Vanessa B. Sheppard, Leigh Anne Faul, George Luta, Jonathan D. Clapp, Judy Huei-yu Wang, Claudine Isaacs, Michelle Tallarico, and Jeanne S. Mandelblatt, Georgetown University Medical Center and Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Rachel L. Yung and Eric P. Winer, Dana-Farber Cancer Institute, Boston, MA; Gretchen Kimmick, William T. Barry, Brandelyn N. Pitcher, and Harvey J. Cohen, Duke University Medical Center; William T. Barry and Brandelyn N. Pitcher, Cancer and Leukemia Group B Statistical Center, Durham; Hyman B. Muss, University of North Carolina Chapel Hill, Chapel Hill, NC; Clifford Hudis, Memorial Sloan-Kettering Cancer Center, New York, NY; and Arti Hurria, City of Hope, Los Angeles, CA.

Published online ahead of print at www.jco.org on June 16, 2014.

Supported by Grants No. CA84131, CA124924, CA127617 and CA96940 (J.S.M.) and No. CA154848 (V.B.S.) from the National Cancer Institute (NCI), National Institutes of Health (NIH); in part by the Clinical and Molecular Epidemiology (now Nontherapeutic Subject Registry) and Biostatistics and Bioinformatics Shared Resources at Georgetown-Lombardi Comprehensive Cancer Center, funded by NCI NIH Grant No. P30CA51008; and in part by NCI NIH Grants No. CA31946 to Cancer and Leukemia Group B (CALGB) and No. CA33601 to the CALGB Statistical Center (for CALGB 369901 research); and in part by a grant to support patient accrual from Amgen Pharmaceuticals to the CALGB Foundation.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

The content of this manuscript is solely the responsibility of the authors and does not represent the official views of the National Cancer Institute, National Institutes of Health, or Cancer and Leukemia Group B (CALGB). CALGB is presently part of the Alliance for Clinical Trials in Oncology.

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

Corresponding author: Vanessa B. Sheppard, PhD, Georgetown University, Lombardi Comprehensive Cancer Center, 3300 Whitehaven Blvd, Suite 4100, Washington, DC 20007; e-mail: vis3@georgetown.edu.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3222w-2318w/\$20.00

DOI: 10.1200/JCO.2013.51.7367

Frailty and Adherence to Adjuvant Hormonal Therapy in Older Women With Breast Cancer: CALGB Protocol 369901

Vanessa B. Sheppard, Leigh Anne Faul, George Luta, Jonathan D. Clapp, Rachel L. Yung, Judy Huei-yu Wang, Gretchen Kimmick, Claudine Isaacs, Michelle Tallarico, William T. Barry, Brandelyn N. Pitcher, Clifford Hudis, Eric P. Winer, Harvey J. Cohen, Hyman B. Muss, Arti Hurria, and Jeanne S. Mandelblatt

ABSTRACT

Purpose

Most patients with breast cancer age ≥ 65 years (ie, older patients) are eligible for adjuvant hormonal therapy, but use is not universal. We examined the influence of frailty on hormonal therapy noninitiation and discontinuation.

Patients and Methods

A prospective cohort of 1,288 older women diagnosed with invasive, nonmetastatic breast cancer recruited from 78 sites from 2004 to 2011 were included (1,062 had estrogen receptor–positive tumors). Interviews were conducted at baseline, 6 months, and annually for up to 7 years to collect sociodemographic, health care, and psychosocial data. Hormonal initiation was defined from records and discontinuation from self-report. Baseline frailty was measured using a previously validated 35-item scale and grouped as prefrail or frail versus robust. Logistic regression and proportional hazards models were used to assess factors associated with noninitiation and discontinuation, respectively.

Results

Most women (76.4%) were robust. Noninitiation of hormonal therapy was low (14%), but in prefrail or frail (v robust) women the odds of noninitiation were 1.63 times as high (95% CI, 1.11 to 2.40; $P = .013$) after covariate adjustment. Nonwhites (v whites) had higher odds of noninitiation (odds ratio, 1.71; 95% CI, 1.04 to 2.80; $P = .033$) after covariate adjustment. Among initiators, the 5-year continuation probability was 48.5%. After adjustment, the risk of discontinuation was higher with increasing age ($P = .005$) and lower for stage $\geq$ IIB (v stage I) disease ($P = .003$).

Conclusion

Frailty is associated with noninitiation of hormonal therapy, but it does not seem to be a major predictor of early discontinuation in older patients.

J Clin Oncol 32:2318-2327. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Women age ≥ 65 years (ie, older patients) constitute nearly half of patients with breast cancer.^{1,2} This group will account for an increasing absolute number of patient cases over the coming decades because of the aging of the US population. Most of these older women (approximately 70%) will have **estrogen receptor (ER)**–positive breast cancers.³⁻⁵ Adjuvant hormonal therapy decreases recurrence⁶ and breast cancer–specific mortality in ER-positive cancers.⁶

Current guidelines recommend that women with ER-positive disease receive adjuvant hormonal therapy for at least 5 years,⁷ but older women have been found to initiate therapy less often and discontinue treatment more frequently than younger

women.^{4,8-10} Factors similar to those noted for younger women^{4,11} also affect older women's use of hormonal treatment, including patient attitudes,¹² difficulties in discussing treatment with providers,³ and financial barriers.¹³

A unique aspect of treatment in older patients is the considerable heterogeneity in functional status, level of comorbidity, accumulated health deficits, and probability of competing causes of death.^{14,15} The concept of frailty has been used to capture these domains as distinct from chronologic age.¹⁶ However, most prior investigations of noninitiation and discontinuation have been based on data available in tumor registries or administrative databases and have only captured limited data on frailty.^{8,9,13,17} Frailty might affect patterns of hor-

Fig 1. Study sample of older women with estrogen receptor (ER) –positive breast cancer. (*) A total of 1,703 participants were registered for the study. This is a correction from a 2012 publication indicating 1,704 participants.¹⁸ A duplicate entry for a participant was deleted; prior analyses only included this individual once.

monal therapy use and the balance of its risks and benefits. We used data from a large national prospective cohort of older patients with breast cancer to examine whether baseline frailty influenced noninitiation and discontinuation of hormonal therapy independent of chronologic age. We also explored whether sociodemographic characteristics and health care interactions affected hormonal therapy patterns.

PATIENTS AND METHODS

This analysis used data from a national cohort study of patterns of systemic therapy in older women.^{18,19} The study was conducted at 78 hospitals or practices affiliated with the Cancer and Leukemia Group B (CALGB) cooperative group, presently part of the Alliance for Clinical Trials in Oncology.¹⁸ The protocol met Health Insurance Portability and Accountability Act standards and was approved by CALGB and the institutional review boards at all sites.

