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EPIDEMIOLOGY

Influence of adherence to adjuvant endocrine therapy on disease-free and overall survival: a population-based study in Catalonia, Spain

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Abstract

Objective To assess adherence to endocrine therapy and its relation to recurrence and mortality in women with early breast cancer.

Methods This is a retrospective cohort study in population-based cancer registries in two Catalonian provinces of Spain. We included all cases of invasive stage I–III breast cancer diagnosed from 2007 to 2011 and with follow-up to 2017. Adherence to endocrine therapy was measured by means of prescription refills. Patients were considered non-adherent if they filled less than 80% of their prescriptions. After collecting data from patients' medical records, we analysed clinical variables and their relation with adherence by means of logistic and Cox regression models.

Results The study included 2413 women. Five-year adherence was 84.5%; the greatest risk for non-adherence was in women under 50 years of age, diagnosed with stage III cancer, treated with neoadjuvant therapy, or receiving tamoxifen or sequential treatment. Adverse effects were associated with greater adherence. Non-adherence was significantly and independently associated with recurrence (hazard ratio [HR] 1.71, 95% confidence interval [CI] 1.16–2.51) and all-cause mortality (HR 2.11, 95% CI 1.62–2.74), after adjusting for age and tumour stage.

Conclusions Although non-adherence was relatively infrequent in this population-based study, its impact on the risk of recurrence and mortality was considerable. Clinicians should make efforts to ensure therapeutic adherence during clinical follow-up of women with breast cancer.

Keywords Adherence · Breast cancer · Recurrence · Mortality · Population-based cancer registry · Adjuvant endocrine therapy

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Introduction

Endocrine therapy (tamoxifen and/or aromatase inhibitors) is a cornerstone of adjuvant treatment for hormone receptor-positive breast cancer, as reflected in clinical practice guidelines [1, 2]. A wide body of research has demonstrated the benefit of these medications for reducing the risk of recurrence and subsequent mortality [3, 4]. The recommended duration of therapy is at least 5 years, with some authors arguing that the long-term risk of recurrence justifies treatment for up to 10 years as long as the balance between risk and benefit is favourable [5–7].

To obtain the good outcomes achieved in clinical trials, treatment adherence must be optimal; however, different studies in clinical practice settings have shown that this can be variable, with considerable room for improvement. One literature review reported that adherence ranged from 47 to

97% in women with breast cancer, and over 5 years mean adherence was just 56% [8]. The review highlighted the difficulties in comparing results obtained by heterogeneous assessment methods, which included patient self-report, medication electronic monitoring systems (MEMS), prescription refill data, and medicine possession ratio. Indeed, results can vary substantially depending on the indicators used, as one study demonstrated by comparing three techniques to measure adherence in a multicentre cohort study in women with breast cancer; observed adherence ranged from 74.7 to 94.7% [9], with prescription refill data showing the lowest (and probably most realistic) rates [10].

Previous studies using cancer registry data from Scotland [11, 12] and other data sources in the United States [13] have found an association between mortality and non-adherence to endocrine treatment. Other authors have pointed to the increased costs that non-adherence incurs on the health system [14]. Taken together, this research underlines the need to address adherence during patient evaluation and follow-up. The aim of this study is to assess the association that adherence to hormone treatment has with recurrence, mortality, and other related factors in women diagnosed with stage I–III breast cancer in two population-based cancer registries.

Methods

We designed a retrospective cohort study in two population-based cancer registries (Girona and Tarragona) in Catalonia, Spain (761,248 women, with an age adjusted incidence rate (world population) of 69.2 per 100,000 population) [15, 16]. Included patients were women diagnosed from 2007 to 2011 with incident, invasive, and ductal in situ breast cancer (stage I–III). All patients had a confirmed histological diagnosis, coded as C50.0–C50.9, D05.1, D05.7, or D05.9 according to the International Classification of Diseases, 10th revision (ICD-10). Staging followed the TNM 6th edition in patients diagnosed in 2007–2009 and the 7th edition in those diagnosed in 2010–2011.

