Variations in Guideline-Concordant Breast Cancer Adjuvant Therapy in Rural Georgia

Gery P. Guy Jr., Joseph Lipscomb, Theresa W. Gillespie, Michael Goodman, Lisa C. Richardson, and Kevin C. Ward

Objective. To examine factors associated with guideline-concordant adjuvant therapy among breast cancer patients in a rural region of the United States and to present an advancement in quality-of-care assessment in the context of multiple treatments.

Data Sources. Chart abstraction on initial therapy received by 868 women diagnosed with primary, invasive, early-stage breast cancer in a largely rural region of southwest Georgia.

Study Design. Using multivariable logistic regression, we examined predictors of adjuvant chemo-, radiation, and hormonal therapy regimens defined as guideline-concordant according to the 2000 National Institutes of Health Consensus Development Conference Statement.

Principal Findings. Overall, 35.2 percent of women received guideline-concordant care for all three adjuvant therapies. Higher socioeconomic status was associated with receiving guideline-concordant care for all three adjuvant therapies jointly, and for chemotherapy. Compared with private insurance, having Medicaid was associated with guideline-concordant chemotherapy. Unmarried women were more likely to be nonconcordant for chemotherapy and radiation therapy. Increased age predicted nonconcordance for adjuvant therapies jointly, for chemotherapy, and for hormonal therapy.

Conclusions. A number of factors were independently associated with receiving guideline-concordant adjuvant therapy. Identifying and addressing factors that lead to nonconcordance may reduce disparities in treatment and survival.

Key Words. Quality assessment, quality of care, rural health, breast cancer, cancer care

Adjuvant therapy is an important component in the management of breast cancer. Receipt of indicated adjuvant chemotherapy, radiation, and hormonal therapy significantly reduces disease recurrence and improves survival among women with early-stage breast cancer (Clarke et al. 2005; Early Breast Cancer Trialists' Collaborative Group 2005). The National Institutes of Health (NIH)

and a number of other leading medical organizations have developed evidence-based guidelines and recommendations regarding the use of adjuvant therapy for breast cancer (Eifel et al. 2001; National Comprehensive Cancer Network 2014).

Despite the documented health benefits and recommendations, receipt of adjuvant therapy varies by several nonclinical factors such as race, health insurance, socioeconomic status (SES), and treatment facility characteristics (Griggs et al. 2007; Byers et al. 2008; Wu et al. 2008, 2012; Bhargava and Du 2009; Buist et al. 2009; Yen et al. 2010; Freedman et al. 2011). For example, black women have been shown to be less likely to receive adjuvant chemotherapy (Bhargava and Du 2009; Freedman et al. 2011) and hormonal therapy (Freedman et al. 2011). Compared with private insurance, having Medicaid insurance has been shown to be associated with lower rates of guideline-concordant chemotherapy (Wu et al. 2012). SES has been shown to be associated with breast cancer treatment patterns (Griggs et al. 2007; Byers et al. 2008; Wu et al. 2012), with patients of lower SES experiencing reduced rates of guideline-concordant chemo- and hormonal therapy (Wu et al. 2012). Receipt of adjuvant therapy may depend on treatment facility characteristics, with higher rates of guideline-concordance reported at American College of Surgeons' Commission on Cancer (CoC)-approved cancer centers (Wu et al. 2012). Increasing age is inversely associated with adjuvant therapy use (Buist et al. 2009; Yen et al. 2010).

Although previous studies have provided insight into the factors potentially influencing receipt of adjuvant therapy, little is known about the delivery of adjuvant therapy in nonmetropolitan settings. Rural breast cancer patients may be less likely to receive new treatments due to slower adoption of new technologies in rural locations. Rural patients may also face additional barriers to treatment, such as a lack of experienced providers, lack of technological support, and longer travel distances (Arrington et al. 2013). The present study examines the delivery of adjuvant therapy for breast cancer in the largely rural region of southwest Georgia (SWGA). Specifically, we examine the factors

Address correspondence to Gery P. Guy Jr., Ph.D., M.P.H., Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Highway NE, MS-F76 Chamblée, GA 30341; e-mail: irm2@cdc.gov. Joseph Lipscomb, Ph.D., Michael Goodman, M.D., M.P.H., and Kevin C. Ward, Ph.D., are with the Department of Health Policy and Management, Rollins School of Public Health, Winship Cancer Institute, Emory University, Atlanta, GA. Theresa W. Gillespie, Ph.D., M.A., is with the Department of Surgery, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA. Lisa C. Richardson, M.D., M.P.H., is with the Division of Blood Disorders, Centers for Disease Control and Prevention, Atlanta, GA.

associated with receiving guideline-concordant (1) adjuvant chemotherapy, (2) adjuvant radiation therapy, and (3) adjuvant hormonal therapy, considered both individually and for all adjuvant therapies jointly, among SWGA breast cancer patients.

This study presents an innovative approach to constructing a summary measure of “guideline-concordance” when there are multiple possible treatment components (here, different types of adjuvant therapy following breast cancer surgery) and the recommended treatment package for a patient is conditional on her particular clinical circumstances. Whether a patient is guideline-concordant, so defined, becomes an important indicator of the quality of cancer care. Because the summary measure is a two-level (Yes/No) variable, the patient- and provider-level determinants of variations in guideline-concordance can thus be investigated directly through binary logistic regression. In addition, this study examines guideline-concordance in breast cancer treatment within an important and relatively understudied segment of the U.S. population.

METHODS

Study Population

The study population consisted of all women residing in the 33-county region of SWGA who were diagnosed with a first primary, invasive, early-stage (American Joint Committee on Cancer [AJCC] stage I, II, and IIIA) breast cancer from 2001 through 2003, and who received at least their first 12 months of postdiagnosis treatment within the region. Incident breast cancer cases were identified from the Georgia Cancer Registry. A customized electronic data collection instrument and trained onsite abstractors were used to identify and code information from medical records. As receipt of neoadjuvant therapy may impact decisions regarding adjuvant therapy, we excluded patients receiving neoadjuvant therapy ($n = 62$) (Giordano et al. 2006; Richardson et al. 2006; Lipscomb et al. 2012).

