VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Discontinuation and Nonadherence to Adjuvant Hormonal Therapy in a Cohort of 8,769 Early-Stage Breast Cancer Patients

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Submitted September 1, 2009; accepted March 22, 2010; published online ahead of print at www.jco.org on June 28, 2010.

Supported by Grants No. RSGT-08-009-01-CPHPS from the American Cancer Society (D.L.H.); R01 CA105274 from the National Cancer Institute (L.H.K.); and BC043120 from the Department of Defense (A.I.N.); and Contract No. N01-PC-35136 from the Surveillance, Epidemiology and End Results Rapid Response Surveillance Study (S.L.G.).

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

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0732-183X/10/2827-4120/$20.00

DOI: 10.1200/JCO.2009.25.9655

ABSTRACT

Purpose
While studies have found that adjuvant hormonal therapy for hormone-sensitive breast cancer (BC) dramatically reduces recurrence and mortality, adherence to medications is suboptimal. We investigated the rates and predictors of early discontinuation and nonadherence to hormonal therapy in patients enrolled in Kaiser Permanente of Northern California health system.

Patients and Methods
We identified women diagnosed with hormone-sensitive stage I-III BC from 1996 to 2007 and used automated pharmacy records to identify hormonal therapy prescriptions and dates of refill. We used Cox proportional hazards regression models to analyze factors associated with early discontinuation and nonadherence (medication possession ratio $< 80\%$) of hormonal therapy.

Results
We identified 8,769 patients with BC who met our eligibility criteria and who filled at least one prescription for tamoxifen (43%), aromatase inhibitors (26%), or both (30%) within 1 year of diagnosis. Younger or older age, lumpectomy (*v* mastectomy), and comorbidities were associated with earlier discontinuation, while Asian race, being married, earlier year at diagnosis, receipt of chemotherapy or radiotherapy, and longer prescription refill interval were associated with completion of 4.5 years of therapy. Of those who continued therapy, similar factors were associated with full adherence. Women age younger than 40 years had the highest risk of discontinuation (hazard ratio, 1.51; 95% CI, 1.23 to 1.85). By 4.5 years, 32% discontinued therapy, and of those who continued, 72% were fully adherent.

Conclusion
Only 49% of patients with BC took adjuvant hormonal therapy for the full duration at the optimal schedule. Younger women are at high risk of nonadherence. Interventions to improve adherence and continuation of hormonal therapy are needed, especially for younger women.

J Clin Oncol 28:4120-4128. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Lack of adherence to prescribed medications is a well-known problem in the medical literature.[1,2] Many patients fail to fill the initial prescription (noninitiation), to take the drug on a daily basis as prescribed (nonadherence), or to continue long-term with the drug (early discontinuation), and such departures from optimal drug use frequently result in treatment failure.[1]

Oncology has made notable strides in the development of effective treatments to improve cancer survival. It is, therefore, surprising that adherence appears to be almost as significant a problem in oncology for these potentially life-saving medications, such as chemotherapy, as for other diseases.[3-9] One of the most dramatic and important additions to the treatment of breast cancer (BC) has been adjuvant hormonal therapy for hormone-sensitive BC, with impressive reductions in recurrence and mortality.[10,11] These oral agents include tamoxifen and aromatase inhibitors (AIs) and are typically prescribed for 5 years or longer. Nonetheless, it is surprising to find that, despite the dramatic efficacy of hormonal agents, there is a discontinuation rate of approximately 7% to 10% per year for tamoxifen and AIs.[12-19] Reports indicate that only 40% to 60% of patients with BC finish their recommended courses of hormonal therapy, despite the fact that randomized trials show higher recurrence rates and worse survival with < 5 years of treatment.[18,20-23]

Prior studies on predictors of adherence have either focused on the elderly, on patients taking tamoxifen, and on those who had limited clinical, insurance and follow-up information, and/or were underpowered to compare rates among different ethnic groups. These studies as a whole suggest that possible predictors of nonadherence include African American race, the severity of adverse effects, older age, tumor stage, prior receipt of adjuvant chemotherapy, having a surgeon rather than a medical oncologist prescribe the drug, and the extent to which the patient and physician believe in the drug's efficacy.[12,16,19,24,25]

To provide a more comprehensive understanding of the patient and clinical factors associated with discontinuation and nonadherence to hormonal therapy, we compared the rates and predictors of early discontinuation and nonadherence for both tamoxifen and AIs over a 10-year period in women who were enrolled in a large prepaid integrated health system, Kaiser Permanente of Northern California (KPNC). The KPNC population is large, diverse, and representative of all age groups. The participants all have a prescription health plan and access to health care.

PATIENTS AND METHODS

Data Source

KPNC provides health care services to more than 3 million members in 14 counties in Northern California. This population is racially and ethnically diverse and closely resembles the socioeconomic makeup of the geographic area it serves.[26,27]

KPNC maintains a cancer registry that reports to the Surveillance, Epidemiology, and End Results (SEER) program supported by the National Cancer Institute. The KPNC cancer registry provides high-quality information on tumor histology, hormone receptor status (positive $>$ 10%), stage of disease, first course of treatment, and survival, along with patient demographic characteristics.

