Noninitiation of Adjuvant Chemotherapy in Women With Localized Breast Cancer: The Breast Cancer Quality of Care Study

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Submitted April 24, 2012; accepted August 2, 2012; published online ahead of print at www.jco.org on September 24, 2012.

Supported by a Department of Defense Breast Cancer Center of Excellence Award (No. BC043120; A.I.N.), National Cancer Institute (NCI) R01 (Grant No. CA105274), Department of Defense Center for Biobehavioral Breast Cancer Research Award (L.H.K.), NCI R25 fellowship (Grant No. CA094601; N.L.), Department of Defense Grant No. DAMD-17-01-1-0334 (D.H.B.), NCI R01 (Grant No. CA100598; C.B.A.), NCI R01 (Grants No. CA124924 and CA127617; J.S.M.), NCI U10 (Grant No. CA84131; J.S.M.), and NCI K05 (Grant No. CA96940; J.S.M.). D.L.H. and C.B.A. are recipients of funding from the Breast Cancer Research Foundation.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3031-3800/\$20.00

DOI: 10.1200/JCO.2012.43.8168

ABSTRACT

Purpose

For some women, adjuvant chemotherapy for nonmetastatic breast cancer decreases recurrences and increases survival; however, patient-physician decisions regarding chemotherapy receipt can be influenced by medical and nonmedical factors.

Patients and Methods

We used a prospective cohort design and multivariate modeling to investigate factors related to noninitiation of chemotherapy among women with newly diagnosed breast cancer recruited from three US sites. We interviewed patients at baseline and during treatment on sociodemographic, tumor, and treatment decision-making factors. Patients were categorized according to National Comprehensive Cancer Network guidelines as those for whom chemotherapy was definitely indicated, clinically discretionary, or discretionary based on age greater than 70 years.

Results

Of 1,145 patients recruited, chemotherapy was clinically indicated for 392 patients, clinically discretionary for 459 patients, discretionary because of age for 169 patients, and not indicated for 93 patients; data were insufficient for 32 patients. Chemotherapy rates were 90% for those in whom chemotherapy was clinically indicated, 36% for those in whom it was discretionary because of clinical factors, and 19% for those in whom it was discretionary based on age greater than 70 years. Nonreceipt of chemotherapy was associated with older age, more negative beliefs about treatment efficacy, less positive beliefs about chemotherapy, and more concern about adverse effects. In the two discretionary groups, clinical predictors of worse outcome (greater tumor size, positive nodes, worse grade, and estrogen receptor- and progesterone receptor-negative status) were associated with increased chemotherapy initiation.

Conclusion

Utilization of adjuvant chemotherapy was most common among patients who, based on clinical criteria, would most likely benefit from it, patients with more positive than negative beliefs regarding treatment efficacy, and patients with few concerns about adverse effects.

J Clin Oncol 30:3800-3809. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Over the last three decades, advances in the use of adjuvant chemotherapy, radiation therapy, and hormonal therapy have improved breast cancer survival significantly.^{1,2} Unfortunately, not all patients receive appropriate and timely treatment³⁻⁵; some patients fail to receive the recommended therapy at all,⁶ whereas others delay initiation⁷⁻⁹ or discontinue therapy early.^{3,10,11} Deviations from recommended adjuvant therapy have been associated with worse survival,^{3,7,8} and

interventions to improve compliance may lead to improved survival.

Chemotherapy after surgery has led to reduced risk of recurrence and death for women with resectable breast cancer,² depending on the clinical characteristics of the disease and age of the patient. For example, older women, particularly women who are hormone receptor positive, seem less likely to benefit from chemotherapy; for such women, hormonal therapy alone is effective.^{2,12,13} For patients with nonmetastatic breast cancer, guidelines developed by the National Comprehensive Cancer Network

(NCCN) specify the clinical and demographic characteristics of those who should or should not receive chemotherapy and of those for whom it is a judgment call or discretionary.¹⁴

More than two thirds of premenopausal women with breast cancer,^{15,16} but only 15% to 30% of older women age ≥ 65 years, receive adjuvant chemotherapy.^{13,15,17-19} A few studies have explored reasons for nonreceipt of adjuvant chemotherapy and identified factors related to the patient, the physician, and patient-physician communication. However, these studies have been limited by small sample size, selection bias, or use of administrative databases, such as the Surveillance, Epidemiology, and End Results–Medicare database. One recent analysis of an administrative database¹⁶ used treatment guidelines to identify patients younger than age 70 who should receive chemotherapy and found that 65% received adjuvant therapy. However, they did not distinguish patients for whom therapy was definitive from those for whom it was discretionary, and they did not have information on patient preference.

The Breast Cancer Quality of Care Study (BQUAL) is a multisite prospective cohort study whose goal is to identify reasons for noninitiation, delay, and early discontinuation of adjuvant chemotherapy and hormonal therapy among women with resected breast cancer. In this article, we present data on nonreceipt of chemotherapy on both patients for whom it is clearly indicated and patients for whom the benefit is small or unknown. We also report on the association of demographic, clinical, and psychosocial factors and patient perceptions regarding decision making with receipt of chemotherapy.

PATIENTS AND METHODS

The BQUAL study has been previously described.²⁰ Briefly, between 2006 and 2010, we recruited adult women, age 20 years and older, who were newly diagnosed with primary breast cancer (stages I to III), from three sites (New York City [Columbia University Medical Center and Mount Sinai School of Medicine], metropolitan Detroit [Henry Ford Health System], and northern California [Kaiser Permanente of Northern California]). Women with a history of any cancer other than nonmelanoma skin cancer were excluded, as were women with a history of significant memory deficit, non-English speakers, or patients unable to provide informed consent. All patients were required to have a telephone.

