Endocrine Therapy Initiation From 2001 to 2008 Varies by Age at Breast Cancer Diagnosis and Tumor Size

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Abstract

Purpose: To evaluate tamoxifen and aromatase inhibitor (AI) initiation over time and by patient characteristics among women diagnosed with breast cancer in a community setting.

Methods: We conducted a retrospective cohort study of 1,501 women age ≥ 18 years diagnosed with stages I to II invasive, hormone receptor–positive breast cancer from 2001 to 2008 in an integrated delivery system. Using automated pharmacy dispensings, we determined endocrine therapy receipt within 12 months of diagnosis. We used generalized linear models to estimate adjusted relative risks (RRs) with 95% CIs for any endocrine therapy use (v none), tamoxifen use (v none), AI use (v none), and AIs first (v tamoxifen). Each model adjusted for age, stage, body mass index, tumor size, lymph node status, comorbidities, other treatment, and diagnosis year.

Results: Tamoxifen use was at its highest (56.9%) in 2001 and then decreased; AI use was lowest in 2001 (5.5%) and then peaked in 2005 (36.8%). In multivariate models, women age ≥ 65 years were less likely to use any endocrine therapy compared with women age 55 to 64 years (age 65 to 74 years: RR, 0.86; 95% CI, 0.78 to 0.96; age ≥ 75 years: RR, 0.71; 95% CI, 0.61 to 0.81). Women age ≥ 75 years were significantly less likely to begin AIs versus no treatment (RR, 0.46; 95% CI, 0.32 to 0.64) and versus tamoxifen (RR, 0.67; 95% CI, 0.46 to 0.97). Women with tumor sizes 1.0 to 1.9 cm and ≥ 2.0 cm were significantly more likely to use any endocrine therapy compared with women with tumor sizes < 1.0 cm (RR, 1.41; 95% CI, 1.23 to 1.61 and RR, 1.52; 95% CI, 1.27 to 2.81, respectively).

Conclusion: Differential initiation over time, as well as by age and tumor size, suggests patient preferences and provider recommendations for endocrine therapy vary, despite guideline recommendations.

Introduction

Approximately 80% of women diagnosed with invasive breast cancer have hormone receptor (HR) –positive disease, making a large proportion of women with breast cancer potential candidates for adjuvant endocrine therapy.[1,2] Clinical trials consistently demonstrate that tamoxifen or aromatase inhibitor (AI) use significantly improves disease-free survival and overall breast cancer mortality.[3,4] Current National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend AI therapy for 5 years after completion of primary therapy or for 2 to 3 years after 2 to 3 years of tamoxifen for postmenopausal women.[1,2,5,6] NCCN guidelines also recommend that adjuvant endocrine therapy be considered for women with HR-positive breast cancer "regardless of menopausal status, age, or HER2 status of the tumor."[2(pMS-25)]

We do not know how well these recommendations are currently followed in community practice, even though they stem from the results of large, high-quality clinical trials. Diffusion studies show that AI and tamoxifen were used before the development of guidelines,[7-9] so patterns of use in the community may not conform to guidelines. Factors such as age, disease severity, and medical insurance or access to health care—all of which are inherently controlled for in clinical trials—may influence treatment selection in a real-world setting. In fact, a few studies using data before 2005 have shown that endocrine therapy initiation ranges between 15% to 84% in various populations of women with estrogen receptor (ER) –positive tumors.[8,10-12] Understanding cancer treatment patterns in the community is critical to evaluating quality of care for women with breast cancer and may provide valuable information for future comparative effectiveness studies. A better understanding of who does and does not use different yet similarly effective treatments may help us more accurately estimate the effectiveness of these drugs in the general population and improve breast cancer survival.

The purpose of this article is to describe women's initiation of endocrine therapy over time and by demographic and tumor characteristics. We hypothesized that overall use of endocrine therapy would increase over time, corresponding to recent increases in AI use. Our study minimized one major factor that might normally bias treatment selection; all women in the study population were insured with comprehensive benefits and full access to health care through Group Health, an integrated health care delivery system in Washington. This provided an opportunity to conduct an unbiased examination of the selection factors that influence adjuvant endocrine therapy initiation.