Clinical records provided data on sociodemographic variables, tumour characteristics (stage of tumour at diagnosis, histological grade, multifocality and/or multicentricity of tumour), hormone receptor status, diagnosis and staging procedure, surgical treatment (sentinel node biopsy, type of breast surgery), axillary treatment (lymphadenectomy or sentinel lymph-node biopsy), postoperative complications, neoadjuvant and adjuvant treatment (chemotherapy and adjuvant endocrine therapy), and adjuvant radiotherapy. We used the hospital discharge minimum data set to assess comorbidity [17]. Review of patients' clinical records supplied further information on recurrence, defined as detection of a locoregional or distant breast cancer relapse or a second primary ipsilateral or contralateral breast tumour [18]. To standardise data collection from clinical records, we used a specific data extraction form, accompanied by instructions containing pertinent definitions. Two specially trained data managers reviewed the clinical records and collected the data. Recurrence was assessed over total patient follow-up, defined as the date of diagnosis to 31 December 2015 (end date of clinical history review). To determine vital status, we consulted the National Death Index linkage. Survival time was estimated from the date of first prescription of endocrine therapy to the date of death or to February 2017 (study end).

We defined adherence as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [19]. Thus, any change in drug between tamoxifen and aromatase inhibitor was considered a continuation of treatment. We estimated adherence as the proportion of days covered by a filled drug prescription over the treatment period (up to 5 years from the date of first prescription), deeming a cumulative adherence rate of 80% or more as satisfactory. The primary outcome in the analysis was disease-free survival, defined as survival from the date of first prescription of endocrine therapy to the date of the first evidence of recurrence or death from any cause. Patients lost to follow-up were censored. Overall survival was measured from the date of first prescription to death from any cause or censoring point at last follow-up. Data on endocrine therapy prescription refills for breast cancer were collected for the entire study period (2007–2017) from the community pharmacy database, which is mandatory for drug reimbursement in Catalonia.

To assess the factors related to adherence, we performed univariate analyses of categorical variables using a χ^2 test. An unconditional logistic regression model was fitted to estimate the odds ratios (OR) and 95% confidence intervals (CI) for mortality, recurrence, and adherence to oral hormone therapy, adjusting for clinical features. Survival analysis was by means of the Kaplan–Meier method, and adherence results were compared using the log-rank test. Cox multivariate analysis was used to calculate the hazard ratio (HR) and 95% CIs for recurrence and survival according to age at diagnosis, registry, year of diagnosis, and stage. Analyses were performed using SPSS (version 21) and R (version 2.14.0) software. The ethics committee of Bellvitge Hospital approved the study protocol on 25 April 2013.

Results

Figure 1 presents the flow chart for the study population. Of the 3819 women with invasive breast cancer, 2956 presented positive hormone receptors (ER+). Cases of stage IV cancer were excluded from this group, as were the 4.9% of women with no prescription record of endocrine therapy (probably because they were treated in the private