The KPNC Patient Demographic Database contains key demographic characteristics of KPNC enrollees, including their medical record number, date of birth, sex, and specific member characteristics. Socioeconomic status (SES) was determined by geocoding patients' addresses, assigning a census tract code, and linking the data to Census 2000 information on education, poverty, and income to derive a composite score.[28]

The Pharmacy Information Management System records each ordered and filled prescription at all KPNC outpatient and inpatient pharmacies. This database contains cost, prescribing practitioner, and medication information, including the name of the drug, National Drug Code, date of prescription, and date of refill. During this timeframe, copayment amounts were similar for all patients.

The Outpatient Summary Clinical Record contains information on all outpatient encounters at KPNC hospitals, medical centers, and medical offices. The database includes Common Procedure Terminology–based codes and diagnosis codes that are based on the International Classification of Disease (ICD), as well as additional KPNC-specific codes to provide additional detail.

Sample Selection

We identified all women in the KPNC database who were pathologically diagnosed with stage I-III BC between January 1, 1996, and June 30, 2007. We restricted our sample to patients who were classified as having tumors that were positive for estrogen receptor and/or progesterone receptor and who received at least one prescription for oral hormonal therapy (tamoxifen, anastrozole, exemestane, or letrozole) within 12 months of diagnosis and before the diagnosis of recurrent disease. Age at diagnosis was categorized as $<$ 50 years, 50 to 65 years, or $>$ 65 years. Year at diagnosis was categorized as $\leq$ 2001 or $>$ 2001. Race/ethnicity was classified as white, black, Asian, or Hispanic.

Patient SES

We generated an aggregate SES score from education, poverty, and income data from census data, following the method adapted by Du et al.[19] Patients were ranked on a scale of 1 to 5, where 1 was the lowest value, based on a formula incorporating these variables weighted equally.

Comorbid Disease

To assess the prevalence of comorbid disease in our cohort, we used the Klabunde adaptation of the Charlson comorbidity index.[29,30] KPNC inpatient and outpatient claims were searched for ICD-9-Clinical Modification (ICD-9-CM) diagnostic codes. Each condition was weighted, and patients were assigned a score based on the Klabunde-Charlson index.[30]

Prescription Refill Interval

Prescription refill was categorized into 30-, 60-, and 90-day intervals. Patients were placed in a category based on the most common prescription interval during the follow-up period.

Outcomes

We categorized patients as having discontinued therapy if 180 days elapsed from the prior prescription without a refill. Of those who continued, we categorized patients as being adherent if the number of pills dispensed in prescriptions from the date of the first prescription to the end of follow-up covered at least 80% of the days in that entire period (ie, a medication possession ratio [MPR] of $\geq$ 80%). The number of pills for each prescription was estimated from the date of the first prescription to the date of the subsequent prescription, which fell into 30-, 60-, and 90-day intervals. We assumed that participants could refill prescriptions 7 days earlier for a 60-day prescription and 14 days earlier for a 90-day prescription. The total number of pills dispensed for each patient was determined by adding all the intervals between prescriptions plus an additional 30, 60, or 90 days for the last prescription based on prior interval pattern (Appendix Table A1, online only).

Follow-Up and Censoring

Follow-up was available through December 31, 2008. Due to uncertainties with regard to intent of refills in the last 6 months, we report data out to 4.5 years rather than 5 years. We censored a patient at the date of death (n = 307), the date dis-enrolled in KPNC (n = 435), date of recurrence based on metastatic ICD-9 codes (196.x, 197.x, or 198.x; n = 37), or after 4.5 years elapsed from the date of first prescription.

Statistical Analysis

We used univariate and multivariate Cox proportional hazards regression models to analyze the association between rates of discontinuation of hormonal therapy with patient clinical and demographic factors. These analyses were also performed separately for each type of hormonal therapy (tamoxifen *v* AIs). The same approach was taken to analyze the association between clinical and demographic factors and nonadherence in patients who continued on therapy.

We generated Kaplan-Meier curves to show discontinuation and nonadherence in patients receiving hormonal therapy. For patients who were nonadherent at the time of censoring, the date of nonadherence was the date when MPR of a patient first became less than 80%. This was determined by examining MPRs at successive intervals. The exact date of nonadherence was then calculated using the interval where MRP first became $\geq$ 80% and the prior interval. All analyses were conducted using SAS, Version 9.13 (SAS Institute, Cary, NC).

RESULTS

There were 15,143 women diagnosed with hormone receptor–positive stage I-III BC in the KPNC system between January 1, 1996, and June 30, 2007. Among these women, we identified 8,790 women (58%) who filled at least one prescription for either an AI or tamoxifen within 12 months of their BC diagnosis and before the diagnosis of recurrent disease. Of these, 21 patients were excluded

Table 1. Baseline Characteristics of Patients Diagnosed With Hormone Receptor–Positive Breast Cancer, Stages I-III, Who Received Adjuvant Endocrine Therapy, KPNC, 1996-2006