Each participant was interviewed by phone three times by trained research assistants. The baseline interview was conducted within 3 months of diagnosis or before receipt of a third cycle of chemotherapy; the second interview was conducted 4 to 6 weeks later; and the third interview was conducted 12 to 24 weeks after diagnosis. Participants with hormone-sensitive breast cancer completed additional follow-up surveys every 6 months for the first 2 years and then annually until conclusion of the study. Each participant provided written informed consent and Health Insurance Portability and Accountability Act authorization before study entry.

Patients were grouped into the following four categories according to NCCN guidelines available in 2006¹⁴ (Table 1): patients younger than 70 years of age for whom adjuvant chemotherapy was definitely indicated; patients younger than 70 years of age for whom chemotherapy was discretionary based on clinical criteria; patients for whom chemotherapy was discretionary because of age greater than 70 years; and patients for whom chemotherapy was not indicated. In 2008, the NCCN guidelines for the treatment of breast cancer were updated to include *Oncotype DX* (Genomic Health, Redwood City, CA).²¹ This information, as well as information on nodal micrometastasis from the 2006 guidelines, was not available and not used to categorize patients. Chemotherapy initiation was determined by self-report based on questions in the interview at baseline and in the two follow-up interviews. Self-report of chemotherapy receipt has been shown to have an accuracy of 98% or

Table 1. Guidelines for Use of Adjuvant Chemotherapy for Women With Resected Localized Breast Cancer Based on the 2006 NCCN* Guidelines¹⁴

Chemotherapy Clinically Indicated	ER/PR	HER2	Tumor Size (cm)	Nodes
No	+	+	≤ 0.5	Neg
	+	Neg	≤ 0.5	Neg, micro†
	+	Neg	0.5-1.0	Neg
	Neg	+	≤ 0.5	Neg
	Neg	Neg	≤ 0.5	Neg
Yes‡	+	+	> 1.0	Neg
	+	+	> 1.0	+
	+	Neg	> 0.5	Neg
	+	Neg	> 0.5	+
	Neg	+	> 1.0	Neg
	Neg	+	> 1.0	+
	Neg	Neg	> 1.0	Neg
	Neg	Neg	> 1.0	+
Discretionary	+	+	≤ 0.5	Micro†
	+	+	0.6-1.0	Neg
	+	Neg	> 0.5	Neg
	+	Neg	> 0.5	Neg
	Neg	+	≤ 0.5	Micro†
	Neg	+	0.6-1.0	Neg
	Neg	Neg	≤ 0.5	Micro†
	Neg	Neg	0.6-1.0	Neg

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Micro, microscopic metastasis; NCCN, National Comprehensive Cancer Network; Neg, negative; PR, progesterone receptor.

*In the 2008 NCCN guideline update, *Oncotype DX* was added.²¹ In a separate sensitivity analysis (see Results), year of diagnosis (2006 to 2007 and 2008 to 2010) was examined as a covariate, and we found no difference in our results (data not shown).

†Information related to microscopic metastasis was not available.

‡Chemotherapy is discretionary when the patient is age 70 years or older.

better.²²⁻²⁵ All study procedures were approved by the institutional review board of each recruitment site as well as by the US Army Medical Research and Materiel Command Office of Research Protections and Human Research Protection Office.

Study Variables

Demographic and tumor factors. Demographic characteristics, including age, race/ethnicity, educational attainment, annual household income, employment, marital status, and site of recruitment, were collected at baseline. Tumor characteristics (American Joint Committee on Cancer stage, tumor grade and size, nodal status, and estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 status) and comorbidities reported from 12 months before diagnosis to 3 months after diagnosis were abstracted from the medical record or obtained from administrative databases; comorbidities were used to derive a Charlson comorbidity index score.²⁶

Chemotherapy-related factors. Factors related to chemotherapy included self-reported referral to a medical oncologist; whether the participant was under the care of a medical oncologist; whether chemotherapy was discussed, offered, or recommended; and if so, by whom.

Chemotherapy decision making. The extent of desired involvement in the chemotherapy decision-making process was determined using a modified version of a questionnaire developed and validated by Llewellyn-Thomas et al.²⁷ Women were also asked how difficult the decision to receive chemotherapy had been and who, if anyone other than the physician, assisted them in making their decision. Patients were asked to indicate the importance of several considerations that factored into the decision to undergo chemotherapy.²⁸ These considerations included physical appearance; nausea and vomiting; negative beliefs about chemotherapy effectiveness; positive beliefs, such as

Table 2. Demographics and Clinical and Tumor Characteristics (univariate) of Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, Categorized According to 2006 NCCN Guidelines for Indications for Adjuvant Chemotherapy

