Original Study

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Identification of Subgroups of Early Breast Cancer Patients at High Risk of Nonadherence to Adjuvant Hormone Therapy: Results of an Italian Survey ☆

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Abstract

The aim of this study was the identification of subgroups of patients at higher risk of nonadherence to adjuvant hormone therapy for breast cancer. Using recursive partitioning and amalgamation (RECPAM) analysis, the highest risk was observed in the group of unmarried, employed women, or housewives. This result might be functional in designing tailored intervention studies aimed at improvement of adherence.

Background: Adherence to adjuvant endocrine therapy (HT) is suboptimal among breast cancer patients. A high rate of nonadherence might explain differences in survival between clinical trial and clinical practice. Tailored interventions aimed at improving adherence can only be implemented if subgroups of patients at higher risk of poor adherence are identified. Because no data are available for Italy, we undertook a large survey on adherence among women taking adjuvant HT for breast cancer. **Patients and Methods:** Patients were recruited from 10 cancer clinics in central Italy. All patients taking HT for at least 1 year were invited, during one of their follow-up visit, to fill a confidential questionnaire. The association of sociodemographic and clinical characteristics of participants with adherence was assessed using logistic regression. The RECPAM method was used to evaluate interactions among variables and to identify subgroups of patients at different risk of nonadherence. **Results:** A total of 939 patients joined the study and 18.6% of them were classified as nonadherers. Among possible predictors, only age, working status, and switching from tamoxifen to an aromatase inhibitor were predictive of nonadherence in multivariate analysis. RECPAM analysis led to the identification of 4 classes of patients with a different likelihood of nonadherence to therapy, the lowest being observed in retired women with a low level of education, the highest in the group of unmarried, employed women, or housewives. **Conclusion:** The identification of these subgroups of "real life" patients with a high prevalence of nonadherers might be functional in designing intervention studies aimed at improving adherence.

Identification of Patients at High Risk of Nonadherence to Therapy

Introduction

Nonadherence with drug therapy, in chronic conditions such as hypertension, diabetes mellitus, and postmenopausal osteoporosis has long been recognized as a major issue in health care, especially when self-administration of oral medicines is required.[1] Obviously, a less than optimal adherence to therapy might lead to worsening of the disease and this could be erroneously attributed by the clinician to the lack of activity of the drug.[2]

The availability of oral drugs for the treatment of cancer has increased in recent years, and it is estimated that approximately 25% of all anticancer agents currently in development will be available as oral formulations.[3] Largely, this phenomenon follows patient preferences, dictated by convenience.[4,5] Indeed, the avoidance of frequent trips to health care facilities, insertion of central venous lines, discomfort from infusion, and risks of associated adverse events, are not trivial advantages of oral cytotoxic therapies over traditional, intravenously administered ones. The downside to this is that health care professionals no longer directly monitor treatment administration, thus justifying the increased concern among oncologists about adherence of patients to oral treatment.[6]

The issue of adherence is especially important for the adjuvant endocrine therapy (HT) of early breast cancer, that relies on oral drugs administered for 5 or more years.[7] In fact, although perceived as strongly motivated by the life-threatening nature of their disease, women taking oral HT were found to be nonadherent to therapy in 15% to 50% of the cases, and more often in real life than in the clinical trial setting.[8] Moreover, low adherence to HT has been associated with shorter survival.[9] Because the rate of adherence appears to decrease with increasing duration of therapy,[10] this problem might become even more serious considering recent findings of further reduction of mortality from breast cancer with longer HT treatment.[11]

Interventions aimed at promoting adherence have been tested in several studies, but a recent review concluded that none of them were effective.[12] One of the reasons for these disappointing results is that interventions were quite generic and not adapted to the need of the patient.[13] It is, therefore, necessary to identify subgroups of patients with a higher risk of poor adherence to put tailored interventions in place.[1] It is well known that side effects of HT are main determinants of suboptimal adherence to HT. However, it has been found that the latter is a multidetermined behavior, being influenced by socioeconomic- and health care system-related factors among others,[6,14] it is likely that the characteristics of these patients differ from country to country. Because no data of this kind are available for Italy, we carried out a large survey on adherence among women taking adjuvant HT for breast cancer, and the results are reported herein.

