OXFORD

JNCI J Natl Cancer Inst (2022) 114(12): djac120

https://doi.org/10.1093/jnci/djac120
First published online August 2, 2022
Article

Mediators of Racial Disparities in Heart Dose Among Whole Breast Radiotherapy Patients

Christina Hunter Chapman, MD [1,2], Reshma Jagsi, MD, DPhil,[1] Kent A. Griffith, MS,[1] Jean M. Moran, PhD,[1] Frank Vicini, MD,[3] Eleanor Walker, MD,[4] Michael Dominello, DO,[5] Eyad Abu-Isa, MD,[6] James Hayman, MD,[1] Anna M. Laucis, MD,[1] Melissa Mietzel, MS,[1] and Lori Pierce, MD [1,*]; on behalf of the Michigan Radiation Oncology Quality Consortium

[1]Rogel Comprehensive Cancer Center at the University of Michigan, Ann Arbor, MI, USA; [2]Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI, USA; [3]GenesisCare, Farmington Hills, MI, USA; [4]Henry Ford Hospital, Detroit, MI, USA; [5]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; and [6]Ascension Providence Hospital, Southfield, MI, USA

[*]**Correspondence to:** Lori J. Pierce, MD, University of Michigan Rogel Comprehensive Cancer Center, Rm 4308, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA (e-mail: ljpierce@med.umich.edu).

Abstract

Background: Racial disparities in survival of patients with cancer motivate research to quantify treatment disparities and evaluate multilevel determinants. Previous research has not evaluated cardiac radiation dose in large cohorts of breast cancer patients by race nor examined potential causes or implications of dose disparities. **Methods:** We used a statewide consortium database to consecutively sample 8750 women who received whole breast radiotherapy between 2012 and 2018. We generated laterality- and fractionation-specific models of mean heart dose. We generated patient- and facility-level models to estimate race-specific cardiac doses. We incorporated our data into models to estimate disparities in ischemic cardiac event development and death. All statistical tests were 2-sided. **Results:** Black and Asian race independently predicted higher mean heart dose for most laterality-fractionation groups, with disparities of up to 0.42 Gy for Black women and 0.32 Gy for Asian women (left-sided disease and conventional fractionation: 2.13 Gy for Black women vs 1.71 Gy for White women, $P < .001$, 2-sided; left-sided disease and accelerated fractionation: 1.59 Gy for Asian women vs 1.27 Gy for White women, $P = .002$). Patient clustering within facilities explained 22%-30% of the variability in heart dose. The cardiac dose disparities translated to estimated excesses of up to 2.6 cardiac events and 1.3 deaths per 1000 Black women and 0.7 cardiac events and 0.3 deaths per 1000 Asian women vs White women. **Conclusions:** Depending on laterality and fractionation, Asian women and Black women experience higher cardiac doses than White women. This may translate into excess radiation-associated ischemic cardiac events and deaths. Solutions include addressing inequities in baseline cardiac risk factors and facility-level availability and use of radiation technologies.

Whole breast radiotherapy (RT) increases the risk of ischemic cardiac events (1), with incidence and mortality risk further increased by baseline cardiac risk factors. This underscores the importance of minimizing cardiac dose among women with breast cancer. Dose-reducing strategies exist, including early diagnosis (reduced need for internal mammary nodal treatment) and cardiac dose-reducing radiation techniques (2). If applied consistently, these strategies can minimize cardiac dose for all patients. If applied inconsistently, however, cardiac dose may be unnecessarily elevated among specific demographic subgroups. Disparities in cardiac dose may be particularly harmful for racial and ethnically minoritized women, given the increased prevalence of cardiac risk factors (3).

Despite the importance of reducing cardiac dose, studies show statistically significant patient-level variation in cardiac dose (4). Research is needed to understand and correct factors causing unwarranted variation in cardiac dose and investigate whether racial disparities exist. Factors that mediate cardiac dose (4) may be unevenly distributed between racial and ethnic subpopulations. Although some mediators may be nonmodifiable (eg, year of diagnosis), multilevel, modifiable mediators may exist across the cancer continuum. Prediagnosis mediators

Received: December 21, 2021; **Revised:** March 22, 2022; **Accepted:** June 9, 2022

ARTICLE

such as body mass index, breast volume, and comorbidities are considered modifiable because they are influenced by forces like structural racism (5) that drive disparities in social determinants of health. Cancer workup and treatment mediators, which can also be modifiable, include disease stage and use of cardiotoxic systemic therapies. Radiation technique mediators include deep inspiration breath hold (DIBH) use and other RT technical delivery factors [eg, 3-dimensional vs intensity modulated radiation therapy (IMRT) (4) use]. Cardiac dose may also be mediated through institutional practices attributable to treatment facility. This may be evident by examining factors like the type of practice (academic or community) of the facility or observing attenuation of the disparity when accounting for institution common practice by clustering patients within treating facilities.

We therefore used a statewide consortium to explore racial differences in cardiac dose. Our findings are designed to inform multilevel strategies to mitigate disparities in cardiac event risk among women with breast cancer.

Methods

Data Collection and Sampling

The Michigan Radiation Oncology Quality Consortium (MROQC) is a state-wide collaborative designed to improve patients' experiences with RT (4). Deidentified patient-level clinical and radiation data are collected in a centralized database (6). This study was considered institutional review board exempt due to quality assurance status.

We queried the MROQC database for RT dosimetry to examine racial differences in mean heart dose (MHD) among women treated with whole breast RT at 25 institutions between January 1, 2012, or January 1, 2014 (heart dose collection began earlier in left- vs right-sided plans) and August 31, 2018. Given that MHD is dependent on disease laterality and fractionation, we generated separate models based on disease laterality (right vs left) and receipt of conventional (CWBI) vs accelerated whole breast irradiation (AWBI).

Race was self-reported (71.0%) and, if missing, was extracted from the hospital's electronic medical record (29.0%). Given the missingness (34.4%) and low prevalence of Hispanic, Latina, and Latinx ethnicity, we omitted ethnicity from the analysis. For the final analysis, we included Asian, Black, and White racial groups and removed others (American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Arab or Middle Eastern groups, unknown or not reported and other, please specify, 3.6% of the sample).

Statistical Analysis

Given that MHD is a skewed (nonnormal) distribution, we used linear regression but modeled the MHD natural logarithm. We estimated average MHD by centering age at 60 years, year in 2015, minimum dose covering 50% of the breast (D50) at 48 Gy (mean), continuous covariates at or near their mean or median value, and other categorical values as appropriate to facilitate interpretation.