Population

Participants were registered between January 1, 2004, and April 1, 2011. Eligible participants were age ≥ 65 years, diagnosed with invasive (≥ 1 cm) nonmetastatic breast cancer, spoke English or Spanish, and had sufficient cognitive function to complete interviews.^{20,21} Women were < 20 weeks from their last definitive surgery and had not initiated hormonal therapy. There were 1,703 women registered for the study (Fig 1); of these, 1,526 were eligible. A total of 1,288 baseline interviews (84.4%) were completed. This analysis was restricted to women with ER-positive tumors ($n = 1,062$).

Data Collection

Clinical research associates assessed patients, confirmed eligibility, obtained consent, and performed record review, including determination of ER status using standard criteria. Patients completed a 45-minute baseline structured telephone interview. Anchored on the baseline interview date, patients

completed 15- to 20-minute follow-up interviews at 6 months and annually thereafter for up to 7 years.

Measures

Outcomes were noninitiation and discontinuation of adjuvant hormonal therapy over 5 years (recommended duration during study period). Initiation of any type of adjuvant hormonal therapy (and start date) was based on medical records. Discontinuation was based on patient self-report. The stopping or censoring date was set at the midpoint between consecutive interviews.²² Women who died or experienced recurrence were censored at the date of the event based on medical records. Women who stopped > 18 months before the recurrence date were classified as discontinuing.

Frailty, the primary predictor, was measured by adapting the 35-item scale (Appendix Table A1, online only) developed by Searle et al,²³ previously validated to predict mortality in community-dwelling elders. It includes self-reported items relating to limitations in basic and instrumental activities of daily living, sensory deficits, functioning, and prediagnosis comorbidity. Because we excluded women with cognitive impairment, this item was not included in our adaptation. To evaluate the separate contributions of age and frailty, age was not included.^{23,24} Each deficit item was rated between 0 and 1, where a higher score indicated greater frailty (Cronbach's $\alpha = 0.77$). Scores were calculated for participants missing $< 10\%$ of items (1% missing $\geq 10\%$; Appendix, online only). Values for nonmissing items were summed and divided by the total number of items, yielding a final score between 0 and 1; four deficits necessitated scoring of intermediate levels, and weights were applied per published methods.²³ Frailty scores were categorized based on cut points related to mortality outcomes^{16,23} as follows: robust, 0 to < 0.2 ; prefrail, 0.2 to < 0.35 ; and frail ≥ 0.35 to 1. Given the sample distributions, we collapsed groupings into robust versus prefrail or frail.

Other selected measures were based on the adherence model of health behavior^{25,26} and included sociodemographic, psychosocial, attitudinal, patient-provider interaction, health care setting, and clinical (surgery, American Joint Committee on Cancer [version 6] stage, and chemotherapy use) factors relevant to adherence to medication regimens.

Sociodemographic factors included age, marital status, and race (white ν nonwhite). As a proxy for wealth, we assessed education, insurance, prescription drug coverage, and home ownership. Psychosocial and attitudinal factors included perceived ageism in cancer care (eg, “physicians treat older women [age > 65 years] and younger women [age < 65 years] the same”; $\alpha = 0.81$),²⁷ fatalism (eg, “if someone is meant to get breast cancer, she will get it no matter what she does”; $\alpha = 0.58$),²⁸ optimism (eg, “I hardly expect things to go my way”; $\alpha = 0.72$),²⁹ and emotional ($\alpha = 0.96$) and tangible ($\alpha = 0.93$) support subscales of the Medical Outcomes Study scale.³⁰

Patient perceptions of patient-physician communication were assessed using the Makoul scale and Primary Care Assessment Survey (PCAS). The seven-item Makoul scale³¹ addresses the role of patients and providers during information exchange (eg, “physician gave me all of the information I needed about my breast cancer”; $\alpha = 0.80$). Patients’ ratings of provider communication were also assessed with PCAS items (eg, “how often did you leave your physician’s office with unanswered questions?” $\alpha = 0.95$).³² Other PCAS subscales, including patients’ ratings of the medical oncologists’ knowledge about them ($\alpha = 0.84$), interpersonal treatment (eg, “physician’s caring and concern”; $\alpha = 0.96$), and thoroughness of examinations (eg, “thoroughness of physician’s physical examination of you”) and trust (eg, “I completely trust my physician’s judgments about my medical care”; $\alpha = 0.78$), were added to the survey in 2008 and were not available for all women. Factors related to setting of care included health maintenance organization (yes ν no) and National Cancer Institute–designated comprehensive cancer center status (yes ν no).

Statistical Analysis

Univariable associations between hormonal noninitiation and variables of interest were assessed using t and χ^2 tests. Variables related to noninitiation at a level of $P \leq .10$ were considered in the multivariable logistic regression model. Frailty was included as the main predictor, whereas age, race, and stage were retained for face validity regardless of statistical significance. Backward elimination using a significance level of $P = .05$ was used to determine the final model. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test.

We used Kaplan-Meier survival curves to estimate the probability of continuation over time overall and for subgroups of interest (eg, by frailty category). The log-rank test was used to compare the distributions of time with discontinuation between groups of interest. Cox proportional hazards models assessed the univariable relationships between time to discontinuation and covariates. Patients were censored at death ($n = 23$). We included patients with recurrent disease ($n = 54$); 41 were censored at the time or date of recurrence, and 13 were classified as nonadherent because they discontinued therapy > 18 months before their recurrence date. On the basis of routine clinical treatment and diagnostic timeframes, the 18-month window was selected so as not to count women who stopped therapy because of a recurrence as having discontinued therapy prematurely. We used the 18-month window as a conservative approach, because we had dates of recurrence from records, whereas dates of hormonal therapy discontinuation were based on self-report in annual interviews.

Variable selection for inclusion in the multivariable hazards model was based on a significance level of .10 in univariable analysis. Backward elimination at the .05 significance level was used to determine the final Cox proportional hazards regression model; frailty index was included in the final model as the main predictor. We used Kolmogorov-type supremum tests to test the proportional hazards assumption for each variable included in the final model.³³ A competing-risk analysis was not performed, given the small number of women who died or experienced recurrence and to enhance the comparability of our results to those of related studies.

