The Effect of Hospital Volume on Breast Cancer Mortality

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Objective: The aim of this study was to determine whether hospital volume was associated with mortality in breast cancer, and what thresholds of case volume impacted survival.

Background: Prior literature has demonstrated improved survival with treatment at high volume centers among less common cancers requiring technically complex surgery.

Methods: All adults (18 to 90 years) with stages 0-III unilateral breast cancer diagnosed from 2004 to 2012 were identified from the American College of Surgeons National Cancer Data Base (NCDB). A multivariable Cox proportional hazards model with restricted cubic splines was used to examine the association of annual hospital volume and overall survival, after adjusting for measured covariates. Intergroup comparisons of patient and treatment characteristics were conducted with X^2 and analysis of variance (ANOVA). The log-rank test was used to test survival differences between groups. A multivariable Cox proportional hazards model was used to estimate hazard ratios (HRs) associated with each volume group.

Results: One million sixty-four thousand two hundred and fifty-one patients met inclusion criteria. The median age of the sample was 60 (interquartile range 50 to 70). Hospitals were categorized into 3 groups using restricted cubic spline analysis: low-volume (<148 cases/year), moderate-volume (148 to 298 cases/year), and high-volume (>298 cases/year). Treatment at high volume centers was associated with an 11% reduction in overall mortality for all patients (HR 0.89); those with stage 0-I, ER+/PR+ or ER+/PR- breast cancers derived the greatest benefit.

Conclusions: Treatment at high volume centers is associated with improved survival for breast cancer patients regardless of stage. High case volume could serve as a proxy for the institutional infrastructure required to deliver complex multidisciplinary breast cancer treatment.

Keywords: breast cancer, hospital volume, mortality

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Breast cancer is the most common cancer diagnosis among women in the United States, comprising 29% of all newly diagnosed female cancers each year.[1] The contemporary treatment of breast cancer has become increasingly complex. Heterogeneous tumor biology drives diverse systemic therapy strategies, surgical and radiation treatment plans are often interdependent, and a large and growing body of research guides nuanced clinical practices. As a result, many oncology providers and treatment centers now focus on subspecialty breast cancer care.

Previously published literature has established a relationship between hospital volume and cancer outcomes.[2,3] Higher volume treatment centers have reported a lower 30-day operative mortality and improved long-term survival, especially among less common malignancies requiring complex surgical care (pancreas and esophageal cancer and sarcomas). Similar findings have been identified for breast cancer.

The American Society for Clinical Oncology and American College of Surgeons Commission on Cancer (CoC) encourage women with breast cancer to inquire about specialization and practitioner experience when identifying quality comprehensive cancer care.[4,5] Published data support these recommendations, demonstrating improved 5-year mortality among women with breast cancer treated by surgeons defined as "high volume."[6] Patients are faced with decisions not only about which cancer treatments to choose but also where to receive this care.

Thus, we sought to determine whether annual hospital breast cancer volume impacted the overall survival (OS) among women with nonmetastatic breast cancer, and which subsets of breast cancer patients would benefit most from seeking care at high volume centers. Furthermore, using novel statistical methods, we aimed to define which thresholds of case volume provided best discrimination between groups. We hypothesized that treatment at higher volume hospitals is associated with improved survival among curable breast cancer patients, and that certain subgroups of patients would derive the greatest benefit.

METHODS

The data source for this study was the National Cancer Data Base (NCDB) maintained by the American College of Surgeons and the American Cancer Society. The NCDB data are derived from hospital registry data on more than 1500 CoC-accredited facilities and represents 70% of newly diagnosed cancers in the United States.[4] Following IRB approval, the database was queried for all adults (men and women) between the ages of 18 and 90 years who were diagnosed with unilateral stage 0-III in situ or invasive breast cancer from 2004 to 2012. Patients who had bilateral breast cancers or unknown laterality were excluded. Information on epidermal growth factor Her-2 status was omitted due to limited data availability in the NCDB database. The consort diagram describing inclusion and exclusion criteria is included as Fig. 1.

Collected covariates included age at diagnosis, gender, race, education, ethnicity, insurance status, income level, comorbidity score, stage at diagnosis, hormone receptor status, surgery type, hormone therapy after surgery, hospital type and geographic location, time from diagnosis to surgery (in days), use of radiation, use of chemotherapy, distance traveled to treating hospital, treatment received at more than 1 CoC facility, and tumor size. Race and ethnicity were combined to create 6 categories: non-Hispanic White, non-Hispanic Black, non-Hispanic other, Hispanic White, Hispanic

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The authors have no commercial interests to disclose with regard to the presented research.