Demographic or Characteristic	Chemotherapy Clinically Indicated, Age < 70 Years (n = 392)					P	Chemotherapy Discretionary, Age < 70 Years (n = 459)					P	Chemotherapy Discretionary, Age ≥ 70 Years (n = 169)					P
	Initiated (n = 353, 90%)		Did Not Initiate (n = 39, 10%)		Initiated (n = 167, 36%)		Did Not Initiate (n = 292, 64%)		Initiated (n = 38, 22%)		Did Not Initiate (n = 131, 78%)							
	No. of Patients	%	No. of Patients	%	No. of Patients		%	No. of Patients	%	No. of Patients	%		No. of Patients	%				
Age, years					< .001					< .001					.04			
< 40	32	9	0	0		14	8	5	2		—	—	—	—				
40-49	89	25	5	13		54	32	40	14		—	—	—	—				
50-59	144	41	12	31		59	35	97	33		—	—	—	—				
60-69	88	25	22	56		40	24	150	51		—	—	—	—				
70-79	—	—	—	—		—	—	—	—		35	92	100	76				
80+	—	—	—	—		—	—	—	—		3	8	31	24				
Race					.65					.59					.43			
Asian	32	9	5	13		17	10	29	10		0	0	7	5				
African American/Black	68	19	9	23		23	14	38	13		7	18	17	13				
Hispanic	23	7	1	3		13	8	15	5		1	3	1	1				
White	223	63	24	62		113	68	204	70		30	79	105	80				
Other	7	2	0	0		1	1	6	2		0	0	1	1				
Year of diagnosis					.87					.10					.99			
2006-2007	113	32	12	31		55	33	75	26		9	24	31	24				
2008-2010	240	68	27	69		112	67	217	74		29	76	100	76				
Education					.33					.41					.92			
≤ High school graduate	71	20	12	31		46	28	66	23		11	29	38	29				
College	181	51	20	51		77	46	136	47		19	50	69	53				
Graduate school	99	28	7	18		44	26	90	31		8	21	24	18				
Household income					.09					.11					.22			
< \$15,000-\$24,999	31	9	6	15		14	8	26	9		12	32	36	8				
\$25,000-\$49,999	62	18	10	26		27	16	67	23		9	24	52	16				
\$50,000-\$89,999	111	31	14	36		67	40	84	29		11	29	21	40				
≥ \$90,000	130	37	6	15		55	33	103	35		4	11	10	27				
Refused	19	5	3	8		4	2	12	4		2	5	12	9				
Employment status					.005					< .001					.47			
Full time	110	31	14	36		80	48	103	35		0	0	5	4				
Part time	31	9	4	10		19	11	40	14		3	8	9	7				
Retired	67	19	15	38		17	10	89	30		32	84	112	86				
Not currently working	145	41	6	15		51	31	60	21		3	8	5	4				
Marital status					.30					.77					.054			
Married	186	53	24	62		89	53	156	53		15	39	31	24				
Not married	120	34	13	33		57	34	93	32		13	34	73	56				
Unknown	47	13	2	5		21	13	43	15		10	26	27	21				
Site of recruitment					.13					.02					.69			
CUMC/MSSM	78	22	4	10		30	18	27	9		2	5	4	3				
KPNC	244	69	33	85		122	73	233	80		27	71	101	77				
HFHS	31	9	2	5		15	9	32	11		9	24	26	20				
AJCC stage					.06					< .001					< .001			
I	47	13	4	10		92	55	250	86		7	18	81	62				
II	217	61	32	82		68	41	36	12		21	55	41	31				
III	78	22	3	8		1	1	0	0		8	21	3	2				
Unknown	11	3	0	0		6	4	6	2		2	5	6	5				
Grade					< .001					< .001					.0015			
Well differentiated	37	10	14	36		23	14	116	40		2	5	36	27				
Moderately differentiated	141	40	15	38		91	54	142	49		18	47	69	53				
Poorly differentiated	163	46	9	23		43	26	15	5		14	37	19	15				
Unknown	12	3	1	3		10	6	19	7		4	11	7	5				
Node status					.16					—					< .001			
Positive	263	75	33	85		0	0	0	0		23	61	17	13				
Negative	90	26	6	15		167	100	292	100		15	39	114	87				

(continued on following page)

Table 2. Demographics and Clinical and Tumor Characteristics (univariate) of Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, Categorized According to 2006 NCCN Guidelines for Indications for Adjuvant Chemotherapy (continued)

Demographic or Characteristic	Chemotherapy Clinically Indicated, Age < 70 Years (n = 392)				P	Chemotherapy Discretionary, Age < 70 Years (n = 459)				P	Chemotherapy Discretionary, Age ≥ 70 Years (n = 169)				P
	Initiated (n = 353, 90%)	Did Not Initiate (n = 39, 10%)	No. of Patients	%		Initiated (n = 167, 36%)	Did Not Initiate (n = 292, 64%)	No. of Patients	%		Initiated (n = 38, 22%)	Did Not Initiate (n = 131, 78%)	No. of Patients	%	
Tumor size, cm					.49					< .001					< .001
0-0.5	144	41	19	49		86	52	244	84		13	34	93	71	
> 0.5-1.0	182	52	17	44		72	43	45	15		22	58	32	24	
> 1.0	18	5	3	8		9	5	3	1		3	8	5	4	
Unknown	9	3	0	0		—	—	—	—		0	0	1	1	
ER/PR status					.14					.03					.06
Positive	205	58	29	74		157	94	286	98		30	79	118	90	
Negative	147	42	10	26		10	6	6	2		7	18	13	10	
Unknown	1	< 1	0	0		—	—	—	—		1	3	0	0	
HER2 status					.01					< .001					< .001
Positive	69	20	2	5		33	20	8	3		8	21	4	3	
Negative	257	73	30	77		123	74	250	86		27	71	116	89	
Unknown	27	8	7	18		11	7	34	12		3	8	11	8	
Charlson comorbidity score					.45					.03					.55
0-1	324	92	38	97		163	97	270	92		30	79	109	82	
≥ 2	27	8	1	3		4	2	22	8		8	21	22	17	
Unknown	2	1	0	0		1	1	0	0		0	0	0	0	

Abbreviations: CUMC/MSSM, Columbia University Medical Center/Mount Sinai School of Medicine in New York City; AJCC, American Joint Committee on Cancer; BQUAL, Breast Cancer Quality of Care Study; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HFHS, Henry Ford Health System in the metropolitan Detroit area; KPNC, Kaiser Permanente of Northern California; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor.

not having to worry about the cancer coming back; finances and the ability to pay for treatment; and beliefs of family and friends about chemotherapy.