Variables related to health care interactions were statistically significant in univariable analyses, so a sensitivity analysis was performed among participants with data on these PCAS items ($n = 660$; ie, those enrolled after survey was modified in late 2008); using backward elimination, we ended up with the same final model. We also used the Kaplan-Meier method to examine whether patterns of discontinuation were similar for women receiving tamoxifen and aromatase inhibitors. Analyses were conducted using SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

Participants’ ages ranged from 65 to 91 years (mean, $72.8 \pm$ standard deviation, 6.05 years). Most had prescription coverage and owned their own home (Table 1). The average frailty score was 0.14 ($\pm$ standard deviation, 0.10). Overall, 76.4% had scores in the robust range (0 to < 0.2); 18.7% were considered prefrail (0.2 to < 0.35); only 4.9% were considered frail (≥ 0.35 ; Table 1).

Noninitiation of Hormonal Therapy

The rate of noninitiation of adjuvant hormonal therapy was 14%. Among those who initiated, 79% received an aromatase inhibitor, and 21% received tamoxifen or another selective ER modulator (Table 2). Several factors were related to noninitiation of treatment in univariable analyses (Table 1), including age (odds ratio [OR], 1.04; 95% CI, 1.01 to 1.07 per 1-year increase; $P = .007$), nonwhite race (ν white; OR, 1.69; 95% CI, 1.04 to 2.75; $P = .034$), and frailty or prefrailty versus robustness (OR, 1.77; 95% CI, 1.21 to 2.58; $P = .003$). There was a trend toward Medicare prescription coverage being related to treatment initiation. Neither patient-provider nor clinical factors were related to initiation of hormonal therapy. In multivariable analyses (Table 1), age and race remained significant. The odds of noninitiation were also higher in the prefrail or frail group (OR, 1.63; 95% CI, 1.11 to 2.40; $P = .013$) compared with the robust group, after considering age, race, and stage.

Discontinuation of Hormonal Therapy

The median follow-up time from initiation was 3 years (range, 0.5 to 7 years). The continuation rate by 5 years was 48.5% and was slightly lower among the frail group than the robust group (41% ν 50%; log-rank $P = .045$; Fig 2). In univariable analyses (Table 2), the point estimate for frailty suggested a trend toward a higher risk of discontinuing therapy among prefrail or frail women compared with robust women (hazard ratio, 1.32; 95% CI, 0.99 to 1.78; $P = .060$). Several variables were significantly associated with discontinuation in univariable analyses, including older age, being unmarried, not owning a home, perceiving more ageism, being less optimistic, and having less emotional and tangible support. Disease stage $\geq$ IIB (ν I) was associated with continuing therapy. Also, chemotherapy was inversely associated with discontinuation. Continuation curves from the Kaplan-Meier method (exploratory analysis; log-rank $P = .076$) did not suggest evidence of statistical differences with respect to discontinuation between women receiving tamoxifen versus those receiving aromatase inhibitors (data not shown).

Among the subset who were asked about health care interactions, features of the patient-oncologist relationship (eg, trust in physician and so on) were associated with discontinuation in univariable analyses, with those who rated the oncologist’s thoroughness, knowledge of the patient, and trustworthiness higher (ν lower) being less likely to discontinue treatment ($P < .05$). After considering covariates, frailty became nonsignificant (hazard ratio, 1.24; 95% CI, 0.92 to 1.67; $P = .150$). However, the direction of the point estimate remained similar to unadjusted estimates (Table 2).

DISCUSSION

To our knowledge, this is the first study to explore the role of frailty in adjuvant hormonal therapy use among older women. This study demonstrates that the overwhelming majority of older women initiated adjuvant

Hormonal Therapy in Older Women

Table 1. Sample Characteristics and ORs for Associations With Noninitiation of Adjuvant Hormonal Therapy Among Older Women With Breast Cancer

Characteristic	Total Sample (N = 1,062)		Initiation of Hormonal Therapy				Noninitiation of Hormonal Therapy (n = 1,051)					
			No (n = 149)		Yes (n = 913)		Unadjusted			Adjusted*		
	No.	%	No.	%	No.	%	OR	95% CI	P	OR	95% CI	P
Age, years†							1.04	1.01 to 1.07	.007	1.03	1.00 to 1.06	.029
Mean	72.78		74.02		72.57							
SD	6.05		6.73		5.89							
65-74	680	64.0	83	55.7	597	65.4						
75-79	225	21.2	31	20.8	194	21.2						
≥ 80	157	14.8	35	23.5	122	13.4						
Race												
White	945	89.0	125	83.9	820	89.8		Referent				
Nonwhite	117	11.0	24	16.1	93	10.2	1.69	1.04 to 2.75	.034	1.71	1.04 to 2.80	.033
Marital status												
Married	596	56.4	74	49.7	522	57.6		Referent				
Not married	460	43.6	75	50.3	385	42.4	1.37	0.97 to 1.94	.073			
Missing		6		0		6						
Home ownership												
Yes	917	86.5	125	83.9	792	86.9		Referent				
No	143	13.5	24	16.1	119	13.1	1.28	0.79 to 2.06	.314			
Missing	2		0		2							
Insurance												
Medicare plus private	818	77.0	111	74.5	707	77.4		Referent				
Medicare plus Medicaid	129	12.1	18	12.1	111	12.2	1.03	0.60 to 1.77	.690			
Medicare only	115	10.8	20	13.4	95	10.4	1.34	0.80 to 2.26	.325			
HMO												
No	885	83.6	125	85.6	760	83.2	1.20	0.73 to 1.96	.473			
Yes	174	16.4	21	14.4	153	16.8		Referent				
Missing	3		3		0							
Medicare Part D or insurance drug coverage												
Yes	794	74.8	102	68.5	692	75.8		Referent				
No	268	25.2	47	31.5	221	24.2	1.44	0.99 to 2.10	.057			
Education, years												
> 12	614	57.8	91	61.1	523	57.3		Referent				
≤ 12	448	42.2	58	38.9	390	42.7	0.85	0.60 to 1.22	.385			
Setting of care												
Community	762	71.8	109	73.2	653	71.6		Referent				
Cancer center	299	28.2	40	26.8	259	28.4	0.93	0.63 to 1.37	.696			
Surgery												
Lumpectomy	729	68.7	105	70.5	624	68.4		Referent				
Mastectomy	332	31.3	44	29.5	288	31.6	0.91	0.62 to 1.33	.617			
Missing	1		0		1							
AJCC-6 stage												
I	507	47.7	74	49.7	433	47.4		Referent				
IIA	325	30.6	41	27.5	284	31.1	0.84	0.56 to 1.27	.381	0.83	0.55 to 1.26	.393
≥ IIB	230	21.7	34	22.8	196	21.5	1.02	0.65 to 1.58	.641	0.96	0.61 to 1.51	.857
Chemotherapy												
No	707	67.1	98	67.6	609	67.1		Referent				
Yes	346	32.9	47	32.4	299	32.9	0.98	0.67 to 1.42	.903			
Missing		9		4		5						
Frailty score‡												
Robust	803	76.4	98	66.7	705	78.0		Referent				
Prefrail	197	18.7	35	23.8	162	17.9	1.77	1.21 to 2.58	.003	1.63	1.11 to 2.40	.013
Frail	51	4.9	14	9.5	37	4.1						
Missing	11		2		9							
Communication							1.03	0.81 to 1.30	.833			
Mean	4.17		4.19		4.17							
SD	0.75		0.74		0.76							
Missing	68		14		54							