Definition of Guideline-Concordant Adjuvant Therapy

We examined the following four binary outcomes: guideline-concordant receipt of adjuvant chemotherapy, guideline-concordant receipt of adjuvant radiation therapy, guideline-concordant receipt of adjuvant hormonal therapy, and guideline-concordant receipt of all three adjuvant therapies.

Concordance was defined on the basis of the guidelines developed from the 2000 NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer (Eifel et al. 2001), which were issued closely to the time of the study population's diagnosis. These guidelines for adjuvant therapy were established based on tumor size, lymph node status, histology type, estrogen/progesterone (ER/PR) status, type of surgery received, and patient age (Table 1).

We first determined whether adjuvant therapy would be recommended from the guidelines based on individual tumor, patient, and surgical characteristics and then categorized each woman into one of three categories (concordant, discordant, discretionary) as it relates to her receipt of guideline-concordant therapy for each of the three individual modalities. Among women for whom the guidelines recommended adjuvant therapy, those receiving the therapy were considered guideline-concordant. Similarly, women for whom the guidelines recommended no adjuvant therapy were considered guideline-concordant if the specified therapy was not received. The assignment of guideline-discordance followed similar rules. Patients for whom the guidelines did not make a clear yes/no recommendation for a given therapy were considered discretionary and were excluded from the denominator of modality specific analyses. Discretionary guidelines include those with recommendations stating the following: the decision should be individualized; the decision should consider the survival benefit, toxicity, existing comorbidities, and mortality from other causes; or the benefits of therapy are unclear.

A hierarchy was then used to determine joint guideline-concordance. First, women who were guideline-concordant across all three individual therapies were considered jointly guideline-concordant. Second, women who were guideline-discordant for any of the three therapies were considered to be jointly guideline-discordant. The remaining women with discretionary guidelines for any individual modality were excluded from the denominator of the joint guideline-concordant analyses (Figure 1).

Explanatory Variables of Interest

Explanatory variables for analyses of guideline-concordant adjuvant therapy included age at diagnosis, race, marital status, insurance status, SES, urban/rural status, number of comorbidities at diagnosis, AJCC stage at diagnosis, tumor grade, ER/PR status, treatment facility, distance to the treatment facility, and type of surgery performed (Table 2). SES was examined at the residential census tract level and categorized into >20, 10–20, and <10 percent of the population living below the federal poverty level in 2000. Insurance status

Table 1: Adjuvant Treatment for Invasive Breast Cancer Based on the 2000 NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer

<i>Chemotherapy Recommendations</i>		
Age	Tumor Characteristics	Recommendation
Age ≤70 years	Lymph node positive or tumor size ≥1 cm	Yes
Age ≤70 years	Lymph node negative and tumor size <1 cm	Discretionary: Decision should be individualized
Age >70 years		Discretionary: Decision should consider the survival benefit, toxicity, existing comorbidities, and mortality from noncancer causes
<i>Radiation Therapy Recommendations</i>		
Surgery type	Tumor Characteristics	Recommendation
Breast conserving surgery		Yes
Mastectomy	≥4 positive lymph nodes or tumor size ≥5 cm	Yes
Mastectomy	1–3 positive lymph nodes and tumor size <5 cm	Discretionary: Benefits unclear
Mastectomy	Lymph node negative and tumor size <5 cm	No
<i>Hormonal Therapy Recommendations</i>		
Estrogen/Progesterone status		Recommendation
Positive		Yes
Negative		No

was categorized into four groups as follows: private insurance, Medicare only, Medicaid/Medicaid pending, and uninsured. The private insurance group included cases with Medicare plus private insurance and/or CHAMPUS or VA coverage, because these plans represent either privately purchased insurance or insurance provided by the military, which functions in a similar manner to private insurance. Treatment facility was the primary center where cancer care was received in SWGA; facilities A–D are the four American College of Surgeons’ CoC-approved hospitals in SWGA, while “Other” indicates the patient received her cancer care primarily at some other non-CoC facility in SWGA. For patients treated in more than one facility, the hospital where the patient was diagnosed was chosen, as this facility is likely where the treatment plan was created and where the majority of care was received.

Distance to the facility was the distance, in miles, between the geographic centroid of the patient’s residential zip code and the patient’s main treatment facility, using the Great Circle Distance geocoding algorithm

Figure 1: Receipt of Guideline-Concordant Therapy among Women with Early-Stage Breast Cancer Diagnosed and Treated in Southwest Georgia, 2001–2003

Notes. Discretionary guidelines include those with recommendations stating the following: the decision should be individualized; the decision should consider the survival benefit, toxicity, existing comorbidities, and mortality from other causes; or the benefits of therapy are unclear. Missing cases includes women with missing data resulting in an inability to determine guideline-concordance.

published by the North American Association of Central Cancer Registries (2014). Distance was categorized into <5, 5–22, and >22 miles. All models controlled for the implementation of the Breast and Cervical Cancer Prevention and Treatment Act (BCCPTA) program, which was implemented in Georgia in July 2001.

Statistical Analyses

We assessed the association between each of the explanatory variables and guideline-concordance for adjuvant therapy, both individually and combined, using chi-square tests. Multivariable logistic regression models were used to identify factors independently associated with receipt of guideline-concordant therapy. Logistic regression results were expressed as adjusted odds ratios, with corresponding 95 percent confidence intervals (CI). *p* values were

Table 2: Characteristics of Women with Early-Stage Invasive Breast Cancer Diagnosed and Treated in Southwest Georgia, 2001–2003

