Use of hormonal therapy in senior breast cancer patients treated with or without radiotherapy

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ABSTRACT

Purpose

Breast cancer treatment guidelines state that radiotherapy (RT) can reasonably be omitted in selected women 70 years of age and older if they take adjuvant endocrine therapy (AET) for 5 years. We aimed to assess persistence and adherence to AET in women 70 years of age and older, and to examine differences between RT receivers and non-receivers.

Methods

Quebec's medical service and pharmacy claims databases were used to identify seniors undergoing breast-conserving surgery (1998–2005) and initiating AET. Cox proportional hazards models were used to identify predictors of AET non-persistence.

Results

Of 3180 women who initiated AET (mean age: 77.5 years), 28% did not receive RT. During the subsequent 5 years, 32% of patients who initiated AET did not persist, 2% filled only a single prescription, and 22% switched medications. Compared with RT receivers, non-receivers discontinued more often (35.5% vs. 30.1%) and earlier (1.4 years vs. 1.6 years). They also became nonadherent earlier (medication possession ratio < 80% at year 3 vs. at year 5). Predictors of non-persistence included RT omission [hazard ratio (HR): 1.26; 95% confidence interval (CI): 1.09 to 1.46]; age (HR per decade increase: 1.15; 95% CI: 1.01 to 1.31); new medications (HR per medication: 1.01; 95% CI: 1.00 to 1.02); and hospitalizations during AET, (HR per hospitalization: 1.08; 95% CI: 1.05 to 1.11). In a subanalysis of RT non-receivers, significant predictors included hospitalizations (HR: 1.07; 95% CI: 1.02 to 1.12) and medications at AET start (HR: 0.94; 95% CI: 0.91 to 0.97).

Conclusions

Suboptimal use of AET was observed in at least one third of women. In RT non-receivers, AET use was worse than it was in RT receivers. Initiation of new medications and hospitalizations increased the risk of non-persistence.

KEY WORDS

Adjuvant endocrine therapy, persistence, adherence, radiotherapy, breast cancer, seniors

1. INTRODUCTION

The National Comprehensive Cancer Network clinical practice guidelines state that, after breast-conserving surgery (BCS), women 70 years of age and older with early-stage breast cancer can forego radiotherapy (RT) if they receive adjuvant endocrine therapy (AET) for 5 years^{1–3}. When taken for 5 or more years, AET represents a low-risk, easily administered treatment that constitutes an ideal strategy for reducing the impact of disease in women with hormone receptor-positive breast cancer⁴. However, the effectiveness of AET depends on optimal AET use, which has at least two dimensions: persistence (continuing to take the medication for as long as prescribed) and adherence (taking the medication as prescribed)⁵. Deviations from optimal AET use may curb its expected preventive and curative benefits⁶, and prior research has shown that women at the extremes of age range—that is, those less than 40 years or more than 75 years of age—are particularly likely to be non-persistent and nonadherent⁷.

The decision to omit RT is often based on the assumption that patients 70 years of age and older will be taking their AET according to guidelines and accruing maximal benefit from it. However, little is known about actual AET use in this age group. Approximately 30% of incident breast cancer cases

occur after the age of 70 years, and elderly women are the fastest-growing segment of the population⁸. Understanding the patterns and predictors of AET use in this group might allow clinicians to determine which women can and cannot safely forego RT without incurring an avoidably high risk of recurrence and decreased overall survival⁹.

Senior residents in Quebec are eligible for enrollment in the public prescription drug insurance plan. The provincial health insurance agency, RAMQ, keeps administrative databases containing records of the prescription drug and medical services use by its beneficiaries. When linked, those databases provide a unique opportunity to study patterns and to identify predictors relating to health care and medication access and use that are less likely to be confounded by socioeconomic inequities^{10,11}. The purposes of the present study were to assess AET use (in terms of rates and predictors of persistence and adherence) over 5 years in women 70 years of age and older with early-stage breast cancer treated with BCS, and to examine differences in AET use among patients in Quebec who had and had not received RT.

2. METHODS

2.1 Setting and Data Sources

The source population consisted of senior residents living in Quebec and enrolled in the public health and prescription drug insurance plan. Data for the study were available from 1997 to 2007 and were acquired through anonymous linkage of these administrative databases:

- The RAMQ medical services database, containing records of fee-for-service claims for physician visits¹²
- The RAMQ prescription claims database¹²
- The RAMQ registrant database, containing demographic information (name, sex, dates of birth and death, postal code, and material deprivation index)
- The Quebec Ministry of Health and Social Services discharge abstract database (MED-ÉCHO)¹², which captures administrative and clinical information on nearly all hospital discharges in the province

Quebec's material deprivation index, provided to RAMQ by the National Institute of Public Health of Quebec¹³, is calculated using data from the Canadian census¹⁴. Ethics approval for the study was obtained from the Research Ethics Office at McGill University and the provincial Access to Information Office.