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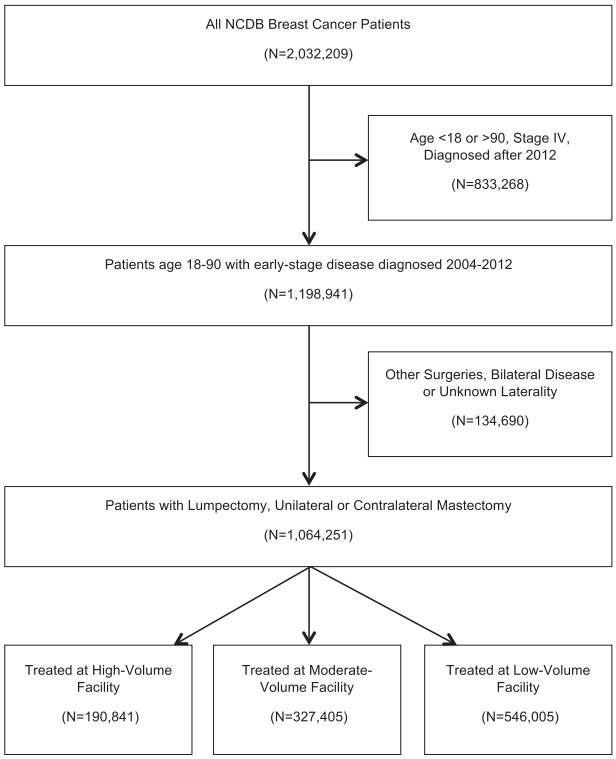

FIGURE 1. Study population selection criteria from NCDB database. The study population was selected form the National Cancer Database and included breast cancer patients who were diagnosed from 2004 to 2012 who underwent lumpectomy, unilateral, or contralateral mastectomy. The final cohort sample size was 1,064,251.

Black, and Hispanic other. Due to the paucity of data on Asians, American Indians/Alaskan Natives, and Native Hawaiian/Pacific Islanders, these racial categories were collapsed into non-Hispanic other and Hispanic other. Insurance status was composed of 3 categories—private, government, and none. Income level was dichotomized into <$35,000 and ≥$35,000.

Hormone receptor status was based on estrogen (ER) and progesterone (PR) receptors and was coded as a combined ER/PR status with 4 possible values: ER+/PR+, ER+/PR-, ER-/PR+, or ER-/PR-. Surgery type included lumpectomy, unilateral mastectomy, and contralateral mastectomy. The use of radiation, chemotherapy, and hormone therapy was dichotomized as yes or no. Chemotherapy was further divided into neoadjuvant and adjuvant. NCDB designations of hospital type as academic, comprehensive, community, or integrated were applied. Twenty-five hospitals had multiple hospital type designations, and among these, the most representative designation was selected. Hospital locations were based on the 4 NCDB assigned geographic regions of Midwest, Northeast, South, and West. Comorbidity score was based on the Charlson-Deyo score and divided into 3 groups with scores of 0, 1, and ≥2. Age, distance travelled to treating hospital, and tumor size remained as continuous variables throughout the analysis.

The average annual hospital volume was calculated as the number of breast cancer cases treated at a given facility divided by the number of years the facility had participated in the NCDB. OS was defined as time from diagnosis to death or last follow-up. Patients who did not die were censored at the date of last follow-up. Mortality was not limited to breast cancer related mortality but rather defined as all-cause mortality.

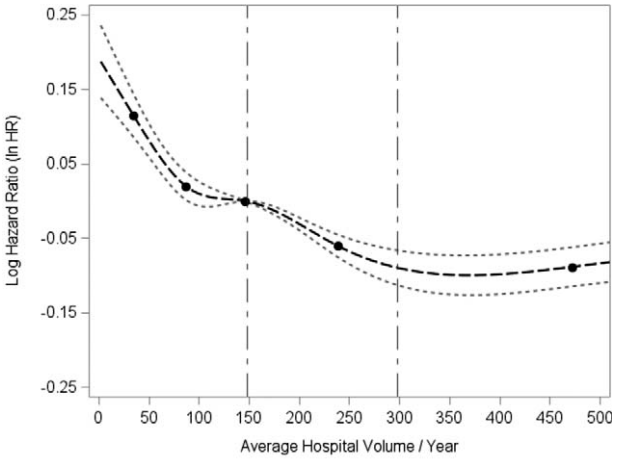

FIGURE 2. Scatter plot of log HR by average annual hospital volume with restricted cubic spline fit. Relationship between risk of death and annual hospital volume after adjustment for known covariates. Black dashed line represents the restricted cubic spline (RCS) fit with knots indicated by black dots. Gray dotted lines represent the 95% confidence interval for the RCS fit.