Patients and Methods

Patients

Participants were recruited from 10 cancer clinics mainly located in central Italy and treating at least 100 breast cancer patients per year. Women taking adjuvant HT for breast cancer were identified among patients attending regular follow-up visits. All patients treated for at least 1 year were approached by their oncologists during one of the routine appointments and invited to join the survey. Patients were asked to anonymously complete a structured questionnaire and to drop it into a ballot box. Because it was not possible for the physician to verify if the questionnaire was completely filled, the number of respondents might be different for each question. The questionnaire included items regarding sociodemographic characteristics (age, marital status, number of children, area of residence, level of education, type of work) and medical history (year and type of surgery, radiation and chemotherapy, details on duration and type of hormone therapy).

To verify adherence, patients had to indicate how often they did not take the tablets during the past month and if the drug was taken at the same time each day. Other questions were included to assess reasons for not taking the medications (intentionally or unintentionally), beliefs about the effectiveness of the hormone therapy, number of medications taken each day, presence of a depressed mood. All the questions were posed in a nonjudgmental form. Patients who reported to have not regularly taken their medication at least 4 times during the past month were retained as nonadherers.

The study was approved by the independent Ethics Committees of participating institutions and written informed consent was obtained from each participant. The consent procedure was approved by the same Ethics Committees.

Statistical Analysis

Prevalence of nonadherence to therapy according to patient characteristics was determined and the association with each covariate was expressed in terms of unadjusted odds ratio (OR) with the 95% confidence interval (CI). A multiple logistic regression was used to identify characteristics independently associated with nonadherence to therapy. Covariates resulting as statistically significant in univariate analysis were introduced in the final model. The recursive partitioning and amalgamation (RECPAM) tree-based methods was used to evaluate interactions among the different variables and to identify distinct and homogeneous subgroups of patients with different risk of nonadherence.[15] Patient age served as the global predictor (ie, its effect was considered to be equally important in all subgroups indentified using the method). A further multivariate logistic regression analysis with the RECPAM classes forced-in the model was run, testing all other characteristics not entering the tree. A P value < .05 was considered for statistical significance. All analyses were performed using SAS release 9.1 (SAS Institute, Cary, NC).

Results

A total of 939 patients joined the study. The overall participation rate was > 90%. Sociodemographic characteristics of the patients are detailed in Table 1. Median age was 62 years (interquartile range, 52-71 years) and most patients were postmenopausal (70%). More than 81% (N° = 764) of participants were married and 378 (40%) had a secondary or higher education. With respect to working status, 348 (37%) were retired, 366 (39%) were housewives, and 200 (21%) employed.

Clinical characteristics of participants are reported in Table 2. Breast-conserving surgery was more than twice as common as mastectomy, and approximately half of the patients had received previous adjuvant chemotherapy. Most participants were taking aromatase inhibitors (71%), and among them only 11% had switched from tamoxifen.

Table 1	Sociodemographic Characteristics of Participants
Variable	**n (%)**
Age Category, Years	
≤45	89 (9.5)
46-60	325 (34.6)
61-70	252 (26.8)
>70	260 (27.7)
Missing	13 (1.4)
Region of Residence	
Abruzzi	307 (32.7)
Lazio	557 (59.3)
Umbria	43 (4.6)
Others	32 (3.4)
Marital Status	
Married	764 (81.4)
Unmarried/divorced	160 (17.0)
Missing	15 (1.6)
Number of Offspring	
0	113 (12.0)
≥1	805 (85.7)
Missing	21 (2.3)
Level of Education	
No education/elementary	295 (31.4)
Middle school	216 (23.0)
≥High school	378 (40.3)
Missing	50 (5.3)
Work Status	
Retired	348 (37.1)
Housewife	366 (38.9)
Employed	200 (21.3)
Missing	25 (2.7)

