treatment, and adverse events during chemotherapy (dose delay, dose reduction, early treatment discontinuation, hospitalization).

Demographic and overall health data

Patients completed a questionnaire in which they self-reported their age, race, education, employment status, marital status, and history of falls in the past 6 months.

Statistical considerations

Fisher's exact tests and two-sample t-tests were used to compare the distributions of baseline patient characteristics between Black and White participants. With the available sample sizes per group, Fisher's exact tests would have adequate power (> 80%) to detect symptom severity differences of about 20% (nQuery advisor 4.0). Modified Poisson regression [43, 44] was used to estimate the unadjusted and adjusted relative risks of moderate, severe, or very severe (MSVS) symptom severity and chemotherapy-related adverse events and the corresponding 95% confidence intervals. All analyses were performed using SAS statistical software v9.4 (Cary, NC). Significance level was set at 0.05, and *p-value*s are reported.

Results

Patient characteristics

In a sample of 294 women with newly diagnosed Stage I–III breast cancer scheduled to receive (neo)adjuvant chemotherapy, 226 (77%) are White and 68 (23%) are Black (Table 1). Higher proportions of Black women were less educated (27% vs. 12% high school or less) ($p = 0.006$), not married (63% vs. 39%) ($p = 0.0007$), had obesity (Body Mass Index/BMI or 30 or higher) (68% vs. 29%) ($p < 0.0001$), and had a higher average number of comorbidities [2.2 (SD 1.6) vs. 1.5 (SD 1.5)] ($p = 0.003$). A higher proportion of Black as compared to White patients had hormone receptor negative (HR–) and HER2 negative (triple negative) tumors (38% vs. 26%) and a lower proportion had HR + /HER2– tumors (31% vs. 50%) ($p = 0.03$).

The four primary chemotherapy regimens were as follows: 30% doxorubicin/cyclophosphamide followed/preceded by paclitaxel (AC-T), 19% docetaxel/carboplatin plus anti-HER-2 therapy (TCH), 16% docetaxel/cyclophosphamide plus/minus anti-HER-2 therapy (TC), and

Table 1 Study Participants Baseline Characteristics

Variable	Overall $N=294$	White $N=226$ (77%)	Black $N=68$ (23%)	*p-value*
Demographics and overall health indicators				
Age	57.6 (SD 13.1)	58.0 (SD 13.2)	56.4 (SD 12.7)	0.40
Education				**.006**
High school or less	45 (16%)	27 (12%)	18 (27%)	
More than high school	244 (84%)	196 (88%)	48 (73%)	
Employed more than 32 h/week				.22
No	200 (70%)	158 (72%)	42 (64%)	
Yes	86 (30%)	62 (28%)	24 (36%)	
Married				**.0007**
No	129 (45%)	87 (39%)	42 (63%)	
Yes	159 (55%)	135 (61%)	24 (37%)	
Body Mass Index/BMI	29 (SD 6.1)	28 (SD 5.9)	33 (SD 5.3)	**< .001**
Underweight (BMI < 18.5)	3 (1%)	3 (2%)	0 (0%)	**< .0001**
Normal (BMI 18.5–24)	56 (26%)	54 (32%)	2 (4%)	
Overweight (BMI 25–29)	75 (35%)	62 (37%)	13 (28%)	
Obese (BMI 30 or greater)	81 (38%)	49 (29%)	32 (68%)	
Comorbidities	1.7 (SD 1.6)	1.5 (SD 1.5)	2.2 (SD 1.6)	**0.003**
History of falls in the past 6 months				.18
None	245 (88%)	187 (87%)	58 (94%)	
1 or more	32(12%)	28 (13%)	4 (6%)	
Breast cancer diagnosis and treatment				
Breast cancer stage				.61
I	71 (24%)	55 (24%)	16 (24%)	
II	151 (51%)	119 (53%)	32 (48%)	
III	70 (24%)	51 (23%)	19 (28%)	
HER2				.27
Negative	218 (75%)	171 (76%)	47 (69%)	
Positive	74 (25%)	53 (24%)	21 (31%)	
Hormone receptor (HR)				.24
Negative	62 (38%)	45 (35%)	17 (47%)	
Positive	101 (62%)	82 (65%)	19 (53%)	
Breast cancer phenotype				**.03**
HR-/HER2-	84 (29%)	58 (26%)	26 (38%)	
HR-/HER2 +	34 (12%)	24 (11%)	10 (15%)	
HR + /HER2-	134 (46%)	113 (50%)	21 (31%)	
HR + /HER2 +	40 (14%)	29 (13%)	11 (16%)	
Lymph node biopsy				.45
Axillary	84 (30%)	61 (28%)	23 (34%)	
Sentinel	200 (70%)	155 (72%)	45 (66%)	
Chemotherapy timing				.12
Neoadjuvant	108 (38%)	80 (36%)	28 (41%)	
Adjuvant	177 (61%)	139 (63%)	38 (56%)	
Both	3 (1%)	1 (1%)	2 (3%)	

Table 1 (continued)