Hospital Volume Groups

To determine the hospital volume groups, we created a multivariable Cox proportional hazards model (Model 1) with restricted cubic splines (RCS, Fig. 2). Covariates in the model included gender, race/ethnicity, insurance status, income level, comorbidity score, stage at diagnosis, ER-status, PR-status, surgery type, hospital type, hospital location, use of radiation, use of chemotherapy, distance traveled to treating hospital, age, and tumor size. The use of RCS allows for a flexible multivariable model that accounts for the nonlinear relationship between average annual hospital volume and survival without assuming the location or existence of potential cutpoints.[7] Due to the large sample size, a 5-knot model, with knots placed at the 5th, 28th, 50th, 73rd, and 95th percentiles, was used to better define the relationship between annual hospital volume and survival.[8] Alternative models considered included 3 and 4-knot models and free knot models, specifically thin-plate splines and adaptive splines.[9,10] Final model selection was based on the Akaike Information Criteria (AIC). Results from our model identified 2 ranges of values of average annual hospital volume that corresponded to changes in the log hazard ratio (HR). Further analysis was conducted with bootstrap simulation with a Monte Carlo Markov Chain procedure that estimated 147.22 [95% confidence interval (95% CI) 126.32–149.14] and 297.26 (95% CI 257.87–328.69) as the points within each of the ranges that corresponded to the maximum change in log HR.[11] On the basis of the estimated points (147 and 297), 3 hospital volume groups were created—low-volume (<148 cases/year), moderate-volume (148 to 298 cases/year), and high-volume (>298 cases/year).

Univariate Analysis of Volume groups

For the 3 volume groups (low, moderate, and high), sociodemographic variables, clinical variables, geographic location, and facility type were summarized by frequencies (%) for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. A descriptive analysis was conducted comparing