Quality of patient-physician communication. Patients' perceptions of the quality of their patient-physician communication was assessed using the following four face valid items: receiving sufficient information on which to base a treatment decision, obtaining an adequate explanation of the treatment's risks and benefits, if the patient's opinions and preferences regarding chemotherapy were elicited and considered, and if the physician believed that pre-existing conditions precluded chemotherapy use.

Psychosocial factors. To assess pretreatment expectations for adverse effects, participants were asked to indicate, on a visual analog scale (range, 1 to 10), their expectations for fatigue, nausea, hearing loss, and pain, as well as how bothersome they expected chemotherapy adverse effects to be.²⁹ Participants were also asked to complete the social support subscale of the Medical Outcomes Study³⁰ measure and to indicate the number of close friends and family members in whom they could confide. Participants were queried about their beliefs regarding chemotherapy (eg, "You are less likely to have the cancer come back if you have chemotherapy"). We also assessed optimistic disposition with the Life Orientation Test,³¹ fatalistic beliefs using that subscale of the Mental Adjustment to Cancer scale,³² and impact of a breast cancer diagnosis as a stressful life event using the Impact of Events Scale.³³ These measures were all collected at baseline. Four to 6 weeks after baseline, in the first follow-up survey, we evaluated medical literacy,³⁴ medical mistrust,³⁵ and quality of care using the Interpersonal Processes of Care measures.³⁶

Outcome Measure

The patient's initiation of chemotherapy was determined by self-report, a method that has been found to have 98% to 100% agreement with chart abstraction.²²⁻²⁵ Patients were asked whether a physician discussed chemotherapy with them, whether chemotherapy had been prescribed, and whether they had made a decision to undergo chemotherapy. The questions were first asked at baseline and, for patients who reported that chemotherapy had not been discussed or prescribed, again in follow-up questionnaires (up to 6

months after diagnosis). After a participant indicated her decision was made, the questions were no longer asked.

Data Analysis

Comparison between chemotherapy initiators and noninitiators was conducted using Fisher's exact or χ^2 tests for categorical variables and *t* tests for continuous variables. Cronbach's α was used to assess internal consistency and reliability of scale measures. We conducted multivariable logistic regression analyses to assess the relationship of chemotherapy initiation with demographic characteristics, clinical characteristics, treatment received, decision-making scales, patient-physician communication scales, and psychosocial factors. We conducted two sensitivity analyses—one to evaluate the impact of beginning chemotherapy before the baseline interview and another to assess the influence of year of diagnosis and changes in the NCCN guidelines on outcomes. Only variables found to have a *P* < .10 in the univariate analyses were included in the multivariate models. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

We identified and contacted 1,479 women with newly diagnosed nonmetastatic breast cancer between May 2006 and June 2010. Of these, 122 women (8.2%) refused to participate, and 212 women (14.3%) were found to be ineligible. We categorized the remaining 1,145 women according to NCCN guidelines¹⁴ (Table 1) into the following four groups: 392 patients (34.2%) for whom chemotherapy was clinically indicated; 459 patients (40.1%) less than 70 years for whom chemotherapy was discretionary; 169 patients (14.8%) for whom chemotherapy was discretionary because of age (> 70 years); and 93 patients (10.9%) for whom chemotherapy was not

Table 3. Treatment, Decision-Making, and Psychosocial Characteristics of Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, and Categorized According to NCCN Guidelines for Indications for Adjuvant Chemotherapy