Characteristic	All Patients (N = 8,769)		Tamoxifen Only (n = 3,802)		Aromatase Inhibitors Only (n = 2,313)	
	No.	%	No.	%	No.	%
Discontinued by 4.5 years	2,790	32	1,460	38	659	29
Nonadherent by 4.5 years	1,666	28*	702	30*	465	28*
Age at diagnosis, years						
< 50	1,472	16.8	910	23.9	89	3.9
50-64	3,609	41.2	1,312	34.5	1,082	46.8
≥ 65	3,688	42.1	1,580	41.6	1,142	49.4
Year at diagnosis						
> 2001	4,885	55.7	1,294	34.0	2,244	97.0
≤ 2001	3,884	44.3	2,508	66.0	69	3.0
Race/ethnicity						
White	6,687	76.2	2,869	75.5	1,762	76.2
Black	488	5.6	225	5.9	121	5.2
Hispanic	630	7.2	260	6.8	169	7.3
Asian	964	11.0	448	11.8	261	11.3
Marital status						
Unmarried	3,525	40.2	1,525	40.1	1,006	43.5
Married	5,244	59.8	2,277	59.9	1,307	56.5
Socioeconomic status						
Lowest quintile	1,129	12.9	511	13.4	286	12.4
2nd quintile	2,090	23.8	867	22.8	580	25.1
3rd quintile	1,993	22.7	864	22.7	516	22.3
4th quintile	1,662	19.0	764	20.1	448	19.4
Highest quintile	1,895	21.6	796	20.9	483	20.9
Comorbidity score						
0	7,650	87.2	3,295	86.7	1,964	84.9
1	915	10.4	413	10.9	288	12.5
≥ 2	204	2.3	94	2.5	61	2.6
Tumor size, cm						
0-< 1	2,377	27.1	1,102	29.0	686	29.7
1-2	3,929	44.8	1,711	45.0	982	42.5
> 2	1,969	22.5	765	20.1	562	24.3
Unknown	494	5.6	224	5.9	83	3.6
Tumor grade						
Low (1 or 2)	6,310	72.0	2,726	71.7	1,692	73.2
High (3 or 4)	1,475	16.8	610	16.0	392	17.0
Unknown	984	11.2	466	12.3	229	9.9
Lymph node involvement						
Negative	7,961	90.8	3,577	94.1	2,002	86.6
Positive	808	9.2	225	5.9	311	13.5
Surgery						
Mastectomy	3,190	36.4	1,454	38.2	715	30.9
Lumpectomy	5,407	61.7	2,292	60.3	1,537	66.5
No/unknown	172	2.0	56	1.5	61	2.6
Chemotherapy						
No/unknown	6,415	73.2	2,932	77.1	1,761	76.1
Yes	2,354	26.8	870	22.9	552	23.9
Radiation						
No/unknown	4,622	52.7	2,020	53.1	1,207	52.2
Yes	4,147	47.3	1,782	46.9	1,106	47.8
Prescription refill interval, days						
30	1,764	20.1	957	25.2	321	13.9
60	1,323	15.1	902	23.7	69	3.0
90	5,682	64.8	1,943	51.1	1,923	83.1
Types of endocrine therapy						
Tamoxifen only	3,802	43.4	—	—	—	—
Aromatase inhibitors only	2,313	26.4	—	—	—	—
Anastrozole only	1,964	84.9				
Letrozole only	133	5.8				
Exemestane only	19	0.8				
Tamoxifen and aromatase inhibitors	2,654	30.3	—	—	—	—

Abbreviation: KPNC, Kaiser Permanente of Northern California.
*Denominator is the number of patients that continued on treatment.

Table 2. Univariate and Multivariate Analysis of Predictors of Endocrine Therapy Discontinuation Among Women Diagnosed With Stage I-III Hormone Receptor–Positive Breast Cancer Who Initiated Adjuvant Hormonal Therapy, KPNC, 1996-2006