We generated 6 sequential patient- or multilevel models for each subpopulation based on the phase of the cancer continuum (covariates shown in Table 2 and the Supplementary Methods and Tables; available online): 1) nonmodifiable, 2) prediagnosis, 3) cancer workup and pre-RT treatment, 4) radiation oncology, 5) clustering within facilities, and 6) facility type. P values less than .05 were considered statistically significant (2-sided). To quantify the amount of variability in MHD attributable to facility differences in practice, we calculated intraclass correlational and variance partitioning coefficients.

To quantify the clinical significance of disparities in cardiac dose, we applied our dosimetric data to existing models (1) to quantify differences in cumulative risk (by age 80 years) of 1) development of at least 1 radiation-related acute coronary event and 2) radiation-related death from ischemic cardiac disease. Details for our method to quantify cumulative risk are presented in the Supplementary Methods (available online).

Statistics were performed using the SAS System version 9.4 (Cary, NC, USA).

Results

Table 1 shows the characteristics of the 8750 women treated with whole breast radiotherapy between 2012 and 2018. The final sample was comprised of 1.9% Asian women, 18.3% Black women, and 79.9% White women. Black women (63.5%) and Asian women (62.4%) were more likely to be treated at academic institutions than White women (29.4%). Asian women were younger (mean age 54.9 years vs 60.8 years for Black women and 61.9 years for White women). Black women had larger mean breast and lumpectomy bed volumes, were less likely to be treated using DIBH, 3-dimensional conformal radiotherapy (vs IMRT), and AWBI, and were more likely to have triple negative disease, obesity, and at least 1 cardiac risk factor (Black women = 89.1%; Asian women = 43.0%; White women = 69.6%).

Left-Sided Conventional Fractionation

Regression results by race are shown in Table 2, with the complete list of covariates shown in Supplementary Table 3 (available online). The estimated MHD for the baseline for White women was approximately 1.7-1.8 Gy for all models. In Model 1, which included race, age, year, and triple-negative disease, heart dose was statistically significantly higher for Black women (24.5%, 95% CI = 19.9% to 29.2%, $P < .001$) but not Asian women (−2.7%, 95% CI = −16.5% to 11.1%). For Black women, controlling for prediagnosis (body mass index, breast volume, comorbidities, smoking) and workup or pre-RT treatment (disease stage, chemotherapy or trastuzumab) had minimal influence on the disparity (Model 2: 23.5%, 95% CI = 18.8% to 28.3% and Model 3: 22.5%, 95% CI = 17.8% to 27.2%). Controlling for radiation technique (breast D50, DIBH use, IMRT use, positioning, nodal treatment, and boost use) reduced cardiac dose (Model 4: 15.5%, 95% CI = 11.0% to 19.9%, $P < .001$). Controlling for clustering within facilities further reduced dose (Model 5: 8.3%, 95% CI = 3.5% to 13.1%, $P < .001$), but further controlling for academic or teaching status had minimal impact (Model 6: 8.3%, 95% CI = 3.5% to 13.1%, $P < .001$). Estimates for Asian women changed minimally across models.

Left-Sided Accelerated Fractionation

The estimated MHD for the baseline White women increased from 1.27 in Model 1 to 1.56 in Model 5. In Model 1, heart dose was statistically significantly higher for Black women (20.1%, 95% CI = 14.9% to 25.3%, $P < .001$) and Asian women (24.9%, 95% CI = 8.9% to 40.3%, $P < .001$) (details shown in Supplementary Table 3, available online). Controlling for societal factors,

Table 1. Sample characteristics, all patients, stratified by race

Variable	All patients	Asian women	Black women	White women	P^a for White vs Black women	P^a for White vs Asian women	P^b continuous variables
Year of radiotherapy completion, No. (%)							
2012	315 (3.6)	4 (2.4)	67 (4.2)	244 (3.5)	.05	.10	
2013	556 (6.4)	11 (6.7)	107 (6.7)	438 (6.3)			
2014	1517 (17.3)	27 (16.4)	313 (19.6)	1177 (16.9)			
2015	1852 (21.2)	29 (17.6)	335 (20.9)	1488 (21.3)			
2016	1945 (22.2)	34 (20.6)	325 (20.3)	1586 (22.7)			
2017	1720 (19.7)	32 (19.4)	314 (19.6)	1374 (19.7)			
2018	845 (9.7)	28 (17.0)	139 (8.7)	678 (9.7)			
Academic (teaching) treating institution, No. (%)					<.001	<.001	
No	5576 (63.7)	62 (37.6)	584 (36.5)	4930 (70.6)			
Yes	3174 (36.3)	103 (62.4)	1016 (63.5)	2055 (29.4)			
Age							
Total No.	8750	165	1600	6985			
Mean (SD), y	61.6 (10.8)	54.9 (10.7)	60.8 (11.2)	61.9 (10.6)			<.001
Median [IQR], y	61.8 [53.9-69.1]	52.4 [46.4-63.9]	60.8 [53.0-68.5]	62.2 [54.3-69.4]			.001
Age groups, No. (%)					<.001	<.001	
<50 y	1310 (15.0)	59 (35.8)	281 (17.6)	970 (13.9)			
50 to <60 y	2539 (29.0)	56 (33.9)	457 (28.6)	2026 (29.0)			
60 to <70 y	2921 (33.4)	35 (21.2)	527 (32.9)	2359 (33.8)			
70+ y	1980 (22.6)	15 (9.1)	335 (20.9)	1630 (23.3)			
Weight							
Total No.	8731	164	1598	6969			
Mean (SD), kg	80.5 (19.1)	62.0 (10.2)	86.9 (19.9)	79.5 (18.6)			<.001
Median [IQR], kg	77.8 [66.6-90.9]	59.4 [54.4-69.4]	84.5 [73.4-97.5]	76.7 [65.8-89.8]			<.001
BMI							
Total No.	8653	163	1593	6897			
Mean (SD), kg/m^2	30.3 (7.0)	24.8 (4.0)	32.6 (7.2)	30.0 (6.9)			<.001
Median [IQR], kg/m^2	29.3 [25.2-34.3]	24.4 [21.8-27.5]	31.8 [27.8-36.5]	28.8 [24.9-33.8]			<.001
BMI categories, No. (%)					<.001	<.001	
Underweight <18.5 kg/m^2	156 (1.8)	9 (5.5)	13 (0.8)	134 (1.9)			
Normal 18.5 to <25 kg/m^2	2016 (23.0)	84 (50.9)	198 (12.4)	1734 (24.8)			
Overweight 25 to <30 kg/m^2	2609 (29.8)	52 (31.5)	417 (26.1)	2140 (30.6)			
Obesity I 30 to <35 kg/m^2	2020 (23.1)	20 (12.1)	452 (28.3)	1548 (22.2)			
Obesity II 35 to <40 kg/m^2	1110 (12.7)	0(0)	298 (18.6)	812 (11.6)			
Obesity III >40 kg/m^2	839 (9.6)	0(0)	222 (13.9)	617 (8.8)			
Breast total volume							
Total No.	8724	165	1596	6963			
Mean (SD), cc	1143.3 (643.5)	710.8 (375.2)	1359.5 (774.8)	1104.1 (601.0)			<.001
Median [IQR], cc	1023.4 [685.8-1471.7]	627.4 [446.4-896.8]	1219.3 [814.8-1736.5]	993.4 [675.0-1419.6]			<.001
Lumpectomy bed total volume							
Total No.	8491	158	1564	6769			
Mean (SD), cc	41.5 (71.5)	28.1 (32.1)	67.5 (98.9)	35.8 (62.8)			<.001
Median [IQR], cc	22.7 [11.5-46.1]	18.3 [9.2-34.5]	34.2 [14.4-81.2]	21.3 [11.1-41.4]			<.001
Smoking status, No. (%)					<.001	<.001	
Never smoker	4988 (57.0)	144 (87.3)	858 (53.6)	3986 (57.1)			
Former smoker	2767 (31.6)	14 (8.5)	499 (31.2)	2254 (32.3)			
Current smoker	995 (11.4)	7 (4.2)	243 (15.2)	745 (10.7)			
Comorbidities count categories, No. (%)					<.001	<.001	
Not reported	3 (0.0)	0(0)	1 (0.1)	2 (0.0)			
0	3708 (42.4)	101 (61.2)	380 (23.8)	3227 (46.2)			
1	2948 (33.7)	39 (23.6)	588 (36.8)	2321 (33.2)			
2	1492 (17.1)	23 (13.9)	435 (27.2)	1034 (14.8)			
3+	599 (6.8)	2 (1.2)	196 (12.3)	401 (5.7)			