	<i>No. of Patients (N = 844)</i>	<i>% of Sample</i>
Age at diagnosis (years)		
<50	175	20.7
50–64	314	37.2
65+	355	42.1
Race*		
White	593	70.3
Black	251	29.7
Marital status		
Married	432	51.9
Not married	401	48.1
Insurance status		
Private + Medicare w/supplemental + VA/CHAMPUS	593	70.3
Medicare only (no supplemental)	116	13.7
Medicaid or Medicaid pending	76	9.0
Uninsured (self-pay/charity)	59	7.0
Socioeconomic status: % in census tract below poverty level		
>20%	432	51.9
10–20%	284	34.1
<10%	117	14.1
Rural status		
Metro	158	18.7
Nonmetro	686	81.3
Comorbid conditions [†]		
None	440	52.1
1 or more	404	47.9
AJCC stage at diagnosis		
I	431	51.1
II	321	38.0
IIIA	92	10.9
Grade		
Well differentiated	158	20.6
Moderately differentiated	310	40.5
Poorly/undifferentiated	298	38.9
Estrogen/progesterone status		
ER– and PR–	166	23.2
ER+ or PR+	551	76.9
Treatment site		
A	338	40.1
B	167	19.8
C	133	15.8
D	89	10.6
Other	117	13.9

continued

Table 2. *Continued*

	No. of Patients (N = 844)	% of Sample
Distance to treatment site		
<5 miles	258	30.6
5–22 miles	307	36.4
>22 miles	279	33.1
Surgery		
Breast conserving surgery	283	33.5
Mastectomy	553	66.2
Guideline-concordance		
Jointly guideline-concordant	163	35.2
Adjuvant chemotherapy	308	63.4
Adjuvant radiation therapy	559	80.9
Adjuvant hormonal therapy	560	78.1

Notes: Numbers for all characteristics do not sum to the total due to missing data.

*Race was defined as two-level variable that includes non-Hispanic whites (white) and non-Hispanic blacks (black), as all other racial/ethnic groups together constituted only 0.8% of the incident breast cancer cases in SWGA in 2001–2003.

†Comorbidities at the time of diagnosis include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, dementia, hemiplegia, AIDS, diabetes, diabetes with end organ damage, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, any tumor, leukemia, lymphoma, and metastatic solid tumor.

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor.

two-sided, with $p < .05$ considered significant. Analyses were conducted with *Stata, version 13.0* (Stata Corporation, College Station, TX, USA).

Additional sensitivity analyses were conducted using multiple imputation to account for missing ER/PR status ($n = 128$). ER/PR status was imputed using all available independent variables from the original model.

RESULTS

Among the 1,289 SWGA women diagnosed with breast cancer in 2001–2003, most (85.0 percent) were treated within the study region. Among these women, 907 were diagnosed with invasive, early-stage breast cancer. After excluding 62 women receiving neoadjuvant therapy, 844 cases met our study inclusion criteria; nearly half of these women were age ≥ 65 years (42.1 percent), most were white (70.3 percent), and most had private health insurance

(70.3 percent). The majority of patients resided in high poverty areas (51.9 percent), in nonmetropolitan settings (81.3 percent), and received treatment at CoC-approved facilities (86.1 percent). Overall, 35.2 percent of women with clear indications for treatment recommendations were guideline-concordant for all three adjuvant therapies; meanwhile 63.4 percent were concordant for adjuvant chemotherapy, 80.9 percent for adjuvant radiation therapy, and 78.1 percent for adjuvant hormonal therapy (Table 2).

Guideline-Concordant for All Three Adjuvant Therapies Jointly

Women age 50–64 years (OR = 0.45; 95 percent CI, 0.25–0.82) and ≥ 65 years (OR = 0.12; 95 percent CI, 0.06–0.27) were less likely to be jointly guideline-concordant compared to those age < 50 years (Table 3). Those residing in low-poverty areas were more likely to be jointly guideline-concordant (OR = 3.53; 95 percent CI, 1.43–8.68). Relative to women diagnosed with stage I, those diagnosed with stage II (OR = 3.71; 95 percent CI, 2.11–6.53) or stage IIIA (OR = 3.24; 95 percent CI, 1.48–7.08) breast cancer were more likely to be jointly guideline-concordant. Generally, women treated at CoC facilities were more likely to be guideline-concordant for all three therapies.

Guideline-Concordant Chemotherapy

Women age 50–64 years (OR = 0.29; 95 percent CI, 0.15–0.58) and ≥ 65 years (OR = 0.30; 95 percent CI, 0.13–0.71) were less likely to be guideline-concordant for chemotherapy compared to those age < 50 years. Women with Medicaid or Medicaid pending health insurance were more likely to be concordant for chemotherapy (OR = 4.07; 95 percent CI, 1.47–11.27), compared with those privately insured. Women residing in low-poverty areas were more likely to be concordant for chemotherapy (OR = 3.66; 95 percent CI, 1.17–11.49). Unmarried women were less likely to be concordant for chemotherapy (OR = 0.42; 95 percent CI, 0.21–0.84). Relative to stage I, those diagnosed with stage II (OR = 8.97; 95 percent CI, 4.82–16.69) or stage IIIA (OR = 23.27; 95 percent CI, 4.95–109.51) breast cancer were more likely to be concordant for chemotherapy. Those diagnosed with a higher tumor grade were more likely to be concordant for chemotherapy (OR = 2.90; 95 percent CI, 1.14–7.40). Generally, women treated at CoC facilities were more likely to be concordant for chemotherapy.

Table 3: Adjusted Odds Ratios for Receipt of NIH Consensus Development Conference Statement Adjuvant Chemotherapy, Hormonal Therapy, and Radiation Therapy