TABLE 1. Patient Demographics and Treatment Summary Statistics

	All Patients (N = 1,064,251)	**High-volume (>298 Cases/Year) (N = 190,841)**	**Moderate-volume (148–298 Cases/Year) (N = 327,405)**	**Low-volume (<148 Cases/Year) (N = 546,005)**	***P*†**
Socio-demographic					
Age, y					<0.0001
≤40	61,133 (5.7%)	13,130 (6.9%)	19,980 (6.1%)	28,023 (5.1%)	
41–55	342,476 (32.2%)	67,468 (35.4%)	110,088 (33.6%)	164,920 (30.2%)	
56–69	382,912 (36%)	67,784 (35.5%)	117,194 (35.8%)	197,934 (36.3%)	
≥70	277,730 (26.1%)	42,459 (22.2%)	80,143 (24.5%)	155,128 (28.4%)	
Median (IQR)	60 (50–70)	58 (49–68)	59 (50–69)	61 (51–71)	
Gender					<0.0001
Female	1,056,157 (99.2%)	189,599 (99.3%)	325,241 (99.3%)	541,317 (99.1%)	
Male	8094 (0.8%)	1242 (0.7%)	2164 (0.7%)	4688 (0.9%)	
Race/Ethnicity					<0.0001
Non-Hispanic White	794,859 (74.7%)	135,676 (71.1%)	246,365 (75.2%)	412,818 (75.6%)	
Non-Hispanic Black	105,691 (9.9%)	21,122 (11.1%)	29,872 (9.1%)	54,697 (10%)	
Non-Hispanic Other	37,746 (3.5%)	7416 (3.9%)	14,606 (4.5%)	15,724 (2.9%)	
Hispanic White	46,652 (4.4%)	8886 (4.7%)	14,466 (4.4%)	23,300 (4.3%)	
Hispanic Black	1182 (0.1%)	407 (0.2%)	303 (0.1%)	472 (0.1%)	
Hispanic other	2286 (0.2%)	491 (0.3%)	577 (0.2%)	1218 (0.2%)	
Insurance status					<0.0001
Private	592,164 (55.6%)	119,561 (62.6%)	193,857 (59.2%)	278,746 (51.1%)	
Government	439,253 (41.3%)	67,440 (35.3%)	125,973 (38.5%)	245,840 (45%)	
None	18,992 (1.8%)	2513 (1.3%)	4597 (1.4%)	11,882 (2.2%)	
Income level					<0.0001
<$35,000	261,685 (24.6%)	35,925 (18.8%)	65,162 (19.9%)	160,598 (29.4%)	
≥$35,000	765,301 (71.9%)	147,695 (77.4%)	250,627 (76.5%)	366,979 (67.2%)	
Education level					<0.0001
≤80% high school graduation rate	346,982 (32.6%)	54,865 (28.7%)	92,969 (28.4%)	199,148 (36.5%)	
>80% high school graduation rate	679,891 (63.9%)	128,701 (67.4%)	222,798 (68%)	328,392 (60.1%)	
Distance traveled (mi) – Median (IQR)	8.4 (4–17.4)	10 (4.9–20.4)	8.7 (4.4–17.6)	7.6 (3.5–16.1)	<0.0001
Comorbidity score					<0.0001
0	909,281 (85.4%)	166,186 (87.1%)	282,309 (86.2%)	460,786 (84.4%)	
1	128,547 (12.1%)	20,671 (10.8%)	37,706 (11.5%)	70,170 (12.9%)	
≥2	26,423 (2.5%)	3984 (2.1%)	7390 (2.3%)	15,049 (2.8%)	
Clinical					
Stage at diagnosis					<0.0001
0	261,382 (24.6%)	49,578 (26%)	83,139 (25.4%)	128,665 (23.6%)	
I	491,991 (46.2%)	87,922 (46.1%)	149,641 (45.7%)	254,428 (46.6%)	
II	247,817 (23.3%)	43,715 (22.9%)	75,918 (23.2%)	128,184 (23.5%)	
III	63,061 (5.9%)	9626 (5%)	18,707 (5.7%)	34,728 (6.4%)	
Tumor size (cm) – Median (IQR)	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.5 (0.9–2.5)	<0.0001
ER status					<0.0001
Positive	799,344 (75.1%)	142,958 (74.9%)	247,583 (75.6%)	408,803 (74.9%)	
Negative	184,810 (17.4%)	32,625 (17.1%)	56,531 (17.3%)	95,654 (17.5%)	
PR status					<0.0001
Positive	687,040 (64.6%)	121,725 (63.8%)	212,841 (65%)	352,474 (64.6%)	
Negative	283,544 (26.6%)	50,917 (26.7%)	87,067 (26.6%)	145,560 (26.7%)	
ER/PR status combined					<0.0001
ER+/PR+	677,015 (63.6%)	120,093 (62.9%)	209,890 (64.1%)	347,032 (63.6%)	
ER+/PR−	109,368 (10.3%)	20,106 (10.5%)	33,721 (10.3%)	55,541 (10.2%)	
ER−/PR+	9632 (0.9%)	1576 (0.8%)	2879 (0.9%)	5177 (0.9%)	
ER−/PR−	173,282 (16.3%)	30,625 (16%)	53,129 (16.2%)	89,528 (16.4%)	
Treatment					
Surgery					<0.0001
Lumpectomy	676,223 (63.5%)	117,190 (61.4%)	205,075 (62.6%)	353,958 (64.8%)	
Unilateral mastectomy	274,419 (25.8%)	49,836 (26.1%)	83,846 (25.6%)	140,737 (25.8%)	
Contralateral mastectomy	113,609 (10.7%)	23,815 (12.5%)	38,484 (11.8%)	51,310 (9.4%)	
Reconstruction					<0.0001
None	929,294 (87.3%)	155,853 (81.7%)	278,782 (85.1%)	494,659 (90.6%)	
Implant	49,835 (4.7%)	13,591 (7.1%)	18,040 (5.5%)	18,204 (3.3%)	
Tissue	45,426 (4.3%)	12,093 (6.3%)	16,636 (5.1%)	16,697 (3.1%)	
Combined (Implant + Tissue)	16,239 (1.5%)	4843 (2.5%)	5647 (1.7%)	5749 (1.1%)	
Reconstruction (NOS)	23,457 (2.2%)	4461 (2.3%)	8300 (2.5%)	10,696 (2%)	
Radiation	610,291 (57.3%)	106,114 (55.6%)	185,617 (56.7%)	318,560 (58.3%)	<0.0001

TABLE 1. (*Continued*)