(continued)

Table 1. (continued)

Variable	All patients	Asian women	Black women	White women	P[a] for White vs Black women	P[a] for White vs Asian women	P[b] continuous variables
Hypertension, No. (%)					<.001	<.001	
Not reported	3 (0.0)	0(0)	1 (0.1)	2 (0.0)			
No	4619 (52.8)	115 (69.7)	504 (31.5)	4000 (57.3)			
Yes	4128 (47.2)	50 (30.3)	1095 (68.4)	2983 (42.7)			
Diabetes, No. (%)					<.001	<.001	
Not reported	3 (0.0)	0(0)	1 (0.1)	2 (0.0)			
No	7366 (84.2)	140 (84.8)	1168 (73.0)	6058 (86.7)			
Yes	1381 (15.8)	25 (15.2)	431 (26.9)	925 (13.2)			
Cardiac risk factor, No. (%)					<.001	<.001	
No	2394 (27.4)	94 (57.0)	175 (10.9)	2125 (30.4)			
Yes	6356 (72.6)	71 (43.0)	1425 (89.1)	4860 (69.6)			
AJCC 7th ed. Stage of Disease, No. (%)					<.001	.63	
Not reported	38 (0.4)	0(0)	8 (0.5)	30 (0.4)			
0	1722 (19.7)	34 (20.6)	378 (23.6)	1310 (18.8)			
1	4429 (50.6)	79 (47.9)	682 (42.6)	3668 (52.5)			
2	2311 (26.4)	48 (29.1)	473 (29.6)	1790 (25.6)			
3	250 (2.9)	4 (2.4)	59 (3.7)	187 (2.7)			
Final surgical margins, No. (%)					.69	.49	
Not reported	137 (1.6)	7 (4.2)	20 (1.3)	110 (1.6)			
Close	1182 (13.5)	20 (12.1)	215 (13.4)	947 (13.6)			
Negative	7143 (81.6)	130 (78.8)	1318 (82.4)	5695 (81.5)			
Positive	288 (3.3)	8 (4.8)	47 (2.9)	233 (3.3)			
Triple-negative disease, No. (%)					<.001	.16	
Not reported	22 (0.3)	1 (0.6)	3 (0.2)	18 (0.3)			
No	7885 (90.1)	146 (88.5)	1326 (82.9)	6413 (91.8)			
Yes	843 (9.6)	18 (10.9)	271 (16.9)	554 (7.9)			
Chemotherapy (excluding trastuzumab), No. (%)					<.001	.002	
Not reported	35 (0.4)	0(0)	2 (0.1)	33 (0.5)			
No	6053 (69.2)	100 (60.6)	988 (61.8)	4965 (71.1)			
Yes	2662 (30.4)	65 (39.4)	610 (38.1)	1987 (28.4)			
Trastuzumab, No. (%)					.005	.13	
Not reported	35 (0.4)	0(0)	2 (0.1)	33 (0.5)			
No	7910 (90.4)	145 (87.9)	1422 (88.9)	6343 (90.8)			
Yes	805 (9.2)	20 (12.1)	176 (11.0)	609 (8.7)			
Hormone therapy, No. (%)					.07	.09	
Not reported	1968 (22.5)	44 (26.7)	336 (21.0)	1588 (22.7)			
No	2295 (26.2)	49 (29.7)	454 (28.4)	1792 (25.7)			
Yes	4487 (51.3)	72 (43.6)	810 (50.6)	3605 (51.6)			
IMRT, No. (%)					<.001	.10	
No	4625 (52.9)	106 (64.2)	478 (29.9)	4041 (57.9)			
Yes	4125 (47.1)	59 (35.8)	1122 (70.1)	2944 (42.1)			
Delivery type/fractionation, No. (%)					<.001	.16	
3DRT/CWBI	2336 (26.7)	58 (35.2)	305 (19.1)	1973 (28.2)			
3DRT/AWBI	2289 (26.2)	48 (29.1)	173 (10.8)	2068 (29.6)			
IMRT/CWBI	2110 (24.1)	33 (20.0)	632 (39.5)	1445 (20.7)			
IMRT/AWBI	2015 (23.0)	26 (15.8)	490 (30.6)	1499 (21.5)			
Deep inspiration breath hold, No. (%)					<.001	.49	
No	7383 (84.4)	133 (80.6)	1475 (92.2)	5775 (82.7)			
Yes	1367 (15.6)	32 (19.4)	125 (7.8)	1210 (17.3)			
Nodal radiotherapy treatment, No. (%)					<.001	.01	
Without nodal trt or Axillary (I/II) only	7730 (88.3)	137 (83.0)	1356 (84.8)	6237 (89.3)			
	587 (6.7)	12 (7.3)	171 (10.7)	404 (5.8)			