	Jointly Guideline-Concordant*		Adjuvant Chemotherapy*		Adjuvant Radiation Therapy*		Adjuvant Hormonal Therapy*	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age at diagnosis (years)								
<50	1.00		1.00		1.00		1.00	
50-64	0.45 (0.25-0.82)	.009	0.29 (0.15-0.58)	<.001	0.74 (0.34-1.60)	.443	0.75 (0.41-1.37)	.353
65+	0.12 (0.06-0.27)	<.001	0.30 (0.13-0.71)	.006	0.56 (0.27-1.16)	.121	0.50 (0.28-0.90)	.021
Race								
White	1.00		1.00		1.00		1.00	
Black	1.42 (0.80-2.57)	.253	1.01 (0.51-1.99)	.975	1.07 (0.58-1.95)	.831	1.27 (0.74-2.16)	.383
Marital status								
Married	1.00		1.00		1.00		1.00	
Not married	0.65 (0.36-1.15)	.137	0.42 (0.21-0.84)	.014	0.48 (0.27-0.86)	.013	1.16 (0.73-1.84)	.537
Insurance status								
Private + Medicare w/ supplemental + VA/CHAMPUS	1.00		1.00		1.00		1.00	
Medicare only (no supplemental)	1.05 (0.43-2.57)	.922	0.72 (0.28-1.89)	.507	1.06 (0.50-2.22)	.885	1.12 (0.60-2.11)	.719
Medicaid or Medicaid pending	1.52 (0.66-3.49)	.321	4.07 (1.47-11.27)	.007	2.30 (0.75-7.08)	.146	0.66 (0.29-1.48)	.314
Uninsured (self pay/charity)	0.56 (0.23-1.41)	.220	0.68 (0.26-1.81)	.439	0.90 (0.34-2.37)	.828	0.56 (0.24-1.30)	.175
Socioeconomic status: % in census tract below poverty level								
>20%	1.00		1.00		1.00		1.00	
10-20%	0.99 (0.55-1.78)	.978	1.31 (0.68-2.51)	.415	0.82 (0.46-1.48)	.518	1.16 (0.72-1.87)	.532
<10%	3.53 (1.43-8.68)	.006	3.66 (1.17-11.49)	.026	1.90 (0.69-5.21)	.213	0.74 (0.35-1.56)	.425

continued

Table 3. Continued

	Jointly Guideline-Concordant*		Adjuvant Chemotherapy*		Adjuvant Radiation Therapy*		Adjuvant Hormonal Therapy*	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
	N = 421		N = 395		N = 526		N = 641	
Rural status								
Metro	1.00		1.00		1.00		1.00	
Nonmetro	1.72 (0.67–4.46)	.262	1.98 (0.64–6.15)	.240	1.14 (0.44–2.94)	.789	1.21 (0.55–2.67)	.643
Comorbid conditions								
None	1.00		1.00		1.00		1.00	
1 or more	0.82 (0.47–1.43)	.484	0.96 (0.51–1.78)	.885	0.87 (0.50–1.52)	.622	1.00 (0.63–1.57)	.986
AJCC stage at diagnosis								
I	1.00		1.00		1.00		1.00	
II	3.71 (2.11–6.53)	<.001	8.97 (4.82–16.69)	<.001	0.52 (0.29–0.95)	.033	2.63 (1.61–4.28)	<.001
IIIA	3.24 (1.48–7.08)	.003	23.27 (4.95–109.51)	<.001	0.18 (0.08–0.40)	<.001	1.25 (0.60–2.63)	.554
Grade								
Well differentiated	1.00		1.00		1.00		1.00	
Moderately differentiated	1.44 (0.61–3.37)	.403	0.81 (0.35–1.87)	.619	0.68 (0.31–1.48)	.334	1.41 (0.84–2.36)	.195
Poorly/undifferentiated	2.29 (0.93–5.66)	.072	2.90 (1.14–7.40)	.025	0.43 (0.18–1.00)	.051	1.37 (0.73–2.57)	.328
Estrogen/progesterone status								
ER– and PR–	1.00		1.00		1.00		1.00	
ER+ or PR+	0.74 (0.39–1.40)	.358	0.61 (0.28–1.32)	.212	0.90 (0.46–1.75)	.760	0.45 (0.24–0.85)	.014
Treatment site								
A	1.00		1.00		1.00		1.00	
B	0.66 (0.28–1.59)	.355	0.86 (0.30–2.45)	.772	0.83 (0.32–2.11)	.690	0.47 (0.23–0.97)	.040
C	0.58 (0.24–1.39)	.225	0.39 (0.14–1.06)	.064	2.32 (0.79–6.78)	.124	0.94 (0.43–2.06)	.887

continued

Table 3. Continued

	Jointly Guideline-Concordant*		Adjuvant Chemotherapy*		Adjuvant Radiation Therapy*		Adjuvant Hormonal Therapy*	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
D	0.25 (0.10–0.64)	.003	0.21 (0.08–0.58)	.003	0.78 (0.32–1.89)	.580	0.62 (0.30–1.31)	.220
Other	0.21 (0.07–0.67)	.008	0.18 (0.05–0.66)	.009	0.29 (0.11–0.75)	.011	0.15 (0.07–0.34)	<.001
Distance to treatment site								
<5 miles	1.00		1.00		1.00		1.00	
5–22 miles	1.19 (0.59–2.40)	.618	1.06 (0.48–2.31)	.892	1.22 (0.61–2.42)	.579	0.47 (0.26–0.83)	.009
>22 miles	1.53 (0.65–3.59)	.332	1.03 (0.39–2.72)	.960	1.04 (0.45–2.44)	.924	0.45 (0.22–0.92)	.029
Type of surgery								
Mastectomy	1.00		1.00		1.00		1.00	
Breast conserving surgery	1.30 (0.74–2.27)	.357	0.65 (0.35–1.22)	.179	0.48 (0.27–0.85)	.012	1.17 (0.73–1.86)	.515
BCCPTA implemented								
No	1.00		1.00		1.00		1.00 (1.05–2.96)	.033
Yes	0.72 (0.37–1.41)	.340	0.64 (0.30–1.40)	.265	0.90 (0.45–1.81)	.775	1.76 (1.05–2.96)	
c index (probability of concordance)	0.8431		0.8830		0.7598		0.7289	

*Defined as receiving or not receiving the therapy consistent with the 2000 NIH Consensus Development Conference Statement. AJCC, American Joint Committee on Cancer; BCCPTA, Breast and Cervical Cancer Prevention and Treatment Act; ER, estrogen receptor; PR, progesterone receptor.

Guideline-Concordant Radiation Therapy

Unmarried women were less likely to be guideline-concordant for radiation therapy (OR = 0.48; 95 percent CI, 0.27–0.86). Relative to stage I, those diagnosed with stage II (OR = 0.52; 95 percent CI, 0.29–0.95) or stage IIIA (OR = 0.18; 95 percent CI, 0.08–0.40) breast cancer were less likely to be concordant for radiation therapy. Those undergoing breast conserving surgery (OR = 0.48; 95 percent CI, 0.27–0.85) were less likely to be concordant for radiation therapy, compared to having a mastectomy. Women treated at CoC facilities were more likely to be guideline-concordant for radiation therapy.