Methods

Study Setting and Population

We conducted a retrospective cohort study of women age ≥ 18 years who were diagnosed with early-stage invasive breast cancer (American Joint Committee on Cancer Version 5 stage I, IIA, or IIB) from 1990 to 2008. All participants were part of the COMBO (Commonly Used Medications and Breast Cancer Outcomes) study. We obtained a waiver of consent to review electronic data and abstract medical records, and all study pro-

cedures were approved by the institutional review board at Group Health.

Women in the COMBO study had been enrolled continuously in Group Health for at least 12 months before and after their breast cancer diagnosis unless they died (n = 4,428) and received care from Group Health–owned and –operated facilities. For this analysis, we limited our sample to women diagnosed from 2001 to 2008 because AIs were not used at Group Health before 2001 (n = 1,927). We excluded women who died within 1 year of diagnosis (n = 28), did not have definitive breast cancer surgery as primary treatment (n = 32), had ER-negative or progesterone receptor (PR) –negative disease (n = 307), or unknown ER and PR status (n = 104). These exclusion criteria were not mutually exclusive, and our final sample for this analysis was 1,501 women. We used age ≥ 55 years as a proxy for postmenopausal status for some analyses, even though age at menopause may vary widely among women undergoing breast cancer treatment (particularly chemotherapy), and thus women younger than 55 years of age may be postmenopausal and eligible for tamoxifen or AI therapy.[13]

Data Collection

We identified patient cases of breast cancer by linking Group Health enrollees with the Western Washington Surveillance, Epidemiology, and End Results (SEER) registry. Group Health has linked with SEER since 1974 for primary cancer diagnoses and tumor characteristics. We used the detailed electronic administrative data of Group Health on outpatient pharmacy dispensings, enrollment, and demographics to identify our outcomes and covariates for this analysis.

Tamoxifen and AI Use

The outcome for this study was first use of endocrine therapy after diagnosis, either tamoxifen or AIs. All tamoxifen and AI data were collected using electronic pharmacy data, which has been shown to be 97% complete.[14,15] Pharmacy use is captured for all Group Health enrollees who fill prescriptions at Group Health–owned and –operated pharmacies and for all Group Health enrollees with a drug benefit who fill prescriptions at outside pharmacies. A recent unpublished survey of women from the COMBO study demonstrates 92% almost always fill their prescriptions at Group Health pharmacies. This also includes Medicare Part D enrollees, starting in 2006, who likely increased capture of pharmacy data because more enrollees were offered a drug benefit through Group Health rather than obtaining prescriptions elsewhere. With a goal of capturing all use and avoiding inclusion of tamoxifen or AI use for recurrence, we defined use as one or more dispensings of one drug within 12 months of diagnosis. Because we were primarily interested in initiation of each drug, using one or more dispensings allowed us to include women who may have stopped using that drug because of intolerable adverse effects. Limiting our definition to 12 months after diagnosis reduced the possibility of misclassifying anyone who used tamoxifen or AIs for breast cancer recurrence instead of their primary diagnosis. This definition is consistent with that in a recent study.[16] We defined women as having any endocrine therapy use if they had one or more dispensings of either tamoxifen or AIs within 12 months of diagnosis; nonusers had no dispensings of tamoxifen or AIs. If a woman switched drugs at any point, she was classified as a user of tamoxifen or AIs based on what she filled first (n = 74).

Covariates

Variables of interest included demographic and breast cancer tumor characteristics. These data were collected from electronic administrative databases including enrollment files (age, length of enrollment, comorbidities or Charlson score,[17] pharmacy copayment), Group Health Breast Cancer Surveillance project data[18] (education, body mass index [BMI]), and SEER data (date of diagnosis, race, ethnicity, stage at diagnosis, tumor size, lymph node status, ER status, PR status, definitive surgical procedure, chemotherapy, radiation therapy).