(continued)

Table 1. (continued)

Variable	All patients	Asian women	Black women	White women	P[a] for White vs Black women	P[a] for White vs Asian women	P[b] continuous variables
Supra or infraclavicular nodal treatment							
Internal mammary trt w/or w/o SCV/IVC trt	433 (4.9)	16 (9.7)	73 (4.6)	344 (4.9)			
Boost to lumpectomy bed, No. (%)					<.001	.03	
No	1556 (17.8)	21 (12.7)	167 (10.4)	1368 (19.6)			
Yes	7194 (82.2)	144 (87.3)	1433 (89.6)	5617 (80.4)			
Treatment position, No. (%)					<.001	.03	
Prone	595 (6.8)	3 (1.8)	181 (11.3)	411 (5.9)			
Supine	8155 (93.2)	162 (98.2)	1419 (88.7)	6574 (94.1)			
D50 to the Breast							
Total No.	8624	165	1578	6881			
Mean (SD)	48.2 (4.4)	48.1 (4.3)	49.5 (4.9)	47.9 (4.3)			<.001
Median [IQR]	47.2 [44.4-51.9]	47.3 [44.5-51.4]	48.6 [45.3-52.5]	46.9 [44.2-51.7]			.38

[a]P values for the comparison of White with Black women and White with Asian women using the χ^2 test statistic for categorical data. 3DCRT = 3-dimensional conformal radiotherapy; AWBI = accelerated whole breast irradiation; BMI = body mass index; CWBI = conventionally fractionated whole breast irradiation; ICV = infraclavicular; IMRT = intensity modulated radiation therapy; IQR = interquartile range; SCV = supraclavicular; trt = treatment; w/ = with; w/o = without.
[b]t test statistic for continuous data.

health-care system, staging, and workup factors, and radiation technique factors had minimal influence on these disparities. Controlling for clustering within facilities further reduced the estimated mean cardiac dose modestly for Asian women (Model 4: 23.6% vs Model 5: 15.5%, 95% CI = 2.6% to 28.5%, $P = .008$) and substantially for Black women (Model 4: 17.2%, Model 5: 6.9%, 95% CI = 1.4% to 12.4%, $P = .01$). Further controlling for academic or community status had minimal impact.

Right-Sided Conventional Fractionation

The estimated MHD for the baseline White women was approximately 0.67 Gy for all models. There were no racial disparities across Models 1 through 6 for any racial group.

Right-Sided Accelerated Fractionation

The estimated MHD for the baseline White women was approximately 0.60 Gy for all models. In Model 1, heart dose was statistically significantly higher for Asian women (14.4%, 95% CI = 0.4% to 28.4%, $P = .04$) and Black women (6.8%, 95% CI = 1.4% to 12.2%, $P = .01$). Across all 6 models, heart dose was higher for Black women vs White women ($P < .049$). There was no trend across the models for Asian women or Black women (Asian women: Models 1–6, range = 9.7%-14.4%; Black women: Models 1–6, range = 5.6%-12.4%).

Mediators of Cardiac Dose

In the final models (Model 6), the following factors were predictors for higher heart dose regardless of laterality or fractionation: supine positioning, earlier year of diagnosis, higher breast volume, IMRT, and breast D50. For conventional fractionation, lack of DIBH and nodal RT (both IMN and supraclavicular or infraclavicular without IMNs) were associated with higher cardiac dose. Other factors were statistically significantly associated with elevated cardiac dose depending on the model.

Variance Partitioning for Facility-Level Contribution

The intraclass correlation ranged from 25.5% for right-sided CWBI to 29.2% for right-sided ABWI, with left-sided intraclass correlations of 26.7% for both fractionation types. The variance partitioning coefficients for the full models (Model 6) ranged from 23.1% for right-sided CWBI to 31.9% for left-sided CWBI. Accounting for covariates reduced the residual variance by larger amounts for the left-sided models than for right-sided models (Table 3).

Unexplained Disparity

For Black women with left-sided disease, one-third (33.7%-33.9%) of the disparity remained unexplained in Model 6. For Asian women, the covariates explained little of the disparity, with 55.6%-78.4% of the Model 1 disparity remained unexplained in Model 6.

Estimated Impact on Cardiac Events

Figure 1A shows Model 1 cardiac doses by race for left-sided conventionally fractionated RT (Asian women = 1.66 Gy, Black women = 2.13 Gy, White women = 1.71 Gy). Accounting for all mediators included in Models 2-6 reduced heart dose among Black women to 1.92 Gy (vs 1.77 Gy for White women) and had minimal change for Asian women. Figure 1B shows Model 1 cardiac doses by race for left-sided AWBI (Asian women = 1.59 Gy, Black women = 1.53 Gy, White women = 1.27 Gy). Accounting for all mediators included in Models 2-6 reduced disparities in heart dose among Asian women and Black women (1.79 Gy and 1.66 Gy, respectively, vs 1.55 Gy for White women).

Using data from Darby et al. (1), we estimated that the disparity (after accounting for only nonmodifiable covariates, Model 1) currently experienced by Black women undergoing CWBI for left-sided disease results in an excess of 2.6 ischemic cardiac events and 1.3 cardiac deaths by age 80 years per 1000 women (Figure 2, events: Asian women = 6.12, Black women =