(continued on following page)

Table 1. Sample Characteristics and ORs for Associations With Noninitiation of Adjuvant Hormonal Therapy Among Older Women With Breast Cancer (continued)

Characteristic	Total Sample (N = 1,062)		Initiation of Hormonal Therapy				Noninitiation of Hormonal Therapy (n = 1,051)					
			No (n = 149)		Yes (n = 913)		Unadjusted			Adjusted*		
	No.	%	No.	%	No.	%	OR	95% CI	P	OR	95% CI	P
Knowledge about patient§							0.97	0.92 to 1.03	.317			
Mean	21.52		20.90		21.58							
SD	4.99		4.98		4.98							
Missing	327		91		236							
Thoroughness of care§							1.03	0.77 to 1.37	.837			
Mean	5.23		5.25		5.23							
SD	0.94		0.78		0.95							
Missing	319		90		229							
Trust in physician§							0.94	0.88 to 1.02	.125			
Mean	28.39		27.73		28.45							
SD	3.45		4.12		3.39							
Missing	317		89		228							
Optimism							0.93	0.73 to 1.18	.548			
Mean	4.25		4.22		4.26							
SD	0.74		0.74		0.74							
Missing	30		7		23							
Ageism							0.98	0.90 to 1.07	.670			
Mean	5.01		4.93		5.02							
SD	2.26		2.30		2.26							
Missing	150		26		124							
Fatalism							0.91	0.67 to 1.24	.567			
Mean	0.28		0.25		0.28							
SD	0.63		0.58		0.63							
Missing	73		17		56							
Emotional support							1.00	0.79 to 1.27	.988			
Mean	4.34		4.34		4.34							
SD	0.76		0.81		0.75							
Missing	52		13		39							
Tangible support							0.94	0.76 to 1.16	.543			
Mean	4.41		4.37		4.42							
SD	0.83		0.91		0.82							
Missing	54		13		41							
Treatment communication							1.01	0.97 to 1.06	.567			
Mean	45.07		45.43		45.03							
SD	5.66		5.22		5.71							
Missing	266		74		192							

NOTE. Bold font indicates statistical significance ($P \leq .05$; excluding race and age).

Abbreviations: AJCC-6, American Joint Committee on Cancer (version 6); HMO, health maintenance organization; OR, odds ratio; PCAS, Primary Care Assessment Survey; SD, standard deviation.

*Blank cells indicate variable was removed through backward elimination and not included in final regression model.

†Age was employed as continuous variable in unadjusted and adjusted models; results of Hosmer-Lemeshow test ($P = .51$) provided support for goodness-of-fit of final logistic regression model.

‡Frailty was used as robust versus prefrail or frail in analysis.

§Item is PCAS subscale³² and was only added to patient interview in 2008, so data were not available for all participants in our sample; analyses using this variable were conducted as sensitivity analyses.

||Refers to patient involvement in communication about therapy.

hormonal therapy, but nearly half discontinued treatment before 5 years. Advancing age was related to noninitiation and discontinuation of adjuvant hormonal therapy. Even after considering chronologic age, women who were frail or prefrail tended to have higher odds of noninitiation. We did not find a significant relationship between discontinuation and frailty. Nonwhite race played a larger role in noninitiation than in discontinuation of therapy. Type of regimen, attitude, psychosocial factors, and health care interactions were not consistently associated with noninitiation or discontinuation in this sample.

The rate of initiation that we observed was higher than those in prior reports^{3,34} and may reflect the fact that this cohort was recruited from a cooperative group setting. The rates of discontinuation in this population were similar to those reported in other older cohorts.^{8,9,17,35}

Although prior studies have considered age,^{3,8,9,12,13,17} comorbidity,^{3,8,9,12,17} or functional status,^{3,12} none have included the multidimensional construct of frailty.³⁶ Frailty encompasses daily functioning, physiologic, cognitive, and emotional reserves. Although

Hormonal Therapy in Older Women

Table 2. HRs for Discontinuing Adjuvant Hormonal Therapy Among Older Women Who Initiated Hormonal Therapy