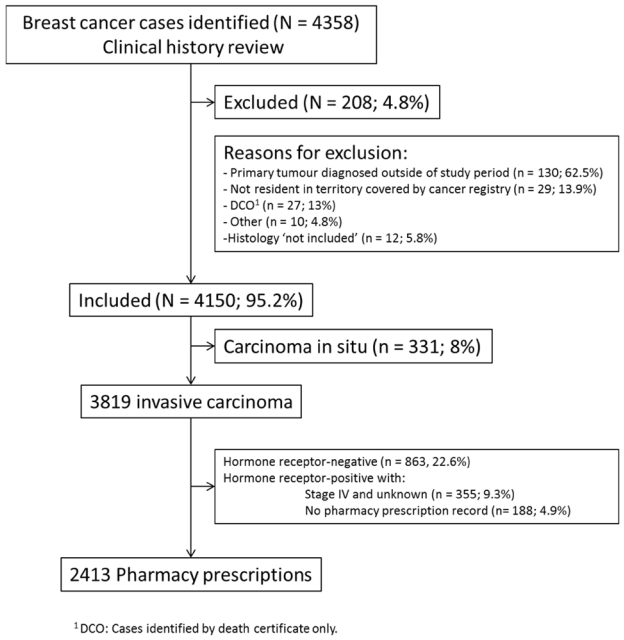

Fig. 1 Flowchart

healthcare system; this group did not show any differences in pretreatment clinical variables compared with the rest of the study population). Finally, 2413 women were included in the analysis. Median (interquartile range; IQR) follow-up time was 4.5 years (2.5) for recurrence and 6.6 years (2.5) for mortality.

Table 1 describes patients' characteristics, treatment regimens, and clinical outcomes according to adherence to endocrine therapy, taking 80% as the threshold to define adequate adherence. Cumulative adherence at 5 years was 84.5%. The lowest adherence rates were in women aged under 50 years, those with stage III tumours, those who received neoadjuvant treatment, and those receiving tamoxifen or sequential therapy. Likewise, women who experienced a relapse or died during follow-up showed lower adherence.

Table 2 presents the results from the logistic regression analysing adherence as an outcome variable and adjusting for age, tumour stage, and cancer registry. Comorbidity was not associated with adherence. The probability of adherence was higher in the presence of adverse effects, after adjusting for age and tumour stage.

The association that adherence had with recurrence and all-cause mortality was analysed by Cox regression (Table 3; Figs. 2, 3). The time from diagnosis to initiation of endocrine therapy was strongly associated with stage and treatment strategy, so we did not consider this variable for inclusion in the model to avoid over-adjustment. Non-adherence was associated with a significantly increased risk of recurrence (HR 1.71, 95% CI 1.16–2.51) and death (HR 2.11, 95% CI 1.62–2.74).

Discussion

The aim of adjuvant endocrine therapy in stage I–III cancer is to reduce the risk of recurrence, contralateral breast cancer, and cancer-related death. Achieving this clinical objective requires patients to adhere to their medical prescriptions. The difference between a prescribed treatment regimen and the treatment that patients actually receive can have an impact on the clinical benefits. The present study, in breast cancer patients included in two disease registries and followed for 5 years, shows that non-adherence to endocrine therapy increases the risk of recurrence by 71% and doubles the risk of all-cause mortality. These observational data corroborate similar results from clinical trials—an important finding given that prior research, using comparable definitions of adherence, follow-up times, and population-based registry data, has shown an association only with all-cause mortality, not with recurrence [11, 12]. Likewise, the Kaiser Permanente population study did not observe an association with recurrence, but only with mortality [13]. Another study, this time based on data from the Dutch cancer registry [20], observed a 26% lower risk of a breast cancer event in patients whose treatment adherence rates were over 80%. Our study uses population-based data to confirm that non-adherence has an impact on the risk of recurrence as well as all-cause mortality. These results underline the need to evaluate and reduce the risk of non-adherence during clinical follow-up of breast cancer patients.

Although our follow-up times differed for the outcomes of recurrence and death, we observed an impact on both variables over a relatively short period of time, even for a tumour site (like the breast) associated with high survival rates. A longer study period would permit a more precise evaluation of the impact of non-adherence to endocrine treatment on the evolution of breast cancer. The difference between risk of recurrence and death—in our study as well as in other observational research—is remarkable. To properly assess it, it is important to consider both the difference in follow-up (2 years longer follow-up for risk of death than for recurrence), and the fact that mortality data include all causes of death, not only breast cancer-specific deaths.