Table 2. Single and multilevel models explaining mean heart dose

Laterality and fractionation/intercept and race	Model 1 (age, tx year, triple-negative status)		Model 2 (Model 1 + BMI, breast volume, comorbidities, smoking status)		Model 3 (Model 2 + disease stage, chemotherapy receipt, trastuzumab receipt)		Model 4 (Model 3 + breast D50, DIBH, nodal radiotherapy, IMRT use, prone positioning, boost use)		Model 5 (Model 4 + clustering within facilities)		Model 6 (Model 5 + academic/teaching status)	
	Mean heart dose (95% CI)	*P*[a]	Mean heart dose (95% CI)	*P*[a]	Mean heart dose (95% CI)	*P*[a]	Mean heart dose (95% CI)	*P*[a]	Mean heart dose (95% CI)	*P*[a]	Mean heart dose (95% CI)	*P*[a]
Left-sided conventional												
Intercept (baseline estimate), Gy	1.71 (1.67 to 1.75)	<.001	1.81 (1.70 to 1.92)	<.001	1.71 (1.60 to 1.83)	<.001	1.66 (1.55 to 1.77)	<.001	1.79 (1.57 to 2.04)	<.001	1.77 (1.53 to 2.05)	<.001
Race group												
Asian, %	−2.7 (−16.54 to 11.14)	.70	−1.5 (−15.26 to 12.33)	0.84	0.0 (−13.67 to 13.58)	0.99	1.2 (−11.27 to 13.73)	0.85	2.8 (−8.65 to 14.21)	.63	2.8 (−8.67 to 14.19)	.64
Black, %	24.5 (19.90 to 29.16)	<.001	23.5 (18.79 to 28.26)	<.001	22.5 (17.82 to 27.22)	<.001	15.5 (11.03 to 19.91)	<.001	8.3 (3.51 to 13.13)	<.001	8.3 (3.45 to 13.08)	<.001
White (referent)		<.001[b]		<.001[b]		<.001[b]		<.001[b]		.003[b]		.003[b]
Left-sided accelerated												
Intercept (baseline estimate), Gy	1.27 (1.24 to 1.30)	<.001	1.33 (1.25 to 1.41)	<.001	1.33 (1.25 to 1.42)	<.001	1.50 (1.40 to 1.60)	<.001	1.56 (1.39 to 1.76)	<.001	1.55 (1.35 to 1.77)	<.001
Race group												
Asian to %	24.9 (8.94 to 40.81)	.002	24.4 (8.58 to 40.29)	.003	24.1 (8.30 to 39.98)	.003	23.6 (8.93 to 38.22)	.002	15.5 (2.59 to 28.48)	.02	15.5 (2.55 to 28.44)	.02
Black to %	20.1 (14.89 to 25.27)	<.001	20.0 (14.70 to 25.27)	<.001	20.3 (14.96 to 25.58)	<.001	17.2 (11.98 to 22.39)	<.001	6.9 (1.38 to 12.41)	.01	6.8 (1.28 to 12.34)	.02
White (referent)		<.001[b]		<.001[b]		<.001[b]		<.001[b]		.004[b]		.004[b]
Right-sided conventional												
Intercept (baseline estimate) to Gy	0.69 (0.67 to 0.71)	<.001	0.72 (0.67 to 0.78)	<.001	0.66 (0.61 to 0.72)	<.001	0.64 (0.59 to 0.69)	<.001	0.66 (0.58 to 0.75)	<.001	0.66 (0.57 to 0.76)	<.001
Race group												
Asian to %	3.6 (−11.12 to 18.32)	.63	4.0 (−10.94 to 18.95)	.60	2.0 (−12.58 to 16.66)	.78	2.3 (−11.53 to 16.20)	.74	−5.0 (−17.81 to 7.92)	.45	−5.0 (−17.86 to 7.88)	.45
Black to %	4.7 (−0.74 to 10.14)	.09	5.2 (−0.51 to 10.83)	.07	4.5 (−1.12 to 10.10)	.12	3.3 (−2.14 to 8.73)	.23	5.6 (−0.29 to 11.43)	.06	5.5 (−0.35 to 11.40)	.07
White (referent)		.23[b]		.19[b]		.29[b]		.48[b]		.12[b]		.12[b]
Right-sided accelerated												
Intercept (baseline estimate)	0.56 (0.54 to 0.58)	<.001	0.60 (0.56 to 0.64)	<.001	0.60 (0.56 to 0.64)	<.001	0.62 (0.58 to 0.67)	<.001	0.62 (0.54 to 0.70)	<.001	0.60 (0.52 to 0.69)	<.001
Race group												
Asian to %	14.4 (0.44 to 28.39)	.04	13.8 (−0.32 to 27.97)	.06	13.9 (−0.26 to 28.04)	.05	9.7 (−3.92 to 23.25)	.16	11.4 (−0.26 to 23.08)	.06	11.3 (−0.37 to 22.97)	.06
Black to %	6.8 (1.37 to 12.24)	.01	8.0 (2.36 to 13.56)	.005	7.8 (2.20 to 13.46)	.006	5.6 (0.03 to 11.25)	.049	12.4 (6.84 to 17.87)	<.001	12.2 (6.72 to 17.76)	<.001
White (referent)		.009[b]		.004[b]		.005[b]		.06[b]		<.001[b]		<.001[b]

[a]Linear regression to 2-sided *P* values. BMI = body mass index; DIBH = deep inspiration breath hold; IMRT = intensity modulated radiation therapy.
[b]Group *P* values. Linear regression to 2-sided *P* values.

Table 3. Variance attributable to patients being clustered by treatment facilities[a]

Population	ICC (empty model (ie no covariates only clustering)) to %	VPC for full model (Model 6) to %	Percent reduction in residual variance (full to empty) to %
Left-sided CWBI	26.7	31.9	19.3
Left-sided AWBI	26.7	29.4	21.4
Right-sided CWBI	25.5	23.1	15.6
Right-sided AWBI	29.2	30.4	10.2

[a]AWBI = accelerated whole breast irradiation; CWBI = conventionally fractionated whole breast irradiation; ICC = intraclass correlation; VPC = variance portioning coefficient.