2.2 Design and Study Population

Our historical prospective cohort study included women 70 years of age and older who were treated with BCS between January 1, 1998, and December 31,

2005, and who initiated AET within 1 year of BCS. Incident BCS procedures were identified using RAMQ procedure codes in MED-ÉCHO (Table I) and primary diagnostic codes from the International Classification of Diseases, 9th revision, adapted for Quebec (ICD-9-QC)¹⁵ corresponding to localized tumour topography (Table II)¹⁶ and confirmed through Quebec's tumour registry. Initiation of AET was ascertained using prescription claims corresponding to AET drugs (Table III).

To ensure that at least 1 year of medical service history after BCS was available for all patients, women who became ineligible for medical insurance in the year after BCS were excluded. The date of BCS was considered the index date. Women who underwent mastectomy (Table II) within 1 year of BCS or who received chemotherapy within 4 months of BCS (Table I) were excluded from the study on the premise that they must have had more advanced breast cancer, making them ineligible for RT exclusion. It was assumed that women who initiated AET had an estrogen receptor-positive breast cancer¹⁷.

2.3 Assessment of Patient Characteristics

Patient characteristics were assessed for the year before BCS and during the time on AET. Age at diagnosis was obtained from the registrant database. The comorbidity profile of each patient was assessed using the Charlson comorbidity index (CCI), calculated using the enhanced ICD-9 coding algorithm published by Quan *et al.*¹⁸ for use with administrative databases.

TABLE I Régie de l'assurance maladie du Québec procedure codes

<i>Procedure</i>	<i>Procedure codes</i>
Breast-conserving surgery ^a	01174, 01175, 01201, 01204, 01205, 01228, 01229
Axillary lymph node dissection	01228, 01231, 01232
Radiotherapy treatment	08520, 08519, 09131, 09133, 09134, 09141, 09143, 09144, 09146, 09172, 08507, 08508, 08509, 08511, 08553, 08564, 08518
Simple or modified radical mastectomy	01230, 01231, 01232
Chemotherapy treatment	0734

^a Partial excision of breast or lumpectomy.

TABLE II International Classification of Diseases, 9th revision, adapted for Quebec

<i>Condition</i>	<i>Code</i>	<i>Description</i>
Localized or regional disease	174	Malignant neoplasm of female breast

TABLE III Drug codes

Drug	ID type ^a	ID numbers ^b
Adjuvant endocrine inhibitor		
Tamoxifen	DIN	2088428, 2237460, 2063778, 812390, 2237596, 2084430, 851965, 851973, 2237459, 2089858, 812404, 2237597, 2296748, 2048485, 2084422, 2063751, 2296721, 1926624, 1926632, 1982281, 839353, 810444, 2048477, 657360, 419052, 1982273, 810452, 638706, 1951947, 657379, 1951939, 839361
Letrozole	DIN	2322315, 2309114, 2347997, 2344815, 2348969, 2338459, 2231384
Exemestane	DIN	2242705
Anastrozole	DIN	2224135
Anticonvulsant	AHFS	281212XX, 281220XX, 281292XX
Antidepressant	AHFS	28160416, 28160420
Benzodiazepine	AHFS	282408XX, 281208XX
Antipsychotic	AHFS	28160804, 28160808, 28160824, 28160832, 28160892, 282800XX, 289200XX
Opioid	AHFS	280808XX, 280812XX

^a Drug identification number (DIN) or American Hospital Formulary Service (AHFS).

^b An “X” in AHFS numbers means any digit (that is, only the first 6 digits are considered).

We adjusted the algorithm by removing the ICD-9 codes for the study condition (Table II), given that all women in the cohort had breast cancer by default. The residence of each woman was classified as rural if the second digit of her postal code was 0; otherwise, it was classified as urban, in accordance with Canada Post Corporation delivery service¹⁹.