Table 2	Clinical Characteristics of Participants
Variable	**n (%)**
Type of Surgery	
Quadrantectomy/segmentectomy	616 (65.6)
Mastectomy	253 (26.9)
Missing	70 (7.5)
Time From Surgery, Years	
≤2	129 (13.7)
3-4	364 (38.7)
≥5	434 (46.3)
Missing	12 (1.3)
Adjuvant Radiotherapy	
Yes	686 (73.1)
No	236 (25.1)
Missing	17 (1.8)
Adjuvant Chemotherapy	
Yes	451 (48.0)
No	448 (47.7)
Missing	40 (4.3)
Menopausal Status at the Start of Endocrine Therapy	
Premenopausal	276 (29.4)
Postmenopausal	655 (69.7)
Missing	8 (0.9)
Time of Adjuvant Endocrine Therapy, Months	
≤18	86 (9.1)
19-36	287 (30.6)
>36	551 (58.7)
Missing	15 (1.6)
Current Endocrine Therapy	
Tamoxifen	239 (25.5)
Aromatase inhibitors	668 (71.1)
Missing	32 (3.4)
Switch From Tamoxifen to Aromatase Inhibitors	
Yes	105 (11.2)
No	806 (85.9)
Missing	28 (2.9)

Overall, our study population appeared to be highly motivated in taking the prescribed drug, as 729 (77.6 %) patients were confident that therapy would be effective in curing cancer. According to the operative definition of adherence adopted in the study, 18.5% of patients were considered to be nonadherers. Basically, nonadherence was largely unintentional, because 94.6% of nonadherers declared to forget to take the tablet or to refill the prescription. Only 9 patients reported to have intentionally discontinued treatment before the completion of 5 years of therapy.

Sociodemographic and clinical characteristics and adherence data were similar among patients from different institutions. Potential predictors of nonadherence identified in univariate and multivariate analysis are reported in Table 3. Only age, working status, and switching from tamoxifen to an aromatase inhibitor were significant predictors of nonadherence in multivariate analysis. Older women showed the highest adherence rate (88.8%). In relation to this reference class, the risk of nonadherence among other age classes was greater. In particular, patients ≤ 45 years of age (OR, 2.56; 95% CI, 1.03-6.34; *P* = .0424) and those between 61 and 70 years of age (OR, 1.93; 95% CI, 1.09-3.41; *P* = .0233) had the greatest odds of being nonadherent. According to the working status, retired

patients showed the lowest percentage of nonadherers (11.8%), and the greatest odds of nonadherence was observed for housewives (OR, 1.92; 95% CI, 1.17-3.15; *P* = .0101). Finally, the risk of nonadherence was greater among patients who switched from tamoxifen to aromatase inhibitors. Notably, no association with adherence was observed for some treatment-related factors, such as type of surgery, time from surgery, previous adjuvant chemotherapy, duration of hormone therapy, and the number of drugs taken.

Recursive partitioning and amalgamation analysis with age as the global predictor led to the identification of 4 classes of patients with a different likelihood of nonadherence (Figure 1). The most important variable for determining the risk of nonadherence was represented by working status, with the lowest prevalence (8.7%) in