The adherence rates observed in our study (84.5%) are high relative to others using prescription refills as the adherence measure, including one multicentre cohort study in Barcelona that reported an adherence rate of 74.7% with this method [9]. Literature reviews have reported adherence rates of 47–97% over 5 years [10] or a mean adherence of 74% [8]. On the other hand, population-based studies in countries like the Netherlands observed rates that were much lower at 49% [21]. Thus, our study population

Table 1 Patient characteristics

	Adherence < 80%		Adherence ≥ 80%		Total ($N = 2413$)	*P* value
	N	% row	*N*	% row	*N*	
Study centre						
Registry 1	184	14.5	1083	85.5	1267	0.18
Registry 2	189	16.5	957	83.5	1146	
Age group (years)						
< 50	150	22.2	526	77.8	676	< 0.001*
50–69	146	13.0	976	87.0	1122	
> 69	77	12.5	538	87.5	615	
Stage at diagnosis						
Stage I	131	13.6	834	86.4	965	0.033*
Stage II	159	15.7	852	84.3	1011	
Stage III	83	19.0	354	81.0	437	
Number of comorbidities						
0 comorbidities	332	15.3	1838	84.7	2170	0.77
1 comorbidities	31	17.3	148	82.7	179	
2 + comorbidities	10	15.6	54	84.4	64	
Year of diagnosis						
2007	62	14.6	362	85.4	424	0.52
2008	64	15.1	359	84.9	423	
2009	94	17.9	432	82.1	526	
2010	79	15.2	442	84.8	521	
2011	74	14.3	445	85.7	519	
Surgery						
Yes	368	15.4	2014	84.6	2382	0.92
No	5	16.1	26	83.9	31	
Type of operation						
Conservative	258	14.9	1470	85.1	1728	0.26
Mastectomy	110	16.8	544	83.2	654	
Neoadjuvant therapy						
No	281	14.0	1725	86.0	2006	< 0.001*
Yes	92	22.6	315	77.4	407	
Type of adjuvant therapy						
HT	49	17.6	230	82.4	279	0.39
CHT	144	14.4	854	85.6	998	
RT	180	15.8	956	84.2	1136	
Type of hormone therapy						
Tamoxifen	120	23.0	402	77.0	522	< 0.001*
Aromatase inhibitors	153	11.3	1199	88.7	1352	
Sequential therapy	88	17.7	408	82.3	496	
Not available/other	12	27.9	31	72.1	43	
Adverse effects						
No	174	17.1	842	82.9	1016	0.053
Yes	199	14.2	1198	85.8	1397	
Exitus						
No	298	14.2	1797	85.8	2095	< 0.001*
Yes	75	23.6	243	76.4	318	
Recurrence						
No	339	15.0	1927	85.0	2266	0.008*
Yes	34	23.1	113	76.9	147	

CHT any combination of chemotherapy, radiotherapy, and hormone therapy; *HT* hormone therapy only; *RT* any combination of radiotherapy, hormone therapy and no chemotherapy

P value: χ^2 test. *Statistical significance set at $P < .05$

Table 2 Prognostic and therapeutic factors associated with adherence

	5-year adherence			
	N	(%) adh	ORa (95% CI)	*P* value
Age (years)				
< 50	676	77.8	1	< 0.001*
50–69	1122	87.0	1.85 (1.43–2.39)*	< 0.001*
> 69	615	87.5	1.99 (1.47–2.68)*	< 0.001*
Tumour stage at diagnosis				
I	965	86.4	1	0.11
II	1011	84.3	0.88 (0.69–1.14)	0.35
III	437	81.0	0.72 (0.53–0.98)*	0.036*
Number of comorbidities				
0	2170	84.7	1	0.34
1	179	82.7	0.75 (0.49–1.14)	0.17
2+	64	84.4	0.79 (0.40–1.59)	0.52
Surgery				
Yes	2382	84.5	1	0.65
No	31	83.9	0.80 (0.30–2.14)	0.65
Type of operation				
Conservative	1728	85.0	1	
Mastectomy	654	83.2	0.98 (0.74–1.28)	0.86
Neoadjuvant therapy				
No	2006	85.9	1	
Yes	407	77.4	0.67 (0.49–0.91)*	0.010*
Type of adjuvant therapy				
HT	279	82.4	1	0.015*
CHT	998	85.5	1.69 (1.15–2.49)*	0.008*
RT	1136	84.2	1.28 (0.89–1.84)	0.19
Type of hormone therapy				
Tamoxifen	522	77.0	1	0.001*
Aromatase inhibitors	1352	88.6	1.98 (1.38–2.84)*	< 0.001*
Sequential therapy	496	82.3	1.29 (0.93–1.79)	0.13
Other	43	72.1	0.78 (0.38–1.60)	0.50
Adverse effects[a]				
No	1016	82.9	1	
Yes	1397	85.7	1.33 (1.06–1.67)*	0.014*
Exitus				
No	2095	85.7	1	
Yes	318	76.4	0.45 (0.33–0.62)*	< 0.001*
Recurrence				
No	2266	85	1	
Yes	147	76.9	0.64 (0.42–0.97)*	0.036*