Characteristic	Initiated (n = 913)		Discontinued (n = 250)		Censored (n = 663)		Discontinuation					
							Unadjusted			Adjusted*		
	No.	%	No.	%	No.	%	HR	95% CI	P	HR	95% CI	P
Age, years†							1.04	1.02 to 1.06	< .001	1.03	1.01 to 1.05	.005
Mean	72.57		73.12		72.34							
SD	5.89		6.11		5.81							
65-74	597	65.4	159	63.6	438	66.1						
75-79	194	21.2	50	20.0	144	21.7						
≥ 80	122	13.4	41	16.4	81	12.2						
Race												
White	820	89.8	224	89.6	596	89.9		Referent				
Nonwhite	93	10.2	26	10.4	67	10.1	1.26	0.84 to 1.89	.264	1.32	0.88 to 1.98	.182
Marital status												
Married	522	57.6	135	54.4	387	58.7		Referent				
Not married	385	42.4	113	45.6	272	41.3	1.32	1.03 to 1.69	.030			
Missing	6		2		4							
Home ownership												
Yes	792	86.9	210	84.0	582	88.0		Referent				
No	119	13.1	40	16.0	79	12.0	1.50	1.07 to 2.11	.018			
Missing	2		0		2							
Insurance												
Medicare plus private	707	77.4	180	72.0	527	79.5		Referent				
Medicare plus Medicaid	111	12.2	39	15.6	72	10.9	1.17	0.83 to 1.65	.380			
Medicare only	95	10.4	31	12.4	64	9.7	1.23	0.84 to 1.79	.296			
HMO												
No	760	83.2	203	81.2	557	84.0	1.00	0.73 to 1.37	.996			
Yes	153	16.8	47	18.8	106	16.0		Referent				
Medicare Part D or insurance drug coverage												
Yes	692	75.8	208	83.2	484	73.0		Referent				
No	221	24.2	42	16.8	179	27.0	1.02	0.73 to 1.43	.911			
Education, years												
> 12	523	57.3	152	60.8	371	56.0		Referent				
≤ 12	390	42.7	98	39.2	292	44.0	1.04	0.81 to 1.34	.770			
Setting of care												
Community	653	71.6	183	73.5	470	70.9		Referent				
Cancer center	259	28.4	66	26.5	193	29.1	0.80	0.60 to 1.06	.114			
Surgery												
Lumpectomy	624	68.4	175	70.0	449	67.8		Referent				
Mastectomy	288	31.6	75	30.0	213	32.2	0.98	0.75 to 1.28	.873			
Missing	1		0		1							
AJCC-6 stage												
I	433	47.4	143	57.2	290	43.7		Referent			Referent	
IIA	284	31.1	71	28.4	213	32.1	0.75	0.57 to 1.00	.051	0.76	0.57 to 1.02	.064
≥ IIB	196	21.5	36	14.4	160	24.1	0.56	0.39 to 0.81	.002	0.57	0.39 to 0.82	.003
Chemotherapy												
No	609	67.1	197	79.1	412	62.5		Referent				
Yes	299	32.9	52	20.9	247	37.5	0.45	0.33 to 0.61	< .001			
Missing	5		1		4							
Type of hormonal therapy												
Aromatase inhibitor	710	79.3	178	74.2	532	81.2		Referent				
SERM	185	20.7	62	25.8	123	18.8	1.28	0.96 to 1.71	.094			
Missing	18		10		8							
Frailty score‡												
Robust	705	78.0	189	76.2	516	78.7		Referent				
Pre frail	162	17.9	51	20.6	111	16.9	1.32	0.99 to 1.78	.060	1.24	0.92 to 1.67	.150
Frail	37	4.1	8	3.2	29	4.4						
Missing	9		2		7							

(continued on following page)

Table 2. HRs for Discontinuing Adjuvant Hormonal Therapy Among Older Women Who Initiated Hormonal Therapy (continued)

Characteristic	Initiated (n = 913)		Discontinued (n = 250)		Censored (n = 663)		Discontinuation					
							Unadjusted			Adjusted*		
	No.	%	No.	%	No.	%	HR	95% CI	P	HR	95% CI	P
Communication							0.87	0.73 to 1.03	.116			
Mean		4.17		4.14		4.18						
SD		0.76		0.79		0.75						
Missing	54		22		32							
Knowledge of patient§							0.97	0.94 to 0.99	.017			
Mean		21.58		21.23		21.74						
SD		4.98		5.19		4.87						
Missing	226		35		201							
Thoroughness of care§							0.84	0.74 to 0.97	.016			
Mean		5.23		5.15		5.27						
SD		0.95		0.99		0.93						
Missing	229		32		197							
Trust in physician§							0.94	0.90 to 0.98	.003			
Mean		28.45		28.06		28.62						
SD		3.39		3.42		3.37						
Missing	228		33		195							
Optimism							0.84	0.71 to 1.00	.048			
Mean		4.26		4.22		4.27						
SD		0.74		0.74		0.73						
Missing	23		9		14							
Ageism							1.07	1.01 to 1.13	.016			
Mean		5.02		5.45		4.86						
SD		2.26		2.47		2.16						
Missing	124		36		88							
Fatalism							1.05	0.85 to 1.31	.644			
Mean		0.28		0.25		0.29						
SD		0.63		0.63		0.63						
Missing	56		17		39							
Emotional support							0.84	0.72 to 1.00	.045			
Mean		4.34		4.30		4.35						
SD		0.75		0.82		0.73						
Missing	39		13		26							
Tangible support							0.85	0.73 to 0.98	.024			
Mean		4.42		4.34		4.45						
SD		0.82		0.88		0.79						
Missing	41		13		28							
Treatment communication							0.98	0.96 to 1.01	.159			
Mean		45.03		44.52		45.27						
SD		5.71		5.49		5.80						
Missing	192		20		172							

NOTE. Bold font indicates statistical significance ($P \leq .05$).

Abbreviations: AJCC-6, American Joint Committee on Cancer (version 6); HMO, health maintenance organization; HR, hazard ratio; PCAS, Primary Care Assessment Survey; SD, standard deviation.

*Blank cells indicate variable was removed through backward elimination and not included in final regression model.

†Age was employed as continuous variable in unadjusted and adjusted models; P values from tests of proportional hazards assumption (Kolmogorov-type supremum tests) ranged from .13 to .55, providing support for proportional hazards assumption.

‡Frailty was used as robust versus prefrail or frail in analysis.

§Item is PCAS subscale³² and was only added to patient interview in 2008, so data were not available for all participants in our sample; analyses using this variable were conducted as sensitivity analyses.

||Refers to patient involvement in communication about therapy.

it is correlated with age,²³ frailty is heterogeneous within age groups and has been validated in multiple studies to predict nursing home placement¹⁶ and mortality in older community populations.^{16,37} The finding that women who were prefrail or frail initiated therapy less often than robust women suggests that there may have been some consideration of the balance of life expectancy and the probability of recurrence within remaining life expectancy. We do not have data to

directly test this idea; however, if true, the relationship between higher frailty and noninitiation could indicate that women and/or their providers are making informed judgments about the risks and benefits. An alternative explanation is that women with greater frailty may have been concerned about adverse effects based on interactions of hormonal therapy and specific comorbidities,³⁸ such as cardio- and/or cerebrovascular disease and risk of thromboembolic events.³⁹ It is also

Fig 2. Probability of continuing hormonal therapy over 5-year follow-up period for older women with estrogen receptor (ER) –positive breast cancer (A) overall and (B) by frailty level. Graphs are based on Kaplan-Meier curves for continuing hormonal therapy among 885 women diagnosed from 2004 to 2011 with ER-positive breast cancer who initiated hormonal therapy.

possible that the primary treatment goal in older women, especially frail patients, may be to avoid recurrence before death resulting from other causes, because older women generally will not die as a result of their breast cancers.^{40,41}

Our data suggest that the frailest women never initiated therapy. This may explain why frailty, while tending to be associated with discontinuation, was not significant in the discontinuation analysis. Overall, the frailty results imply that patterns of noninitiation may reflect appropriate use of adjuvant therapy rather than suboptimal quality of care for older women.³⁵ With the increasing use of geriatric assessment within the oncology setting,^{42–45} new senior adult oncology recommendations from the National Comprehensive Cancer Network,⁷ and the availability of easy-to-use prognostic indices that generate life expectancy estimates,⁴⁶ it should become easier to incorporate discussions about harms and benefits of cancer treatments into routine clinical oncology care with older patients.