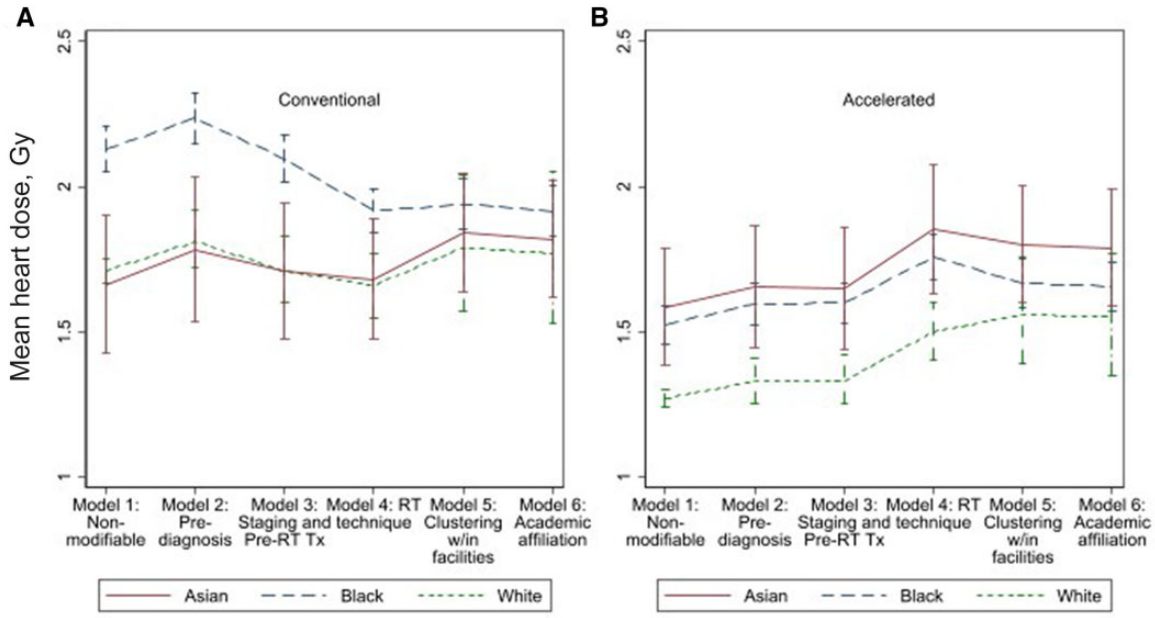

Figure 1. Mean heart dose by race for women with left-sided disease undergoing conventionally fractioned (**A**) and accelerated (**B**) whole breast radiotherapy. Six separate models control for modifiable individual- and facility-level mediators of cardiac dose. For conventionally fractionated whole breast radiotherapy, doses for Black women are elevated compared with those of Asian women and White women. This disparity decreases as radiotherapy (RT) technique and clustering for facilities are controlled for. For accelerated whole breast radiotherapy, doses for Asian and Black women are elevated compared with those of White women. Clustering within facilities accounts for a substantial proportion of the disparity among Black women but only a modest proportion for Asian women. **Error bars** represent 95% confidence intervals. Tx = treatment.

9.52, White women = 6.91; deaths: Asian women = 3.06, Black women = 4.76, White women = 3.46). For Asian women undergoing CWBI for left-sided disease, the combination of similar MHD but lower prevalence of cardiac risk factors resulted in estimates of 0.8 fewer cardiac events and 0.4 deaths per 1000 Asian women vs White women (Figure 2). For women with left-sided disease treated with AWBI, we estimate an excess of 1.7 events and 0.8 death per 1000 Black women and 0.7 events and 0.4 deaths per 1000 women for Asian women vs White women (Figure 2 events: Asian women = 5.83, Black women = 6.82, White women = 5.13; deaths: Asian women = 2.92, Black women = 3.41, White women = 2.57).

Discussion

In this study of cardiac dose among women undergoing whole breast RT, we identified statistically and clinically significant racial disparities. To our knowledge, this the first study examining racial disparities in cardiac dose across institutions. After accounting for nonmodifiable factors, cardiac dose was 7%-25% higher among Asian women and Black women treated with accelerated fractionation (regardless of laterality) and 25% higher among Black women with left sided-disease treated with conventional fractionation. The largest mediators were facility-level variation in practice and individual-level differences in radiation technique. However, disparities were not fully explained, especially for Asian women. When accounting for disparities in baseline cardiac risk factors, the dosimetric disparities translated into an estimated excess of 2.6 ischemic events and 1.3 deaths per 1000 Black women treated with conventional fractionation for left-sided disease compared with White women. Smaller, but notable disparities occurred for Asian women and Black women treated with accelerated fractionation for left-sided disease. These disparities should be addressed.

DIBH use may partially explain these disparities. DIBH reduces dose in up to 67% of women (7-10). In our study, controlling for radiation technique, which included DIBH, reduced the dose disparity for Black women by 30%. DIBH was only used in 14% of Black women vs approximately 30%-45% of Asian women and White women treated with conventional fractionation for left-sided disease. Patient tolerance (11) drives DIBH use (due to the required breath hold) but is unlikely the sole

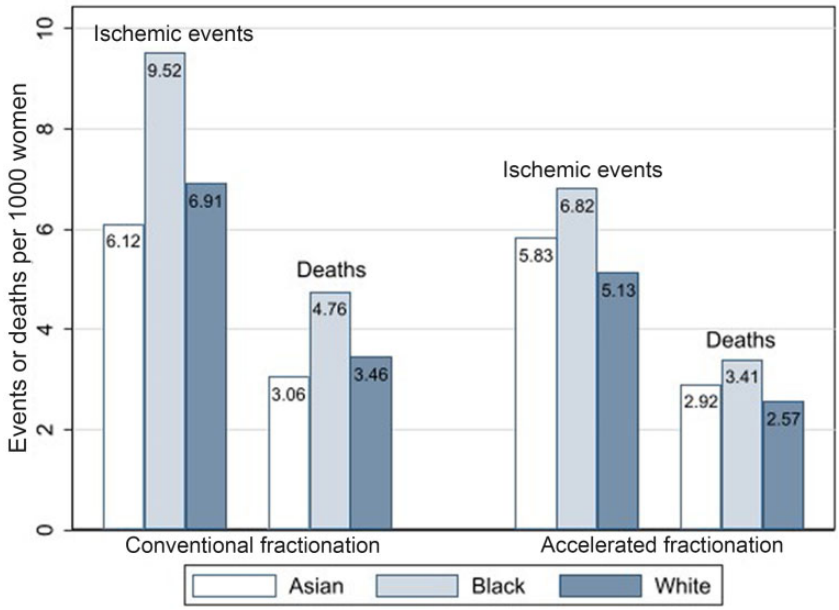

Figure 2. Cumulative risk of death or development of at least 1 of radiation-associated ischemic events for women who received conventionally fractionated or accelerated whole breast irradiation at age 60 years for left-sided disease. This figure shows race-stratified estimates for the number of women experiencing at least 1 radiation-associated ischemic cardiac event or death from an ischemic cardiac event by age 80 years as a result of radiation received at age 60 years. Mean cardiac doses were derived from Model 1, given that these doses most closely reflect the present-day experience. Absolute risks were calculated using the prevalence of 0 vs 1 or more cardiac risk factors.

explanation. Instead, facility availability and/or typical practice may drive DIBH use, because it was not used during the study period at the 2 facilities with the largest proportions of Black women (where 50% of Black women were treated). DIBH is reportedly affordable to most departments (12-14), but inequities in payor mix across facilities may drive disparities. This illustrates how structural racism can drive facility-level disparities.