	All Patients (N = 1,064,251)	High-volume (>298 Cases/Year) (N = 190,841)	Moderate-volume (148–298 Cases/Year) (N = 327,405)	Low-volume (<148 Cases/Year) (N = 546,005)	*P*†
Hormone therapy (after surgery)	517,677 (48.6%)	92,503 (48.5%)	156,276 (47.7%)	268,898 (49.2%)	<0.0001
Chemotherapy	360,255 (33.9%)	67,235 (35.2%)	110,194 (33.7%)	182,826 (33.5%)	<0.0001
Type of chemotherapy*					<0.0001
Neoadjuvant	85,260 (23.7%)	17,623 (26.2%)	28,086 (25.5%)	39,551 (21.6%)	
Adjuvant	250,869 (69.6%)	43,749 (65.1%)	74,601 (67.7%)	132,519 (72.5%)	
Time from diagnosis to surgery (Days) – Median (IQR)	33 (19–56)	37 (22–63)	35 (21–58)	29 (17–51)	<0.0001
Hospital					
Type					<0.0001
Academic	315,556 (29.7%)	88,905 (46.6%)	127,366 (38.9%)	99,285 (18.2%)	
Comprehensive	551,579 (51.8%)	63,092 (33.1%)	161,848 (49.4%)	326,639 (59.8%)	
Community	118,163 (11.1%)	1639 (0.9%)	934 (0.3%)	115,590 (21.2%)	
Integrated network	77,220 (7.3%)	35,497 (18.6%)	37,257 (11.4%)	4466 (0.8%)	
Other	1733 (0.2%)	1708 (0.9%)	0 (0%)	25 (0%)	
Location					<0.0001
Midwest	272,722 (25.6%)	48,982 (25.7%)	66,370 (20.3%)	157,370 (28.8%)	
Northeast	239,674 (22.5%)	45,127 (23.6%)	81,176 (24.8%)	113,371 (20.8%)	
South	360,381 (33.9%)	71,352 (37.4%)	101,422 (31%)	187,607 (34.4%)	
West	191,474 (18%)	25,380 (13.3%)	78,437 (24%)	87,657 (16.1%)	
Treatment received at >1 facility	219,782 (20.7%)	46,659 (24.4%)	70,057 (21.4%)	103,066 (18.9%)	<0.0001

Data presented as N (%) unless otherwise specified. Percentages may not add up to 100 due to rounding or missing values.
*Type of chemotherapy proportions are out of all patients who received chemotherapy.
†*P* value for chi-squared test for categorical variables, and ANOVA for continuous variables.

treatment (surgery, radiation, and chemotherapy) by stage at diagnosis between the 3 volume groups. Intergroup comparisons were conducted using the chi-squared test or analysis of variance (ANOVA) as appropriate. A Kaplan-Meier plot was used to visualize survival differences, and the log-rank test was used to test for differences in OS between the 3 volume groups.

Multivariable Analysis

A multivariable Cox proportional hazards model (Model 2) was created including hospital volume as a 3-level variable defined by cubic splines as described above. Other covariates in this model included gender, race/ethnicity, insurance status, income level, education, comorbidity score, stage at diagnosis, ER/PR-status, surgery type, hospital type, hospital location, use of radiation, use of chemotherapy, use of hormone therapy, distance traveled to treating hospital, age, tumor size, and treatment at multiple facilities. To account for intrahospital dependence, a robust sandwich covariance matrix estimate was utilized.

To determine if an interaction between volume and specific variables exists, subsequent multivariable Cox proportional hazards models (Model 3) were created. An interaction term of volume by hormone receptor status, age, insurance status, income level, education, race/ethnicity, hormone therapy use, or stage was included to determine if the effect of volume on survival differed on the basis of the value of the listed variables. All the covariates used in Model 2 were also included. Adjusted HRs were estimated at each level of the interaction variable for each pairwise volume group comparison (high vs low and moderate vs low). A significance level of 0.01 was used for all statistical tests. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Population Demographics

One million sixty-four thousand two hundred fifty-one patients fulfilled our inclusion criteria. The median age was 60 (IQR 50 to 70). The sample was predominantly female (99.2%) and non-Hispanic white (74.7%). The majority of patients had private insurance (55.6%), an income ≥$35,000 (71.9%), and came from areas of higher education levels defined by the NCDB as high school graduation rates of over 80% (63.9%). Most of the subjects reported no comorbidities (85.4%). Most patients had hormone receptor positive tumors (ER+/PR+ 63.6%), and stage I disease (46.2%) at diagnosis. Approximately half of the subjects received radiation therapy (57.3%) and hormone therapy (48.6%) after surgery. Most patients received their care in a comprehensive hospital as defined by the NCDB (51.8%) (Table 1).

Univariate Intergroup Analysis by Volume

There were 1044 low-volume (51.3% of patients), 181 moderate-volume (30.8% of patients) and 52 high-volume (17.9% of patients) hospitals in the study sample. The median case volume for the low, moderate, and high-volume hospitals was 52 cases (IQR 32 to 86), 194 (IQR168 to 236), and 385 (IQR 333 to 462) per year, respectively (Fig. 2). The patients in the hospital volume groups did not differ substantially by age, race/ethnicity, gender, comorbidity, stage, hormone receptor status, and hormone therapy.