Our results also suggest that race was more important in noninitiation than in discontinuation patterns of care. This finding is in concert with others that found that nonwhites were less likely to initiate therapy.^{34,47–49} However, Neugut et al⁴ did not find racial

differences in initiation in their sample of largely health maintenance organization–insured women. Because we focused only on older women in largely fee-for-service settings and had limited race variability, this will be an important area for future investigation. It was encouraging that when nonwhite women did initiate hormonal therapy, they were no more likely to discontinue than whites.

Contrary to other reports,^{4,50} we did not find that type of hormonal regimen, attitudes about treatment, or patient-physician interactions influenced noninitiation. We expected to see greater discontinuation related to aromatase inhibitors compared with other classes of therapy as a result of their higher reported musculoskeletal adverse effects³⁸ and potential interactions with arthritis and other common comorbidities in older women. The similarity in patterns of discontinuation for women receiving tamoxifen and aromatase inhibitors may indicate good tolerance of aromatase inhibitors in older women. Alternatively, because most patients started on aromatase inhibitors, we may not have been able to detect treatment-specific effects. We also lacked data on whether women who started on tamoxifen switched to aromatase inhibitors over the follow-up period. Because a high rate of older women did ultimately discontinue hormonal therapy, future investigation should consider regimen-specific adverse effects, symptoms, and interactions with other illnesses.

Our data suggest that components of oncologist-patient interactions were related to discontinuation. Unfortunately, for administrative reasons, we only had data on a subset of the sample for these measures, so we cannot draw conclusions about this important aspect of adherence. Although several patient attitudes seemed important in predicting discontinuation, they did not remain significant after considering age, frailty, and other factors. Of note, those with more advanced stage disease were less likely to discontinue, perhaps reflecting communication about or understanding of greater potential benefits versus risks.

Strengths of this study include its focus on older women, prospective design, detailed patient-reported data, inclusion of key constructs posited to influence noninitiation and discontinuation of hormonal therapy, and inclusion of frailty. Despite important strengths, several caveats should be considered. First, this was a secondary analysis, so borderline levels of significance could represent either lack of power or type I error resulting from examination of multiple hypotheses. Although the results for frailty were suggestive, these results should be confirmed in other studies. Next, hormonal therapy initiation was based on medical records and confirmed through self-report, but discontinuation was only measured via annual self-report. Generally, the direction of any self-report bias has been associated with an underestimation of the actual rates of early discontinuation.^{51–53} However, previous reports found strong agreement between self-report and pharmacy records^{12,22} and between self-report and medical records.^{12,22,50,54} Because participants were screened for cognitive status, and those with impairment were excluded, it is unlikely that there was systematic misclassification of self-report by frailty index. Third, we only considered baseline frailty (and not changes over time). Also, several factors could have limited the representativeness and variability of the observed range of frailty scores, including the exclusion of women with cognitive impairment, healthy volunteer effects, and the cooperative group setting.¹⁸ These constraints are likely to underestimate the true effects of frailty on noninitiation in the general older population of patients with breast

cancer. Finally, the median length of follow-up of 3 years is also a limitation.

This study illustrates the potential value of considering measures of aging beyond chronologic age in understanding patterns of care for older patients with cancer. Results suggest that consideration of frailty for therapy initiation may be useful to clarify oncology treatment goals and provide data for informed decision making about the balance of benefits and risks of long-term cancer regimens among the growing older patient population.^{44,55,56}

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

REFERENCES

1. Surveillance Epidemiology and End Results: SEER Stat fact sheets: Breast cancer. <http://seer.cancer.gov/statfacts/html/breast.html>
2. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. *CA Cancer J Clin* 63:11-30, 2013
3. Demissie S, Silliman RA, Lash TL: Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. *J Clin Oncol* 19:322-328, 2001
4. Neugut AI, Hillyer GC, Kushi LH, et al: Non-initiation of adjuvant hormonal therapy in women with hormone receptor-positive breast cancer: The breast cancer quality of care study (BQUAL). *Breast Cancer Res Treat* 134:419-428, 2012
5. Silliman RA, Guadagnoli E, Rakowski W, et al: Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer. *J Clin Oncol* 20:2680-2688, 2002
6. Davies C, Godwin J, Gray R, et al: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *Lancet* 378:771-784, 2011
7. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: Senior adult oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
8. Owusu C, Buist DS, Field TS, et al: Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. *J Clin Oncol* 26:549-555, 2008
9. Hershman DL, Shao T, Kushi LH, et al: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat* 126:529-537, 2011
10. Barron TI, Connolly R, Bennett K, et al: Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer* 109:832-839, 2007
11. Cluze C, Rey D, Huiart L, et al: Adjuvant endocrine therapy with tamoxifen in young women

with breast cancer: Determinants of interruptions vary over time. *Ann Oncol* 23:882-890, 2012

12. Fink A, Gurwitz J, Rakowski W, et al: Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *J Clin Oncol* 22:3309-3315, 2004
13. Riley GF, Warren JL, Harlan LC, et al: Endocrine therapy use among elderly hormone receptor-positive breast cancer patients enrolled in Medicare part D. *Medicare Medicaid Res Rev* 1:e1-e25, 2011
14. van de Water W, Bastiaannet E, Hille ET, et al: Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: A TEAM study analysis. *Oncologist* 17:55-63, 2012
15. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA* 285:885-892, 2001
16. Rockwood K, Mitnitski A, Song X, et al: Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. *J Am Geriatr Soc* 54:975-979, 2006
17. Partridge AH, Wang PS, Winer EP, et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol* 21:602-606, 2003
18. Mandelblatt JS, Sheppard VB, Hurria A, et al: Breast cancer adjuvant chemotherapy decisions in older women: The role of patient preference and interactions with physicians. *J Clin Oncol* 1:3146-3156, 2010
19. Mandelblatt JS, Faul LA, Luta G, et al: Patient and physician decision styles and breast cancer chemotherapy use in older women: Cancer and Leukemia Group B Protocol 369901. *J Clin Oncol* 30:2609-2614, 2012
20. Davis PB, Morris JC, Grant E: Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. *J Am Geriatr Soc* 38:129-135, 1990
21. Kawas C, Karagiozis H, Resau L, et al: Reliability of the Blessed Telephone Information-Memory-