Table 3	Univariate and Multivariate Analysis of Factors Predicting Nonadherence to Endocrine Therapy							
	Adherers, n (%)	Nonadherers, n (%)	Univariate LR			Multivariate LR		
Variable			OR	95% CI	*P*	OR	95% CI	*P*
Age, Years								
≤45	62 (71.3)	25 (28.7)	3.2	1.74-5.87	.0002	2.56	1.03-6.34	.0424
46-60	254 (79.4)	66 (20.6)	2.06	1.28-3.32	.003	1.52	0.76-3.04	.2355
61-70	198 (80.2)	49 (19.8)	1.96	1.19-3.24	.0085	1.93	1.09-3.41	.0233
>70	222 (88.8)	28 (11.2)	1			1		
Marital Status								
Married	619 (82.7)	129 (17.3)	1			1		
Unmarried/divorced	115 (74.7)	39 (25.3)	1.63	1.08-2.45	.0199	1.42	0.82-2.34	.1693
Number of Offspring								
0	84 (74.3)	29 (25.7)	1.64	1.04-2.60	.0348	1.34	0.78-2.32	.2926
≥1	647 (82.6)	136 (17.4)	1			1		
Level of Education								
No education/elementary	248 (86.7)	38 (13.3)	1			1		
Middle school	170 (80.2)	42 (19.8)	1.61	1.00-2.61	.0512	1.23	0.71-2.14	.4581
≥High school	289 (77.9)	82 (22.1)	1.85	1.22-2.82	.0041	1.37	0.82-2.29	.2278
Work Status								
Retired	300 (88.2)	40 (11.8)	1			1		
Housewife	275 (77.3)	81 (22.7)	2.21	1.46-3.34	.0002	1.92	1.17-3.15	.0102
Employed	151 (77.0)	45 (23.0)	2.24	1.4-3.57	.0008	1.58	0.85-2.95	.1462
Type of Surgery								
Quad/segmentectomy	494 (81.2)	114 (18.7)	1.02	0.69-1.49	0.9376			
Mastectomy	198 (81.4)	45 (18.6)	1					
Time From Surgery, Years								
≤2	106 (84.1)	20 (15.9)	1					
3-4	282 (78.5)	77 (21.5)	1.45	0.84-2.48	.1799			
≥5	350 (83.1)	71 (16.9)	1.08	0.63-1.85	.7932			
Adjuvant Radiotherapy								
Yes	539 (80. 5)	131 (19.5)	1.24	0.83-1.84	.2864			
No	194 (83.6)	38 (16.4)	1					
Adjuvant Chemotherapy								
Yes	353 (80.0)	88 (20.0)	1.20	0.85-1.84	.2864			
No	365 (82.77)	76 (17.23)	1					
Menopausal Status at the Start of Endocrine Therapy								
Premenopausal	212 (77.3)	62 (22.7)	1.45	1.02-2.05	.0395	0.76	0.44-1.31	.3213
Postmenopausal	529 (83.1)	107 (16.9)	1			1		
Adjuvant Endocrine Therapy, Months								
≤18	70 (82.3)	15 (17.7)	1					
19-36	227 (80.1)	54 (19.9)	1.11	0.59-2.09	.7458			
>36	438 (81. 6)	99 (18.4)	1.05	0.58-1.92	.8614			
Current Endocrine Therapy								
Tamoxifen	184 (77.3)	54 (22.7)	1.44	1.00-2.07	.0513			
Aromatase inhibitors	544 (83.0)	111 (17.0)	1					
Switch From Tamoxifen to Aromatase Inhibitors								
Yes	75 (71.4)	30 (28.6)	1.95	1.23-3.09	.047	1.80	1.08-3.01	.0248
No	657 (83.0)	135 (17.0)	1			1		

Abbreviations: LR = logistic regression; Quad =quadrantectomy.

Table 4	Logistic Regression Model With Forced-In RECPAM Classes	
Variable	**OR (95% CI)**	***P***
RECPAM Class		
1	4.79 (2.43-9.45)	<.0001
2	2.68 (1.52-4.72)	.0007
3	2.58 (1.26-5.92)	.0097
4	1	
Switch Therapy		
Yes	1.78 (1.08-2.92)	.0240
No	1	

Abbreviation: RECPAM = recursive partitioning and amalgamation.