Patients receiving treatment at low-volume centers (Table 1) were more likely to have government insurance (45% low, 38.5% moderate, and 35.3% high), income <$35,000 (low 29.4%, moderate 19.9%, and high 18.8%), and lower educational attainment (≤80% high school graduation rate: low 36.5%, moderate 28.4%, and high 28.7%).

The rates of lumpectomy and unilateral mastectomy, chemotherapy, endocrine therapy, and radiation therapy did not differ between the 3 volume groups for any stage. However, across all stages, treatment at higher volume centers resulted in a slightly increased likelihood of contralateral mastectomy (high 12.5%, moderate 11.8%, and low 9.4%). Individuals receiving treatment at high-volume centers (Table 1) had the longest time from diagnosis to surgery.

Comparison of OS between the groups demonstrated a survival benefit for treatment at high-volume centers (log-rank

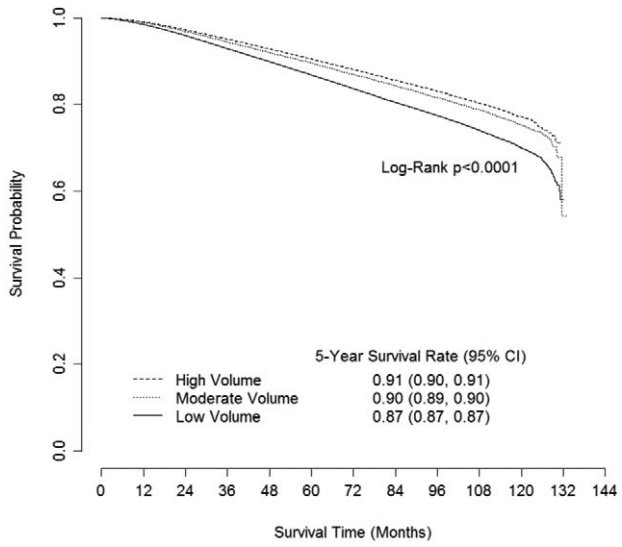

FIGURE 3. Unadjusted Kaplan-Meier curve for overall survival (N = 1,058,198). Relationship between hospital volume and unadjusted overall survival by months (log-rank $P < 0.0001$).

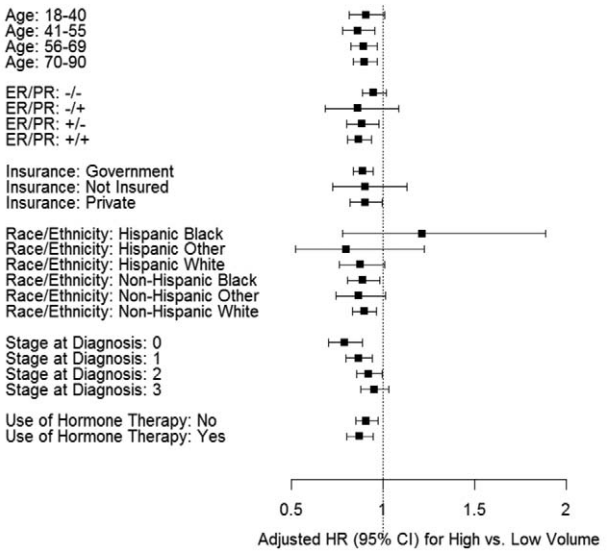

FIGURE 4. Adjusted hazard ratios for high versus low-volume facilities by subgroup. Relationship between hospital volume and risk of death based on age, tumor subtype, insurance status, race/ethnicity, stage at diagnosis, and use of hormone therapy.

$P < 0.0001$) (Fig. 3). Specifically, patients at high-volume centers had a reduced risk of death when compared with low-volume hospitals (5-year OS rate 0.91 vs 0.90 and 0.87, respectively). Ten-year OS was 0.77, 0.75, and 0.70 for high, moderate, and low-volume hospitals, respectively, data not shown.