2.4 Assessment of Patterns of Health Service and Medication Use

The number and types of prescription medications dispensed to members of the cohort were assessed using the RAMQ prescription claims database at baseline (3 months before AET initiation) and from the date of AET initiation onward, using drug codes from the American Hospital Formulary Service²⁰. Specifically, we characterized the cohort’s use of anticonvulsants, antidepressants, benzodiazepines, antipsychotics, and opioids (Table III). An “AET

switch” was defined as the dispensing of an AET (tamoxifen, letrozole, exemestane, or anastrozole) different from the one originally initiated during follow-up. Using MED-ÉCHO, the number of hospital admissions was assessed from the date of AET initiation for as long as the patient remained on AET. Receipt of RT was ascertained from the presence of claims in the RAMQ medical services database for RAMQ procedure codes (Table I) corresponding to treatment with RT and assessed up to 1 year after diagnosis, per guideline recommendations.

2.5 Assessment of Non-persistence

We considered that patients had become non-persistent to AET (that is, they had discontinued it) if 60 days had elapsed without a refill since the prior prescription. The 60-day time period was chosen because nearly all prescriptions (94.5%) were dispensed for 30 days. In Quebec, pharmacists have an incentive to split a 90-day prescription into three 30-day supplies so that they receive three dispensing fees, for a grand total that is higher than the fee they would receive if they dispensed only once²¹.

2.6 Assessment of Adherence

Adherence was measured using the medication possession ratio (MPR), defined as the percentage of eligible days in the 5-year follow-up period during which a woman had a supply of AET, as ascertained by the presence of prescription claims^{22–25}. We adjusted the MPR by accounting for overlaps (early refills) and gaps (late refills). If an overlap was noted in the supply days of two prescriptions, the days of overlap were added to the end of the second prescription. If a gap was noted between two prescriptions, those days were not included in the count of days of AET supply. We descriptively report the mean annual MPR and the proportion of patients who maintained a MPR of 80% or higher per year. Although patients are often assumed to be “adherent,” no clinically significant adherence threshold for AET has been established for breast cancer patients to date^{7,25–29}. However, adherence of less than 80% has been shown to be associated with poorer survival⁹.

2.7 Follow-Up and Censoring

Women were followed for 5 years from the date of AET initiation. Censoring occurred if a woman did not experience the outcome before the end of the observation period (5 years), if she died or was lost to follow-up, or if December 31, 2007, was reached (end of available data) before the end of the 5-year follow-up period, whichever came first. Loss to follow-up most commonly resulted when patients ceased to be eligible for drug or medical insurance for various reasons (moving out of the province, for instance).

2.8 Statistical Analysis

We first examined differences in baseline characteristics between the women who had and had not received RT. Those analyses used chi-square or two-sample *t*-tests (for categorical and continuous variables respectively). We used Cox proportional hazards regression to evaluate the crude and adjusted associations between predictors and non-persistence (time to first discontinuation) and to estimate non-persistence hazard ratios (HRs) and 95% confidence intervals (CIs). Subsequently, a stepwise selection of significant variables was performed, keeping age and CCI score in the model.

Women entered the cohort dynamically and contributed person-years at risk until they experienced the outcome or were censored. Collinearity between variables was assessed using a Pearson correlation matrix. No variables were excluded from the model because of correlations with other variables (Pearson coefficient of ≥ 0.5). Interaction terms between time to discontinuation and number of drugs at baseline, number of new drugs started, and admissions while on AET were introduced to the model one at a time, but none of those variables was found to be significant.

Kaplan–Meier curves were constructed to compare time to AET non-persistence (discontinuation) between RT receivers and non-receivers. In a secondary analysis, we examined predictors of non-persistence in the sub-cohort of women who did not receive RT. All *p* values are for two-tailed tests, with statistical significance defined as $p \leq 0.05$. The SAS software application (version 9.3; SAS Institute, Cary, NC, U.S.A.) was used for all analyses.

3. RESULTS

3.1 Cohort Characteristics

Between January 1, 1998, and December 31, 2005, 3573 women 70 years of age and older who underwent BCS for localized breast cancer in Quebec were alive, insured, and had initiated AET within 1 year after their surgery. Of those women, 168 (4.7%) received chemotherapy and 225 (6.3%) underwent mastectomy within 1 year after BCS and were thus excluded. The remaining 3180 women (mean age: 77 ± 5.2 years) constituted the study population.