Variable	Overall $N=294$	White $N=226$ (77%)	Black $N=68$ (23%)	*p-value*
Chemotherapy regimen – drug combinations				**.04**
AC-T (doxorubicin/cyclophosphamide before/after paclitaxel)	87 (30%)	67 (30%)	20 (30%)	
AC-TC (doxorubicin/cyclophosphamide before/after paclitaxel/carboplatin)	22 (8%)	19 (8%)	3 (4%)	
TC (docetaxel/cyclophosphamide plus/minus anti-HER-2 therapy)	80 (27%)	69 (31%)	11 (16%)	
TCH (docetaxel/carboplatin plus anti-HER-2 therapy)	46 (16%)	32 (14%)	14 (21%)	
Other	56 (19%)	37 (17%)	19 (28%)	
Chemotherapy regimen				.67
Not anthracycline-based	164 (56%)	125 (55%)	39 (59%)	
Anthracycline-based	128 (44%)	101 (45%)	27 (41%)	
Taxane				.57
Paclitaxel/Nab-Paclitaxel	142 (52%)	107 (50%)	35 (56%)	
Docetaxel	133 (48%)	105 (50%)	28 (44%)	
Assessments and Health Behavior at baseline				
Timed Up and Go (TUG) – ≥ 14 s				.11
No	238 (88%)	189 (90%)	49 (82%)	
Yes	32 (12%)	21 (10%)	11 (18%)	
Short Physical Performance Battery/SPPB—range 0 = worst to 12 = best performance	10.5 (SD 1.8)	10.8 (SD 1.5)	9.4 (SD 2.4)	**< .0001**
Blessed Orientation Memory Concentration Test/BOMC—lower cognition score ≥ 5				**.003**
< 5	221 (79%)	179 (83%)	42 (65%)	
≥ 5	60 (21%)	37 (17%)	23 (35%)	
Patient-Reported Outcomes (PRO) Scales				
Mental Health Index/MHI—range 0–43				.10
Depressed score ≥ 12				
Not depressed	198 (74%)	158 (77%)	40 (66%)	
Depressed	69 (26%)	48 (23%)	21 (34%)	
Mental Health Index/MHI—range 0–20				.08
Anxious score ≥ 6				
Not anxious	151 (54%)	111 (51%)	40 (65%)	
Anxious	127 (46%)	105 (49%)	22 (35%)	
Instrumental Activities of Daily Living/IADL—range 0–14				**.009**
< 14 = limitations	43 (15%)	26 (12%)	17 (27%)	
14 = no limitations	236 (85%)	190 (88%)	46 (73%)	
Physical Function—range 0–20				.73
< 20 = lower function	153 (67%)	120 (67%)	30 (64%)	
20 = high function	77 (33%)	60 (33%)	17 (36%)	
Social Activity Limitation score–range 0–100				.45
< 50 = less social activity limitation	177 (76%)	141 (77%)	36 (72%)	
≥ 50 = more social activity limitation	55 (24%)	41 (23%)	14 (28%)	
Social Support-Emotional—range 0–100				.42
< 50 = lower support	9 (4%)	6 (3%)	3 (6%)	
≥ 50 = higher support	218 (96%)	171 (97%)	47 (94%)	
Social Support-Tangible (range 0–100)				1.00
< 50 = lower support	13 (6%)	10 (6%)	3 (6%)	
≥ 50 = higher support	216 (94%)	168 (94%)	48 (94%)	

Table 1 (continued)

Variable	Overall $N=294$	White $N=226$ (77%)	Black $N=68$ (23%)	*p-value*
Functional Assessment of Cancer Therapy/FACT-General (higher score = higher wellbeing)				.07 .38
Physical well-being (range 0–28)	24.9 (SD 3.8)	25.1 (SD 3.7)	24.0 (SD 4.3)	**.02** .17
Social/family wellbeing (range 0–28)	24.6 (SD 4.7)	24.7 (SD 4.7)	24.1 (SD 4.7)	
Emotional wellbeing (range 0–24)	19.2 (SD 3.8)	18.9 (SD 4.0)	20.1 (SD 3.1)	
Functional wellbeing (range 0–28)	21.0 (SD 5.6)	21.2 (SD 5.3)	20.2 (SD 6.4)	
Functional Assessment of Chronic Illness Therapy/FACIT-Fatigue (reverse scored so that higher score = less fatigue) (range 0–52)	43.1 (SD 8.8)	43.1 (SD 8.8)	43.1 (SD 8.6)	1.00

Figures in bold are statistically significant

8% doxorubicin/ cyclophosphamide followed/preceded by paclitaxel and carboplatin (AC-TC) [45]. Nineteen percent of patients received a regimen other than these four. As expected, due to the interaction of race and cancer phenotype, chemotherapy regimen varied by race ($p=0.04$).

Measures of function and quality of life

Table 1 presents pre-chemotherapy values for assessments conducted by research staff and outcome measures completed by patients. In univariate analysis, a higher proportion of Black patients had poorer physical function (Short Physical Performance Battery scores [9.4 (SD 2.4 vs. 10.8 (SD 1.5] ($p<0.0001$)), and a higher proportion of Black patients had poorer cognitive function (Blessed Orientation Memory Concentration scores of 5 or higher on this cognitive status screening test) (35% vs. 17%) ($p=0.003$)). A higher proportion of Black patients reported limitations in Instrumental Activities of Daily Living (IADL score < 14) (27% vs. 12%) ($p=0.009$). The mean score for Functional Assessment of Cancer Therapy-General (FACT-G) Emotional Well-Being was higher (better) in Black patients (20.1, SD 3.1) as compared to White patients (18.9, SD 4.0) ($p=0.02$) on a 0–24 scale.

Symptom severity

Figures 1 and 2 present the proportion of patients who reported moderate, severe, or very severe (MSVS) symptom *severity* at any time during chemotherapy and, separately, MSVS symptom *interference with daily activities*. Figure 1 presents MSVS severity and interference percentages for patients who received anthracycline-based chemotherapy regimens, and Fig. 2 for patients receiving non-anthracycline regimens.

Among patients who received *anthracycline-based* regimens, a higher proportion of Black as compared to White patients reported more severe lymphedema (41% vs. 20%, $p=0.04$), and a lower proportion reported severe diarrhea (15% vs. 39%), $p=0.02$) (Fig. 1). To further explore the lymphedema differences, multivariable analyses were done separately to compare patients having axillary dissection vs. sentinel node biopsy, and to explore the impact of BMI [46]. After controlling for type of axillary surgery, Black patients were found to have 91% increased risk for lymphedema (RR 1.91, 95% CI 1.03, 3.55) ($p=0.04$) compared to White patients. In multivariable analysis adding BMI as a potential moderator of lymphedema, race was no longer significant at the $p=0.05$ level (Black RR 1.76, 95% CI 0.97, 3.21) ($p=0.06$).