Multivariable Analysis

Results from our multivariable Cox proportional hazards model confirmed the survival benefit of treatment at a high-volume center. Patients receiving treatment for breast cancer at high-volume centers had an 11% lower overall mortality than those treated at low-volume centers (HR 0.89, 95% CI 0.84–0.96). Hispanic ethnicity was protective with a ≥20% reduction in overall mortality. The protective effects of ethnicity were more prominent in Hispanic white patients (HR 0.78, 95% CI 0.73–0.83) and Hispanic other patients (HR 0.70, 95% CI 0.58–0.865) than non-Hispanic white patients. Conversely, non-Hispanic black patients had the worst outcomes with a 20% higher mortality regardless of hospital volume (HR 1.20, 95% CI 1.16–1.23). Male gender (HR 1.24, 95% CI 1.16–1.32), multiple comorbidities (≥2) (HR 2.28, 95% CI 2.20–2.37), and uninsured status (HR 1.52, 95% CI 1.42–1.64) were associated with worse outcomes.

In multivariable models that included an interaction term, there was no significant interaction between hospital volume and age, income level, insurance, hormone therapy use, or race/ethnicity. However, these models also revealed that the impact of hospital volume on survival differed on the basis of stage and hormone receptor status. Patients with ER receptor positive tumors had an 11% to 13% lower overall mortality at high versus low-volume centers (ER+/PR+ HR 0.87, 95% CI 0.81–0.94, ER+/PR- HR 0.89 95% CI 0.80–0.98) than those with ER receptor negative tumors (ER-/PR+ HR 0.86 95% CI 0.68–1.09; ER-/PR- HR 0.95 95% CI 0.89–1.02). The additional benefit of care at high versus low-volume centers was more pronounced among patients with stage 0 (HR 0.79, 95% CI 0.70–0.89) and stage I (HR 0.87, 95% 0.80–0.94) breast cancer, than stages II and III (Fig. 4).

DISCUSSION

This study is the largest series to date to evaluate the volume-outcome relationship in the contemporary treatment of breast cancer, and the first to define hospital volume based on its association with clinical outcomes. In this evaluation of over 1 million women with stage 0-III breast cancer, we found that treatment at higher volume centers was independently predictive of improved OS (5-year OS 0.91 vs 0.87 and 10-year OS 0.77 vs 0.70 for high vs low volume, respectively), with the greatest benefit seen in patients with earlier stage, ER-receptor positive cancers.

Previous smaller studies have reported improved outcomes among breast cancer patients treated at higher volume centers, although published definitions of ''high-volume'' have varied widely.[12–15] On review of New York State data from 1984 to 1989, Roohan et al[16] demonstrated that patients receiving treatment for breast cancer at high-volume hospitals (≥150 breast surgeries performed per year) had a significantly improved survival at 5 years when compared with patients treated at lower volume centers. The authors also reported that higher mortality was associated with lower case volumes (19% in moderate-volume hospitals = 51 to 150 breast surgeries per year; 30% in low-volume hospitals = 11 to 50 breast surgeries per year; 60% in very low-volume hospitals = ≤10 breast surgeries per year).[16] Skinner et al[17] demonstrated that though hospital case volume was not directly associated with improved 5-year survival among breast cancer patients, volume was more influential on improving mortality than cancer center designation.

Other authors have evaluated breast cancer survival in relation to surgeon volume. A meta-analysis of breast cancer patients between 1988 and 2000 compared the relationship of both hospital and surgeon volume to OS.[18] Although surgeon volume was significantly associated with improved OS, the relationship between hospital volume and outcome could not clearly be established based on the heterogeneous definitions of high volume hospitals. Using a Medicare claims cohort of 987 surgeons from 1994 to 1995, Neuner

et al[19] demonstrated that only 2% of surgeons were performing a volume of breast cancer operations that correlated with lower breast cancer mortality.

We chose to focus on hospital volume instead of practitioner volume in order to better reflect the multidisciplinary nature of contemporary breast cancer treatment. In this setting, survival is driven by all components of care and less dependent on a single provider or modality.[20] Multiple studies have suggested that treatment at high-volume centers is associated with the receipt of evidence-based care, including multidisciplinary consultations, and more frequent use of breast conservation, adjuvant chemotherapy, and radiation.[6,13,15,19,20,21] Kong et al[15] demonstrated that use of sentinel lymph node biopsy was the aspect of care that most notably differed between high versus low-volume centers, and correlated with more frequent use of adjuvant therapy (including chemotherapy, radiation, and endocrine therapy) in their series. A similar phenomenon could explain the improved survival among hormone-receptor positive breast cancers seen in our study; favorable biology leaves a greater chance for cure, and decisions about systemic therapy in this population are nuanced and multifactorial. Our findings demonstrate that receipt of surgery, systemic therapy, hormone therapy, and radiation therapy was similar regardless of hospital volume; though these differences were statistically significant based on the large sample size, we believe they were not clinically meaningful. Patients treated at higher volume centers were more likely to receive neoadjuvant versus adjuvant chemotherapy (26.2% vs 21.6%, $P < 0.0001$), undergo contralateral prophylactic mastectomy (12.5% vs 9.4%, $P < 0.0001$), and breast reconstruction (18.3% vs 9.4%, $P < 0.0001$); however, these aspects of treatment have not been shown to impact survival in breast cancer patients. It is unlikely that a hospital's ability to treat more patients explains the survival benefit seen at high-volume centers, but more likely that high volume acts as a surrogate for tailored breast cancer care that we are unable to delineate through analysis of this large dataset.

