

# Assessing Predictors of Tamoxifen Nonadherence in Patients with Early Breast Cancer

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**Abstract:** Adjuvant endocrine therapy (AET) is generally proposed to all patients with hormone receptor-positive breast cancer to reduce the risk of recurrence and death. Adherence to therapy is crucial. However, non-adherence to AET is common, with estimates of up to 50% of patients not successfully completing a five-year course of treatment, and it is significantly associated with lower survival rates and a higher risk of recurrence. Currently, no gold standard is available to assess adherence. Several studies, most of them retrospective in nature, have used both direct and indirect methods to monitor the adherence to therapy in breast cancer. The indirect method is more widely used, and it is based on pharmacy prescription refills and patient administered questionnaires. On the other hand, direct methods such as a measurement of the level of the drug or its metabolites in blood or urine are much more precise, but more expensive and not routinely implemented. In this review, we analyzed the results of the major studies focused on the adherence to tamoxifen in breast cancer patients. We identified several factors associated with poor adherence, such as the side effects of therapy, the lack of shared decision-making between the physician and patient, the context in which the discussion takes place, and whether the patients are enrolled in a clinical trial. Moreover, we discussed possible methods to improve adherence to adjuvant therapy in breast cancer.

**Keywords:** adherence, adjuvant endocrine therapy, tamoxifen, breast cancer

## Introduction

Poor adherence to medications is an international problem and is believed to lead to 200,000 premature deaths in Europe annually.<sup>1</sup> This has had severe economic consequences, impacting the healthcare system, since patient non-adherence leads to additional medical treatments, emergency visits, and hospital admissions.<sup>2</sup> Currently, the gold standard is not available to assess adherence. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has focused on research into this unmet need, and has widened their definition of adherence to now include factors such as physiological and social issues.<sup>3</sup> The World Health Organization (WHO) defines adherence as “the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider” underlining the need to consider varying factors, which may impact patient non-adherence.<sup>4</sup> In breast cancer patients, adjuvant treatment is used to prevent the risk of recurrence. Currently, 75–80% of early-stage breast cancer patients are candidates for hormonal therapy, which may be continued for several years.<sup>5,6</sup> Breast cancer prognosis has significantly improved over time, and the longer survival rates require dedicated strategies to manage long-term sequelae of breast cancer treatments.<sup>7</sup> Therefore, adherence to therapy is of the utmost

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importance. Adjuvant endocrine therapy (AET) is generally proposed for all patients with endocrine-sensitive early breast cancer to reduce the risk of recurrence and death. Different options, including tamoxifen and aromatase inhibitors, with or without LHRH analogue (if premenopausal) should be discussed with the patients according to the stage and biological features of the breast cancer, concomitant disease, age, and patient preferences.<sup>8–11</sup> Moreover, several data support that the prolongation of hormonal therapy (ie 10 years of hormonal treatment) is associated with a statistically improved outcome.<sup>12–15</sup>

All guidelines recommend that clinicians should consider adverse side effects, patient preferences, and pre-existing conditions when discussing adjuvant strategies in breast cancer.<sup>8</sup>

In order to monitor adherence to breast cancer therapy, both direct and indirect methods exist. The indirect method is more widely used, and it is based on pharmacy prescription refills and patient-administered questionnaires. This method may overestimate adherence, since patient self-reports can be particularly inaccurate, and pharmacy prescriptions do not necessarily reflect the true consumption of medication, since patients may collect their treatment and not actually take them. On the other hand, direct methods, such as a measurement of the level of the drug or its metabolites in blood or urine, are much more precise, but more expensive and not routinely implemented.

Several studies have attempted to analyze adherence in breast cancer patients. The majority are retrospective and use an indirect method to identify non-adherence. These studies aimed to understand factors related to non-adherence in endocrine therapy. The percentage of non-adherence changed between studies, and ranged between 30%–60%.<sup>16–21</sup>

The aims of this review were to analyze factors associated with poor adherence to tamoxifen and to discuss possible methods to improve adherence to adjuvant therapy in breast cancer.