Characteristic	All Patients (N = 8,769)			Tamoxifen Only (n = 3,802)			Aromatase Inhibitors Only (n = 2,313)		
	Univariate HR	Multivariate HR	Multivariate 95% CI*	Univariate HR	Multivariate HR	Multivariate 95% CI*	Univariate HR	Multivariate HR	Multivariate 95% CI*
Discontinued by 4.5 years									
No.	2,790			1,460			659		
%	32			38			29		
Age at diagnosis, years									
< 50	1.24	1.27	1.13 to 1.43	1.22	1.23	1.05 to 1.43	1.09	1.17	0.76 to 1.80
50-64	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
≥ 65	1.28	1.10	1.01 to 1.20	1.14	1.07	0.94 to 1.21	1.39	1.11	0.93 to 1.31
Year at diagnosis									
> 2001	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
≤ 2001	0.80	0.64	0.58 to 0.71	0.85	0.73	0.65 to 0.83	0.58	0.53	0.34 to 0.83
Race/ethnicity									
White	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Black	1.06	0.97	0.82 to 1.14	0.90	0.88	0.70 to 1.11	1.39	1.00	0.72 to 1.39
Hispanic	0.89	0.86	0.74 to 1.00	0.87	0.82	0.66 to 1.01	0.81	0.79	0.56 to 1.10
Asian	0.87	0.86	0.76 to 0.98	0.84	0.80	0.67 to 0.95	0.92	1.00	0.78 to 1.29
Marital status									
Unmarried	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Married	0.76	0.82	0.76 to 0.88	0.85	0.85	0.77 to 0.95	0.68	0.81	0.69 to 0.96
Socioeconomic status									
Lowest quintile	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
2nd quintile	0.88	0.91	0.80 to 1.04	0.93	0.90	0.76 to 1.08	0.81	0.90	0.69 to 1.17
3rd quintile	0.84	0.89	0.78 to 1.01	0.88	0.87	0.73 to 1.04	0.67	0.76	0.57 to 1.00
4th quintile	0.98	1.02	0.89 to 1.16	0.99	1.02	0.86 to 1.22	0.92	1.03	0.78 to 1.34
Highest quintile	0.86	0.91	0.80 to 1.04	0.93	0.92	0.77 to 1.10	0.82	0.91	0.69 to 1.20
Comorbidity score									
0	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
1	1.23	1.12	1.00 to 1.26	1.04	1.00	0.85 to 1.18	1.41	1.23	0.99 to 1.52
≥ 2	1.41	1.28	1.02 to 1.60	1.34	1.33	0.99 to 1.79	1.34	1.01	0.63 to 1.61
Tumor size, cm									
0-< 1	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
1-2	0.90	0.95	0.87 to 1.04	0.94	0.91	0.80 to 1.02	0.94	0.95	0.79 to 1.15
> 2	0.89	0.97	0.86 to 1.08	0.90	0.87	0.74 to 1.02	0.99	1.08	0.86 to 1.36
Unknown	0.71	0.82	0.68 to 1.00	0.81	0.84	0.66 to 1.08	0.78	0.78	0.49 to 1.25
Tumor grade									
Low (1 or 2)	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
High (3 or 4)	0.95	0.98	0.88 to 1.08	0.95	0.98	0.84 to 1.13	0.94	0.95	0.76 to 1.19
Unknown	0.97	0.94	0.84 to 1.06	0.90	0.87	0.74 to 1.02	1.09	1.11	0.86 to 1.44
Lymph node involvement									
Negative	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Positive	0.84	0.96	0.82 to 1.13	1.05	1.13	0.88 to 1.45	0.94	1.00	0.76 to 1.32
Surgery									
Mastectomy	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Lumpectomy	1.11	1.24	1.12 to 1.38	1.05	1.17	1.01 to 1.36	1.21	1.34	1.07 to 1.67
None/unknown	1.42	1.33	1.02 to 1.74	0.98	0.80	0.48 to 1.34	2.29	2.03	1.33 to 3.11
Chemotherapy									
No	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Yes	0.79	0.88	0.79 to 0.99	0.98	0.96	0.82 to 1.13	0.76	0.83	0.66 to 1.04
Radiation									
No	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Yes	0.94	0.82	0.75 to 0.91	0.92	0.84	0.72 to 0.97	0.96	0.82	0.67 to 1.00
Prescription refill interval, days									
30	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
60	0.38	0.38	0.34 to 0.43	0.38	0.38	0.33 to 0.44	0.30	0.32	0.21 to 0.49
90	0.41	0.36	0.33 to 0.40	0.43	0.38	0.34 to 0.43	0.17	0.18	0.15 to 0.21
Types of endocrine therapy									
Tamoxifen only	1.00	1.00	—	—	—	—	—	—	—
Aromatase inhibitor only	0.99	0.90	0.80 to 1.00	—	—	—	—	—	—
Both	0.54	0.54	0.50 to 0.59	—	—	—	—	—	—

NOTE. Missing data were characterized as unknown. All variables in the multivariate analysis were adjusted for each other.
Abbreviations: KPNC, Kaiser Permanente of Northern California; HR, hazard ratio.
*CI associated with multivariate HR.

Table 3. Univariate and Multivariate Analysis of Predictors of Nonadherence to Endocrine Therapy for Women Diagnosed With Stage I-III Hormone Receptor–Positive Breast Cancer Who Continued Adjuvant Hormonal Therapy (discontinued patients removed), KPNC, 1996-2006