Guideline-Concordant Hormonal Therapy

Women age ≥ 65 years (OR = 0.50; 95 percent CI, 0.28–0.90) were less likely to be guideline-concordant for hormonal therapy compared to those < 50 years. Relative to stage I, those diagnosed with stage II (OR = 2.63; 95 percent CI, 1.61–4.28) were more likely to be guideline-concordant for hormonal therapy. Women with ER/PR positive were less likely to be concordant for hormonal therapy (OR = 0.45; 95 percent CI, 0.24–0.85). Relative to those residing within 5 miles of their treatment center, those 5–22 miles away (OR = 0.47; 95 percent CI, 0.26–0.83), and > 22 miles away (OR = 0.45; 95 percent CI, 0.22–0.92), were less likely to be guideline-concordant for hormonal therapy. Generally, patients treated at CoC facilities were more likely to be guideline-concordant for hormonal therapy.

Sensitivity Analyses

In analyses using multiple imputation for cases with missing ER/PR receptor status (thereby allowing these cases to be included in the regression analyses), our results for the association between patient, clinical, and area characteristics were similar across each of the models. These findings suggest that our results are robust to the treatment of women with missing data on ER/PR status.

DISCUSSION

To our knowledge, this is the most comprehensive examination of guideline-concordant adjuvant therapy among early-stage breast cancer patients in a largely rural region of the United States. Despite established consensus

guidelines, a substantial number of women in our study did not receive guideline-concordant adjuvant therapy. Among women diagnosed with early-stage breast cancer in southwest Georgia between 2001 and 2003, 35.2 percent of women received guideline-concordant adjuvant chemotherapy, radiation therapy, and hormonal therapy combined, while guideline-concordance for individual treatment modalities ranged from 63.4 to 80.9 percent. The rates of guideline-concordance for individual therapies found in this study are similar to those observed in a previous study examining guideline-concordant chemotherapy and hormonal therapy across seven states (Wu et al. 2012). However, no study to our knowledge has examined guideline-concordance to all three adjuvant therapies jointly.

A number of factors were independently associated with receiving guideline-concordant adjuvant therapy. Higher socioeconomic status was associated with being guideline-concordant for chemotherapy and all three adjuvant therapies together. Compared to private insurance, having Medicaid or Medicaid pending insurance was associated with receiving guideline-concordant chemotherapy. Being unmarried was associated with nonconcordant chemotherapy and radiation therapy. Increased age was associated with nonconcordant chemotherapy, hormonal therapy, and all three adjuvant therapies jointly.

Our results indicating lower use of guideline-concordant adjuvant therapy in high poverty areas are consistent with other studies documenting differences in breast cancer therapy among vulnerable populations (Newman et al. 2002; Field et al. 2005; Blackman and Masi 2006; Byers et al. 2008). Many factors may influence the use of adjuvant therapy in vulnerable populations, such as access to a regular source of care and accessibility to treatment facilities. Lower socioeconomic status has been shown to be a risk factor for all-cause mortality after cancer diagnosis, largely due to later stage at diagnosis and less aggressive treatment (Byers et al. 2008). Given these disparities in treatment, and persistent outcome disparities in women of lower socioeconomic status (Newman et al. 2002; Field et al. 2005), attention to such patterns may provide opportunities to address and eliminate such disparities.

Previous studies have shown that marital status, felt to serve as a proxy for social support, influences the receipt of medical care, including treatment and survival among cancer patients (Goodwin et al. 1987; Osborne et al. 2005; Voti et al. 2006). In this study, we found that unmarried women were less likely to receive guideline-concordant chemotherapy and radiation therapy. Social support may be especially important for these therapies, as they

are administered over multiple visits, requiring commitment not only from the patient but also her support network. Unmarried women may be more likely to decline therapy given concerns about who might be able to help them with postoperative care or transportation (Silliman et al. 1997). Physicians may share these concerns and offer definitive therapy less often to unmarried women (Osborne et al. 2005).

An interesting finding of this study was that women with Medicaid or Medicaid pending insurance were more likely to receive guideline-concordant chemotherapy compared to women with private insurance. Contrary to these findings, previous research has shown that women insured by Medicaid are less likely than women with other types of insurance to receive appropriate treatment (Bradley, Given, and Roberts 2002; Ward et al. 2008). Further investigation of the impact of health insurance is warranted. However, our findings may be explained, in part, by the BCCPTA program implemented in July 2001 by the Centers for Disease Control and Prevention, which provides Medicaid coverage for uninsured women upon diagnosis of breast or cervical cancer through the National Breast and Cervical Cancer Early Detection Program. In Georgia, enrollment in Medicaid for women with breast cancer was shown to increase significantly following the implementation of the BCCPTA program (Adams et al. 2009).

In this study, we did not find a significant association between race and receipt of guideline-concordant therapy. There is a great deal of literature examining black–white differences in breast cancer treatment. While a number of studies have found lower rates of adjuvant therapy among black women compared with white women (Bickell et al. 2006; Giordano et al. 2006; Bhargava and Du 2009; Freedman et al. 2011), others have found no such difference (Elkin et al. 2006; Kimmick et al. 2006; Lund et al. 2008). It is possible that the influence of race on therapy receipt may be different in regions such as SWGA that are characterized by overall low levels of income, considerable distance from major metropolitan areas, and large proportions of rural residents that include both blacks and whites.

Among women in our study who were not guideline-concordant for any one of the individual therapies, 91.0 percent of the time guideline-discordance resulted from adjuvant therapy being recommended but not received. Thus, certain clinical factors such as receiving breast conserving surgery and being ER/PR positive provide ample opportunity to be guideline-discordant as radiation therapy and hormonal therapy are recommended in each case, respectively. This may explain, in part, the association between guideline-concordant radiation therapy and receiving a mastectomy compared with breast

conserving surgery, and the association between guideline-concordant hormonal therapy and being ER/PR negative.