Characteristic	Chemotherapy Clinically Indicated, Age ≤ 70 Years (n = 392)					Chemotherapy Discretionary, Age ≤ 70 Years (n = 459)					Chemotherapy Discretionary, Age ≥ 70 Years (n = 169)					Range of Possible Values
	Initiated (n = 353, 90%)		Did Not Initiate (n = 39, 10%)		P	Initiated (n = 167, 36%)		Did Not Initiate (n = 292, 64%)		P	Initiated (n = 38, 22%)		Did Not Initiate (n = 131, 78%)		P	
	No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%		
Chemotherapy-related factors																
Referred to a medical oncologist	345	98	37	95	.26	161	96	279	96	.81	38	100	121	92	.12	
Under the care of a medical oncologist	353	100	38	97	.10	167	100	288	99	.30	38	100	123	94	.20	
Chemotherapy discussed	347	98	38	97	.52	164	98	238	82	< .001	38	100	94	72	< .001	
Chemotherapy offered or recommended	345	98	21	54	< .001	156	93	79	27	< .001	38	100	14	11	< .001	
Recommended by (the most)					.59					.04					< .001	
Surgeon	129	37	6	29		33	21	12	15		11	29	5	4		
PCP	2	1	0	0		0	0	0	0		0	0	0	0		
Medical oncologist	201	58	15	71		114	73	64	81		26	68	7	5		
Other	13	4	0	0		8	5	0	0		1	3	2	2		
Chemotherapy decision making†																
Chemotherapy decision- making beliefs					< .001					.04					.47	
Doctor should make the decision	93	26	6	15		47	28	54	18		13	34	38	29		
Doctor and patient make the decision together	135	38	11	28		53	32	115	39		17	45	52	40		
Patient should make the decision	123	35	22	56		67	40	123	42		8	21	41	31		
Level of chemotherapy decision difficulty					< .001					< .001					< .001	
Difficult	87	25	15	38		60	36	68	23		11	29	8	6		
Neither difficult nor easy	44	12	6	15		25	15	30	10		4	11	11	8		
Easy	218	62	14	36		81	49	163	56		23	61	96	73		
Missing	4	1	4	10		1	1	31	11		0	0	16	12		
Persons involved in chemotherapy decision*																
Family and friends	216	61	20	51	.23	106	63	156	53	.04	20	53	45	34	.06	
Husband/partner	136	39	9	23	.08	59	35	94	32	.54	8	21	11	8	.04	
Parent/child/grandchild	69	20	6	15	.67	39	23	45	15	.04	12	32	29	22	.28	
Other relative	59	17	4	10	.37	34	20	36	12	.03	3	8	6	5	.42	
Other medical professional	9	3	3	8	.11	4	2	4	1	.47	0	0	3	2	.35	
Other	68	19	11	28	.20	38	23	50	17	.14	5	13	13	10	.56	
Decision-making considerations††																
Physical	0.56	0.76	1.05	0.80	< .001	0.71	0.83	0.82	0.85	.22	0.65	0.79	0.94	0.82	.03	0-2
Negative balance	0.83	1.12	2.50	1.22	< .001	1.05	1.25	2.43	1.14	< .001	0.86	0.82	2.50	1.08	< .001	0-5
Positive balance	2.88	0.37	1.79	1.19	< .001	2.86	0.39	1.82	1.09	< .001	2.89	0.31	1.50	1.11	< .001	0-3
Concrete considerations	1.09	1.19	1.26	1.29	.40	1.01	1.23	1.07	1.23	.66	0.82	0.93	1.12	1.19	.16	0-5
Family and friends	0.40	0.49	0.34	0.48	.51	0.47	0.50	0.30	0.46	< .001	0.37	0.49	0.28	0.45	.30	0-1
Chemotherapy-related patient- physician communication††																
Communication quality scale	13.89	2.49	12.89	2.16	.02	14.07	2.45	13.6	2.90	.08	13.6	2.59	12.5	2.72	.04	3-18
Psychosocial factors‡																
Pretreatment expectations‡																
Fatigue	6.09	2.25	7.08	2.38	.011	6.28	2.12	7.33	2.02	< .001	5.92	2.25	6.98	2.22	.01	0-10
Nausea	4.72	2.76	6.43	2.26	< .001	4.58	2.76	7.18	2.22	< .001	3.49	2.50	6.52	2.88	< .001	0-10
Hearing loss	0.85	1.71	1.48	2.11	.047	0.85	1.79	1.77	2.50	< .001	1.00	1.83	2.15	2.74	.02	0-10
Pain	3.49	2.58	4.73	2.36	.005	3.79	2.68	5.26	2.67	< .001	3.46	2.43	4.86	2.87	.009	0-10
Adverse effects	5.63	2.46	7.41	2.09	< .001	5.84	2.33	7.46	2.15	< .001	4.92	2.54	6.90	2.60	< .001	0-10

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Table 3. Treatment, Decision-Making, and Psychosocial Characteristics of Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, and Categorized According to NCCN Guidelines for Indications for Adjuvant Chemotherapy (continued)

Characteristic	Chemotherapy Clinically Indicated, Age < 70 Years (n = 392)					Chemotherapy Discretionary, Age < 70 Years (n = 459)					Chemotherapy Discretionary, Age ≥70 Years (n = 169)					Range of Possible Values
	Initiated (n = 353, 90%)		Did Not Initiate (n = 39, 10%)		P	Initiated (n = 167, 36%)		Did Not Initiate (n = 292, 64%)		P	Initiated (n = 38, 22%)		Did Not Initiate (n = 131, 78%)		P	
	No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%		
No. of close friends/relatives†	14.84	11.13	12.05	6.98	.13	14.01	13.73	13.98	13.88	.98	14.63	9.61	11.81	9.02	.10	Write in
MOS Social Support Index§	4.34	0.66	3.96	0.84	.0012	4.26	0.72	4.23	0.66	.64	4.39	0.62	4.20	0.65	.12	1-5
Chemotherapy beliefs†	3.08	0.50	2.48	0.68	< .001	3.09	0.48	2.67	0.56	< .001	3.13	0.53	2.52	0.61	< .001	1-4
Life Orientation Test††	19.88	4.02	18.82	4.44	.12	20.7	4.21	19.5	4.10	.003	20.2	3.92	20.4	3.85	.69	3-28
Fatalism†	19.79	3.04	19.85	2.30	.91	19.1	3.38	18.2	3.20	.78	20.6	3.18	21.1	3.05	.38	8-32
Impact of Events Scale†	14.98	9.85	13.90	8.01	.51	15.0	10.7	12.4	8.49	.006	14.6	10.2	10.5	8.80	.02	0-75
Medical literacy	7.39	1.53	7.50	1.25	.68	7.28	1.36	7.32	1.43	.76	7.03	1.85	7.56	1.57	.08	0-12
Group-Based Medical Mistrust Scale	21.03	7.30	22.58	8.73	.23	20.3	6.58	21.1	6.81	.25	18.4	6.57	20.0	6.23	.16	13-65
Interpersonal Processes of Care																
Communication																
Lack of clarity	2.10	0.78	2.11	0.87	.93	2.15	0.73	2.16	0.70	.88	1.84	0.72	1.93	0.80	.53	1-5
Eliciting concerns	4.37	0.62	4.22	0.69	.19	4.36	0.68	4.32	0.59	.52	4.47	0.53	4.38	0.61	.40	1-5
Explained results	4.37	0.78	4.19	0.84	.19	4.34	0.81	4.45	0.72	.13	4.57	0.75	4.40	0.79	.24	1-5
Decision making																
Working together	4.14	1.22	4.16	0.88	.93	4.21	1.00	4.39	0.72	.03	4.28	1.02	4.09	1.02	.33	1-5
Interpersonal style																
Compassion	4.35	0.71	4.19	0.83	.18	4.25	0.80	4.33	0.69	.30	4.46	0.75	4.42	0.64	.72	1-5
Discrimination by race	1.20	0.48	1.22	0.58	.77	1.20	0.52	1.18	0.46	.73	1.13	0.36	1.14	0.37	.95	1-5
Disrespectful staff	1.23	0.46	1.39	0.62	.05	1.21	0.48	1.25	0.47	.40	1.07	0.22	1.21	0.47	.09	1-5