Among women who received regimens that were *not anthracycline-based*, a higher proportion of Black patients as compared to White reported peripheral neuropathy (41% vs. 23%, $p=0.04$) (Fig. 2). To further explore this finding, multivariable analyses were conducted separately for taxane regimen (paclitaxel vs. docetaxel) and diabetes at baseline. After controlling for type of taxane, Black patients were found to have a 73% increased risk for peripheral neuropathy (RR 1.73, 95% CI 0.99, 3.00) ($p=0.053$) as compared to White patients. And, after controlling for a diabetes, Black patients were 2.04 times as likely to report MSVS peripheral neuropathy (RR 2.04, 95% CI 1.24,3.35) ($p=0.005$) as compared to White patients.

Symptom interference with daily activities

How symptoms interfered with daily activities or "things you usually do" is presented in Figs. 1 and 2 (Table 2). There were no significant differences between Black and White patients in the proportion reporting symptom interference associated with *anthracycline-based* chemotherapy regimens. However, among women receiving *non-anthracycline-based* regimens, a higher proportion of Black patients reported interference from peripheral neuropathy (28% vs.

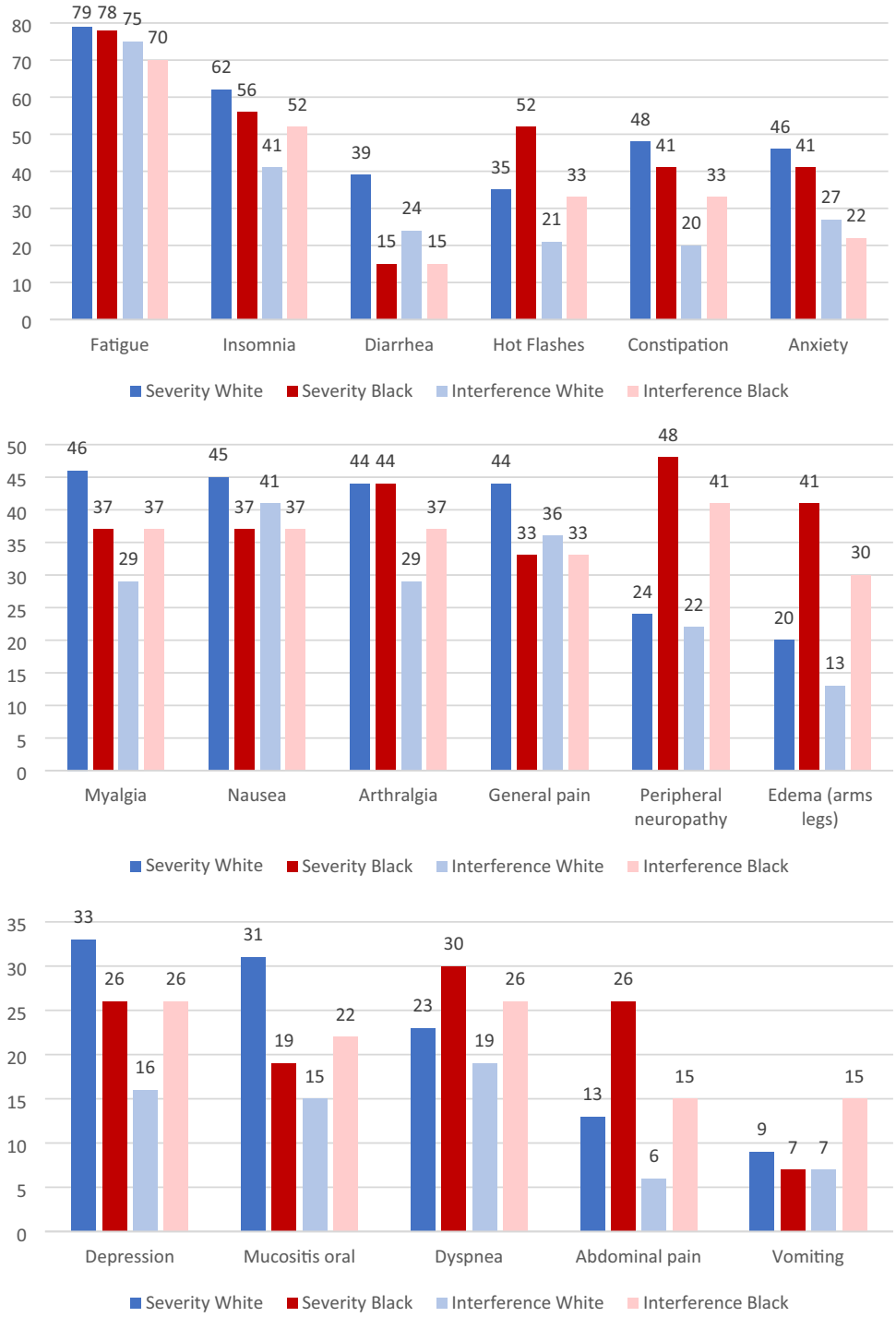

Fig. 1 Patient-reported "moderate, severe, very severe" symptom *severity* and symptom *interference with daily activities* (%)—anthracycline-based chemotherapy

11%) ($p=0.02$), lymphedema (28% vs. 13%) ($p=0.05$), and diarrhea (62% vs. 35%) ($p=0.005$).