Employment or Leadership Position: Arti Hurria, Alliance Pharma (U)
Consultant or Advisory Role: Gretchen Kimmick, Pfizer (C); Claudine Isaacs, Novartis (C); Arti Hurria, GTx (C) **Stock Ownership:** None
Honoraria: Gretchen Kimmick, Pfizer **Research Funding:** Eric P. Winer, Genentech, Roche; Arti Hurria, Celgene, GlaxoSmithKline **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Vanessa B. Sheppard, George Luta, Gretchen Kimmick, William T. Barry, Eric P. Winer, Harvey J. Cohen, Hyman B. Muss, Jeanne S. Mandelblatt
Administrative support: Vanessa B. Sheppard
Provision of study materials or patients: Arti Hurria
Collection and assembly of data: Jonathan D. Clapp, Gretchen Kimmick, William T. Barry, Brandelyn N. Pitcher, Arti Hurria, Jeanne S. Mandelblatt
Data analysis and interpretation: Vanessa B. Sheppard, Leigh Anne Paul, George Luta, Jonathan D. Clapp, Rachel L. Yung, Judy Huei-Yu Wang, Claudine Isaacs, Michelle Tallarico, Brandelyn N. Pitcher, Clifford Hudis, Harvey J. Cohen, Jeanne S. Mandelblatt
Manuscript writing: All authors
Final approval of manuscript: All authors

Concentration test. *J Geriatr Psychiatry Neurol* 8:238-242, 1995

22. Lash TL, Fox MP, Westrup JL, et al: Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat* 99:215-220, 2006
23. Searle SD, Mitnitski A, Gahbauer EA, et al: A standard procedure for creating a frailty index. *BMC Geriatr* 8:24-2318-8-24, 2008
24. Schoufour JD, Mitnitski A, Rockwood K, et al: Development of a frailty index for older people with intellectual disabilities: Results from the HA-ID study. *Res Dev Disabil* 34:1541-1555, 2013
25. Gritz ER, Bastani R: Cancer prevention: Behavior changes—The short and the long of it. *Prev Med* 22:676-688, 1993
26. Sheppard VB, Adams IF, Lamdan R, et al: The role of patient-provider communication for black women making decisions about breast cancer treatment. *Psychooncology* 20:1309-1316, 2011
27. Mandelblatt JS, Bierman AS, Gold K, et al: Constructs of burden of illness in older patients with breast cancer: A comparison of measurement methods. *Health Serv Res* 36:1085-1107, 2001
28. Powe BD: Cancer fatalism among elderly Caucasians and African Americans. *Oncol Nurs Forum* 22:1355-1359, 1995
29. Scheier MF, Carver CS, Bridges MW: Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the life orientation test. *J Pers Soc Psychol* 67:1063-1078, 1994
30. Sherbourne CD, Stewart AL: The MOS social support survey. *Soc Sci Med* 32:705-714, 1991
31. Makoul G, Arntson P, Schofield T: Health promotion in primary care: Physician-patient communication and decision making about prescription medications. *Soc Sci Med* 41:1241-1254, 1995
32. Safran DG, Taira DA, Rogers WH, et al: Linking primary care performance to outcomes of care. *J Fam Pract* 47:213-220, 1998
33. Lin DY, Wei LJ, Ying Z: Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 80:557-572, 1993

34. Kimmick G, Anderson R, Camacho F, et al: Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *J Clin Oncol* 27:3445-3451, 2009
35. McCowan C, Shearer J, Donnan PT, et al: Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer* 99:1763-1768, 2008
36. Fried LP, Ferrucci L, Darer J, et al: Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 59:255-263, 2004
37. Koller K, Rockwood K: Frailty in older adults: Implications for end-of-life care. *Cleve Clin J Med* 80:168-174, 2013
38. Gaillard S, Stearns V: Aromatase inhibitor-associated bone and musculoskeletal effects: New evidence defining etiology and strategies for management. *Breast Cancer Res* 13:205, 2011
39. Baum M, Budzar AU, Cuzick J, et al: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet* 359:2131-2139, 2002
40. Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst* 92:550-556, 2000
41. Van Leeuwen BL, Rosenkranz KM, Feng LL, et al: The effect of under-treatment of breast cancer in women 80 years of age and older. *Crit Rev Oncol Hematol* 79:315-320, 2011
42. Soubeyran P, Fonck M, Blanc-Bisson C, et al: Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* 30:1829-1834, 2012
43. Hurria A, Togawa K, Mohile SG, et al: Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. *J Clin Oncol* 29:3457-3465, 2011
44. Pal SK, Katheria V, Hurria A: Evaluating the older patient with cancer: Understanding frailty and the geriatric assessment. *CA Cancer J Clin* 60:120-132, 2010
45. Kendal WS: Dying with cancer: The influence of age, comorbidity, and cancer site. *Cancer* 112:1354-1362, 2008
46. Schonberg MA, Davis RB, McCarthy EP, et al: External validation of an index to predict up to 9-year mortality of community-dwelling adults aged 65 and older. *J Am Geriatr Soc* 59:1444-1451, 2011
47. Livaudais JC, Hershman DL, Habel L, et al: Racial/ethnic differences in initiation of adjuvant hormonal therapy among women with hormone receptor-positive breast cancer. *Breast Cancer Res Treat* 131:607-617, 2012
48. Bickell NA, Wang JJ, Oluwole S, et al: Missed opportunities: Racial disparities in adjuvant breast cancer treatment. *J Clin Oncol* 24:1357-1362, 2006
49. Banerjee M, George J, Yee C, et al: Disentangling the effects of race on breast cancer treatment. *Cancer* 110:2169-2177, 2007
50. Liu Y, Malin JL, Diamant AL, et al: Adherence to adjuvant hormone therapy in low-income women with breast cancer: The role of provider-patient communication. *Breast Cancer Res Treat* 137:829-836, 2013
51. Murphy CC, Bartholomew LK, Carpentier MY, et al: Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. *Breast Cancer Res Treat* 134:459-478, 2012
52. Font R, Espinas JA, Gil-Gil M, et al: Prescription refill, patient self-report and physician report in assessing adherence to oral endocrine therapy in early breast cancer patients: A retrospective cohort study in Catalonia, Spain. *Br J Cancer* 107:1249-1256, 2012
53. Farmer KC: Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 21:1074-1090, 1999; discussion 1073
54. Liu Y, Diamant AL, Thind A, et al: Validity of self-reports of breast cancer treatment in low-income, medically underserved women with breast cancer. *Breast Cancer Res Treat* 119:745-751, 2010
55. Extermann M, Meyer J, McGinnis M, et al: A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. *Crit Rev Oncol Hematol* 49:69-75, 2004
56. Extermann M, Hurria A: Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 25:1824-1831, 2007

GLOSSARY TERMS

aromatase inhibitors: inhibitors used in treating breast cancer in postmenopausal women. Aromatase inhibitors inhibit the conversion of androgens to estrogens by the enzyme aromatase, thus depriving the tumor of estrogenic signals. Because of decreased production of estrogen, estrogen receptors, which are important in the progression of breast cancer, cannot be activated.