Statistical Analysis

We used generalized linear models with a log link, Poisson distribution, and robust SEs to estimate rates and relative risks (RRs) of endocrine therapy use. Rates of initiation were estimated for each diagnosis year, and we tested for trends in initiation over time. We estimated the adjusted RR and 95% CI for:

- Any endocrine therapy use versus no use of either drug relative to patient demographics and tumor characteristics.
- Tamoxifen use first versus no use of either drug relative to demographics and tumor characteristics.
- AI use first versus no use of either drug relative to demographics and tumor characteristics; this analysis was limited to women age ≥ 55 years.
- Direct comparison of AI use first versus tamoxifen use first, also limited to women age ≥ 55 years; we excluded 164 additional women from this analysis who had one of the following contraindications to AI or tamoxifen use within the 12 months before breast cancer diagnosis: deep vein thrombosis, osteoporotic fracture, pulmonary embolus, or stroke.

All models were adjusted for age, stage, tumor size, lymph nodes, comorbidities, surgical treatment, chemotherapy, radiation therapy, BMI, and diagnosis year, because these were significantly associated with any endocrine therapy use in unadjusted models. Pharmacy copayment, race, ethnicity, and education were not significantly related to endocrine therapy use, so we did not include these variables in the final multivariate models. All analyses were conducted in Stata (StataCorp, College Station, TX), and two-sided *P* values less than .05 were considered statistically significant.

Results

Among 1,501 women diagnosed with HR-positive breast cancer between 2000 and 2008, 680 (45%) were tamoxifen-first users, 368 (25%) were AI-first users, and 453 (30%) used neither drug (Table 1). Most endocrine therapy nonusers were age 65 to 74 years (28.0%) or 75 years or older (36.4%), diagnosed

Table 1. Demographic and Clinical Characteristics of Women With Early-Stage Hormone Receptor–Positive Breast Cancer by Endocrine Therapy Initiation Within 12 Months of Diagnosis From 2001 to 2008

Characteristic	No Tamoxifen or Als		Tamoxifen First		Als First		Total	
	No.*	%	No.*	%	No.*	%	No.*	%
Total No. of patients	453		680		368		1,501	
Age at diagnosis, years								
< 45	18	4.0	61	9.0	11	3.0	90	6.0
45-54	52	11.5	192	28.2	62	16.8	306	20.4
55-64	91	20.1	169	24.9	159	43.2	419	27.9
65-74	127	28.0	146	21.5	93	25.3	366	24.4
≥ 75	165	36.4	112	16.5	43	11.7	320	21.3
Race								
White	401	88.5	589	87.3	318	86.6	1,308	87.5
Black	10	2.2	16	2.4	12	3.3	38	2.5
American Indian/Alaska Native	15	3.3	17	2.5	15	4.1	47	3.1
Asian	27	6.0	53	7.9	22	6.0	106	6.8
Ethnicity								
Non-Hispanic	414	91.4	617	90.7	344	93.5	1,375	91.6
Hispanic	39	8.6	63	9.3	24	6.5	126	8.4
Education								
High school or less	88	28.4	103	20.1	49	17.4	240	21.8
Some college	110	35.5	191	37.3	118	42.0	419	38.0
College graduate	60	19.4	109	21.3	55	19.6	224	20.3
Postgraduate	52	16.8	109	21.3	59	21.0	220	19.9
BMI, kg/m^2								
< 25.0	125	36.9	168	31.8	69	26.5	362	32.1
25.0-29.9	102	30.1	197	37.2	78	30.0	377	33.4
≥ 30.0	112	33.0	164	31.0	113	43.5	389	34.5
Stage at diagnosis								
I	362	79.9	396	58.2	163	44.3	921	61.4
IIA	66	14.6	186	27.4	127	34.5	379	25.2
IIB	25	5.5	98	14.4	78	21.2	201	13.4
Tumor size, cm								
< 1.0	169	38.1	116	17.1	50	13.6	335	22.5
1.0-1.9	193	43.6	337	49.8	175	47.7	705	47.4
≥ 2.0	81	18.3	224	33.1	142	38.7	447	30.1
Lymph node status								
Negative	410	90.5	494	72.6	217	59.0	1,121	74.7
Positive	43	9.5	186	27.4	151	41.0	380	25.3
Hormone receptor status								
ER and PR positive	417	93.9	619	91.8	355	96.7	1,391	93.7
ER positive, PR negative	23	5.2	45	6.7	12	3.3	80	5.4
ER negative, PR positive	4	0.9	10	1.5	0	0.0	14	0.9
Definitive surgical procedure								
Breast conserving	291	64.2	441	64.9	228	62.0	960	64.0
Mastectomy	162	35.8	239	35.1	140	38.0	541	36.0
Chemotherapy								
No	383	85.5	420	62.4	202	56.3	1,005	67.9
Yes	65	14.5	253	37.6	157	43.7	475	32.1