Adverse events during chemotherapy

In Table 3, clinician notes on causes for adverse events during chemotherapy are presented. Twenty-three percent of patients experienced at least one dose delay between chemotherapy infusions (25% Black vs. 22% White). Thirty-two percent had at least one dose reduction (40% Black vs. 30% White). Eighteen percent has early treatment discontinuation (26% Black vs. 14% White), and 18% had at least one hospitalization (22% Black vs. 16% White). Reasons for these adverse events during chemotherapy include neutropenia, neutropenic fever, anemia, thrombocytopenia, nausea/vomiting, fatigue, infection/sepsis, and allergic reaction.

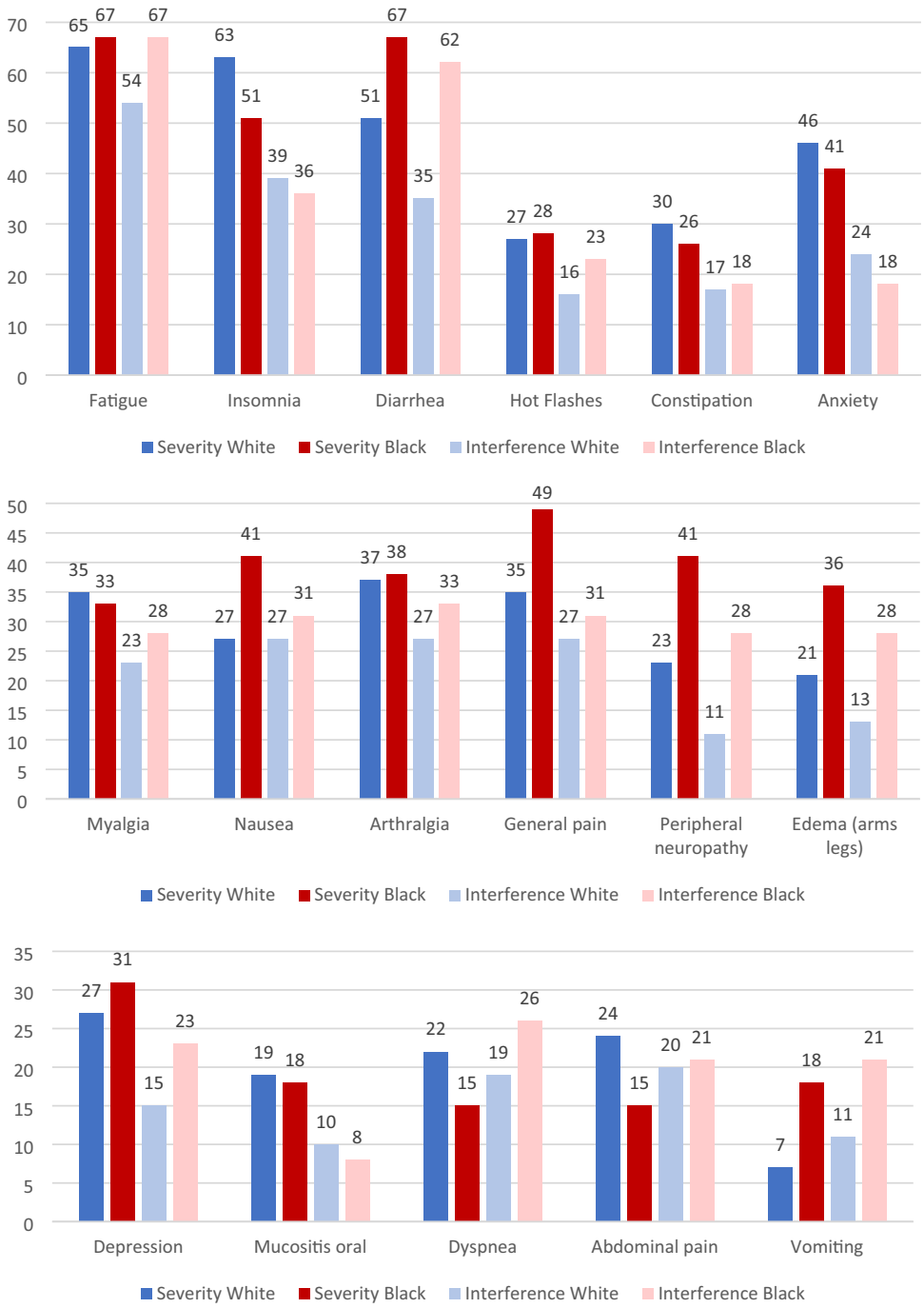

Fig. 2 Patient-reported "moderate, severe, very severe" symptom *severity* and symptom *interference with daily activities* (%)—non-anthracycline chemotherapy

We conducted an exploratory analysis of relative risks for adverse events during chemotherapy, separately for Black and White patients (Online Appendix 3). Only univariate analyses were conducted, because limited sample size precluded adjusted analysis of each adverse event by race. For example (see Table 2), for anthracycline-based regimens, the number of Black vs. White patients who had dose delay was 4 (17%) vs. 30 (34%), dose reduction 6 (25%) vs. 35 (39%), early treatment discontinuation 8 (33%) vs. 15 (17%), and hospitalization 7 (30%) vs. 20 (22%). And, for non-anthracycline regimens, the numbers of Black vs. White patients who had dose delay was 10 (27%) vs. 14 (14%), dose reduction 18 (49%) vs. 25 (25%), ETD 8 (22%) vs. 11 (11%), and hospitalization 6 (17%) vs. 13 (13%). The directionality and magnitude of univariate relative risks are hypothesis generating and warrant further investigation in a larger sample (Online Appendix 3).