CHT any combination of chemotherapy, radiotherapy, and hormone therapy; *CI* confidence interval; *HT* hormone therapy only; *ORa* odds ratio, adjusted for centre, age group, stage; *RT* any combination of radiotherapy, hormone therapy, and no chemotherapy

*Statistical significance set at $P < .05$

[a]Based on physician report

Table 3 Cox regression for overall survival and recurrence by adherence

Outcome	Adherence *n* (%)		HR (95% CI)*	*P* value
	Yes (*N* = 2040)	No (*N* = 373)		
Exitus	243 (11.9)	75 (20.1)	2.11 (1.62–2.74)	< 0.001
Recurrence	113 (5.5)	34 (9.1)	1.71 (1.16–2.51)	0.007

CI confidence interval, *HR* hazard ratio

*Adjusted for registry, age, stage, and year of diagnosis

shows good adherence, considering the long-term treatment needed for endocrine therapy, though some studies have reported even higher rates [22]. This result is important when weighing the possibility of extending treatment time to 10 years, as recent evidence supports [5, 23, 24]. Our patients are likely more amenable to persisting in their treatment regimen beyond 5 years than patients in other countries where reported adherence is much lower.

Good adherence was associated with the presence of adverse effects, in contrast to findings from other studies [25]. Previous research [8, 26] has also shown mixed results with regard to this association; one possible explanation may reside in the type and intensity of the adverse effects studied. We did not differentiate between these, recording only the occurrence of effects as noted by clinicians. However, our results are consistent with those reported in a multicentre cohort study that also took place in Catalonia [9], which suggests that the association between adverse effects and adherence depends on the specific population under study. Qualitative evidence supports this possibility, showing that some women will persist in their treatment despite relevant adverse effects if they value the treatment objectives more than the harmful effects resulting from the therapy [27]. As reported elsewhere, comorbidity was not associated with adherence in our population. However, we did observe that tamoxifen was associated with a greater risk of non-adherence; this may be related to treatment in pre-menopausal women. Treatment with aromatase inhibitors was related to a higher level of adherence, while sequential therapy showed an intermediate level; these data are consistent with other studies [25, 28].

Overall, our data indicate that the profile of non-adherent patients is poorly defined. Indeed, neither our results nor those from the literature [8] do much to clarify which factors are strongly associated with non-adherence to endocrine treatment. However, they do show the impact that non-adherence may have on the relative risk of recurrence or death. Thus, clinicians should systematically evaluate this aspect during follow-up, especially in young women and those who have received a neoadjuvant treatment regimen.