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Table 1. Demographic and Clinical Characteristics of Women With Early-Stage Hormone Receptor–Positive Breast Cancer by Endocrine Therapy Initiation Within 12 Months of Diagnosis From 2001 to 2008 (Continued)

Characteristic	No Tamoxifen or AIs		Tamoxifen First		AIs First		Total	
	No.*	%	No.*	%	No.*	%	No.*	%
Radiation								
No	195	44.1	231	35.0	117	34.2	543	37.6
Yes	247	55.9	429	65.0	225	65.8	901	62.4
Charlson score								
0	308	68.0	532	78.2	271	73.6	1,111	74.0
1	85	18.8	104	15.3	69	18.8	258	17.2
≥ 2	60	13.2	44	6.5	28	7.6	132	8.8
Year of diagnosis								
2001	66	14.6	114	16.8	12	3.3	192	12.8
2002	79	17.4	99	14.6	31	8.4	209	13.9
2003	62	13.7	112	16.5	29	7.9	203	13.5
2004	49	10.8	78	11.5	42	11.4	169	11.3
2005	55	12.1	73	10.7	75	20.4	203	13.5
2006	61	13.5	74	10.9	64	17.4	199	13.3
2007	40	8.8	71	10.4	63	17.1	174	11.6
2008	41	9.1	59	8.7	52	14.1	152	10.1
Pharmacy copayment (per 30-day supply), $								
0-5	50	15.7	107	18.4	48	14.0	205	16.5
7-10	170	53.3	306	52.5	176	51.5	652	52.4
15-25	99	31.0	170	29.2	118	34.5	387	31.1

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.
* Numbers may not add to totals because of missing data.

with stage I breast cancer (79.9%) with tumor sizes < 1.0 cm (38.1%) and/or negative lymph nodes (90.5%). Tamoxifen-first and AI-first users tended to be younger, and a greater proportion were diagnosed with stage IIB breast cancer, had tumors > 2.0 cm in size, and/or had positive lymph nodes compared with nonusers. Surgical treatment did not differ by endocrine therapy use; however, a greater proportion of tamoxifen and AI users received either chemotherapy or radiation therapy compared with nonusers.

Adjusted rates of first tamoxifen use, first AI use, any endocrine therapy use, and nonuse over time are shown in Figure 1. Users of any endocrine therapy increased from 63.4% in 2001 to 75.1% in 2005 and then decreased to 67.1% in 2008. Tamoxifen use was highest in 2001 (56.9%) but dropped to 34.5% in 2005 and remained fairly steady thereafter. AI use accounted for only 5.5% of women in 2001 but had increased to 36.8% by 2005; it then dropped to 26.3% in 2008. Appendix Figure A1 (online only) shows similar patterns of use over time limited to women age ≥ 55 years. Trend tests for each exposure over time were statistically significant (*P* < .001) for both figures.

In multivariable models (Table 2), women age 65 to 74 years and ≥ 75 years were significantly less likely to use any endocrine therapy compared with women age 55 to 64 years (RR, 0.86; 95% CI, 0.78 to 0.96 and RR, 0.71; 95% CI, 0.61 to 0.81, respectively). RR for the association between age ≥ 75 years