Abbreviations: BQUAL, Breast Cancer Quality of Care Study; MOS, Medical Outcomes Study; NCCN, National Comprehensive Cancer Network; PCP, primary care physician.

*More than one response was possible; total is greater than 100%.

†Data collected at baseline.

‡Values represent mean scores and standard deviations.

§MOS measure of social support.

indicated. The remaining 32 women had missing tumor data and could not be categorized. We found that 90% of patients (353 of 392 patients) in the indicated group received chemotherapy, whereas 36% (167 of 459 patients; age < 70 years) and 19% (32 of 169 patients; age > 70 years) of patients in the two discretionary groups received chemotherapy. Only three (3.2%) of 93 patients for whom chemotherapy was not indicated received chemotherapy; these patients are not discussed further.

Table 2 lists the demographic, clinical, and selected treatment characteristics of the remaining three groups separated into those who initiated or did not initiate chemotherapy. In all three groups, patients who initiated chemotherapy were younger, had tumors with higher stage or worse grade, or were more likely to be human epidermal growth factor receptor 2 positive than patients who did not initiate chemotherapy. Among patients younger than 70 years, chemotherapy initiation was associated with being retired, and for the subgroup in whom it was discretionary, chemotherapy initiation was associated with fewer comorbidities and negative ER/PR status. For those older than 70 years, initiation was associated with positive nodes.

Table 3 lists the results of a univariate analysis of various treatment-related, decision-related, and psychosocial factors and their associations with receipt of chemotherapy for the three groups. In all three groups, patients who reported difficulty making a decision about

chemotherapy, strong negative beliefs about treatment (eg, that chemotherapy is not always effective) or weak positive beliefs (eg, fewer worries about tumor recurrence) about it, low quality of communication with physicians, or strong expectations of adverse effects (eg, fatigue, nausea, pain) were less likely than other patients to initiate chemotherapy. In the two groups younger than 70 years, noninitiators believed more that the patient role in decision making should be greater than the physician's role. Spouse, family, and friend support in chemotherapy decision making, the social support index, and the number of close friends and relatives were not associated with chemotherapy initiation in any of the three groups.

In multivariable regression analysis (Table 4), in all three groups, initiation of chemotherapy was strongly associated with younger age and with strong negative beliefs and weak positive beliefs about the efficacy of treatment. Among patients for whom chemotherapy was recommended, chemotherapy initiation was also associated with increased household income, poorly differentiated tumor grade, and higher levels of social support. For the group for whom chemotherapy was discretionary, initiation was also associated with moderately or poorly differentiated tumor grade, negative ER/PR status, larger tumor size, treatment at Columbia University as compared with Kaiser Permanente of Northern California or Henry Ford Health System, higher levels of intrusive thoughts about cancer, and lower levels of

Table 4. Results of Logistic Regression Analysis for Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, Categorized According to NCCN Guidelines for Indications for Adjuvant Chemotherapy, With the End Point of Initiation of Chemotherapy

Factor	Chemotherapy Clinically Indicated, Age < 70 Years (n = 392)			Chemotherapy Discretionary, Age < 70 Years (n = 459)			Chemotherapy Discretionary, Age ≥ 70 Years (n = 169)		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Age, years									
< 40	Ref			Ref					
40-49*				0.89	0.25 to 3.19	.86			
50-59	0.65	0.20 to 2.08	.46	0.42	0.12 to 1.45	.17			
60-69	0.17	0.04 to 0.65	.0095	0.17	0.05 to 0.62	.007			
70-79							Ref		
80+							0.14	0.03 to 0.75	.02
Household income									
<\$15,000-\$24,999	Ref								
\$25,000-\$49,999	2.53	0.68 to 9.33	.16						
\$50,000-\$89,999	2.15	0.63 to 7.32	.22						
≥ \$90,000	6.35	1.60 to 25.2	.009						
Refused	2.44	0.44 to 13.6	.31						
Employment status									
Full time	Ref			Ref					
Part time	2.19	0.54 to 8.84	.27	0.70	0.32 to 1.56	.39			
Retired	2.02	0.58 to 7.08	.27	0.46	0.21 to 1.01	.052			
Not currently working	3.43	1.12 to 10.5	.03	1.15	0.64 to 2.05	.64			
Marital status									
Single							Ref		
Married							3.58	0.97 to 13.2	.06
Unknown							3.06	0.31 to 29.8	.07
AJCC stage									
I	Ref								
II	0.77	0.23 to 2.56	.67						
III	2.88	0.54 to 15.3	.22						
Unknown									
Grade									
Well differentiated	Ref			Ref			Ref		
Moderately differentiated	2.42	0.95 to 6.16	.06	2.92	1.61 to 5.32	< .001	1.32	0.24 to 7.24	.75
Poorly differentiated	4.52	1.62 to 12.7	.004	7.43	3.09 to 17.8	< .001	3.25	0.49 to 21.3	.22
Unknown				1.45	0.52 to 4.05	.48	3.06	0.31 to 29.8	.34
HER2 status									
Positive	Ref			Ref			Ref		
Negative	0.12	0.02 to 0.96	.05	0.18	0.05 to 0.60	< .001	0.13	0.02 to 0.79	.03
Unknown	0.06	0.007 to 0.60	.02	0.05	0.01 to 0.26	< .001	0.31	0.03 to 3.47	.34
ER/PR status									
Positive				Ref			Ref		
Negative				6.78	2.03 to 22.6	.0019	1.89	0.44 to 8.10	.39
Tumor size, cm									
0-0.5				Ref			Ref		
> 0.5-1.0				4.64	2.66 to 8.10	< .001	2.97	1.02 to 8.69	.05
> 1.0				9.69	2.01 to 26.7	.0047	3.81	0.50 to 29.1	.20
Node status									
Positive							Ref		
Negative							0.06	0.02 to 0.18	< .001
Site of recruitment									
CUMC/MSSM				Ref					
KPNC				0.46	0.23 to 0.93	.03			
HFHS				0.63	0.24 to 1.66	.35			
Treatment and decision making†									
Chemotherapy decision-making beliefs									
Doctor should make the decision	Ref			Ref					
Doctor and patient should make the decision together	1.02	0.20 to 5.28	.98	0.50	0.20 to 1.22	.13			
Patient should make the decision	0.49	0.11 to 2.27	.36	0.63	0.26 to 1.50	.29			