Characteristic	All Patients (N = 5,979)			Tamoxifen Only (n = 2,342)			Aromatase Inhibitors Only (n = 1,654)		
	Univariate HR	Multivariate HR	95% CI*	Univariate HR	Multivariate HR	95% CI*	Univariate HR	Multivariate HR	95% CI*
Nonadherent by 4.5 years									
No.	1,666			702			465		
%	28			30			28		
Age at diagnosis, years									
< 50	1.11	1.08	0.93 to 1.25	1.24	1.15	0.93 to 1.43	0.64	0.62	0.35 to 1.12
50-64	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
≥ 65	1.12	1.06	0.94 to 1.18	1.24	1.21	1.01 to 1.45	1.05	1.02	0.83 to 1.24
Year at diagnosis									
> 2001	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
≤ 2001	0.86	0.83	0.74 to 0.94	0.84	0.82	0.68 to 0.98	0.60	0.59	0.31 to 1.13
Race/ethnicity									
White	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Black	1.31	1.23	1.01 to 1.51	1.24	1.27	0.94 to 1.72	1.80	1.45	1.00 to 2.11
Hispanic	1.11	1.06	0.88 to 1.27	0.86	0.79	0.58 to 1.08	1.53	1.49	1.10 to 2.02
Asian	1.01	1.02	0.87 to 1.19	1.11	1.11	0.89 to 1.40	0.94	0.97	0.72 to 1.33
Marital status									
Unmarried	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Married	0.81	0.86	0.77 to 0.95	0.80	0.81	0.70 to 0.95	0.79	0.86	0.71 to 1.05
Socioeconomic status									
Lowest quintile	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
2nd quintile	0.81	0.88	0.74 to 1.04	0.88	0.95	0.74 to 1.23	0.71	0.86	0.62 to 1.18
3rd quintile	0.84	0.92	0.78 to 1.08	0.88	0.94	0.73 to 1.21	0.86	1.02	0.75 to 1.40
4th quintile	0.80	0.85	0.71 to 1.01	0.74	0.78	0.60 to 1.02	0.78	0.91	0.65 to 1.28
Highest quintile	0.83	0.90	0.76 to 1.06	0.84	0.90	0.70 to 1.17	0.76	0.92	0.66 to 1.28
Comorbidity score									
0	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
1	1.23	1.20	1.03 to 1.40	1.16	1.12	0.88 to 1.42	1.40	1.34	1.03 to 1.75
≥ 2	1.60	1.53	1.15 to 2.04	1.55	1.61	1.03 to 2.51	1.73	1.56	0.96 to 2.54
Tumor size, cm									
0-< 1	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
1-2	1.04	1.04	0.92 to 1.18	1.19	1.15	0.95 to 1.39	0.96	0.97	0.77 to 1.21
> 2	1.17	1.13	0.97 to 1.31	1.17	1.09	0.86 to 1.39	1.10	1.11	0.84 to 1.47
Unknown	1.24	1.33	1.08 to 1.64	1.38	1.45	1.06 to 1.99	1.10	1.14	0.70 to 1.87
Tumor grade									
Low (1 or 2)	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
High (3 or 4)	1.02	0.97	0.85 to 1.11	0.95	0.92	0.74 to 1.14	1.00	0.95	0.74 to 1.23
Unknown	1.04	1.01	0.87 to 1.18	1.04	1.01	0.81 to 1.27	0.93	0.94	0.68 to 1.29
Lymph node involvement									
Negative	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Positive	1.22	1.20	1.02 to 1.42	1.35	1.42	1.05 to 1.93	0.99	0.95	0.71 to 1.26
Surgery									
Mastectomy	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Lumpectomy	1.02	1.14	1.00 to 1.31	1.05	1.12	0.91 to 1.39	1.21	1.39	1.08 to 1.78
No/unknown	1.31	1.14	0.81 to 1.59	1.43	1.02	0.59 to 1.76	1.69	1.69	0.94 to 3.02
Chemotherapy									
No	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Yes	1.03	1.02	0.89 to 1.17	1.07	1.02	0.82 to 1.28	1.05	1.16	0.89 to 1.51
Radiation									
No	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
Yes	0.92	0.90	0.79 to 1.02	0.96	0.94	0.76 to 1.16	0.97	0.87	0.69 to 1.09
Prescription refill interval, days									
30	1.00	1.00	—	1.00	1.00	—	1.00	1.00	—
60	0.32	0.32	0.27 to 0.38	0.33	0.32	0.26 to 0.41	0.50	0.54	0.29 to 1.01
90	0.51	0.47	0.42 to 0.53	0.54	0.49	0.40 to 0.59	0.53	0.57	0.42 to 0.77
Types of endocrine therapy									
Tamoxifen only	1.00	1.00	—	—	—	—	—	—	—
Aromatase inhibitors only	1.05	0.95	0.82 to 1.10	—	—	—	—	—	—
Both	0.79	0.75	0.66 to 0.84	—	—	—	—	—	—

NOTE. Missing data were characterized as unknown. All variables in the multivariate analysis were adjusted for each other.
Abbreviations: KPNC, Kaiser Permanente of Northern California; HR, hazard ratio.
*CI associated with multivariate HR.

because of unknown race (Appendix Figure A1, online only). Of the 8,769 patients, 3,802 (43%) received only tamoxifen, while 2,313 (29%) received only an AI, and 2,654 (30%) received both types of medication at least once during the study period (Table 1). The population was diverse, with 11.0% of the patients of Asian race, 7.2% Hispanic, 5.6% black, and 76.2% white. The proportion of patients filling prescriptions for AIs increased starting in 2001; by 2008, 63% of patients with hormone-sensitive BC were taking AIs. Of those taking an AI, 1,964 (84.9%) took anastrozole alone, 152 (6.6%) took letrozole or exemestane alone, and 197 (8.5%) took more than one AI.

Over the 4.5 year follow-up period, 2,790 (32%) discontinued and, of the 5,979 patients who continued, 28% were nonadherent (19% of total). We performed a Cox proportional hazards analysis to determine predictors of early discontinuation. We found that younger age or older age (compared with the 50- to 65-year-old age group), lumpectomy and unknown surgery (*v* mastectomy), and having more comorbid conditions were associated with discontinuation of hormonal therapy, while Asian/Pacific Islander ethnicity, being married, earlier year at diagnosis, prior receipt of adjuvant chemotherapy, receipt of adjuvant radiation therapy, and longer prescription refill interval were associated with the completion of 4.5 years of hormonal therapy. Similar results were obtained for either tamoxifen or AIs (Table 2). Women who took both AIs and tamoxifen at least once during the study period were less likely to discontinue therapy early. However, the discontinuation rates were similar for those who took either tamoxifen or AIs alone.