Recommended practice guidelines, when followed, may improve quality of care by reducing unwarranted variations in treatment (Smith and Hillner 2001; Walter et al. 2004). However, equating practice guideline-concordance with quality of care should be done with caution given the role of physician discretion and patient preferences in selecting therapy (Cabana et al. 1999; Walter et al. 2004). For example, patients' beliefs about the efficacy of therapy, especially with regard to its adverse effects, have been shown to be associated with receiving such therapy (Bickell et al. 2009; Jagsi et al. 2010; Neugut et al. 2012). In addition, mistrust of the medical system and lack of knowledge about adjuvant therapy have been associated with patients not initiating adjuvant therapy (Bickell et al. 2009). Patients not receiving recommended radiation therapy have also indicated their physician failed to discuss or recommend therapy (Jagsi et al. 2010). The patient-physician relationship has a profound impact on chemotherapy initiation (Sheppard et al. 2013). Educational efforts and tailored decision aids encouraging communication between patients and providers may be important in improving rates of guideline-concordant adjuvant therapy. Efforts to improve patient education are needed to assist women in seeking and obtaining appropriate medical care. Likewise, efforts are needed to ensure that physicians are aware of current treatment recommendations so that treatment decision making is appropriately informed.

This study is subject to a number of limitations. First, we could not control for patient functional status and physician attitudes and preferences which are known to affect treatment decisions (Mandelblatt et al. 2000; Du et al. 2003). Second, we could not determine if recommended therapy was offered by the provider and declined by the patient or not offered at all. Third, because our study sample comprised women in a single predominantly rural geographic area, our results may not be generalizable to women who live in other areas. Fourth, our results reflect the patterns of care for breast cancer cases diagnosed in SWGA during 2001–2003, thus, raising questions about generalizability over time. However, we are unaware of changes in breast cancer treatment guidelines or third-party reimbursement policies over the past decade that would have significantly altered the receipt of guideline-concordant adjuvant therapy, as defined in these analyses. Fifth, we lacked individual-level information on SES; thus, our SES measure relies on census data. Census-driven measures may not accurately reflect the SES of some patients. However, geographically based estimates are useful markers of social

influence on outcomes because local socioeconomic factors, in combination with individual characteristics, can affect access to health care and its acceptability (Ward et al. 2004; Eschbach, Mahnken, and Goodwin 2005). Lastly, a potential limitation of this study is the issue of determining what comprised guideline-concordant adjuvant breast cancer treatment given the presence of multiple guidelines. However, when comparing the 2000 NIH Consensus Development Conference on Adjuvant Therapy for Breast Cancer consensus statement to other guidelines available at the time of this study, a substantial number of similarities can be noted (Carlson et al. 2000). In fact, it is likely that the NIH recommendations solidified and amplified what was a growing consensus on key issues in breast cancer adjuvant therapy.

Despite these limitations, this study provides important new findings about the dissemination and uptake of breast cancer treatment guidelines within an important and relatively understudied segment of the U.S. population. An important strength of the study is the use of medical record abstraction from a virtually complete census of patients diagnosed and treated for early-stage breast cancer in SWGA over a 3-year period. An additional strength of this study was the ability to examine joint guideline-concordance across all three adjuvant therapies. This approach can be used to investigate the receipt of guideline-concordant care for breast cancer patients in other settings, patients with other types of cancer, and individuals with other chronic conditions involving multiple treatments. Analyses among other breast cancer patient populations, such as those in urban settings, would allow for comparative analyses of guideline-concordant breast cancer adjuvant therapy.

Ensuring the use of guideline-concordant adjuvant therapy may improve breast cancer outcomes. Previous research has shown that nonadherence to breast cancer treatment consensus guidelines is associated with higher recurrence and mortality rates (Lash et al. 2000; Wu et al. 2008). Future studies should determine the impact of the variations in guideline-concordant adjuvant therapy observed in this study, particularly joint guideline-concordance, on breast cancer-specific and overall survival. These findings could have important implications for breast cancer treatment in rural regions of the United States.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: Funding was made possible by cooperative agreement U48 DP000043 for the Emory Prevention Research

Center, from the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosures: None.

REFERENCES

- Adams, E. K., L. N. Chien, C. S. Florence, and C. Raskind-Hood. 2009. "The Breast and Cervical Cancer Prevention and Treatment Act in Georgia." *Cancer* 115 (6): 1300–9.
- Arrington, A. K., L. Kruper, C. Vito, J. Yim, J. Kim, and S. L. Chen. 2013. "Rural and Urban Disparities in the Evolution of Sentinel Lymph Node Utilization in Breast Cancer." *American Journal of Surgery* 206 (5): 674–81.
- Bhargava, A., and X. L. Du. 2009. "Racial and Socioeconomic Disparities in Adjuvant Chemotherapy for Older Women with Lymph Node-Positive, Operable Breast Cancer." *Cancer* 115 (13): 2999–3008.
- Bickell, N. A., J. J. Wang, S. Oluwole, D. Schrag, H. Godfrey, K. Hiotis, J. Mendez, and A. A. Guth. 2006. "Missed Opportunities: Racial Disparities in Adjuvant Breast Cancer Treatment." *Journal of Clinical Oncology* 24 (9): 1357–62.
- Bickell, N. A., J. Weidmann, K. Fei, J. J. Lin, and H. Leventhal. 2009. "Underuse of Breast Cancer Adjuvant Treatment: Patient Knowledge, Beliefs, and Medical Mistrust." *Journal of Clinical Oncology* 27 (31): 5160–7.
- Blackman, D. J., and C. M. Masi. 2006. "Racial and Ethnic Disparities in Breast Cancer Mortality: Are We Doing Enough to Address the Root Causes?" *Journal of Clinical Oncology* 24 (14): 2170–8.
- Bradley, C. J., C. W. Given, and C. Roberts. 2002. "Race, Socioeconomic Status, and Breast Cancer Treatment and Survival." *Journal of the National Cancer Institute* 94 (7): 490–6.
- Buist, D. S., J. Chubak, M. Prout, M. U. Yood, J. L. Bosco, S. S. Thwin, H. T. Gold, C. Owusu, T. S. Field, and V. P. Quinn. 2009. "Referral, Receipt, and Completion of Chemotherapy in Patients with Early-Stage Breast Cancer Older Than 65 Years and at High Risk of Breast Cancer Recurrence." *Journal of Clinical Oncology* 27 (27): 4508–14.
- Byers, T. E., H. J. Wolf, K. R. Bauer, S. Bolick-Aldrich, V. W. Chen, J. L. Finch, J. P. Fulton, M. J. Schymura, T. Shen, and S. Van Heest. 2008. "The Impact of Socioeconomic Status on Survival after Cancer in the United States." *Cancer* 113 (3): 582–91.
- Cabana, M. D., C. S. Rand, N. R. Powe, A. W. Wu, M. H. Wilson, P.-A. C. Abboud, and H. R. Rubin. 1999. "Why Don't Physicians Follow Clinical Practice Guidelines?" *Journal of the American Medical Association* 282 (15): 1458–65.
- Carlson, R. W., B. O. Anderson, W. Bensinger, C. E. Cox, N. E. Davidson, S. B. Edge, W. B. Farrar, L. J. Goldstein, W. J. Gradishar, A. S. Lichter, B. McCormick, L. M.