Table 2 Patient-reported ("moderate", "severe", "very severe" – MSVS) symptom severity, interference with daily activities during chemotherapy, and adverse events during chemotherapy – anthracycline-based (N = 128) and non-anthracycline (N = 164) regimens

Symptom	Severity (percent MSVS)				Interference (percent			
	Anthracycline-based		Not anthracycline-based		Anthracycline-based			
	N (%)	*p-value*	N (%)	*p-value*	N (%)	*p-value*	N (%)	*p-value*
Mean number of symptom reports					–	–	–	–
White	8.9 (SD 4.5)	.10	4.7 (SD 2.7)	.06				
Black	7.4 (SD 3.7)		5.6 (SD 2.7)					
Mean number of symptoms rated MSVS—severity					–	–	–	–
White	6.6 (SD 3.9)	.76	5.6 (SD 3.9)	.43				
Black	6.3 (SD 3.9)		6.2 (SD 4.2)					
Mean number of symptoms rated MSVS – interference	–	–	–	–				
White					4.5 (SD 3.5)	.23	3.9 (SD 3.9)	.12
Black					5.4 (SD 3.9)		5.0(SD 4.0)	
Fatigue, lack of energy –								
White	77 (79%)	1.00	81 (65%)	1.00	75 (75%)	.63	67 (54%)	.20
Black	21 (78%)		26 (67%)		19 (70%)		26 (67%)	
Anxiety								
White	46 (46%)	.67	57 (46%)	.71	27 (27%)	.81	30 (24%)	.51
Black	11 (41%)		16 (41%)		6 (22%)		7 (18%)	
Depression								
White	33 (33%)	.64	34 (27%)	.69	16 (16%)	.26	18 (15%)	.22
Black	7 (26%)		12 (31%)		7 (26%)		9 (23%)	
Insomnia								
White	62 (62%)	.66	78 (63%)	.26	41 (41%)	.38	48 (39%)	.85
Black	15 (56%)		20 (51%)		14 (52%)		14 (36%)	
Hot flashes								
White	35 (35%)	.12	34 (27%)	1.00	21 (21%)	.21	20 (16%)	.34
Black	14 (52%)		11 (28%)		9 (33%)		9 (23%)	
Dyspnea								
White	23 (23%)	.46	27 (22%)	.50	19 (19%)	.43	24 (19%)	.50
Black	8 (30%)		6 (15%)		7 (26%)		10 (26%)	
Aching joints/arthralgia								
White	44 (44%)	1.00	46 (37%)	1.00	34 (34%)	1.00	34 (27%)	.54
Black	12 (44%)		15 (38%)		9 (33%)		13 (33%)	
Aching muscles/myalgia								
White	46 (46%)	.51	43 (35%)	1.00	29 (29%)	.48	29 (23%)	.53
Black	10 (37%)		13 (33%)		10 (37%)		11 (28%)	
Peripheral neuropathy								
White	40 (40%)	.51	28 (23%)	**.04**	22 (22%)	.08	14 (11%)	**.02**
Black	13 (48%)		16 (41%)		11 (41%)		11 (28%)	
Lymphedema/edema limbs								
White	20 (20%)	**.04**	26 (21%)	.09	13 (13%)	.08	16 (13%)	**.05**
Black	11 (41%)		14 (36%)		8 (30%)		11 (28%)	
Abdominal pain								
White	13 (13%)	.13	30 (24%)	.28	6 (6%)	.22	25 (20%)	1.00
Black	7 (26%)		6 (15%)		4 (15%)		8 (21%)	
General pain								
White	44 (44%)	.38	43 (35%)	.13	36 (36%)	1.00	33 (27%)	.68
Black	9 (33%)		19 (49%)		9 (33%)		12 (31%)	

Table 2 (continued)

Symptom	Severity (percent MSVS)				Interference (percent			
	Anthracycline-based		Not anthracycline-based		Anthracycline-based			
	N (%)	*p-value*	N (%)	*p-value*	N (%)	*p-value*	N (%)	*p-value*
Constipation								
White	48 (48%)	.52	37 (30%)	.69	20 (20%)	.19	21 (17%)	.81
Black	11 (41%)		10 (26%)		9 (33%)		7 (18%)	
Diarrhea								
White	39 (39%)	**.02**	63 (51%)	.10	24 (24%)	.43	44 (35%)	**.005**
Black	4 (15%)		26 (67%)		4 (15%)		24 (62%)	
Nausea								
White	45 (45%)	.52	33 (27%)	.11	41 (41%)	.83	33 (27%)	.68
Black	10 (37%)		16 (41%)		10 (37%)		12 (31%)	
Vomiting								
White	9 (9%)	1.00	9 (7%)	.07	7 (7%)	.25	13 (11%)	.17
Black	2 (7%)		7 (18%)		4 (15%)		8 (21%)	
Mucositis oral								
White	31 (31%)	.24	23 (19%)	1.00	15 (15%)	.39	12 (10%)	1.00
Black	5 (19%)		7 (18%)		6 (22%)		3 (8%)	
Adverse events during chemotherapy								
Dose delay					–	–	–	–
White	30 (34%)	.14	14 (14%)	.08				
Black	4 (17%)		10 (27%)					
Dose reduction					–	–	–	–
White	35 (39%)	.24	25 (25%)	**.01**				
Black	6 (25%)		18 (49%)					
Early treatment discontinuation					–	–	–	–
White	15 (17%)	.09	11 (11%)	.16				
Black	8 (33%)		8 (22%)					
Hospitalization					–	–	–	–
White	20 (22%)	.42	13 (13%)	.58				
Black	7 (30%)		6 (17%)					

MSVS = percent "moderate, severe or very severe" symptom severity or symptom interference with daily activities at any time during chemotherapy

Figures in bold are statistically significant

Discussion

This study provides a detailed exploration of patient-reported symptom experience and adverse events during (neo)adjuvant chemotherapy in Black as compared to White women with early breast cancer treated with curable intent. In our sample, 23% of participants are Black, which is representative of the general population of women with early breast cancer. We identified pre-chemotherapy variables that differed significantly between Black and White women—education, marital status, obesity, number of comorbidities, and breast cancer phenotype. We also found significant baseline differences in function (Short Physical Performance Battery), cognition (BOMC), instrumental activities of daily living, and emotional well-being. Most baseline characteristics suggested better well-being among White patients, with the exception of emotional well-being which was higher in Black women.