## Methods

We conducted a review of the results of retrospective and prospective studies testing the adherence to tamoxifen in breast cancer patients. The Medline database was searched for fully published articles using the keywords ‘adherence to tamoxifen’ and ‘non-adherence to tamoxifen’ and ‘cancer’ or ‘breast’. The search was restricted to the English language. Exclusion criteria included the following: pediatric trials, studies referring to adherence in the metastatic

breast cancer setting, editorials, case reports and review articles. For studies with multiple presentations and/or publications, only the latest versions were included in the analysis.

## Studies of Adherence to Tamoxifen and Aromatase Inhibitors in Breast Cancer Patients

Table 1 reports the studies focused on the adherence to tamoxifen.

Historically, the first study by Partridge et al retrospectively evaluated the adherence of 2378 breast cancer patients to tamoxifen, defined as the availability of tamoxifen for more than 80% of their first year of prescribed therapy. The authors reported that 23% of women were classified as non-adherent, and factors related to the poor adherence were the extremes of age (either very young with age less than 45 years, or very old,  $\geq 85$  years), non-white ethnicity, the type of surgery, and the absence of discussion with oncologist.<sup>22</sup>

Van Herk-Sukel et al retrospectively studied 1451 patients treated with adjuvant tamoxifen. A total of 30% of the population discontinued treatment at two years, evaluated as failure to provide a prescription. Associated factors were found to be older age (older than 70), and the presence of two or more comorbidities.<sup>23</sup>

The same method to evaluate discontinuation of tamoxifen was also used by Hershman et al in 8769 patients with breast cancer.<sup>24</sup> The authors found that 30% were defined as non-adherent to tamoxifen at four years. Similar factors, such as the presence of more comorbidities, extreme ages and the type of surgery, were found to be associated with AET discontinuation.

Similar results were reported by Cavazza et al in a larger retrospective analysis of real-world data of 33,921 surviving women starting AET in 2010–2016. Factors associated with negative determinants of adherence to AET (identified with filled prescriptions of AET for  $> 292/365$  days) were as follows: a delayed initiation of treatment after surgery, receiving surgery in a high-volume hospital, and depression status.<sup>25</sup> The type of AET was associated with different adherence behavior; women treated with tamoxifen had a reduction of 31% of adherence at five years compared with those who switched therapies. The adherence rate decreased with a longer follow up, and if women did not receive adjuvant chemotherapy.