In a Cox proportional hazards analysis to determine predictors of nonadherence, African American race, lumpectomy, unknown tumor size, lymph node involvement, and having more comorbid conditions were associated with nonadherence, while earlier year at diagnosis, being married, and longer prescription refill interval were associated with full adherence to hormonal therapy. Women who took both AIs and tamoxifen were slightly more likely to fully adhere to hormone treatment, and adherence rates were also similar for those who took tamoxifen or AIs alone (Table 3).

The percentage of patients who started therapy on a year-by-year basis after initiation, who continued therapy for the year, and who were fully adherent are shown in Figure 1. For all patients who took hormonal therapy, the percentage of patients who continued and fully adhered to therapy was similar from year to year across all 4.5 years. However, more patients discontinued AI therapy by the end of year 4, and more patients became nonadherent to tamoxifen therapy by the end of year 4.5.

Unadjusted Kaplan-Meier curves for continuation and adherence are shown in Figure 2. The proportion of patients who continued therapy decreased from 86% in year 1 to 60% in year 4.5. Of the patients who continued, adherence also fell from 78% in year 1 to 70% in year 4.5. We found that 358 patients (4%) filled only one prescription, and of the patients who continued, 765 patients (13%) had a delay in the first prescription refill and were classified as never adherent.

The multivariate analysis for nonadherence and discontinuation was repeated on all patients, using a more refined age categorization ($<$ 40, 40 to 54, 55 to 64, 65 to 74, and $\geq$ 75 years). We found that patients at the age extremes ($<$ 40 years and $>$ 75 years) were most likely to discontinue hormone therapy or be nonadherent compared

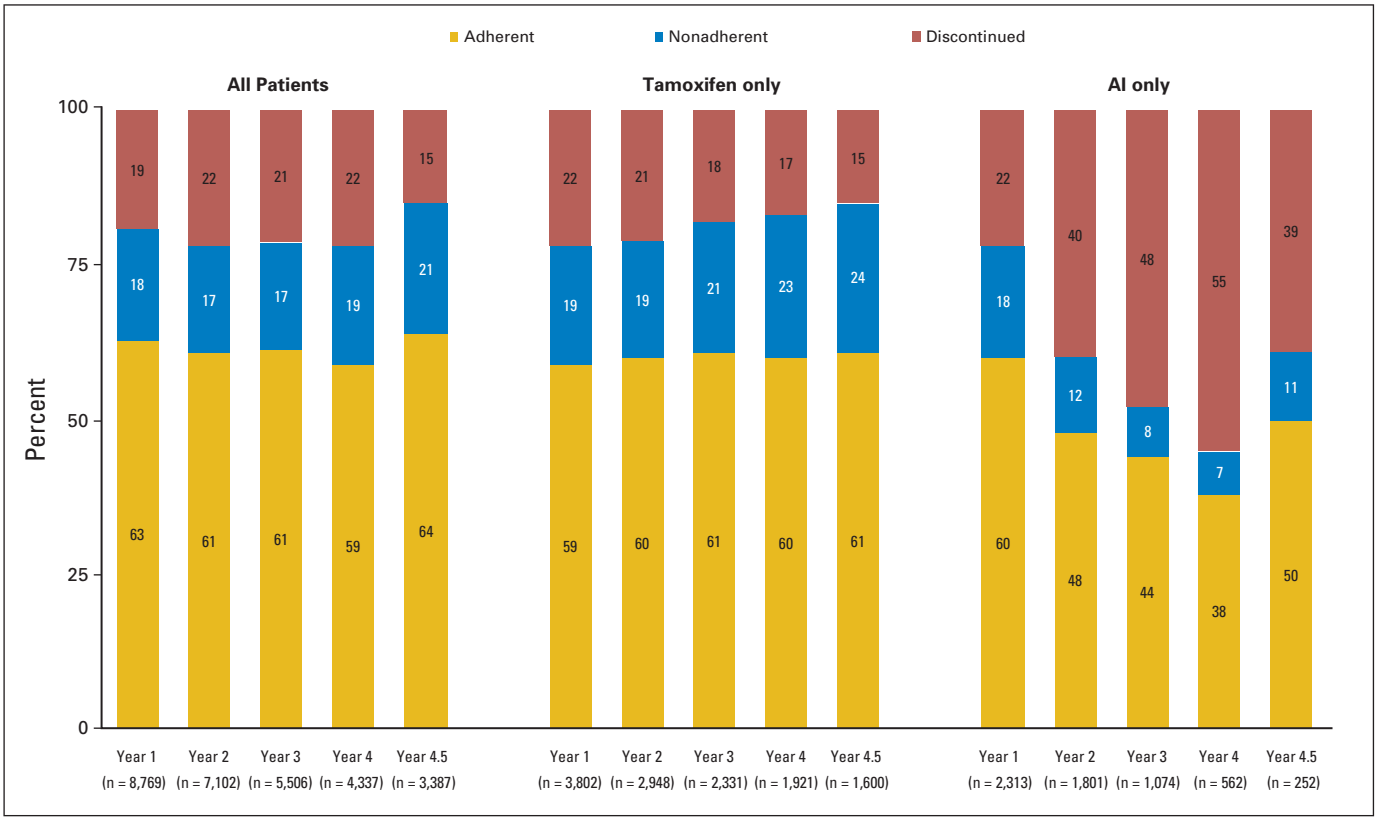

Fig 1. Annual proportions of adherent, nonadherent, and discontinued patients on adjuvant hormonal therapy, of those patients with stage I-III breast cancer who were taking hormonal therapy at the start of the year, Kaiser Permanente of Northern California (KPNC), 1996 to 2006. AI, aromatase inhibitor.