retired women with a low level of education (class 4). This subgroup served as the reference category (OR, 1) for the estimation of OR for other classes. On the opposite side of the regression tree, patients employed or housewives and unmarried represented the subgroup with the highest prevalence of nonadherence (33.7%). The estimated risk of nonadherence for this last subgroup was 4.5 times greater than that of the reference group (OR, 4.61; 95% CI, 2.36-9.28). The other 2 classes of patients, namely those retired with a secondary or higher education (class 3) and married employed or housewives (class 2), displayed a very similar prevalence of nonadherers (18.5% vs. 20.3%) with a risk of approximately 2.4 times greater than the reference gr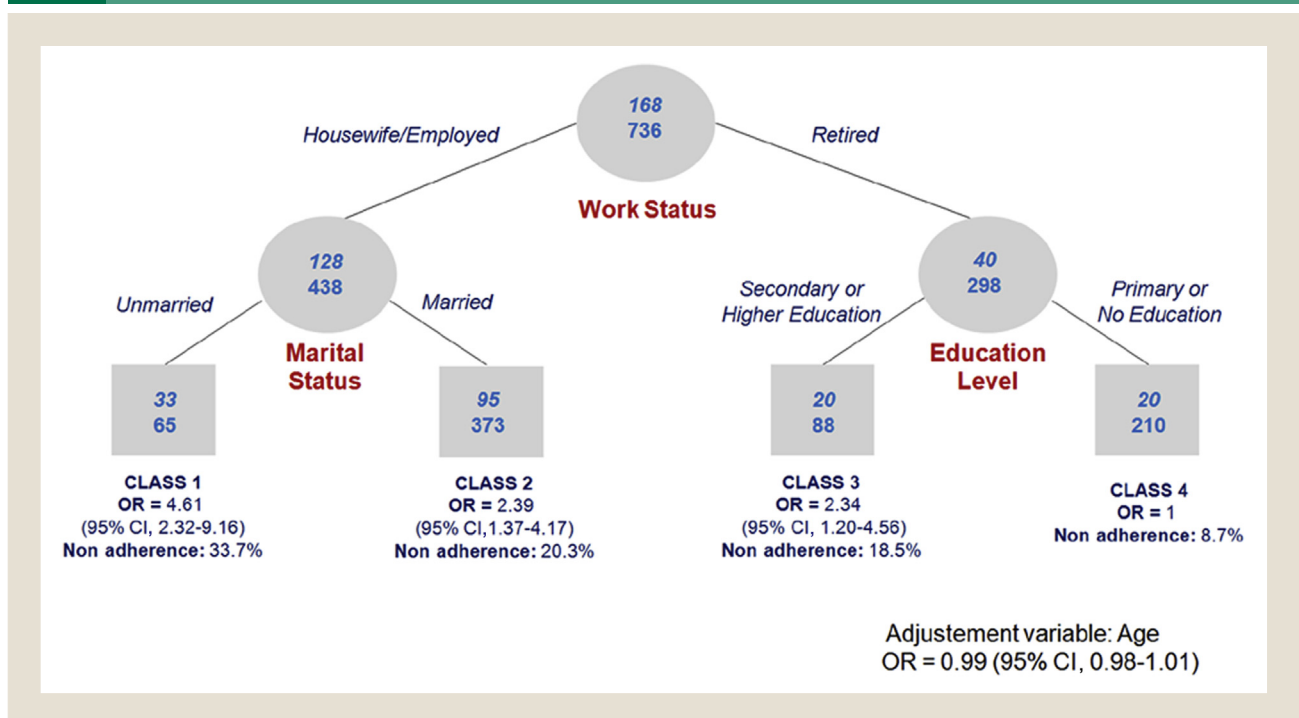oup. A final logistic regression model with RECPAM classes forced-in showed that switching to an aromatase inhibitor was retained in the final model as a globally predictive variable associated with an increased likelihood of nonadherence to therapy (OR, 1.78; 95% CI, 1.08-2.92; *P* = .024; Table 4).