Additional radiation factors beyond DIBH may drive cardiac dose disparities. IMRT was used more commonly in Black women and associated with increased cardiac dose in this and previous MROQC studies (4). Although some IMRT techniques may decrease cardiac dose relative to tangents, others may increase cardiac dose (15) (eg, previous analyses suggested higher MHD with inverse vs forward planning) (4). It is unknown whether IMRT techniques inadvertently increased cardiac dose and mediated the observed racial disparities. Optimal IMRT techniques may be inadvertently underused in Black women, given the literature demonstrating racial disparities in technology dissemination (16-20). However, independent of a causal mechanism, IMRT may simply represent a marker for "unfavorable" anatomy. Physicians may employ IMRT for unfavorable anatomy (extreme anterolateral cardiac location). Even if IMRT is optimized to reduce dose compared with standard tangents, the average dose may exceed that of patients with "favorable" anatomy in whom 3-dimensional techniques are often employed. Future studies should conduct more sophisticated dosimetric analyses and collect data that could illuminate the rationale for IMRT use, because distinguishing between use for unfavorable heart position vs standard treatment would help clarify whether IMRT is contributing to cardiac dose disparities. Further research is needed to optimize IMRT tradeoffs, because minimization of cardiac dose can increase breast dose heterogeneity and noncardiac toxicity or lead to tumor bed undercoverage.

We also found that cardiac dose disparities were mediated through facility-level practice variation. This suggests that Asian women and Black women are more likely to obtain care at facilities whose typical practices result in higher cardiac doses independent of use of techniques like DIBH, proning, and IMRT. These differences are large enough to drive measurable differences in cardiac dose. Clinical judgement was used to determine tradeoffs on an individual patient basis. It remains possible that some of the disparity we observed is due to acceptable provider- or facility-level variation in tradeoff preferences. Nonetheless, disparities in DIBH use and other technical factors (use of proning when DIBH not available or feasible) refute the notion the disparities observed in our study were inevitable and instead suggest that, in many cases, cardiac dose could have been further reduced without compromising breast coverage. Emphasis should therefore be placed not only on availability and use of DIBH and proning techniques but on optimization of planning to reduce cardiac dose regardless of which treatment and planning techniques are employed.

In the short term, facilities may benefit from interfacility collaboration and adherence to national guidelines to facilitate uptake of discuss best practices. Indeed, MRQOC implemented standard cardiac dose constraints in 2015, which were associated with a statewide reduction in cardiac dose (4). However, sustainable solutions must be rooted in an understanding of why racial disparities exist in the first place. The vast majority of individual- and facility-level racial disparities are rooted in structural racism (5). The literature is replete with studies demonstrating that facilities that serve greater numbers of racial and ethnic minoritized patients are typically underresourced, resulting in lower-quality care (21). These disparities are driven by racism in education, housing, employment, and other sectors, which ultimately influence payor mix, reimbursement, and other factors that dictate distribution of facility resources (5). They impede facilities' bandwidth for providing modern, high-quality care, which may explain delayed uptake of technologies like DIBH. However, structural racism may influence application of new medical

research even if no new technology is required. For example, a separate MROQC analysis demonstrated decreased use of hypofractionation among Black women (20) despite the fact that it requires no new technology and only application of newer clinical trial data. The disparity was completely explained by decreased use of hypofractionation among facilities that treated larger proportions of Black women. This is consistent with other studies demonstrating that racial disparities are sometimes explained by delayed incorporation of new research at minority serving facilities (19). These delays may be driven by financial or social exclusion from spaces where advances are published and discussed, or limited time, incentives, or human capital to implement these advances (especially if they are not tied to research, reimbursement, or productivity metrics).

In addition to its impact on institutions, structural and interpersonal racism also acts directly on patients by contributing to disparities in baseline cardiac risk factors. For Black women, disparities in cardiac risk factors magnified the dosimetric disparities we identified. Only 11% of Black women in the study had no cardiac risk factors, which is deeply concerning and speaks to the devastating impact of racism in society. To completely eliminate disparities in cardiac toxicity after RT, solutions must address disparities in radiation technology use and at earlier stages of the cancer continuum (including prediagnosis).

Limitations of our study include the lack of data on Hispanic or Latinx ethnicity, the small numbers of Asian women, and the degree of unexplained disparity for Asian women. Collection of race and ethnicity data must be emphasized to address these disparities. Additionally, our data are limited to a single state. Measuring cardiac dose disparities is challenging because these data are not collected in cancer registries. Single institution and clinical trial data represent alternatives but have limited generalizability to the broader population. Another limitation is that our dose estimates of clinical significance were not biocorrected. Furthermore, the MHDs were at the lower end of the range of doses in the study by Darby et al. (1), which may decrease the confidence in the estimates and suggest less clinical significance. They are also based on European data, which may not fully generalize to our population. Additional unmeasured variables or nuances in measurement that might be missed because of grouping into categories may have affected the identification and quantification of variables mediating cardiac dose. Finally, future efforts to expand the understanding of racial disparities in cancer outcomes should strive to collect the data necessary to directly examine the incidence of cardiac events in large diverse cohorts of patients treated for breast cancer, controlling also for potentially cardiotoxic and cardiopreventive medications received, to build on the findings of the this study focused on cardiac radiation dose.

In conclusion, we identified disparities in cardiac dose among Asian women and Black women undergoing whole breast RT. These disparities are primarily mediated through differences in radiation technique and facility-level practice patterns. Given that these disparities might increase the risk of death and disability from cardiac events, solutions to address them should be prioritized.

Funding

This work was supported by Blue Cross Blue Shield of Michigan and the Blue Care Network of Michigan as part of the BCBSM Value Partnerships Program.

Notes

Role of the funder: The funder had no role in the data collection, study design, analysis, data interpretation, report writing, or decision to submit the paper for publication.