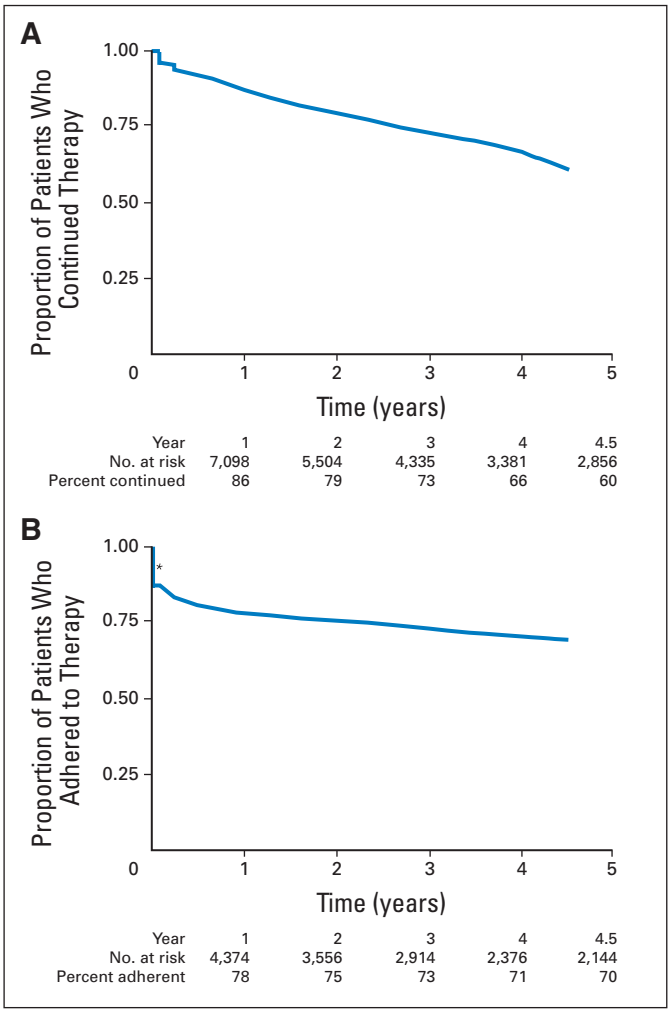

Fig 2. (A) Kaplan-Meier curve for continuation of hormonal therapy among 8,769 patients with stage I-III hormone receptor–positive breast cancer who initiated treatment at Kaiser Permanente of Northern California (KPNC), 1996 to 2006. (B) Kaplan-Meier curve for hormonal therapy adherence among 5,979 patients with stage I-III hormone receptor–positive breast cancer who continued adjuvant treatment at KPNC, 1996 to 2006. (*) 13% of patients never adhered.

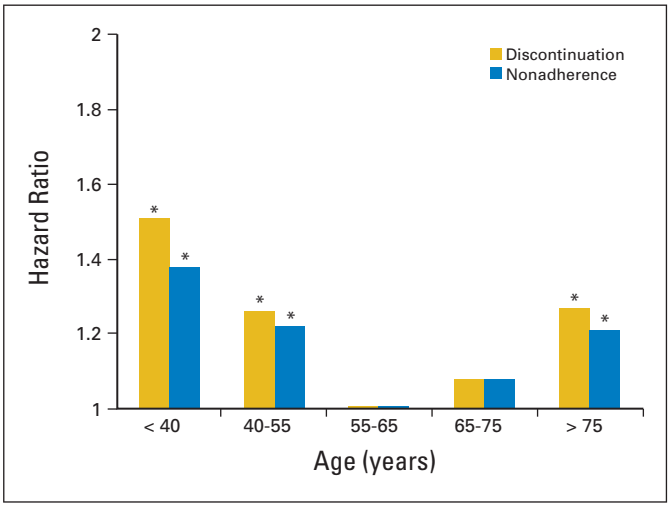

Fig 3. Patient age as a predictor of discontinuation and nonadherence to endocrine therapy among 8,769 women diagnosed with stage I-III hormone receptor–positive breast cancer who initiated adjuvant hormonal therapy at Kaiser Permanente of Northern California (KPNC), 1996 to 2006. (*) $P < .05$.

with patients age 50 to 65 years (Fig 3). There were 202 patients younger than 40 years, and they were the most noncompliant with therapy, being 50% more likely to discontinue therapy and 40% more likely to be nonadherent ($P < .001$).

DISCUSSION

In this large population-based study of women with nonmetastatic BC enrolled in KPNC, we found that approximately 30% of those who began adjuvant hormonal therapy with either tamoxifen or AIs discontinued therapy early. Furthermore, we found that, of those who continued therapy, approximately 70% were fully adherent by the end of the 4.5-year period, indicating that overall only 49% of patients were fully adherent for the entire 4.5 years. We found rates of discontinuation and nonadherence to be similar from year to year. We were surprised to find that women at the extremes of the age range (ie, those < 40 years or > 75 years) were particularly likely to be nonadherent.