**Table 1** Studies of Adherence to Tamoxifen in Breast Cancer Patients

Authors	Patients (N)	FUP Period	Nonadherence Definition	Results in Terms of Nonadherence	Associated factors to Nonadherence
Demissie, 2001 <sup>56</sup>	303	3 yrs	Self-report survey data	15%	Side effects
Partridge, 2003 <sup>22</sup>	2378	4 yrs	Number of days covered by filled prescriptions for tamoxifen in the first year of therapy <80%	23% at 1 yr	Extremes of age; patients less than 45 and 85 years; Nonwhite; mastectomy rather than breast-conserving surgery; NOT seen an oncologist in the year before beginning tamoxifen therapy
Fink, 2004 <sup>38</sup>	516	2 yrs	Self-report survey data	17%	Neutral or negative beliefs about the value of tamoxifen; positive nodes
Grunfeld, 2005 <sup>57</sup>	110	na	Self-report survey data	46%	Side effects, change of routine, belief that there was nothing to be gained from taking tamoxifen
Lash, 2006 <sup>26</sup>	462	5 yrs	Self-report survey data. Failed to complete the recommended 5-year course	31%	Severe side effects, added a prescription
Kahn, 2007 <sup>40</sup>	881	4 yrs	Self-report survey data	21%	Older age and the severity of side effects
McCowan, 2008 <sup>30</sup>	1633	3 yrs	Percentage of days covered by all the prescriptions for each patient dividing it by the duration	10% at 1 yr; 19% at 2 yrs; 32% at 3 yrs	Younger women were more likely to have low adherence
Ma, 2008 <sup>58</sup>	788	na	Not taking as recommended or take < 1 year	30%	Younger age
Owusu, 2008 <sup>59</sup>	961	5 yrs	Discontinuing tamoxifen for more than 60 day	15% at 1 y, 24% at 2 yrs, 33% at 3 yrs	< 70 years or >or= 80 years; breast-conserving surgery (BCS) without radiotherapy; increase in the number of cardiopulmonary comorbidities at 3 years
Rae, 2009 <sup>60</sup>	280	1 yr	Not complete 4 months of therapy	14%	Active CYP2D6 alleles may predict for higher likelihood of tamoxifen discontinuation
van Herk-Sukel, 2010 <sup>23</sup>	1451	5 yrs	Taking the drug during a specific period of time (1–5 yrs) without failure to continue renewals	17% at 1 yr; 30% at 2 yrs 45% at 3 yrs	Older age (older than 70 versus 50–69 years); two or more concomitant diseases (versus no comorbidity)
Dezentje, 2010 <sup>61</sup>	1962	6 yrs	The proportion of days (percentage) covered by tamoxifen in the first year following tamoxifen initiation < 80–90%	Mean of 16% at 3 yrs	Not effect of concomitant CYP2D6 inhibitor use during tamoxifen therapy
Thompson, 2011 <sup>62</sup>	257	na	Medication Possession Ratio (MPR) < 80%	14%	na
Huiart, 2012 <sup>63</sup>	246	3 yrs	Medication Possession Ratio (MPR) < 80%	17% at 1 yr; 29.7% at 2 yrs 39.5% at 3 yrs	Low social support and self-reporting of non-compliance
Pistilli, 2020 <sup>32</sup>	1177	3 yrs	Self-declared /biochemical measuring tamoxifen-serum < 60 ng/mL	16%/12%	Side effects, not receiving neoadjuvant chemotherapy, non-partnered living

Lash et al used a different methodology to analyze adherence. They interviewed 462 patients with breast cancer to evaluate the continued use of tamoxifen.<sup>26</sup>

Of the entire cohort, 31% of enrolled women did not manage to conclude the five years of adjuvant tamoxifen prescribed.

In the small study conducted by Brett et al referred to 32 women (19 adherers and 13 non-adherers) who were interviewed after two or four years of AET, the factors associated with non-adherence to AET were the impact of side effects on their quality of life. Other factors were a feeling of lack of support (mostly when they switched the follow-up from the hospital to their general physician (GP)), unawareness of the risk of recurrences, and of the benefits of AET. Moreover, some women declared that they had interrupted adjuvant therapy to return to normality.<sup>27</sup>

A total of 100 women interviewed by Ziller et al declared full adherence to tamoxifen or aromatase inhibitors, but, after studying prescriptions, 20% of patients resulted non-adherent to tamoxifen. No baseline factors were related to discontinuation.<sup>28</sup>

Different factors related to adherence were identified using prospective studies that were designed in more recent years. Wassermann et al prospectively studied non-adherence behaviors to AET in women under 40 years of age with breast cancer at 30 months, after the initiation of adjuvant endocrine therapy. Patients were evaluated using indirect methods based on three items of poor adherence (ie forgetting to take ET, stopping ET due to feeling unwell, and not having taken therapy in the manner suggested by their doctor in the last three months). More than half (51%) of 384 enrolled patients declared at least one among the three mentioned non-adherence behaviors. A low educational level, low social support, and low confidence in adjuvant ET were factors associated with non-adherence to ET. The most common cause of non-adherence was forgetting to take the pills.<sup>29</sup>

Table 2 reports the studies focused on the adherence to tamoxifen and aromatase inhibitors.