Discussion

A less than optimal adherence to the prescribed medications is a well-known medical issue, especially for chronic diseases requiring treatments lasting several months or years. The increased availability of anticancer drugs in oral formulation undoubtedly results in greater patient convenience. However, taking oral drugs out of the direct control of the medical staff has rendered nonadherence to therapy as challenging in oncology as in other diseases.[6] In this regard, a major area of concern is represented by the adjuvant endocrine treatment of breast cancer.

The results of our survey show that the declared nonadherence of Italian women to HT is in the range of 15% to 50%, as reported in previous studies.[16] The large variability of adherence rate is widely dependent on the different assessment methods.[17] Although no method can be considered optimal,[1] self-reporting through questionnaire might overestimate adherence, being prone to a number of biases such as the response bias and the self-presentation bias.[18] These biases consist of a tendency to respond in a certain way to a questionnaire in an attempt to please the interviewer (response bias)[19] or influence the way the interviewer perceives the interviewed (self-presentation bias).[20] Analysis of prescription refill is

Figure 1	Recursive Partitioning and Amalgamation (RECPAM) Analysis. Tree Growing Algorithm Modeled OR for Nonadherence as Outcome After Multivariate Logistic Regression in Which Age Was a Global Variable. Splitting Variables (Red) Are Shown Between Branches, and Condition Sending Patients to Left or Right Sibling Is on Relative Branch. Class 5 With Lowest Prevalence of Nonadherent Patients Was the Reference Category (OR = 1). Circles Indicate Subgroups of Patients. Squares Indicate RECPAM Classes. Numbers Inside Circles and Squares Represent Number of Patients Adherent or Not (Italic) to Therapy

currently considered a more objective method to estimate adherence to therapy, because it avoids this kind of patient manipulation.[21,22] This method provided more consistent results, with a rate of overall adherence of approximately 50%.[8,9,23] In our study, it was not possible to use prescription refills, because not all the participating institutions could gain access to the pharmacy records. However, we believe that both types of bias were mitigated in our study by the confidential nature of the questionnaire. A possible limitation of our approach is the limited number of items included in the questionnaire. However, this was the result of a trade-off between simplicity and comprehensiveness, so as to not discourage patient participation in the study.

Another important determinant of variation in the rates of adherence is represented by its definition. In most studies, nonadherers were considered those patients taking < 80% of the prescribed dose,[23,24] and this cutoff has been found to be associated with survival.[9,25] We adopted a more relaxed definition, with nonadherers considered those who declared not taking their tablets for at least 4 times during the past month. Whether this extent of nonadherence affects survival is not known at the moment. Notably, other studies have used a very similar definition and the same method of measurement.[26,27] The rate of adherence reported by Oberguggenberger et al[27] is comparable to ours, whereas Atkins and Fallowfield[26] reported a rate of 50%, which probably depended on an even less stringent definition of adherence.

We found an extremely low discontinuation rate probably linked to the setting we chose to conduct the survey. Indeed, it is very likely that patients who have discontinued the treatment are also those no more attending the scheduled follow-up visits. It follows that our study might be affected by such a selection bias. This consideration might also explain why, apparently, in our study the rate of adherence did not decline with the time of HT, which has been consistently observed by others in cancer and chronic diseases.[1,23]

Multiple regression analysis identified several predictors of poor adherence to HT. Among these, age is of major importance. It would be expected that older people are more likely to be nonadherent for a number of reasons, such as cognitive impairment, problems in swallowing tablets, handling them or distinguishing their colors, comorbidities, and a higher number of prescribed medications.[28,29] However, in our study adherence increased with age. Women younger than 45 years had the highest risk of being nonadherent followed by those in the age group of 61 to 70 years. This finding is in agreement with previous studies,[25,26,30] although in others adherence was lower at the extremes of age.[10,23,24] It is now widely recognized that young cancer patients must be regarded as a vulnerable group of patients, because of greater affective distress and greater difficulties in coping with their disease,[31,32] mainly due to the perceived loss of youth, femininity, and fertility associated with side effects of HT.[33] Other authors suggest that the higher rate of adherence among older patients might reflect a survivor bias, because adherent patients might survive longer.[6]