(continued on following page)

Table 4. Results of Logistic Regression Analysis for Patients With Breast Cancer Interviewed Within the BQUAL Study, 2006 to 2010, Categorized According to NCCN Guidelines for Indications for Adjuvant Chemotherapy, With the End Point of Initiation of Chemotherapy (continued)

Factor	Chemotherapy Clinically Indicated, Age < 70 Years (n = 392)			Chemotherapy Discretionary, Age < 70 Years (n = 459)			Chemotherapy Discretionary, Age ≥ 70 Years (n = 169)		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Level of chemotherapy decision difficulty									
Difficult	Ref			Ref			Ref		
Neither difficult nor easy	1.12	0.23 to 5.35	.88	0.85	0.29 to 2.48	.76	0.42	0.05 to 3.91	.45
Easy	2.60	0.67 to 10.1	.17	0.69	0.33 to 1.43	.32	0.31	0.06 to 1.61	.16
Family and friends involved in chemotherapy decision				0.60	0.30 to 1.21	.15	8.58	1.90 to 38.3	.005
Decision-making considerations									
Physical	0.69	0.34 to 1.36	.28				0.95	0.44 to 2.08	.91
Negative balance	0.44	0.29 to 0.68	< .001	0.34	0.25 to 0.45	< .001	0.10	0.04 to 0.27	< .001
Positive balance	6.56	3.27 to 13.2	< .001	5.24	3.00 to 9.14	< .001			
Family and friends				1.17	0.58 to 2.38	.66			
Communication quality scale	1.06	0.85 to 1.32	.61	0.94	0.82 to 1.07	.33	1.15	0.94 to 1.40	.18
Psychosocial characteristics									
Pretreatment expectations†									
Fatigue	0.99	0.75 to 1.31	.95	1.18	0.96 to 1.44	.11	0.98	0.72 to 1.32	.88
Nausea	0.87	0.71 to 1.08	.22	0.67	0.57 to 0.79	< .001	0.61	0.47 to 0.80	< .001
Hearing loss	0.90	0.72 to 1.12	.35	0.87	0.73 to 1.02	.09	0.85	0.64 to 1.13	.25
Pain	1.11	0.90 to 1.37	.34	1.07	0.93 to 1.24	.34	1.00	0.75 to 1.34	.99
Adverse effects	0.72	0.53 to 0.97	.03	0.79	0.65 to 0.96	.02	0.99	0.73 to 1.35	.97
No. of close friends/relatives†							1.01	0.95 to 1.07	.81
MOS Social Support Index†	2.05	1.12 to 3.75	.02						
Chemotherapy beliefs†	2.85	1.16 to 7.01	.02	4.90	2.62 to 9.18	< .001	14.0	3.89 to 50.5	< .001
Life Orientation Test†				1.08	1.00 to 1.16	.05			
Impact of Events Scale†				1.03	1.00 to 1.07	.05	1.11	1.04 to 1.19	.003
Medical literacy							0.75	0.50 to 1.13	.17
Group-Based Medical Mistrust							0.97	0.87 to 1.09	.60
Disrespectful staff	0.89	0.38 to 2.06	.78				0.32	0.06 to 1.68	.18
Working together				0.64	0.43 to 0.94	.02			

Abbreviations: CUMC/MSSM, Columbia University Medical Center/Mount Sinai School of Medicine; AJCC, American Joint Committee on Cancer; BQUAL, Breast Cancer Quality of Care Study; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HFHS, Henry Ford Health System; KPNC, Kaiser Permanente of Northern California; MOS, Medical Outcomes Study; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor; Ref, reference group.

*Those age < 40 and 40 to 49 years are combined as the reference group because of small numbers.

†Data collected at baseline.

expectations for aversive adverse effects, particularly nausea. For the group older than 70 years, chemotherapy initiation was also associated with positive lymph node status.