- Nabell, E. C. Reed, S. M. Silver, M. L. Smith, G. Somlo, R. Theriault, J. H. Ward, E. P. Winer, and A. Wolff. 2000. "NCCN Practice Guidelines for Breast Cancer." *Oncology (Williston Park)* 14 (11A): 33–49.
- Clarke, M., R. Collins, S. Darby, C. Davies, P. Elphinstone, E. Evans, J. Godwin, R. Gray, C. Hicks, and S. James. 2005. "Effects of Radiotherapy and of Differences in the Extent of Surgery for Early Breast Cancer on Local Recurrence and 15-Year Survival: An Overview of the Randomised Trials." *Lancet* 366 (9503): 2087.
- Du, X. L., C. R. Key, C. Osborne, J. D. Mahnken, and J. S. Goodwin. 2003. "Discrepancy between Consensus Recommendations and Actual Community Use of Adjuvant Chemotherapy in Women with Breast Cancer." *Annals of Internal Medicine* 138 (2): 90–7.
- Early Breast Cancer Trialists' Collaborative Group. 2005. "Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer on Recurrence and 15-Year Survival: An Overview of the Randomised Trials." *Lancet* 365 (9472): 1687–717.
- Eifel, P., J. Axelson, J. Costa, J. Crowley, W. Curran, Jr., A. Deshler, S. Fulton, C. Hendricks, M. Kemeny, and A. Kornblith. 2001. "National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1-3, 2000." *Journal of the National Cancer Institute* 93 (13): 979–89.
- Elkin, E. B., A. Hurria, N. Mitra, D. Schrag, and K. S. Panageas. 2006. "Adjuvant Chemotherapy and Survival in Older Women with Hormone Receptor-Negative Breast Cancer: Assessing Outcome in a Population-Based, Observational Cohort." *Journal of Clinical Oncology* 24 (18): 2757–64.
- Eschbach, K., J. D. Mahnken, and J. S. Goodwin. 2005. "Neighborhood Composition and Incidence of Cancer among Hispanics in the United States." *Cancer* 103 (5): 1036–44.
- Field, T. S., D. S. Buist, C. Doubeni, S. Enger, H. Fouayzi, G. Hart, E. J. Korner, L. Lamerato, D. J. Bachman, and J. Ellis. 2005. "Disparities and Survival among Breast Cancer Patients." *JNCI Monographs* 2005 (35): 88–95.
- Freedman, R. A., K. S. Virgo, Y. He, A. L. Pavluck, E. P. Winer, E. M. Ward, and N. L. Keating. 2011. "The Association of Race/Ethnicity, Insurance Status, and Socio-economic Factors with Breast Cancer Care." *Cancer* 117 (1): 180–9.
- Giordano, S. H., Z. Duan, Y.-F. Kuo, G. N. Hortobagyi, and J. S. Goodwin. 2006. "Use and Outcomes of Adjuvant Chemotherapy in Older Women with Breast Cancer." *Journal of Clinical Oncology* 24 (18): 2750–6.
- Goodwin, J. S., W. C. Hunt, C. R. Key, and J. M. Samet. 1987. "The Effect of Marital Status on Stage, Treatment, and Survival of Cancer Patients." *Journal of the American Medical Association* 258 (21): 3125–30.
- Griggs, J. J., E. Culakova, M. E. S. Sorbero, M. van Ryn, M. S. Poniewierski, D. A. Wolff, J. Crawford, D. C. Dale, and G. H. Lyman. 2007. "Effect of Patient Socio-economic Status and Body Mass Index on the Quality of Breast Cancer Adjuvant Chemotherapy." *Journal of Clinical Oncology* 25 (3): 277–84.
- Jagsi, R., P. Abrahamse, M. Morrow, S. T. Hawley, J. J. Griggs, J. J. Graff, A. S. Hamilton, and S. J. Katz. 2010. "Patterns and Correlates of Adjuvant Radiotherapy