In light of socioeconomic influences on breast cancer treatment and outcomes [8] and clinician concerns about the functional status of their patients as they determine the optimal treatment plan [47], pre-chemotherapy profiles of patients in our sample suggested that Black patients may be more vulnerable to toxicity and adverse events during chemotherapy as compared to White patients. Somewhat surprising and reassuring, despite baseline differences,

Table 3 Adverse event during chemotherapy

Adverse event	Total ($N=294$)	Black ($N=68$)	White ($N=226$)
Dose delay between chemotherapy infusions	$N=67$ (23%)	$N=17$ (25%) 1. Neutropenia 6 (35%) 2. Neutropenia Fever 3 (18%) 3. Anemia 2 (12%) 4. Fatigue 1 (6%) 5. Unknown/multiple 4 (24)	$N=50$ (22%) 1. Neutropenia 12 (24%) 2. Neuropathy 6 (12%) 3. Thrombocytopenia 5 (10%) 4. Infection and/or Sepsis 5 (10%) 5. Unknown 22 (44%)
Dose reduction	$N=95$ (32%)	$N=27$ (40%) 1. Neuropathy 7 (26%) 2. Anemia 4 (15%) 3. Neutropenia 3 (11%) 4. Nausea and/or Vomiting 3 (11%) 5. Unknown 10 (37%)	$N=68$ (30%) 1. Neuropathy 24 (35%) 2. Neutropenic Fever 9 (13%) 3. Neutropenia 8 (12%) 4. Nausea and/or Vomiting 4 (6%) 5. Unknown 23 (34%)
Early treatment discontinuation	$N=52$ (18%)	$N=20$ (26%) 1. Neuropathy 6 (30%) 2. Fatigue 3 (15%) 3. Nausea and/or Vomiting 2 (10%) 4. Seizures Preventing Care 2 (10%) 5. Unknown 7 (35%)	$N=32$ (14%) 1. Neuropathy 7 (22%) 2. Neutropenia 3 (9%) 3. Fatigue 3 (9%) 4. Allergic Reaction 3 (9%) 5. Unknown 16 (50%)
Hospitalization	$N=52$ (18%)	$N=15$ (22%) 1. Neutropenic Fever 5 (33%) 2. Infection and/or Sepsis 1 (7%) 3. Seizures Preventing Care 1 (7%) 4. Nausea and/or Vomiting 1 (7%) 5. Unknown 8 (53%)	$N=37$ (16%) 1. Neutropenic Fever 11 (30%) 2. Infection and/or Sepsis 9 (24%) 3. Non-NF Fever 3 (8%) 4. Allergic Reaction 1 (3%) 5. Unknown 13 (35%)

"Unknown" is that the reason was not stated in the clinician notes. "Multiple" is that no one reason was cited as primary among multiple in the clinician notes

our results showed that moderate, severe, and very severe patient-reported symptoms were largely similar between Black and White patients. Notable exceptions were lymphedema (anthracycline-based regimens) and peripheral neuropathy (non-anthracycline regimens) which were reported as more severe among Black patients. In multivariable analysis with factors likely to impact lymphedema, we report 91% increased risk for lymphedema in Black patients after adjusting for type of axillary surgery ($p=0.04$), and a borderline significant greater risk for lymphedema in Black patients after adjusting for BMI ($p=0.06$). It has been previously reported that women with breast cancer and BMI of 30 or higher during treatment are 3.6 times more likely than patients with BMI < 30 to develop lymphedema at 6 months ($p=0.007$) [46]. The role of obesity in lymphedema [48–50] is important in light of higher rates of obesity observed in among Back patients in the current study and in a previous investigation of BMI and related comorbidities in women with early breast cancer [10].

In multivariable analysis controlling for type of taxane (paclitaxel/nab-paclitaxel vs. docetaxel), Black patients had 73% increased risk for peripheral neuropathy as compared to White patients ($p=0.053$). And, after controlling for diabetes at BC diagnosis, Black patients were 2.04 times more likely to report MSVS peripheral neuropathy as White patients ($p=0.005$). In our prior research [10], we have shown significantly higher rates of diabetes in Black as compared to White patients with early breast cancer and we may in fact be observing prediabetes symptoms in our patients with obesity.

Quantitative studies of symptom experience during active treatment in racially diverse women with breast cancer are limited. In a study of women whose chemotherapy regimen included a taxane, 49% had dose reduction due to CIPN—53% of the Black patients as compared to 22% of the White patients ($p<0.001$) [51]. In another study of women treated with early breast cancer between 1985 and 1997, it was noted that Black as compared to White women had lower chemotherapy dose proportion (actual divided by expected doses) (80% vs. 85%) ($p=0.03$) and relative dose intensity (61% vs. 72%) ($p=0.01$) compared to White patients [52]. In multivariable analysis, Black race and BMI were independently associated with first dose reduction [52]. In a study of chemotherapy adherence, women who were less than 100% chemotherapy adherent had a higher number of symptoms (MSAS-SF) ($p=0.018$), but there were no racial differences in 100% adherence by race – 87.5% Non-Hispanic White and 82.4% African American ($p=0.10$) [53]. And, in the Breast Cancer Quality of Care (BQUAL) study, the rate of chemotherapy discontinuation was similar in Black vs. White women (OR 0.70, 95% CI 0.30–1.63) [54].