The study by Yusufov et al attempted to identify predictor factors related to increased risk of non-adherence to AET. A total of 73 women were enrolled before starting AET, assessing psychological and menopausal symptoms at time 0, after 3 and 6 weeks of AET. In this study, the adherence was also evaluated using indirect methods and, from the self-declaration of treatment adherence, only 20% and 26% of women were non adherents at 3 and 6 weeks of starting AET, respectively.<sup>30</sup> Unlike previous studies, no statistically significant difference regarding race, marriage, and employment status was identified to explain adherence and non-adherence amongst women. The majority of non-adherent women described depressive symptoms pre-AET that could

contribute as an important predictor factor to non-adherent behavior to AET.

He et al found different predictor factors for discontinuation of AET in 3395 women who started adjuvant therapy with tamoxifen or aromatase inhibitors.<sup>31</sup> Among these predictors, the major baseline factors were not only the use of antidepressant drugs but also hypnotics, gastrointestinal drugs, and switching therapy to aromatase inhibitors.

Recently, non-adherence to tamoxifen was examined by serum assessment in 1177 French premenopausal patients within the CANTO trial in the first year after the start of adjuvant endocrine treatment.<sup>32</sup> The authors also evaluated the patients' self-declaration of adherence or non-adherence with related reasons and studied its impact on short-term breast cancer survival outcomes. After a median follow-up of 24.2 months since tamoxifen serum assessment, patients who were biochemically nonadherent had significantly shorter DDFS (for distant recurrence or death, adjusted hazard ratio, 2.31; 95% CI, 1.05 to 5.06; P 5 0.036), with 89.5% of patients alive without distant recurrence at 3 years in the nonadherent cohort versus 95.4% in the adherent cohort.

The two methods were significantly associated but with moderate concordance. Biochemical methods and indirect methods identified 16% (188/) and 12% (145) of patients as non-adherent, respectively. Only 50% of self-declared non-adherent patients explained their reasons for discontinuation, which in the majority of cases was due to tamoxifen-related side effects. Similarly to other chronic diseases, social factors were associated with non-adherence to adjuvant treatment, such as non-partnered living. Moreover, increased risk of non-adherence was associated with the onset of symptoms related to tamoxifen. In addition, not receiving neoadjuvant chemotherapy, which is believed to be associated with a decreased awareness of the risk of non-adherence and the gravity of their situation, is another factor found to impact non-adherence. Other studies also found similar results in patients not previously receiving chemotherapy.

## Studies on Psycho-Social Processes Underlying Non-Adherence to Tamoxifen on Breast Cancer Patients

Several studies affirmed that medication non-adherence should be considered as a multi-level concept, and should not be reduced exclusively to clinical (eg, disease and treatments), socio-demographic (eg, age, gender, socio-economic status) and health system-related factors, but also individuals' psychological characteristics should be