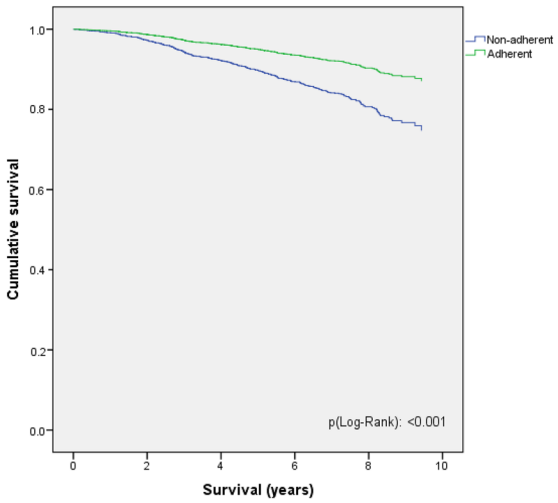

Fig. 2 Overall survival by adherence

N at Risk	at 2 years	4	6	8
Non adherent 373	344	314	213	63
Adherent 2040	1994	1915	1320	504

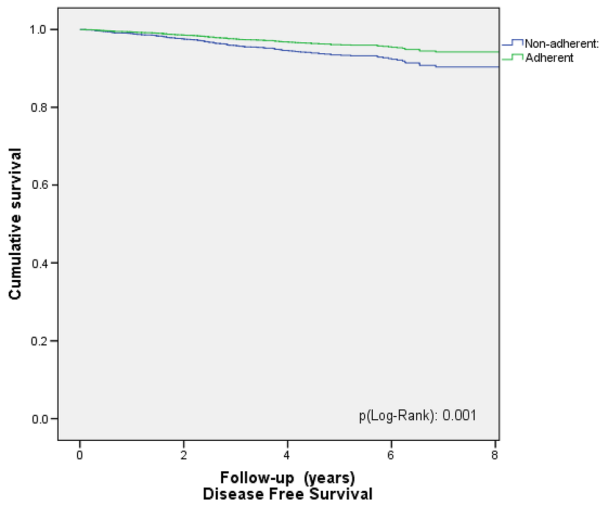

Fig. 3 Recurrence-free survival by adherence

N at Risk	at 2 years	4	6	8
Non adherent 373	313	183	63	2
Adherent 2040	1914	1267	457	28

Readers should keep in mind both the strengths and limitations of this study. Strengths include the population-based nature of the cancer registry data, which minimise the risk of selection bias that is inherent to participant samples in clinical trials. One indicator of the representativeness of the sample is the consistent percentage of women indicated for endocrine therapy relative to other population studies [29]. Other strengths are the long follow-up—close to 5 years—for the primary outcomes, and the use of the most reliable method available for assessing adherence [9, 10]. With regard to limitations, it is necessary to mention the 4.9% of the eligible study sample treated in the private sector, who did not fill their prescriptions in the public system. Although their clinical characteristics were no different from the patients who were analysed, they were excluded from the study. In addition, it was impossible to disaggregate mortality data by cause of death, so the focus of our analysis was on all-cause mortality, similarly to other similar studies [13, 14].

In conclusion, this study confirms the association between poor medication adherence and risk of breast cancer recurrence and all-cause mortality, observed previously

in population-based studies. Until now, the greatest risk of recurrence had been shown in participants of clinical trials [30], who are usually not representative of the population affected by breast cancer. The importance of reproducing trial results in population-based studies is very relevant in order to avoid underestimating the impact of adherence on the population [31]. One illustration of this is that clinical practice guidelines from the European Society of Medical Oncology (ESMO) do not mention the problem of adherence in their discussion of treatment indications [1]. Although only a minority of patients is non-adherent, failure to follow the treatment regimen as prescribed confers a high risk of recurrence and death. Moreover, these patients are frequently unaware of their non-adherence, as most missed doses are not intentional [32]. Both patients and clinicians may overlook the significance of these occasional slip-ups, even though they may easily result in adherence rates of less than 80%. Our results support the conclusion that treatment adherence is an important problem that has a substantial prognostic impact in women with breast cancer. Health professionals should systematically monitor this aspect during patient follow-up, applying corrective strategies to improve adherence and with it, patients' clinical outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not necessary in this study. The Ethics committee of Bellvitge Hospital approved the study protocol on 25 April 2013.

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