and first AI use was particularly low (RR, 0.46; 95% CI, 0.32 to 0.64). Women with tumor sizes from 1.0 to 1.9 cm and ≥ 2.0 cm were significantly more likely to use any endocrine therapy compared with women with tumor sizes < 1.0 cm (RR, 1.41; 95% CI, 1.23 to 1.61 and RR, 1.52; 95% CI, 1.27 to 2.81, respectively); a similar pattern was noted for tumor size and tamoxifen use. Women with positive lymph nodes were more likely to use any endocrine therapy (RR, 1.31; 95% CI, 1.11 to
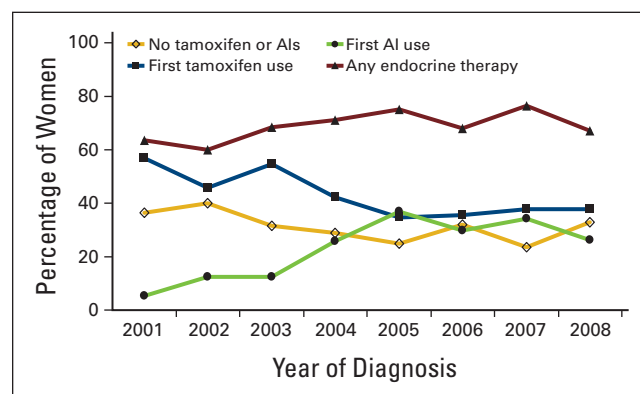

Figure 1. Proportions of endocrine therapy use within 12 months of diagnosis over time (all women age ≥ 18 years); adjusted for age, stage, tumor size, lymph nodes, body mass index, surgical treatment, chemotherapy, radiation therapy, and comorbidities. AI, aromatase inhibitor.

Table 2. Multivariate Associations Between Any Endocrine Therapy, Tamoxifen, or AI Initiation During 12 Months After Breast Cancer Diagnosis

Variable	Any Use *v* None		Tamoxifen First *v* None		AIs First *v* None*	
	RR	95% CI	RR	95% CI	RR	95% CI
Total No. of patients	1,048 *v* 453		680 *v* 453		368 *v* 453	
Age at diagnosis, years						
< 45	0.97	0.84 to 1.12	1.08	0.90 to 1.30	—	—
45-54	1.06	0.97 to 1.15	1.17	1.03 to 1.33	—	—
55-64	1	Reference	1	Reference	1	Reference
65-74	0.86	0.78 to 0.96	0.86	0.73 to 1.01	0.76	0.62 to 0.94
≥ 75	0.71	0.61 to 0.81	0.70	0.58 to 0.84	0.46	0.32 to 0.64
BMI, kg/m^2						
< 25.0	1	Reference	1	Reference	1	Reference
25.0-29.9	1.11	1.01 to 1.22	1.14	1.01 to 1.28	1.28	0.98 to 1.66
≥ 30.0	1.04	0.94 to 1.15	0.98	0.86 to 1.13	1.18	0.91 to 1.52
Stage at diagnosis						
I	1	Reference	1	Reference	1	Reference
IIA	0.99	0.84 to 1.17	0.92	0.74 to 1.15	1.64	0.97 to 2.79
IIB	0.91	0.69 to 1.21	0.78	0.54 to 1.14	1.84	0.76 to 4.49
Tumor size, cm						
< 1.0	1	Reference	1	Reference	1	Reference
1.0-1.9	1.41	1.23 to 1.61	1.52	1.28 to 1.81	1.58	1.17 to 2.12
≥ 2.0	1.52	1.27 to 1.82	1.71	1.35 to 2.17	1.40	0.84 to 2.34
Lymph node status						
Negative	1	Reference	1	Reference	1	Reference
Positive	1.31	1.11 to 1.54	1.48	1.18 to 1.86	1.16	0.71 to 1.87
Definitive surgical procedure						
Lumpectomy	1	Reference	1	Reference	1	Reference
Mastectomy	0.95	0.85 to 1.06	0.94	0.80 to 1.11	0.98	0.75 to 1.28
Chemotherapy						
No	1	Reference	1	Reference	1	Reference
Yes	1.03	0.95 to 1.12	1.04	0.92 to 1.17	0.99	0.80 to 1.22
Radiation therapy						
No	1	Reference	1	Reference	1	Reference
Yes	1.05	0.94 to 1.18	1.08	0.91 to 1.27	1.16	0.89 to 1.52
Charlson score						
0	1	Reference	1	Reference	1	Reference
1	0.99	0.89 to 1.10	0.96	0.83 to 1.11	1.18	0.93 to 1.50
≥ 2	0.92	0.78 to 1.08	0.85	0.67 to 1.08	0.96	0.67 to 1.36
Year of diagnosis						
2001	1	Reference	1	Reference	1	Reference
2002	0.97	0.85 to 1.11	0.93	0.79 to 1.09	1.62	0.88 to 3.00
2003	1.08	0.95 to 1.23	1.06	0.92 to 1.23	1.70	0.90 to 3.22
2004	1.15	0.99 to 1.33	1.11	0.89 to 1.37	2.53	1.42 to 4.51
2005	1.14	0.99 to 1.31	0.94	0.76 to 1.16	3.52	2.00 to 6.18
2006	1.07	0.93 to 1.24	0.97	0.78 to 1.21	2.60	1.49 to 4.56
2007	1.24	1.07 to 1.44	1.04	0.84 to 1.28	3.82	2.17 to 6.73
2008	1.10	0.94 to 1.29	0.95	0.76 to 1.18	3.06	1.72 to 5.47