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ER α and ER β). ER α is one of the most important proteins controlling breast cancer function. ER β is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

Acknowledgment

We thank the women who participated in this study and who generously shared their time and experiences. We also thank the clinical research associates at the study sites who enrolled patients and submitted clinical data; without them, the study would not have been possible. We thank Richard Schilsky, MD, for his support of this research; Wanda Lucas, Trina McClendon, and Meghan McGuckin for their work interviewing patients; Edie Fitts (advocate), the Cancer and Leukemia Group B (CALGB) Statistical Center (John Postiglione, Peggy Edwards, and Lydia Hodgson), and the CALGB Central Office staff who supported these protocols (Kathy Karas, Sara Hoffman, Mary Sherrell, Avis Rodgers, and Donna Johnson); and the principal investigators of Protocol No. 369901 at the CALGB sites for facilitating patient recruitment.

Appendix

Frailty Measure

In this study, we adapted the frailty index of Searle et al²³ to provide a patient self-reported measure of frailty. A total of 35 variables were included in our adapted index, including self-reported items relating to baseline limitations in basic and instrumental activities of daily living, existing sensory deficits, prediagnosis functioning, and prediagnosis comorbidity. Because we excluded women with cognitive impairment, this item was not included in the index. We also did not include age, because we were interested in the contributions of frailty beyond chronologic age to patterns of hormonal therapy use. As described in Appendix Table A1, each item was rated as 0 (no deficit), 0.5 (intermediate value of deficit), or 1 (deficit present) based on the original scale published by Searle et al. Note that in concert with Searle et al, some items with intermediate values were weighted and resulted in a score of 1 or 0. An example would be the ratings for general health (from excellent to poor). These items we applied scoring weights of frailty per Searle et al, methodology that resulted in an overall score for most items of 0 or 1.

Scores were calculated for those missing < 10% of items (1% missing $\geq$ 10%). As in the original scale, values for nonmissing items were summed, divided by the total number of nonmissing items, and standardized to yield a final score between 0 and 1, where a higher score indicates greater frailty. Frailty scores were also categorized based on cut points in the literature related to mortality outcomes: robust, 0 to < 0.2; prefrail, 0.2 to < 0.35; and frail, $\geq$ 0.35 to 1.^{16,23} Given the distribution in the sample, we collapsed groupings into robust versus prefrail or frail for analysis.

Hormonal Therapy in Older Women

Table A1. Items and Scoring for Frailty Index

Item	Value	Format	Score
1. Can take bath/shower ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
2. Can dress/undress self ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
3. Can get in/out of bed ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
4. Can walk ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
5. Health limits moderate activities ^{23*†}	1	Yes, limited a lot	0
	2	Yes, limited a little	1
	3	No, not limited at all	1
6. Can eat ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
7. Take care of own appearance ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
8. Trouble getting to bathroom on time†	1	No	0
	2	Yes	1
	3	Have catheter or colostomy	1
9. Health limits climbing stairs ^{23*†}	1	Yes, limited a lot	0
	2	Yes, limited a little	1
	3	No, not limited at all	1
10. Can go shopping for groceries or clothes ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
11. Can do housework ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
12. Can prepare own meals ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
13. Can take own medicine ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
14. Can handle own money ^{23*†}	1	Without help	0
	2	With some help	1
	3	Completely unable	1
15. General health‡	1	Excellent	0
	2	Very Good	0.25
	3	Good	0.50
	4	Fair	0.75
	5	Poor	1
16. Physical health limits work or activities‡	1	Yes, limited a lot	1
	2	Yes, limited a little	1
	3	No, not limited at all	0
17. Emotional problems limit work or activities‡	1	Yes, limited a lot	1
	2	Yes, limited a little	1
	3	No, not limited at all	0
18. Physical or emotional health interferes with social activities‡	1	All of the time	1
	2	Most of the time	1
	3	A good bit of the time	1
	4	Some of the time	1
	5	A little of the time	0
	6	None of the time	0

(continued on following page)

Table A1. Items and Scoring for Frailty Index (continued)

Item	Value	Format	Score
19. Physical health results in accomplishing less‡	1	Yes, limited a lot	1
	2	Yes, limited a little	1
	3	No, not limited at all	0
20. Emotional problems result in accomplishing less‡	1	Yes, limited a lot	1
	2	Yes, limited a little	1
	3	No, not limited at all	0
21. Have a lot of energy‡	1	All of the time	0
	2	Most of the time	0
	3	A good bit of the time	0
	4	Some of the time	0.5
	5	A little of the time	1
	6	None of the time	1
22. Feel downhearted or blue‡	1	All of the time	1
	2	Most of the time	1
	3	A good bit of the time	1
	4	Some of the time	0.5
	5	A little of the time	0
	6	None of the time	0
23. Feel calm or peaceful‡	1	All of the time	0
	2	Most of the time	0
	3	A good bit of the time	0
	4	Some of the time	0.5
	5	A little of the time	1
	6	None of the time	1
24. Heart disease comorbidity ^{23*†}	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
25. Stroke comorbidity ^{23*†}	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
26. Diabetes comorbidity ^{23*†}	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
27. Arthritis, rheumatism, or other connective tissue disorder comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
28. Emphysema, chronic bronchitis, or asthma comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
29. Chronic liver or kidney disease comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
30. Other cancer/leukemia comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
31. Glaucoma, cataracts, or decreased vision comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1

(continued on following page)

Table A1. Items and Scoring for Frailty Index (continued)

Item	Value	Format	Score
32. Blood pressure comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
33. Osteoporosis comorbidity†	0	No	0
	1	Not at all	1
	2	Somewhat	1
	3	A great deal	1
34. Eyesight†	1	Excellent	0
	2	Good	0
	3	Fair	1
	4	Poor	1
	5	Totally blind	1
35. Hearing†	1	Excellent	0
	2	Good	0
	3	Fair	1
	4	Poor	1
	5	Totally deaf	1

*Song X et al: J Am Geriatr Soc 58:681-687, 2010.

†Fillenbaum GG et al: J Gerontol 36:428-434, 1981.

‡Ware J et al: Med Care 34:220-233, 1996.