In the study cohort, 28% had not received RT, 84% lived in urban areas, 81% started AET with tamoxifen (as opposed to an aromatase inhibitor), 61% had no major comorbidities (CCI score of 0), and only 19% were experiencing severe material deprivation (Table IV). Examination of selected medications revealed that 46% of the cohort had used opioids, 41% had used benzodiazepines, and 8% had used antidepressants in the 3 months before AET initiation. When compared with RT receivers, RT non-receivers were generally older (mean age: 80.9 ± 5.7 years vs. 75.9 ± 4.3 years).

3.2 Descriptive Outcomes

Mean time to AET initiation after BCS was 25 days (range: 14–43 days; Table V). During follow-up, 22% switched AET medications. Overall, 37% of women were censored: 8% died, 4% were lost to follow-up, and data availability ended for 25% at some point before 5 years of follow-up had elapsed. The median follow-up time was 3.7 years (interquartile range: 2.1–5 years).

3.3 Patterns and Predictors of AET Non-persistence

Overall, 32% of women discontinued AET, with 2% of them filling just 1 prescription. Some women discontinued AET permanently (20%); others had multiple initiations and discontinuations (12%). The overall rate of discontinuation was 9.5 episodes per 100 person-years. Compared with RT receivers, non-receivers discontinued more often (36% vs. 30%). More RT non-receivers (2.8% vs. 1.3% of RT receivers) filled just 1 prescription before discontinuing. Compared with RT receivers, RT non-receivers had a higher rate of discontinuation (11.7 episodes vs. 8.7 episodes per 100 person-years). In addition, RT non-receivers discontinued earlier than RT receivers did (median time to first discontinuation: 1.4 years vs. 1.6 years).

On multivariate analysis (Table VI), predictors of AET non-persistence included not having received RT (HR: 1.26; 95% CI: 1.09 to 1.46); age, per 10-year increase (HR: 1.15; 95% CI: 1.01 to 1.31); number of new prescriptions initiated over 5 years (HR: 1.01; 95% CI: 1.00 to 1.02); and hospital admissions over 5 years (HR: 1.08; 95% CI: 1.05 to 1.11). In other words, the risk of discontinuing AET increased by 1% for every additional medication added and by 8% for every additional hospital admission during the 5-year period. On the other hand, rural residence (HR: 0.78; 95% CI: 0.65 to 0.93) and medications at the start of AET (HR: 0.93; 95% CI: 0.92 to 0.95) lowered the risk.

In a secondary analysis of RT non-receivers exclusively, hospital admissions during AET increased the risk for discontinuation (HR: 1.07; 95% CI: 1.02 to 1.12), and an increasing number of medications used at the start of AET decreased the risk (HR: 0.94; 95% CI: 0.91 to 0.97; Table VII). Compared with RT receivers, RT non-receivers became non-persistent significantly faster (Figure 1).

3.4 Patterns of AET Adherence

Over time, the percentage of women considered adherent (Figure 2) and the mean annual MPR (Figure 3) gradually declined for both RT receivers and RT non-receivers, without a considerable difference in the rate of decline between the two groups. However, the mean annual MPR dropped below 80% much earlier for RT non-receivers (year 3) than for RT receivers (year 5, Figure 3).

TABLE IV Demographic and clinical characteristics of the study patients

Characteristic	Received radiotherapy		Overall cohort	p Value ^a
	Yes	No		
Patients (n)	2274	906	3180	
Mean age (years)	75.9±4.3	80.9±5.7	77.4±5.2	<0.0001
Period of diagnosis [n (%)]				0.001
1998–1999	570 (25.1)	281 (31.0)	851 (26.8)	
2000–2002	869 (38.2)	346 (38.2)	1215 (38.2)	
2003–2005	835 (36.7)	279 (30.8)	1114 (35.0)	
Initially assigned AET [n (%)]				0.004
Tamoxifen	1823 (80.2)	765 (84.4)	2588 (81.4)	
Aromatase inhibitor	451 (19.8)	141 (15.6)	592 (18.6)	
CCI score [n (%)] ^b				0.016
0	1426 (62.7)	527 (58.2)	1953 (61.4)	
1–2	742 (32.6)	319 (35.2)	1061 (33.4)	
≥3	106 (4.7)	60 (6.6)	166 (5.2)	
MDI score [n (%)] ^c				0.030
Q1 (most privileged)	447 (19.7)	176 (19.4)	623 (19.6)	
Q2	409 (18.0)	135 (14.9)	544 (17.1)	
Q3	434 (19.1)	166 (18.3)	600 (18.9)	
Q4	479 (21.1)	181 (20.0)	660 (20.8)	
Q5 (most deprived)	413 (18.2)	196 (21.6)	609 (19.2)	
Not available	92 (4.0)	52 (5.7)	144 (4.5)	
Residence [n (%)] ^d				0.738
Rural	363 (16.0)	149 (16.4)	512 (16.1)	
Urban	1911 (84.0)	757 (83.6)	2668 (83.9)	
Prescription medication				
Selected types [n (%)] ^e				
Anticonvulsant	39 (1.7)	20 (2.2)	59 (1.9)	0.353
Antidepressant	166 (7.3)	77 (8.5)	243 (7.6)	0.251
Benzodiazepine	933 (41.0)	381 (42.1)	1314 (41.3)	0.597
Antipsychotic	63 (2.8)	47 (5.2)	110 (3.5)	0.001
Opioid	1079 (47.4)	383 (42.3)	1462 (46.0)	0.008
Mean concomitant (n) ^e	5.9±3.6	6.5±4.1	6.1±3.7	<0.0001
Mean new starts (n) ^f	13.5±8.0	13.0±8.3	13.3±8.1	0.172
Mean hospital admissions during AET (n) ^f	2.0±2.1	2.2±2.2	2.0±2.1	<0.0001