**Table 2** Studies of Adherence to Tamoxifen and Other Endocrine Therapies in Breast Cancer Patients

Authors	Patients (N)	FUP Period	Nonadherence Definition	Results in Terms of Nonadherence	Associated Factors to Nonadherence
Guth, 2008 <sup>51</sup>	287	5 yrs	Discontinued the planned mode of treatment and refused to continue further endocrine therapy.	11%	Follow-up with a general practitioner and adverse events
Kimmick, 2009 <sup>64</sup>	1491	1 yr	Medication Possession Ratio (MPR) < 80%	20%	Married status
Schwartzberg, 2009 <sup>65</sup>	200	na	Self-report survey data	20%	Musculoskeletal symptoms
Ziller, 2009 <sup>28</sup>	100	1 yr	Medication Possession Ratio (MPR) < 80%	20% tam 30% AI	Nothing
Dittmer, 2011 <sup>66</sup>		5 yrs	Self-report survey data	23%	Side-effects
Guth, 2011 <sup>67</sup>	427	1 yr	Discontinued therapy in 5 yrs	9%	Side effects
Nekhlyudov, 2011 <sup>68</sup>	2207	3 yr	Medication Possession Ratio (MPR) < 80%	21% at 1 yrs	Age ≥ 70 years
Hershman, 2011 <sup>24</sup>	8769	4 yrs	Medication Possession Ratio (MPR) < 80%	28%	Younger or older age and an increased number of comorbidities
Huiart, 2011 <sup>63</sup>	13,479	5 yrs	Medication Possession Ratio (MPR) < 80%	29% at 5 yrs	Side effects, younger women, use of tamoxifen
Wigertz, 2012 <sup>69</sup>	1741	3 yrs	Medication Possession Ratio (MPR) < 80%	31%	Unmarried women, switching therapy
Weaver, 2012 <sup>70</sup>	857	5 yrs	Medication Possession Ratio (MPR) < 80%	18% at 1 yr	Studied effect of concomitant use of CYP2D6 enzyme inhibitor medications
He, 2015 <sup>31</sup>	3395	5 yrs	Having any interval between two consecutive dispenses exceeding 180 days during the follow-up	50%	Use of antidepressant, hypnotics, gastrointestinal drugs and switching therapy to aromatase inhibitors
Brett, 2018 <sup>27</sup>	32	4 yrs	Self-report survey data	13/32	Side effects, feeling of unsupported, unawareness of the risk of recurrences and of the benefits of AET
Wasserman, 2019 <sup>29</sup>	384	2, 5 yrs	Self-report survey data	51%	A low educational level, low social support and low- confidence about adjuvant
Yusufov, 2020 <sup>30</sup>	73	6 ws	Self-report survey data	26%	Pre-existing depressive symptoms
Cavazza, 2020 <sup>25</sup>	8400	5 yrs	Medication Possession Ratio (MPR) < 80%	18%	Age ≥ 70 years, delayed initiation of treatment after surgery, receiving surgery in a high-volume hospital and depression status, not receive chemotherapy

**Table 3** Studies on Psycho-Social Processes Underlying Non-Adherence to Tamoxifen

Authors	Year	Type of Study	Patients (N)	Disease Stage	FUP Period	Nonadherence Measure	Nonadherence Rate	Psychological Processes Associated to Nonadherence
Cahir et al. <sup>33</sup>	2015	Qualitative	31	I°-III°	3 Months	Interview	73%	Self-monitoring; Environmental stressors; Knowledge; Medication Beliefs; Time Perspective
Cortier et al. <sup>71</sup>	2018	Survey	125	I°	3 Months	Pill count	36%	Health Beliefs
Cluze et al. <sup>39</sup>	2012	Prospective	218	Not available	10, 16, and 28 months	Two or more consecutive months without dispensed prescription of tamoxifen	42%	Fear of recurrence; Social Support; Patient-Doctor Communication; treatment options
Fink et al. <sup>38</sup>	2004	Cohort	516	I°-III°	3, 6, 15, and 27 months	Interview	21%	Medication Beliefs
Khan et al. <sup>40</sup>	2007	Cohort	881	I°-III°	4-yeras	Single item	21%	involvement in decision-making
Liu et al. <sup>41</sup>	2013	Prospective	303	I°-III°	6, 18, and 36 months	Single item	36%	Patient-centered communication; Self-efficacy
Moon et al. <sup>36</sup>	2019	Longitudinal	345	I°-III°	3, 6 and 12 months	Medication Adherence Rating Scale	50%	Medication beliefs/Self-Confidence in ability to take tamoxifen
Moon et al. <sup>34</sup>	2017	Cross-sectional	777	I°-III°	1–2 years	Medication Adherence Report Scale	44%	Medication Beliefs
Pan et al. <sup>37</sup>	2018	Cohort	116	I°-III°	At 24 months	Single item	14.7%	Medication Beliefs/Optimism
Vaughn et al. <sup>35</sup>	2020	Prospective	89	Not available	Not available	Pill count	Not available	Delay discounting effect
Wassermann et al. <sup>29</sup>	2019	Cohort	384	I°-III°	At 30 months	Three-item	51%	Social-support/Confidence in Decision-Making
Wheeler et al. <sup>47</sup>	2019	Cohort	1280	I°-III°	2-years post-diagnosis-10 years post-diagnosis	Two-item	18.9%	Recurrence risk perception/
Yusufov et al. <sup>30</sup>	2021	Prospective	73	I°-II°	3–6 weeks	Two-item	77.9%	Anxiety/Depression/ Somatosensory Amplification