Disclosures: CC received grants from the National Cancer Institute (to institution), and honoraria from Oregon Health and Science University, the Mayo Clinic, New York University and the National Comprehensive Cancer Institute, AL served as webinar lead for the ACR Commission on Radiation Oncology, KG, JM, LP, RJ, JH and MM received grants (to institution) from the Blue Cross Blue Shield of Michigan which funds the Michigan Radiation Oncology Quality Consortium, EW received grants from Pfizer/American Cancer Society and Genetech, JM received grants to the institution from the National Institutes of Health and Varian Medical Systems and consulting fees from the US Federal Government (Department of Veterans Affairs) for contracting work as a medical physicist, honoraria from MD Anderson Cancer Center, funding for travel from Sun Nuclear QA Symposium for travel, has a patent pending for combined radiation acoustics and ultrasound for radiotherapy guidance and cancer targeting, is chair or vice chair of multiple committees of the American Association of Physicists in Medicine, and has received equipment from Modus Medical, LP has patents from under PFS Genomics, is Chair of the Board of the American Society of Clinical Oncology, is a member of the Breast Cancer Research Foundation Scientific Advisory Board, and receives royalties from UpToDate, and RJ is an uncompensated founding member of TIME'S UP Healthcare, a member of the Board of Directors of ASCO, and co-chair of ASTRO's Ethics Committee, has served as an expert witness for Sherinian and Hasso and Dressman Benzinger LaVelle, has stock options as compensation for her advisory board role in Equity Quotient, a company that evaluates culture in health care companies; has received personal fees from Amgen and Vizient and grants for unrelated work from the National Institutes of Health, the Doris Duke Foundation, the Greenwall Foundation, the Komen Foundation, and has a contract to conduct an investigator initiated study with Genentech.

Author contributions: Conceptualization: CC RJ KG JM AL LP. Data curation: KG MM. Formal analysis: CC KG. Funding acquisition: RJ JM JH MM LP. Investigation: CC RJ KG JM MD JH AL MM EA EW FV LP. Methodology: CC RJ KG JM FV LP. Project administration: CC RJ JM KG MM FV LP. Resources: RJ KG JM MD JH AL MM EA EW FV LP. Software: CC KG. Supervision: RJ KG JM MM FV LP. Validation: RJ KG JM MM LP. Visualization: CC KG. Writing—original draft: CC RJ KG LP. Writing—reviewing and editing: CC RJ KG JM MD JH AL MM EA EW FV LP.

Prior presentations: This work was presented in part at the American Society for Radiation Oncology Annual Meeting, September 15, 2019.

Data Availability

Individual participant data cannot be made publicly available, as anonymization is not possible. This is an analysis of a multi-institution statewide observational dataset in which the data-sharing agreement with each participating institution states that the data belong to the member institutions.

References

1. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987-998.

ARTICLE

2. Jagsi R, Griffith KA, Moran JM, et al. A randomized comparison of radiation therapy techniques in the management of node-positive breast cancer: primary outcomes analysis. *Int J Radiat Oncol Biol Phys*. 2018;101(5):1149-1158.
3. Jha AK, Varosy PD, Kanaya AM, et al. Differences in medical care and disease outcomes among Black and White women with heart disease. *Circulation*. 2003;108(9):1089-1094.
4. Pierce LJ, Feng M, Griffith KA, et al. Recent time trends and predictors of heart dose from breast radiation therapy in a large quality consortium of radiation oncology practices. *Int J Radiat Oncol Biol Phys*. 2017;99(5):1154-1161.
5. Bailey ZD, Krieger N, Agénor M, et al. Structural racism and health inequities in the USA: evidence and interventions. *Lancet*. 2017;389(10077):1453-1463.
6. Moran JM, Feng M, Benedetti LA, et al.; Michigan Radiation Oncology Quality Consortium. Development of a model web-based system to support a statewide quality consortium in radiation oncology. *Pract Radiat Oncol*. 2017;7(3):e205-e213.
7. Yeung R, Conroy L, Long K, et al. Cardiac dose reduction with deep inspiration breath hold for left-sided breast cancer radiotherapy patients with and without regional nodal irradiation. *Radiat Oncol*. 2015;10(1):200.
8. Latty D, Stuart KE, Wang W, et al. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. *J Med Radiat Sci*. 2015;62(1):74-81.
9. Remouchamps VM, Vicini FA, Sharpe MB, et al. Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. *Int J Radiat Oncol Biol Phys*. 2003;55(2):392-406.
10. Bergom C, Currey A, Desai N, et al. Deep inspiration breath hold: techniques and advantages for cardiac sparing during breast cancer irradiation. *Front Oncol*. 2018;8:87.
11. Desai N, Currey A, Kelly T, et al. Nationwide trends in heart-sparing techniques utilized in radiation therapy for breast cancer. *Adv Radiat Oncol*. 2019;4(2):246-252.
12. Bartlett FR, Colgan RM, Carr K, et al. The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol*. 2013;108(2):242-247.
13. Eldredge-Hindy HB, Duffy D, Yamoah K, et al. Modeled risk of ischemic heart disease following left breast irradiation with deep inspiration breath hold. *Pract Radiat Oncol*. 2015;5(3):162-168.
14. Macrie BD, Donnelly ED, Hayes JP, et al. A cost-effective technique for cardiac sparing with deep inspiration-breath hold (DIBH). *Phys Med*. 2015;31(7):733-737.
15. Jagsi R, Moran J, Marsh R, et al. Evaluation of four techniques using intensity-modulated radiation therapy for comprehensive locoregional irradiation of breast cancer. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1594-1603.
16. Peterson ED, Shaw LK, DeLong ER, et al. Racial variation in the use of coronary-revascularization procedures—are the differences real? Do they matter? *N Engl J Med*. 1997;336(7):480-486.
17. McClelland S, 3rd, Kaleem T, Bernard ME, et al. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States-Part 4: Appalachian patients. *Adv Radiat Oncol*. 2018;3(4):471-477.
18. McClelland S, 3rd, Page BR, Jaboin JJ, et al. The pervasive crisis of diminishing radiation therapy access for vulnerable populations in the United States, part 1: African-American patients. *Adv Radiat Oncol*. 2017;2(4):523-531.
19. Samuel CA, Landrum MB, McNeil BJ, et al. Racial disparities in cancer care in the Veterans Affairs health care system and the role of site of care. *Am J Public Health*. 2014;104(Suppl 4):S562-71.
20. Laucis AM, Jagsi R, Griffith KA, et al. The role of facility variation on racial disparities in use of hypofractionated whole breast radiation therapy. *Int J Radiat Oncol Biol Phys*. 2020;107(5):949-958.
21. Hasnain-Wynia R, Baker DW, Nerenz D, et al. Disparities in health care are driven by where minority patients seek care: examination of the hospital quality alliance measures. *Arch Intern Med*. 2007;167(12):1233-1239.