^a Differences by radiotherapy status were evaluated by chi-square or two-sample *t*-tests for categorical or continuous variables respectively.

^b Assessed using the enhanced ICD-9 coding algorithm for medical service databases by excluding ICD-9 codes for breast cancer (because all women in the cohort had that condition by default).

^c Measures deprivation of the goods and conveniences that are part of modern life. Not available for smaller towns and rural communities.

^d Based on second digit of the patient's postal code (0, rural; 1–9, urban). Assessed in the year before initiation of adjuvant endocrine therapy.

^e Assessed in the 3 months before initiation of adjuvant endocrine therapy.

^f Assessed in the 5 years after initiation of adjuvant endocrine therapy.

AET = adjuvant endocrine therapy; CCI = Charlson comorbidity index; MDI = material deprivation index.

4. DISCUSSION

In this prospective historical study of Quebec women 70 years of age and older treated for early-stage breast cancer with BCS, we demonstrated that 5-year persistence and adherence were suboptimal in at least

one third of patients. Women who did not receive RT discontinued AET more often and earlier. In addition, those women became non-adherent earlier than did the RT receivers. Predictors of non-persistence included age, new prescription medications initiated, and hospital admissions during the 5 years of AET. Rural

TABLE V Descriptive outcomes over 5 years

Outcome	Received radiotherapy		Overall cohort (N=3180)
	Yes (n=2274)	No (n=906)	
Adjuvant endocrine therapy (AET) [n (%)]			
Prescriptions filled over 5 years			
1 Only	29 (1.3)	25 (2.8)	54 (1.7)
>1	2245 (98.7)	881 (97.2)	3126 (98.3)
Switched medication	532 (23.4)	154 (17.0)	686 (21.6)
Persisted with therapy for 5 years	751 (33.0)	250 (27.6)	1001 (31.5)
Discontinued therapy	685 (30.1)	322 (35.5)	1007 (31.7)
AET discontinuation			
Rate (n/100 person-years)	8.7	11.7	9.5
Permanent [n (%)]	432 (19.0)	202 (22.3)	634 (19.9)
Re-initiated [n (%)]	253 (11.1)	120 (13.2)	373 (11.7)
Re-discontinued [n (%)]	119 (5.2)	60 (6.6)	179 (5.6)
Died [n (%)]	151 (6.6)	108 (11.9)	259 (8.1)
Lost to follow-up [n (%)] ^a	51 (2.2)	71 (7.8)	122 (3.8)
Reached study end (Dec 31, 2007) before end of 5 year period [n (%)]	636 (28.0)	155 (17.1)	791 (24.9)
Time			
To AET initiation (days)			
Median	26.0	22.0	25.0
IRQ	15–46	12–39	14–43
Follow-up (years) ^b			
Median	4.0	3.1	3.7
IRQ	2.3–5	1.6–5	2.1–5
Observation (years) ^c			
Median	5.0	4.4	4.9
IRQ	3.3–5	2.6–5	3.1–5
To first discontinuation (years)			
Median	1.6	1.4	1.5
Range	0.5–3.6	0.4–2.9	0.5–3.4
5-Year MPR [n (%)] ^d			
Overall	1141 (50.2)	395 (43.6)	1536 (48.3)
With mean MPR ≥80%	895 (78.4)	300 (75.9)	1195 (77.8)
5-Year mean MPR ^d	0.8±0.3	0.8±0.3	0.8±0.3

^a Medical or public drug insurance ended.^b From date of AET initiation and to date of censoring.^c During which patient had continuous drug insurance.^d Calculated only for patients with 5 years of follow-up.