- Receipt after Lumpectomy and after Mastectomy for Breast Cancer.” *Journal of Clinical Oncology* 28 (14): 2396–403.
- Kimmick, G., F. Camacho, K. L. Foley, E. A. Levine, R. Balkrishnan, and R. Anderson. 2006. “Racial Differences in Patterns of Care among Medicaid-Enrolled Patients with Breast Cancer.” *Journal of Oncology Practice* 2 (5): 205–13.
- Lash, T. L., R. A. Silliman, E. Guadagnoli, and V. Mor. 2000. “The Effect of Less Than Definitive Care on Breast Carcinoma Recurrence and Mortality.” *Cancer* 89 (8): 1739–47.
- Lipscomb, J., T. W. Gillespie, M. Goodman, L. C. Richardson, L. A. Pollack, A. B. Ryerson, and K. C. Ward. 2012. “Black–White Differences in Receipt and Completion of Adjuvant Chemotherapy among Breast Cancer Patients in A Rural Region of the US.” *Breast Cancer Research and Treatment* 133 (1): 285–96.
- Lund, M. J., O. P. Brawley, K. C. Ward, J. L. Young, S. S. Gabram, and J. W. Eley. 2008. “Parity and Disparity in First Course Treatment of Invasive Breast Cancer.” *Breast Cancer Research and Treatment* 109 (3): 545–57.
- Mandelblatt, J. S., J. Hadley, J. F. Kerner, K. A. Schulman, K. Gold, J. Dunmore-Griffith, S. Edge, E. Guadagnoli, J. J. Lynch, and N. J. Meropol. 2000. “Patterns of Breast Carcinoma Treatment in Older Women.” *Cancer* 89 (3): 561–73.
- National Comprehensive Cancer Network. 2014. “Clinical Practice Guidelines in Oncology (Version 2.2014)” [accessed on January 21, 2014]. Available at http://www.nccn.org/professionals/physician_gls/recently_updated.asp
- Neugut, A. I., G. C. Hillyer, L. H. Kushi, L. Lamerato, N. Lecoce, S. D. Nathanson, C. B. Ambrosone, D. H. Bovbjerg, J. S. Mandelblatt, and C. Magai. 2012. “Noninitiation of Adjuvant Chemotherapy in Women with Localized Breast Cancer: The Breast Cancer Quality of Care Study.” *Journal of Clinical Oncology* 30 (31): 3800–9.
- Newman, L. A., J. Mason, D. Cote, Y. Vin, K. Carolin, D. Bouwman, and G. A. Colditz. 2002. “African-American Ethnicity, Socioeconomic Status, and Breast Cancer Survival.” *Cancer* 94 (11): 2844–54.
- North American Association of Central Cancer Registries. 2014. “Great Circle Distance Calculator” [accessed on April 4, 2014]. Available at <http://www.naaccr.org/Research/DataAnalysisTools.aspx>
- Osborne, C., G. V. Ostir, X. Du, M. K. Peek, and J. S. Goodwin. 2005. “The Influence of Marital Status on the Stage at Diagnosis, Treatment, and Survival of Older Women with Breast Cancer.” *Breast Cancer Research and Treatment* 93 (1): 41–7.
- Richardson, L. C., L. Tian, L. Voti, A. G. Hartzema, I. Reis, L. E. Fleming, and J. MacKinnon. 2006. “The Roles of Teaching Hospitals, Insurance Status, and Race/Ethnicity in Receipt of Adjuvant Therapy for Regional-Stage Breast Cancer in Florida.” *Journal Information* 96 (1): 160–66.
- Sheppard, V. B., C. Isaacs, G. Luta, S. C. Willey, M. Boisvert, F. W. Harper, K. Smith, S. Horton, M. C. Liu, and Y. Jennings. 2013. “Narrowing Racial Gaps in Breast Cancer Chemotherapy Initiation: The Role of the Patient-Provider Relationship.” *Breast Cancer Research and Treatment* 139 (1): 207–16.

- Silliman, R. A., S. L. Troyan, E. Guadagnoli, S. H. Kaplan, and S. Greenfield. 1997. "The Impact of Age, Marital Status, and Physician-Patient Interactions on the Care of Older Women with Breast Carcinoma." *Cancer* 80 (7): 1326–34.
- Smith, T. J., and B. E. Hillner. 2001. "Ensuring Quality Cancer Care by the Use of Clinical Practice Guidelines and Critical Pathways." *Journal of Clinical Oncology* 19 (11): 2886–97.
- Voti, L., L. C. Richardson, I. Reis, L. E. Fleming, J. MacKinnon, and J. W. W. Coebergh. 2006. "The Effect of Race/Ethnicity and Insurance in the Administration of Standard Therapy for Local Breast Cancer in Florida." *Breast Cancer Research and Treatment* 95 (1): 89–95.
- Walter, L. C., N. P. Davidowitz, P. A. Heineken, and K. E. Covinsky. 2004. "Pitfalls of Converting Practice Guidelines into Quality Measures." *Journal of the American Medical Association* 291 (20): 2466–70.
- Ward, E., A. Jemal, V. Cokkinides, G. K. Singh, C. Cardinez, A. Ghafoor, and M. Thun. 2004. "Cancer Disparities by Race/Ethnicity and Socioeconomic Status." *CA: A Cancer Journal for Clinicians* 54 (2): 78–93.
- Ward, E., M. Halpern, N. Schrag, V. Cokkinides, C. DeSantis, P. Bandi, R. Siegel, A. Stewart, and A. Jemal. 2008. "Association of Insurance with Cancer Care Utilization and Outcomes." *CA: A Cancer Journal for Clinicians* 58 (1): 9–31.
- Wu, X., L. C. Richardson, A. R. Kahn, J. P. Fulton, R. D. Cress, T. Shen, H. J. Wolf, S. Bolick-Aldrich, and V. W. Chen. 2008. "Survival Difference between Non-Hispanic Black and Non-Hispanic White Women with Localized Breast Cancer: The Impact of Guideline-Concordant Therapy." [Erratum appears in J Natl Med Assoc. 2008 Jun; 100(6):659]. *Journal of the National Medical Association* 100 (5): 490–8.
- Wu, X.-C., M. J. Lund, G. G. Kimmick, L. C. Richardson, S. A. Sabatino, V. W. Chen, S. T. Fleming, C. R. Morris, B. Huang, and A. Trentham-Dietz. 2012. "Influence of Race, Insurance, Socioeconomic Status, and Hospital Type on Receipt of Guideline-Concordant Adjuvant Systemic Therapy for Locoregional Breast Cancers." *Journal of Clinical Oncology* 30 (2): 142–50.
- Yen, T. W. F., L. K. Czypinski, R. A. Sparapani, C. Guo, P. W. Laud, L. E. Pezzin, and A. B. Nattinger. 2010. "Socioeconomic Factors Associated with Adjuvant Hormone Therapy Use in Older Breast Cancer Survivors." *Cancer* 117 (2): 398–405.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.