The ''selective referral'' theory, first described by Luft[22] in 1979, describes patient self-selection and physician referrals to hospitals with better outcomes[23]; higher hospital volumes then become linked to improved mortality.[24] Other literature has suggested that elderly and less educated patients may choose to stay closer to home even when their referring physicians recommend treatment at high-volume centers.[25] Furthermore, medically complex or high-risk patients may be referred for care at higher volume specialty centers, which has the potential to correlate volume with worse outcomes. We found that even adjusting for age and comorbidities, high-volume centers continued to have an 11% benefit in 5-year OS.

One important challenge in assessing the volume-outcome relationship relates to lack of standardization around what constitutes ''low'' versus ''high'' breast cancer volume.[12,13,18] Thus, interpretation of findings has been difficult and evaluation of center experience has been a challenge. In our study, we leveraged the data distribution to define hospital volume groups based on their relationship to survival, rather than imposing arbitrary cut-points to define hospital volume groups. The RCS analysis minimizes bias that may arise with arbitrary definitions of treatment facilities, and instead identifies volume cut-points where they appear most clinically informative. Through this method, we discovered that the overwhelming majority of centers as included in the NCDB, fell into the low-volume category, and receipt of care at the 52 centers that treat more than 298 breast cancer cases per year was associated with improved survival. In addition, high-volume treatment facilities were concentrated in the Pacific, Middle Atlantic, East North Central, and East South Central regions, with fewer high-volume hospitals in the West, North and South Central, and Mountain and South Atlantic regions.

Multiple studies have consistently shown a direct inverse relationship between volume and mortality among high-risk surgical procedures for cancer.[3] Our findings suggest that the complex contemporary treatment of breast cancer is no different. As a result, patient safety organizations (ie, The Leap Frog Group) and health care systems alike have invested in high-volume practices.[3,26] On May 18, 2015, Dartmouth Hitchcock Medical Center, The Johns Hopkins Hospital and Health System, and The University of Michigan Health System publically committed to ''Take a Volume Pledge.'' This campaign seeks to restrict surgeons with low-volumes practices from performing high-risk procedures.[27] Opponents of these practices argue that the data do not properly adjust for case mix, are unfairly influenced by selection bias, and may inhibit access to care, all practices at risk of further widening existing health care disparities.[28–30] As the most common malignancy among women in the United States, it is critical that treatment for breast cancer be widely accessible to affected women across the country. Restricting breast cancer patients to treatment at high-volume hospitals is challenging to patients who may be forced to travel, and to the limited number of high volume sites across the country who cannot reasonably provide high quality care to the 200,000 women diagnosed with this disease each year.[5] The use of pooled resources on a regional level, such as virtual consultations and tumor boards, or shared expertise, may bridge this gap. Individual low-volume centers can treat women closer to home, while providing a high-volume infrastructure that could improve breast cancer survival.

Our study has several important limitations. Facilities participating in the NCDB include hospitals that have applied for, and received designation as cancer programs. This may represent a biased sample of facilities committed to high-quality cancer care. Nevertheless, the NCDB captures approximately 70% of new cancer diagnoses and we believe our findings give an accurate sense of the national landscape of breast cancer care. It is also important to note that we were not able to differentiate disease-specific survival from OS based on available data within the NCDB. As a result, our findings may better reflect the volume-outcome relationship among breast cancer patients without competing risks of mortality, where OS is largely driven by breast cancer specific survival.

The CoC considers several variables when assigning designations to cancer treatment facilities, including type of facility, program structure, services provided, and the number of cases accessioned each year.[4] Although cancer center designation includes the volume of recorded cases per year, high-quality breast cancer treatment depends on more than numbers alone. A sophisticated understanding of the growing body of research, enrollment in clinical trials, advances in treatment, and the infrastructure that promotes high-quality cancer care, all contribute to improved survival after breast cancer diagnosis. Breast cancer patients should continue to be encouraged to inquire about programmatic experience and programs must continue to strive toward a multidisciplinary, disease-specific concentration of care.

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