IRQ = interquartile range; MPR = medication possession ratio.

residence and number of concomitant medications at AET initiation lowered the risk of non-persistence.

The high discontinuation rate in this cohort was not surprising. Several studies have observed discontinuation rates ranging between 30% and 50% among women on AET^{6,7,9,30,31}. Older women are more difficult to recruit and follow, and most studies of patients 65 years of age and older therefore have smaller sample sizes^{6,25,27,28,30,32–34}, include women with advanced breast cancer^{30,32,33}, or fail to achieve 5 years of follow-up^{7,26,32}. In addition, almost no

studies have evaluated the persistence and adherence to AET specifically in women 70 years of age and older who forgo RT according to guidelines. Several studies found older age to be a predictor of early AET discontinuation^{6,7}, but that finding has received little attention. Seniors with cancer have complex comorbidities³⁵ and tend to be more socially isolated³⁶, to have low accrual to clinical trials³⁷, and to be less likely to receive treatment because of their age³⁸. Our study focused exclusively on women 70 years of age and older with early-stage cancer, in the context of

TABLE VI Predictors of time to first discontinuation

Predictor	Cox analysis								
	Univariate			Multivariate ^a			Reduced multivariate ^b		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Age (per 10-year increase)	1.20	1.07 to 1.03	0.002	1.16	1.01 to 1.32	0.031	1.15	1.01 to 1.31	0.039
Initially assigned AET									
Tamoxifen	Reference			Reference					
Aromatase inhibitor	0.81	0.67 to 0.98	0.027	0.88	0.72 to 1.08	0.224			
CCI score									
0	Reference			Reference			Reference		
1–2	0.95	0.83 to 1.09	0.485	0.98	0.85 to 1.13	0.774	0.98	0.85 to 1.12	0.729
≥3	1.19	0.91 to 1.56	0.207	1.24	0.93 to 1.64	0.137	1.23	0.93 to 1.62	0.151
Residence									
Rural	0.80	0.67 to 0.95	0.013	0.80	0.66 to 0.96	0.019	0.78	0.65 to 0.93	0.006
Urban	Reference			Reference			Reference		
Prescription medication									
Selected types									
Anticonvulsant	1.07	0.67 to 1.71	0.769	1.22	0.76 to 1.96	0.412			
No anticonvulsant	Reference			Reference					
Antidepressant	0.98	0.77 to 1.25	0.894	1.15	0.89 to 1.48	0.280			
No antidepressant	Reference			Reference					
Benzodiazepine	0.98	0.87 to 1.11	0.763	1.10	0.96 to 1.26	0.164			
No benzodiazepine	Reference			Reference					
Antipsychotic	0.94	0.65 to 1.35	0.731	0.95	0.65 to 1.38	0.779			
No antipsychotic	Reference			Reference					
Opioid	0.91	0.81 to 1.03	0.151	1.00	0.88 to 1.13	0.958			
No opioid	Reference			Reference					
Concomitant	0.96	0.94 to 0.98	<0.0001	0.93	0.91 to 0.95	<0.0001	0.93	0.92 to 0.95	<0.0001
New start	1.01	1.01 to 1.02	0.000	1.01	1.00 to 1.02	0.006	1.01	1.00 to 1.02	0.004
Radiotherapy receipt									
Yes	Reference			Reference			Reference		
No	1.33	1.16 to 1.52	<0.0001	1.26	1.09 to 1.46	0.002	1.26	1.09 to 1.46	0.002
Hospital admissions during AET treatment	1.08	1.06 to 1.11	<0.0001	1.08	1.05 to 1.11	<0.0001	1.08	1.05 to 1.11	<0.0001

^a Adjusted for period of diagnosis and material deprivation index in addition to all other factors presented in the table.

^b Full model reduced by stepwise selection.

HR = hazard ratio; CI = confidence interval; AET = adjuvant endocrine therapy; CCI = Charlson comorbidity index.

the 2005 National Comprehensive Cancer Network guideline¹, and captured nearly all incident patients meeting that description who initiated AET in Quebec.