Of the 1,145 patients who underwent baseline interviews, 781 patients (68.2%) were interviewed before receiving any chemotherapy, and 364 patients (31.8%) received one or two cycles of chemotherapy before the interview. As a sensitivity analysis, we conducted the multivariate analyses including only patients who had no chemotherapy before the baseline interview; the results were similar to the analyses of the full sample (Appendix Table A1, online only). Because the NCCN guidelines were updated in 2008 to include *Oncotype DX*,²¹ we conducted a second sensitivity analysis that included the year of diagnosis (2006 to 2007 and 2008 to 2010) in the multivariate analyses. This variable did not contribute significantly to the model ($P = .51$ for clinically indicated patients, $P = .52$ for chemotherapy discretionary patients; data not shown).

DISCUSSION

Reassuringly, we found that initiation of adjuvant chemotherapy was associated with the strength of the recommendations for its use.

Ninety percent of patients for whom NCCN guidelines definitely recommended chemotherapy initiated chemotherapy, compared with only 36% of patients for whom chemotherapy was discretionary based on clinical criteria and 19% of patients for whom it was discretionary because of older age. Younger age and less negative and more positive beliefs about efficacy of treatment were also associated with initiation. In the two discretionary groups, initiation of chemotherapy was generally associated with clinical predictors of poor outcomes, such as negative ER/PR status, positive lymph nodes, larger tumor size, or worse grade. Unlike other studies, our study did not find that race was a significant predictor of chemotherapy use in any group or overall. In fact, slightly larger proportions of black and Hispanic patients than of white and Asian patients were in the recommended group and initiated chemotherapy overall.

Several studies have explored determinants of initiation of adjuvant chemotherapy, but most have focused on older patients. No prior study has categorized patients into the definitive versus discretionary chemotherapy categories according to guidelines, although in a recent paper by Wu et al,¹⁶ NCCN guidelines were used to distinguish those who were eligible for chemotherapy by grouping definitive and discretionary together into one category. They found

that 72% of eligible patients younger than age 70 initiated chemotherapy, whereas our rate was slightly lower at 61%, likely because of more stringent definitions. We found that only 22% of patients older than age 70 initiated chemotherapy, consistent with prior studies.^{13,15-19} Clinical trials have shown that the elderly benefit from chemotherapy, and age alone may not be the best criterion for making these decisions.³⁷ Hopefully, with improved prognostic tools, such as *Oncotype DX*, decisions will be based on recurrence risk as opposed to age alone.^{13,16}

In a prior BQUAL study of adjuvant hormonal therapy initiation,³⁸ we found that noninitiators preferred to have more input in the decision-making process and not to rely solely on the physician and that the decision to forego adjuvant hormonal therapy was not an easy one. However, those factors were not independently associated with chemotherapy initiation; expectations of adverse effects, especially nausea, seemed to play a greater role in the chemotherapy decision, and beliefs about chemotherapy overall were significant in certain groups. The robust relationship between pretreatment expectations for nausea and reduced likelihood of chemotherapy initiation is consistent with repeated surveys indicating that nausea is ranked as one of the most feared adverse effects of chemotherapy.³⁹ That higher levels of intrusive thoughts about breast cancer may motivate patients to decide in favor of chemotherapy is consistent with previous retrospective studies^{40,41} and a growing appreciation of the role of emotions in decision making.⁴²

Bickell et al⁴³ examined underuse in 258 patients with breast cancer from six New York hospitals in which use of any adjuvant therapy (chemotherapy, hormonal therapy, or radiotherapy) was studied as a single outcome. Of the 64 patients prescribed adjuvant chemotherapy, 87.5% initiated therapy. Overall, increasing age, increased comorbidities, greater mistrust of the medical system, lack of knowledge about adjuvant therapy, and unfavorable beliefs (eg, unwillingness to undergo painful or unpleasant adverse effects) were associated with noninitiation of treatment. Similar factors, especially belief in the efficacy of the medication, have been associated with decreased adherence to adjuvant hormonal therapy in breast cancer.^{44,45}

Unlike other investigators, we did not find an association between noninitiation of chemotherapy and race.^{3,46,47} We may have had insufficient statistical power, or there may have been a strong correlation between race and the behavioral factors assessed. Our recruitment may have been affected by selection bias, given that the sampling frames in Detroit and California were managed care organizations. However, our study is one of the larger multicenter prospective studies examining patient-reported reasons for chemotherapy noninitiation.

This study has a number of strengths. Because we recruited patients with breast cancer from different health care systems, including community practices and academic medical centers, our

findings have good generalizability. There were also excellent recruitment and retention rates. Study participants were recruited prospectively at the time of breast cancer diagnosis or shortly thereafter.

Our study had limitations as well. The patient population was mostly insured, so we could not investigate the association of insurance with chemotherapy initiation. In the latter years of this study, decisions regarding chemotherapy in the intermediate-risk group may have been influenced by *Oncotype DX* results, but we did not have this information to include in our risk categories. We excluded patients who did not have a telephone or did not speak English, which may decrease generalizability. Finally, some patients were not interviewed until after they initiated chemotherapy; however, excluding these patients did not alter our results.

In conclusion, in this prospective cohort study of women with early-stage breast cancer, we found that women for whom adjuvant chemotherapy is definitively recommended generally initiate chemotherapy at a high rate. Among patients for whom it was discretionary, less than half received chemotherapy. As would be expected, younger age and worse prognostic features are associated with increased rates of chemotherapy initiation in these discretionary groups. More positive beliefs about the efficacy of chemotherapy and less negative beliefs about it, especially with regard to adverse effects, were also associated with increased receipt of chemotherapy. These findings suggest that improved patient education may influence chemotherapy decision making. In short, chemotherapy utilization was high among patients for whom it was most likely to be beneficial, and oncologists seemed to be adhering to the guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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