Our study has some important limitations. We did not collect data pertaining to medications used for symptom management including nausea, depression, anxiety or neuropathy, which may have differed among Black and White participants. Second, our sample was not likely representative of the general population of women with breast cancer as our participants were relatively well-educated (84% with more than a high school education) and a majority were treated at academic medical centers. Although our sample included 23% of women who self-identified as Black, it was not a priori powered to make pre-specified comparisons between races. Thus, the results presented here need further examination in additional studies. And, our study warrants replication in a larger sample of women seen in community-based breast cancer clinics, where patterns of offering chemotherapy, patient acceptance of chemotherapy in the treatment plan, and pre-treatment health status may produce a different patient profile.

Patient-reported symptom assessments provide an opportunity for communication with the clinician about symptom experience. In our previous research, we have shown there can be racial differences in how clinicians and their patients rate symptom onset and severity [28]. We found that clinicians significantly underestimated symptom severity in both White and Non-White patients. In 21% of non-White as compared to 10% of White patients, clinicians rated CIPN as "low" severity when patients rated it as "high" ($p=0.04$). Clinicians rated nausea severity "low" when 15% of White patients and 12% of non-White patients rated this symptom's severity "high" ($p=0.05$) [28].

Effective communication about symptom experience provides an opportunity for clinicians to initiate interventions that could mitigate symptom severity, such as medications to reduce nausea, vomiting, depression, or anxiety. Effective communication can also help clinicians ascertain when treatment needs to be discontinued before the side effect becomes debilitating, such as peripheral neuropathy or fatigue. And, effective patient-provider communication is at the core of patient-centered care [55], providing an opportunity for patients to raise concerns about symptoms, understand whether they are treatment-related, learn how common they are, and agree with their clinician on a symptom management plan. Short report forms such as the PRO-CTCAE can facilitate this communication [56] and encourage quality of life and function as clinical endpoints[57,58].

Conclusion

This study contributes to the breast cancer disparities literature by providing a direct comparison of symptom reporting by Black and White patients with breast cancer treated with contemporary (neo)adjuvant chemotherapy regimens.

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Declarations

Conflict of interest The authors declare they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was received from all study participants.

References

1. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A (2016) Breast cancer statistics, 2015: convergence of incidence rates between black and white women. CA Cancer J Clin 66(1):31–42
2. DeSantis CE, Ma J, Gaudet MM et al (2019) Breast cancer statistics, 2019. Cancer 69(6):438–451
3. Tao L, Gomez SL, Keegan TH, Kurian AW, Clarke CA (2015) Breast cancer mortality in African-American and non-hispanic white women by molecular subtype and stage at diagnosis: a population-based study. Cancer Epidemiol Biomarkers Prev 24(7):1039–1045
4. Carey LA, Perou CM, Livasy CA et al (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295(21):2492–2502
5. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL (2018) Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. J Clin Oncol 36(1):25–33
6. Green AK, Aviki EM, Matsoukas K, Patil S, Korenstein D, Blinder V (2018) Racial disparities in chemotherapy administration for early-stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 172(2):247–263
7. Wheeler SB, Spencer JC, Pinheiro LC, Carey LA, Olshan AF, Reeder-Hayes KE (2018) Financial impact of breast cancer in black versus white women. J Clin Oncol 36(17):1695–1701
8. Wheeler SB, Reeder-Hayes KE, Carey LA (2013) Disparities in breast cancer treatment and outcomes: biological, social, and health system determinants and opportunities for research. Oncologist 18(9):986–993
9. Warner ET, Tamimi RM, Hughes ME et al (2015) Racial and ethnic differences in breast cancer survival: mediating effect of tumor characteristics and sociodemographic and treatment factors. J Clin Oncol 33(20):2254–2261
10. Nyrop KA, Deal A, Carey L et al (2021) Obesity, comorbidities and treatment selection in Black and White women with early breast cancer. Cancer 127(6):922–930
11. Gwede CK, Johnson DJ, Daniels SS, Trotti A (2002) Assessment of toxicity in cooperative oncology clinical trials: the long and short of it. J Oncol Manag. 11(2):15–21

12. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v.5. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 10/23/2017, 2017.
13. Basch E, Rogak LJ, Dueck AC (2016) Methods for implementing and reporting Patient-reported Outcome (PRO) measures of symptomatic adverse events in cancer clinical trials. Clin Ther 38(4):821–830
14. Basch E, Dueck AC, Rogak LJ et al (2017) Feasibility assessment of patient reporting of symptomatic adverse events in multicenter cancer clinical trials. JAMA Oncol 3(8):1043–1050
15. Basch E, Pugh SL, Dueck AC et al (2017) Feasibility of patient reporting of symptomatic adverse events via the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) in a chemoradiotherapy cooperative group multicenter clinical trial. Int J Radiat Oncol Biol Phys 98(2):409–418
16. Cowan RA, Suidan RS, Andikyan V et al (2016) Electronic patient-reported outcomes from home in patients recovering from major gynecologic cancer surgery: a prospective study measuring symptoms and health-related quality of life. Gynecol Oncol 143(2):362–366
17. Di Maio M, Basch E, Bryce J, Perrone F (2016) Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol 13(5):319–325
18. National Cancer Institute. PRO-CTCAE ™ version 1.0. 2018. Accessed 12/17/2018.
19. Basch E, Reeve BB, Mitchell SA et al (2014) 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. 106(9):dju244
20. Dueck AC, Mendoza TR, Mitchell SA et al (2015) 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 1(8):1051–1059
21. Reeve BB, Mitchell SA, Dueck AC et al (2014) Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. J Nat Cancer Inst 106(7):dju129
22. Bennett AV, Dueck AC, Mitchell SA et al (2016) Mode equivalence and acceptability of tablet computer-, interactive voice response system-, and paper-based administration of the U.S. National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Health Qual Life Outcomes 14:24
23. Baeksted C, Pappot H, Nissen A et al (2017) Feasibility and acceptability of electronic symptom surveillance with clinician feedback using the Patient-reported outcomes version of common terminology criteria for adverse events (PRO-CTCAE) in Danish prostate cancer patients. J Patient Rep Outcomes 1(1):1–11
24. Stover A, Irwin DE, Chen RC et al (2015) Integrating patient-reported outcome measures into routine cancer care: cancer patients' and clinicians' perceptions of acceptability and value. EGEMS (Washington, DC) 3(1):1169
25. Nyrop KA, Deal AM, Shachar SS et al (2019) Patient-reported toxicities during chemotherapy regimens in current clinical practice for early breast cancer. Oncologist 24(6):762–771
26. Atkinson TM, Hay JL, Dueck AC et al (2018) What do "None," "Mild," "Moderate," "Severe," and "Very Severe" mean to patients with cancer? Content validity of PRO-CTCAE response scales. J Pain Symptom Manage 55(3):e3–e6
27. Gradishar WJ, Anderson BO, Balassanian R et al (2018) Breast cancer, version 4.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 16(3):310–320
28. Nyrop KA, Deal AM, Reeve BB (2020) Congruence of patient- and clinician-reported toxicity in women receiving chemotherapy for early breast cancer. Cancer 126(13):3084–3093
29. Nyrop KA, Deal AM, Reeder-Hayes KE et al (2019) Patient and clinician-reported chemotherapy-induced peripheral neuropathy (CIPN) in early breast cancer: current clinical practice. Cancer 127(7):2945–2954
30. Guralnik L, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF et al (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol Med Sci 49(2):M85–M94
31. Shumway-Cook A, Brauer S, Woollacott M (2000) Predicting the probability of falls in community-dwelling older adults using the timed up and go test. Phys Ther 2000(80):896–903
32. Podsiadlo D, Richardson S (1991) The timed "Up & Go": a test of functional mobility for frail elderly persons. J Am Geriatr Soc 1991(39):142–148
33. Kawas C, Karagiozis H, Resau L, Corrada M, Brookmeyer R (1995) Reliability of the blessed telephone information-memory-concentration test. J Geriatr Psychiatry Neurol 8(4):238–242
34. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H (1983) Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry 140(6):734–739
35. Fillenbaum GG, Smyer MA (1981) The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol 36(4):428–434
36. Pergolotti M, Langer MM, Deal AM, Muss HB, Nyrop K, Williams G (2019) Mental status evaluation in older adults with cancer: development of the Mental Health Index-13. J Geriatr Oncol 10(2):241–245
37. Stewart A, Ware JE (1992) Measuring Functioning and Well-being: the Medical Outcome Study Approach. Duke University Press, Durham NC
38. Sherbourne CD (1991) Social Functioning: Social Activity Limitations Measure. In: Stewart AL, Ware JE (eds) Measuring Functioning and Well-being: The Medical Outcomes Study. Duke University Press, Durham and London, pp 173–181
39. Sherbourne CD, Stewart AL (1991) The MOS social support survey. Soc Sci Med 32(6):705–714
40. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E et al (1993) The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 11(3):570–579
41. Webster K, Cella D, Yost K (2003) The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 1:79
42. Hay JL, Atkinson TM, Reeve BB et al (2014) Cognitive interviewing of the US National Cancer Institute's Patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Qual Life Res 23(1):257–269
43. Greenland S (2004) Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. Am J Epidemiol 160(4):301–305
44. Zou G (2004) A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 159(7):702–706
45. Goetz MP, Gradishar WJ, Anderson BO et al (2019) NCCN guidelines insights: breast cancer, version 3.2018. J Natl Compr Canc Netw 17(2):118–126
46. Ridner SH, Dietrich MS, Stewart BR, Armer JM (2011) Body mass index and breast cancer treatment-related lymphedema. Support Care Cancer 19(6):853–857
47. Mor V, Laliberte L, Morris JN, Wiemann M (1983) The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer 1983(53):2002–2007
48. de Godoy JMP (2019) Systemic subclinical lymphedema due to obesity as the cause of clinical lymphedema: a new concept. Med Hypotheses 131:109312

49. Sudduth CL, Greene AK (2021) Current overview of obesity-induced lymphedema. Adv Wound Care. https://doi.org/10.1089/wound.2020.1337
50. Ugur S, Arıcı C, Yaprak M et al (2013) Risk factors of breast cancer-related lymphedema. Lymphat Res Biol 11(2):72–75
51. Bhatnagar B, Gilmore S, Goloubeva O et al (2014) Chemotherapy dose reduction due to chemotherapy induced peripheral neuropathy in breast cancer patients receiving chemotherapy in the neoadjuvant or adjuvant settings: a single-center experience. Springerplus 3:366
52. Griggs JJ, Sorbero ME, Stark AT, Heininger SE, Dick AW (2003) Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. Breast Cancer Res Treat 81(1):21–31
53. Wells JS, Strickland OL, Dalton JA, Freeman S (2015) Adherence to intravenous chemotherapy in African American and white women with early-stage breast cancer. Cancer Nurs 38(2):89–98
54. Neugut AI, Hillyer GC, Kushi LH et al (2016) A prospective cohort study of early discontinuation of adjuvant chemotherapy in women with breast cancer: the breast cancer quality of care study (BQUAL). Breast Cancer Res Treat 158(1):127–138
55. Basch E (2014) New frontiers in patient-reported outcomes: adverse event reporting, comparative effectiveness, and quality assessment. Annu Rev Med 65:307–317
56. Stover AM, Basch EM (2016) Implementation of symptom questionnaires into oncology workflow. J Oncol Pract 12(10):859–862
57. Bruner DW, Movsas B, Basch E (2012) Capturing the patient perspective: patient-reported outcomes as clinical trial endpoints. Am Soc Clin Oncol Educ Book 32:139–144
58. Basch E (2016) Missing patients' symptoms in cancer care delivery-the importance of patient-reported outcomes. JAMA Oncol 2(4):433–434