Omitting RT after BCS is often based on the assumption that patients will be taking their AET as prescribed and for as long as prescribed. However, as did other studies, our study found that, compared with RT receivers, RT non-receivers were discontinuing more often (35.5% vs. 30.1%) and earlier (1.4 years vs. 1.6 years)^{7,27}. That finding is concerning, because shorter durations of AET have been associated with decreased overall survival. In relation to AET completion of only 2.4 years, McCowan *et al.*⁹ reported a HR for mortality of 1.59 (95% CI: 1.14 to

2.21). Haque *et al.*³⁹ demonstrated an approximately 50% reduction in the risk of subsequent breast cancer for women with the highest adherence to AET. We found that approximately 2.0% of patients filled only a single AET prescription and that 22% switched medications. Early discontinuation and a high frequency of switches might be related to treatment toxicities (in addition to other factors). Unfortunately, few studies have reported on tolerance of AET outside of clinical trials^{40,41}.

It was not surprising that, in our study, the addition of new medications and hospitalizations over time affected persistence with AET. Consequences of an increasing number of medications over time

TABLE VII Predictors of time to first discontinuation in radiotherapy non-receivers (N=906)

Predictor	Cox analysis								
	Univariate			Multivariate ^a			Reduced multivariate ^b		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Age (per 10-year increase)	1.01	0.91 to 1.33	0.328	1.14	0.94 to 1.40	0.192	1.15	0.95 to 1.40	0.160
Initially assigned AET									
Tamoxifen	Reference			Reference					
Aromatase inhibitor	0.90	0.65 to 1.25	0.531	0.93	0.64 to 1.33	0.675			
CCI score									
0	Reference			Reference			Reference		
1–2	0.86	0.68 to 1.09	0.209	0.94	0.73 to 1.20	0.597	0.92	0.72 to 1.17	0.493
≥3	1.04	0.66 to 1.63	0.874	1.21	0.76 to 1.94	0.430	1.22	0.77 to 1.93	0.402
Residence									
Rural	0.90	0.66 to 1.21	0.470	0.85	0.62 to 1.17	0.324			
Urban	Reference			Reference					
Prescription medications									
Selected types									
Anticonvulsant	1.20	0.57 to 2.54	0.637	1.38	0.64 to 2.98	0.419			
No anticonvulsant	Reference			Reference					
Antidepressant	0.23	0.76 to 0.48	0.228	0.91	0.57 to 1.47	0.709			
No antidepressant	Reference			Reference					
Benzodiazepine	1.02	0.81 to 1.27	0.886	1.15	0.91 to 1.46	0.236			
No benzodiazepine	Reference			Reference					
Antipsychotic	0.85	0.49 to 1.48	0.569	0.88	0.50 to 1.58	0.674			
No antipsychotic	Reference			Reference					
Opioid	0.94	0.75 to 1.17	0.563	1.03	0.82 to 1.29	0.832			
No opioid	Reference			Reference					
Concomitant	0.95	0.92 to 0.98	0.001	0.93	0.90 to 0.97	0.000	0.94	0.91 to 0.97	0.000
New start	1.00	0.99 to 1.01	0.966	1.00	0.99 to 1.02	0.89			
Hospital admissions during AET treatment	1.05	1.00 to 1.10	0.045	1.07	1.02 to 1.13	0.01	1.07	1.02 to 1.12	0.004

^a Adjusted for period of diagnosis and material deprivation index in addition to all other factors presented in the table.

^b Full model reduced by stepwise selection.

HR = hazard ratio; CI = confidence interval; AET = adjuvant endocrine therapy; CCI = Charlson comorbidity index.

include adverse drug effects⁴², and hospital admissions can result in an interruption to a woman's daily medication-tracking routine. In addition, such events might be indicators of a change in health status. Owusu *et al.*⁶ reported an association between an increase in CCI score and discontinuation of tamoxifen. Non-urban residence and concomitant medications at AET start lowered the risk of AET discontinuation. Better persistence in rural regions is probably indirectly associated with higher continuity of care. McCusker *et al.*⁴³ suggested that a different mode of organization of primary care practice in rural Quebec areas, characterized by physicians being affiliated with multiple sites and a greater integration of services, ensures access to, and continuity of, care—for example, because of the possibility of seeing the family doctor at an emergency visit. Concomitant medications

were associated with favourable persistence, most probably because of learned medication management habits⁴⁴. In a subanalysis of RT non-receivers (28% of the cohort), only hospitalizations during AET increased the risk for discontinuation; medications at AET start decreased the risk. Surprisingly, in neither group did the presence of comorbidities assessed using the CCI score influence persistence to AET.