We found that the type of HT has no relation with adherence. Data from clinical trials indicate that, compared with tamoxifen, adherence rates are higher for anastrozole,[34] similar for letrozole,[35] and slightly lower for exemestane.[36] In agreement with other studies,[37] we found that patients who have switched from tamoxifen

to an aromatase inhibitor have a higher risk of nonadherence. This appears to be in contrast with the current belief that there is overall better tolerability of at least some type of aromatase inhibitors.[38] However, this concept has been recently challenged and attributed to a partial assessment, in clinical trials, of the side effects of aromatase inhibitors.[39] It should be noted that in our study, side effects of drugs has no relation with adherence, although they were only indirectly assessed.

Another factor associated with an increased risk of nonadherence is represented by the working status, with nonretired patients being at higher risk of nonadherence. In a recently published prospective study, employment status was found to significantly affect adherence to HT in postmenopausal women with early breast cancer, with nonadherers being prevalent among nonretired patients.[40] Interests and commitments related to an active working status might represent barriers to effective self-care and regular drug assumption.[41]

Medication costs, consistently associated with poor adherence to treatment in countries requiring health insurance coverage,[42] were not evaluated in our study because in Italy health care is provided by the National Health Service and oral drugs for the treatment of cancer are subsidized, with no copayment required.

Finally, although the number of patients enrolled in the survey might not be optimal, RECPAM analysis identified 4 subgroups of patients with significant differences in the prevalence of nonadherence based on the interactions of work status, education level, and marital status. We observed the higher risk of nonadherence among nonretired, unmarried women. Being unmarried has been previously reported as a predictor of poor adherence to medical regimens in general[43] and oral hormone therapy in particular.[9,24] This highlights the important role of social support, mainly from spouse and family members, as a factor for improving adherence. The other factor affecting adherence was the level of education, with patients with secondary or higher education showing a higher prevalence of nonadherers. Highly educated patients are expected to be more adherent because they should have a better knowledge of the disease and possess the cultural tools required to independently evaluate the benefits of therapy. However, an inverse association between educational level and adherence to treatment has been reported in other diseases.[44] This might reflect a more cynical belief of educated patients regarding the usefulness of taking adjuvant therapy and a lower level of trust in oncologists' advice. The final logistic model with RECPAM classes forced-in confirmed that switching from tamoxifen to aromatase inhibitors represented an important factor affecting adherence to this class of drugs.

Conclusion

Poor adherence to adjuvant endocrine treatment for breast cancer is a well known problem and it is expected to become a more compelling one in the coming years. Even if causes of nonadherence were not specifically evaluated, results of our study help to define discrete subgroups of "real life" patients with a high prevalence of nonadherence and, to the best of our knowledge, represents the first Italian study of this kind in its specific setting. Therefore, our results might be functional in designing intervention studies, specifically targeting the high-risk patients with the aim of improving their adherence. Likely these studies should be based on comprehensive

interventions combining behavioral, educational, and affective components.[45]

Clinical Practice Points

- Nonadherence to adjuvant endocrine treatment for breast cancer is a well known problem, and it might explain the difference in survival between clinical trial and clinical practice.
- Interventions aimed at promoting adherence have been proven to be ineffective, probably because they were quite generic and not adapted to the needs of the patient.
- We conducted a survey among women on adjuvant HT for breast cancer with the aim to identify discrete subgroups at higher prevalence of nonadherence.
- The results of our study indicate that women being unmarried, employed, or a housewife are at higher risk of nonadherence.
- These findings might be instrumental in designing intervention studies specifically targeting these high-risk patients with the aim of improving their adherence.

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Disclosure

The authors have stated that there are no conflicts of interest.

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