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; RR, relative risk.
* All variables in the table are adjusted for one another.

1.54) or tamoxifen (RR, 1.48; 95% CI, 1.18 to 1.86) relative to women with negative lymph nodes. Surgical procedure, chemotherapy, and radiation therapy were not associated with any endocrine therapy use in multivariable analyses.

Adjusted RRs for AI use compared with tamoxifen use among women age ≥ 55 years with no contraindications are listed in Appendix Table A1 (online only). Women age 65 to 74 years and ≥ 75 years were significantly less likely to use AIs than tamoxifen compared with women age 55 to 64 years (RR, 0.78; 95% CI, 0.60 to 1.00 and RR, 0.67; 95% CI, 0.46 to 0.97, respectively). Women with BMI ≥ 30.0 were more likely to use AIs than tamoxifen (RR, 1.40; 95% CI, 1.06 to 1.87), as were women diagnosed in 2004 or later; no other associations were statistically significant.

Discussion

Our results show that endocrine therapy, specifically AI use, for early-stage HR-positive breast cancer has increased since 2001. Furthermore, initiation of each type of therapy varies by patient characteristics; older women were least likely to begin endocrine therapy, whereas women with tumor sizes ≥ 1.0 cm and/or positive lymph nodes were most likely. Variation in initiation suggests that certain populations may have different preferences for treatment or may receive different recommendations for treatment from their providers, despite guidelines recommending adjuvant endocrine therapy for all women with HR-positive breast cancer.

Almost one third of women in our study diagnosed with breast cancer as recently as 2008 used no endocrine therapy. Lack of use may reflect patient choice, provider recommendations, and/or perceived recurrence risk. Almost 80% of these women had stage I tumors, and 90% had negative lymph nodes. Using Adjuvant! Online, a woman 65 years of age with average comorbidities, tumor size < 1.0 cm, and negative lymph nodes will reduce her recurrence risk by less than 10% and mortality risk by less than 1% if she uses adjuvant endocrine therapy.[19] Although tamoxifen or AI treatment could be beneficial in this case, the potential risks may outweigh the benefits. This follows NCCN guidelines, which make an exception for endocrine therapy treatment in women with tumors < 1 cm and negative lymph nodes.[2] A recently published study of discontinuation and adherence to adjuvant hormonal therapy found an even higher proportion of patients with stages I to III HR-positive disease (42% over all study years, 1996 to 2007) did not start therapy within 12 months after diagnosis, although this study did not evaluate initiation by tumor size or lymph node status.[16] These results should be verified using prospective data collection, given the possibility of discordance between administrative data and patient self-report.

Older women (age ≥ 65 years) were least likely to use any endocrine therapy, even after adjusting for potential confounders including comorbidities. This result is consistent with those of previous studies showing that older women are less likely to receive any cancer treatment at all, including adjuvant endocrine therapy.[12,20-22] The most likely explanation here is that the risks of treating elderly, frail patients largely outweigh the

benefits, and providers are unlikely to recommend treatment.[23,24] However, it is surprising that women between the ages of 65 and 74 years were less likely to receive any endocrine therapy. Differences in medical coverage among Medicare enrollees may play a role here. Medicare Part D, which covers oral cancer drugs, was not enacted until 2006, and even if women have Part D coverage, costs to patients may be higher if the drugs are not preferred by the health plan or cannot be obtained as generics.[25] Therefore, even though all women in our COMBO study population were enrolled in Group Health, prescription drug coverage likely differed among Medicare enrollees, and some may not have had drug coverage at all.