The finding in our study that adherence progressively declined over time is also consistent with earlier observations³⁴. We found that, compared with RT receivers, the non-receivers became nonadherent much earlier (at year 3 vs. at year 5). That observation is concerning because adherence of less than 80% has been associated with poorer survival⁹ and an increased risk of subsequent breast cancer³⁹. It might therefore be helpful to identify interventions

FIGURE 1 Kaplan-Meier curves for persistence to adjuvant endocrine therapy among women 70 years of age and older with localized breast cancer who initiated treatment between 1998 and 2005, stratified by radiotherapy (RT) receipt.

FIGURE 2 Percentage of women 70 years and older attaining an annual medication possession ratio of 80% or greater, stratified by radiotherapy (RT) receipt.

that will specifically improve adherence in women not considered for RT. Several studies have suggested that strengthened physician-patient communication might result in improved patient perceptions and beliefs about the severity of disease or the effectiveness of therapy^{32,45}.

The joint Cancer and Leukemia Group B-Radiation Therapy Oncology Group trial showed statistically significant reductions of 3% and 8% over 5 and 10 years respectively in the rate of locoregional recurrence for women treated with BCS, RT, and AET, compared with women treated with BCS and AET alone^{2,3}. Although the absolute difference in risk reduction may not be clinically relevant in the context of competing morbidity caused by RT, the actual

FIGURE 3 Mean annual medication possession ratio (MPR) among women 70 years of age and older with localized breast cancer who initiated treatment between 1998 and 2005, stratified by radiotherapy (RT) receipt.

difference in risk reduction after adjusting for AET non-persistence and nonadherence outside of clinical trials (that is, in the general population) is unknown. Therefore, despite the practice guideline from the National Comprehensive Cancer Network¹, the omission of RT for women 70 years of age and older with early-stage breast cancer remains a matter of debate. Khan *et al.*⁴¹ suggested that omission of RT might be most appropriate in women more than 80 years of age (rather than in women 70 years of age and older), in women with comorbidities, and in women likely to be compliant with AET.

Further research is required to determine the long-term consequences of suboptimal AET use. Careful consideration both of prior characteristics and of events occurring during the course of therapy is necessary to select the right candidates for RT omission. Haque *et al.*³⁹ demonstrated a significant benefit of taking AET even if women took it irregularly. The ATLAS trial recently showed that continuing AET to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality, particularly after year 10⁴. Therefore, even if women might be struggling physically (from side effects) because of taking AET daily, encouragement to continue their AET for as long as possible may substantially reduce the risk of breast cancer recurrence.

Optimizing persistence is especially important for women not considered for RT. Identification of traceable and modifiable factors such as the ones presented in the present study could trigger appropriate preventive actions when reported in time to health care teams. For example, electronic medical records could be used for surveillance of vulnerable patients. Medication reconciliation could ensure that women continue to take their AET after discharge, and prioritization of new medications could minimize the pill burden.

At the same time, strengthening physician–patient communication has been considered essential³⁴ in improving AET use.

Our study has several limitations. As with other studies that use administrative claims, we were unable to assess physician- or patient-related reasons for nonadherence and discontinuation. We defined medication possession as the presence of medication refills rather than medication at hand. It was not possible to capture women who were prescribed but who did not initiate AET (“primary nonadherence”). In addition, comorbidity as measured by CCI score might underestimate the comorbidity burden in elderly patients using fewer services⁴⁶. Nevertheless, we were able to capture nearly all women who initiated AET during the study period in the province. In addition, the accuracy of the Quebec prescription database has previously been determined to be more than 99% for drug, dispense date, and duration²¹.

5. CONCLUSIONS

We demonstrated that long-term persistence and adherence to AET is suboptimal in at least one third of patients 70 years of age and older with early breast cancer. Use of AET among RT non-receivers was suboptimal and worse than that observed for RT receivers. Predictors of non-persistence included age, new prescription medications initiated, and hospital admissions during the 5 years of AET. Rural residence and greater number of concomitant medications at AET initiation lowered the risk of non-persistence. In the context of the ATLAS and Cancer and Leukemia Group B trials, efforts to optimize persistence and adherence to AET in senior women, especially those not considered for RT, might help to improve long-term treatment outcomes.

6. ACKNOWLEDGMENTS

The Canadian Cancer Society Research Institute, Canadian Institutes of Health Research, and the Fonds de recherche du Québec–Santé provided funding for this study.

7. CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no financial conflicts of interest.

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