Our results are consistent with other studies that have shown high discontinuation and nonadherence rates among women on adjuvant hormonal therapy; however, slight differences are seen based on the methodology used to define adherence, and the patient populations studied. Prior studies were limited to patients older than age 65 years,[31,32] had smaller sample sizes,[12,33] included only patients on Medicaid,[12,33] were unable to censor at the time of insurance disenrollment/progression, defined discontinuation with a shorter time interval from last prescription,[12,31-33] or had < 5 years of follow-up (2.5-4.5 years).[14] Despite these differences, the prior studies all consistently reported discontinuation rates in the range of 30% to 50%.

Most of the population-based studies on quality of cancer chemotherapy have used the SEER-Medicare database and, as a result, have focused on patients older than age 65 years.[7,34,35] Most of the studies on adherence to adjuvant hormonal therapy have also investigated patients in this older age range.[13,16,31,36] Thus, less is known about younger age groups. In our study, we found that, compared with women age 50 to 65 years, younger women were more likely to discontinue therapy early and more likely to be nonadherent. Two prior studies also found younger age to be a predictor of early tamoxifen discontinuation[19,33]; however, this finding has received little attention. Young adults with cancer may be a particularly vulnerable group.[37-39] While this may not reflect our patient population, patients in this age group have the lowest rates of health insurance coverage, frequent delays in diagnosis, and the lowest accrual to clinical trials.[38] Against this background, young adults with cancer have unique challenges—medically, psychosocially, and economically—that are now beginning to be appreciated and addressed and may result in improved treatment quality.[39]

Similar to other studies in the literature,[40,41] our study found longer prescription refill intervals (60 or 90 days *v* 30 days) to be associated with both completion and full adherence to hormonal therapy. However, the link between nonadherence and length of prescription refill may simply reflect greater opportunities to detect poor

adherence when more refills are required. On the other hand, shorter refill intervals may be associated with an increased frequency of nonadherence because of the inconvenience involved in frequent refilling. Further research is needed to explore the impact of prescription refill interval on medication adherence.

Much of the research on health disparities in treatment quality has focused on differences between African American and white women. For example, African American patients receive less aggressive intravenous chemotherapy,[42] have fewer consultations with medical oncologists,[43] and have a significantly higher risk of recurrence than whites.[44] It is estimated that only 50% of African American women appropriate for adjuvant chemotherapy for BC receive it.[45-47] Similar to other studies,[33] after controlling for confounding factors, our study showed that African American women were more likely to be nonadherent to therapy compared with white women, but there was no difference in discontinuation rate.

Interestingly, we found that Asian/Pacific Islander women were significantly less likely than other racial/ethnic groups to discontinue therapy, but there was no difference in rates of nonadherence. In several population-based studies,[48,49] Asian/Pacific Islander women were significantly more likely to undergo mastectomies than white women.[50] There may be treatment differences across subpopulations of Asian/Pacific Islander women and/or treatment differences related to immigration, language, and acculturation factors that we were not able to evaluate in this study. For example, in one study based on Bay Area SEER data, Chinese women were more likely than white women to not receive adjuvant therapy.[50]

Barriers to adherence include failure of the physician to carefully explain benefits and adverse effects, not giving consideration to cost, and a poor therapeutic relationship.[1] With regard to cancer, adherence to hormonal therapy is highly dependent on the communication between physician and patient.[32] We found that 13% of patients who continued hormonal therapy were nonadherent from the first refill. It might be helpful to identify interventions to improve adherence at this time point. Treatment-associated toxicities are another major barrier to the full application of effective cancer treatment. For example, in a survey of 622 postmenopausal women, 30% discontinued AI therapy, and 84% did so because of adverse effects.[51] This may partially explain our high nonadherence rate with AI therapy. We found that 4% of patients filled only one prescription for their hormonal therapy; this early discontinuation may be related to early treatment toxicities, among other factors.

Financial issues, such as lack of coverage for prescriptions, also inhibit full adherence with oral therapies. The total cost of tamoxifen may be as high as $1,200 per year[52] and, before going off patent, AIs cost about $2,300 per year.[53] Factors such as copayments have been shown to influence adherence. Goldman et al[54] found that a doubling of copays for various chronic medications resulted in drops in adherence ranging from 8% to 45%, depending on the medication. Our study, however, was conducted in an equal-access health care system where all of the patients had a pharmacy plan, thus somewhat controlling for insurance status and copays, so that other factors could be examined.

There are several limitations to our study. First, we were unable to determine the reasons for nonadherence and discontinuation. Another limitation was the inability to capture all recurrences with electronic medical data, which may have led to misclassification bias. In addition, assumptions were made to calculate total number of pills dispensed because of the lack of prescription information (dosage and days supplied), which may have resulted in an under- or overestimation of the number of pills dispensed; however, use of prescription claims databases to estimate medication adherence has been validated in other studies.[55]

We found that only 49% of patients with hormone-sensitive BC continue therapy and take medications in the prescribed fashion until the end of the 4.5-year course, whether they are taking tamoxifen or AIs. Further investigation is warranted to determine the association between nonadherence to hormonal therapy and breast cancer–specific mortality. Ultimately, interventions need to be defined to help such patients comply with the full course of adjuvant hormonal therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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