Older age was also the main characteristic associated with decreased AI initiation compared with tamoxifen initiation. Again, this may be related to Medicare prescription drug coverage, but it may also be explained by different adverse effect profiles. For example, older women are at increased risk for osteoporosis, and AIs further increase that risk[26,27]; therefore, some older women might be more likely to choose tamoxifen. However, other adverse effects, such as increased risk for deep vein thrombosis and stroke, could have influenced some women to begin AIs before tamoxifen. We excluded women with a history of conditions that may have influenced their choice of one drug over the other; however, the potential risk for adverse effects among the remaining women could have influenced their choice.

Women diagnosed with more severe disease (tumor size ≥ 1.0 cm or positive lymph nodes) were more likely to use endocrine therapy than women with smaller tumors or negative lymph nodes. These women were potentially at increased risk for breast cancer recurrence, which may have influenced their treatment preferences and/or provider recommendations. Interestingly, other treatment modalities (surgery, chemotherapy, and radiation) were not associated with endocrine therapy initiation. This is surprising, given that other analyses have suggested that women, especially older women, might be more likely to use endocrine therapy instead of more aggressive adjuvant chemotherapy.[10,28,29]

The rapid diffusion of AI use between 2001 and 2005 in our study, even before ASCO guidelines were updated to recommend them in 2004,[30] is consistent with findings of previous studies.[31] Studies show that AI use increased after the ATAC (Arimidex, Tamoxifen, Alone or in Combination) results were first presented at the San Antonio Breast Cancer Symposium in 2001[32,33] and continued to rise thereafter.[7-9] However, our study is the first to our knowledge to investigate diffusion beyond 2005, and we found little change in AI use after the ASCO guidelines[30] were published. In fact, AI use in our study decreased slightly after 2005. We speculate this may be because providers gained a better understanding of the potential risks of use and became more selective in their prescribing. In addition, our study showed that the proportion of women who used AIs from 2005 to 2008 was roughly equal to the proportion who used tamoxifen during the same time period. This finding suggests that in recent years, one drug was not necessarily preferred over the other. However, this contradicts evidence published

since 2005, which demonstrates greater benefits from AIs and supports the use of AIs over tamoxifen as first-line endocrine therapy.[6,34,35] Thus, we may expect use of AIs to increase and tamoxifen to decrease in future years.

Our primary study limitations are that we lacked information on patient preferences for treatment or provider recommendations. Additionally, we had no automated data on whether therapy was prescribed but not filled or number of coprescriptions (which may have affected initiation). We recognize the importance of these factors and their potential effects on treatment decision making. A small study of older adults with breast cancer showed that 29% (most of whom had early-stage disease) refused all or part of their treatment.[36] Thus, treatment refusal among older women may partially explain the proportion of women who used no endocrine therapy in our study. The COMBO study is currently abstracting data on reasons for no use, including whether tamoxifen or AIs were recommended and refused, whether therapy was prescribed, and adverse effects of tamoxifen and AI treatment. Although adverse effects are more often associated with treatment adherence, the potential risk for adverse effects may deter some women from starting endocrine therapy. These data will be important to evaluate in future analyses, particularly on discontinuation and adherence.

Our study also has several strengths. We were able to collect accurate, automated data on tamoxifen and AI use through the Group Health administrative pharmacy database. Automated pharmacy data enabled us to evaluate initiation of these drugs over many years within an integrated delivery system, in which disenrollment is uncommon, and prescription drug coverage is not a barrier for most women. Our results are fairly generalizable to women who receive treatment within a community setting (particularly other integrated delivery systems), because we included all women with early-stage breast cancer who would have been eligible for endocrine therapy; this included women with a range of ages and comorbidities.

Our results show that tamoxifen and AI initiation are not independent of patient demographics and tumor characteristics. Differences in age, tumor size, and lymph node status may

be explained by patient and provider preferences, potential adverse effect profiles, and changes in Medicare prescription coverage. Overall initiation (70%) was lower than expected for an insured population and strongly related to older age and early-stage cancers. We need a better understanding of the factors that affect patient and provider decision making regarding these drugs, particularly when treating older women with early-stage breast cancer.

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