included in the explanatory model<sup>33,34</sup> (Table 3) Commonly, the individual factors refer to a set of psychological and relational processes, such as health beliefs (beliefs about medications, illness susceptibility), emotional wellbeing (anxiety, depression and fear of recurrence), self-efficacy, time perspective, social support, patient–doctor relationship and the patient’s role in clinical decision-making throughout the disease pathway All mentioned factors seem to boost both intentional and unintentional non-adherence in ET and AET.<sup>30,35</sup>

### Patients’ Beliefs and Dispositional Characteristics

Many studies conveyed that modulators of adherence were connected to individual beliefs about medications (belief of medication effectiveness vs distrust toward the medication) and illness susceptibility.<sup>36,37</sup> A qualitative study conducted by Cahir et al showed that a general mistrust of drugs increased the risk of non-adherence. As for endocrine treatments, Fink et al in a longitudinal study on 516 patients with ER-positive tumors reported that 17% of women stopped taking tamoxifen during the 2-year follow-up stage due to

the negative beliefs associated with risks and benefits of tamoxifen.<sup>33,38</sup> More specifically, women were more adherent to tamoxifen when the benefits of the treatment were perceived as outweighing the risks, compared to women who perceived the risks as similar or higher than the benefits. As Cahir et al suggested, nonadherent women seem to attribute a higher value to quality of life than to an increased life expectancy. Authors argued that the expectation of treatment side effects reinforces the tendency to search for confirmatory symptoms. In addition, the prescription of further drug treatments to control side effects might have the paradoxical effect of diminishing motivation to start or continue with treatment. Furthermore, Pan et al conducted a cohort study on 116 women with hormone receptor-positive breast cancer or a ductal carcinoma in situ undergoing AET, measuring psychological predictors of adherence at 2-years.<sup>37</sup> The results identified a significant role of optimism and emotional wellbeing (anxiety and depression). In particular, compared to nonadherent women, adherent women reported lower anxiety and depression, higher drug effectiveness beliefs, lower expected side-effect severity and higher level of optimism. In addition, perceived self-efficacy in handling the expected side-effects was able to affect adherence behavior more than side effects per se. Analogous results were found by Moon et al observing that nonadherent women were more likely to perceive a lower self-confidence in managing the treatment.<sup>36</sup>

### Patients' Preferences and Relational Factors

Two other key variables that affect adherence rate to tamoxifen are connected with a lower involvement in the treatment decisions and patient–doctor relationship.<sup>29,39</sup> Indeed, as reported by Wassermann et al the role (active, passive or collaborative) of women in clinical decisions and their confidence with the decision regarding ET are moderators of adherence. More specifically, lack of shared decision-making between patients and their oncologist and a lower confidence toward the decided treatment were associated with a lower adherence. Accruing evidence suggested that women who feel that their needs and values are recognized, and that their preferences are integrated in the clinical decisions, are more prone to adhere to the prescribed treatment. Similar results were sustained by other studies that, in addition, showed that a poor patient–doctor relationship at the time of diagnosis, as well as a low quality of treatment-related information provided by the oncologist were significantly related to non-adherence.<sup>40</sup> Also, Liu et al highlighted that patient-

centered communication was positively associated with tamoxifen persistence at three years post-diagnosis.<sup>41</sup>

### Patients' Emotional Predictors

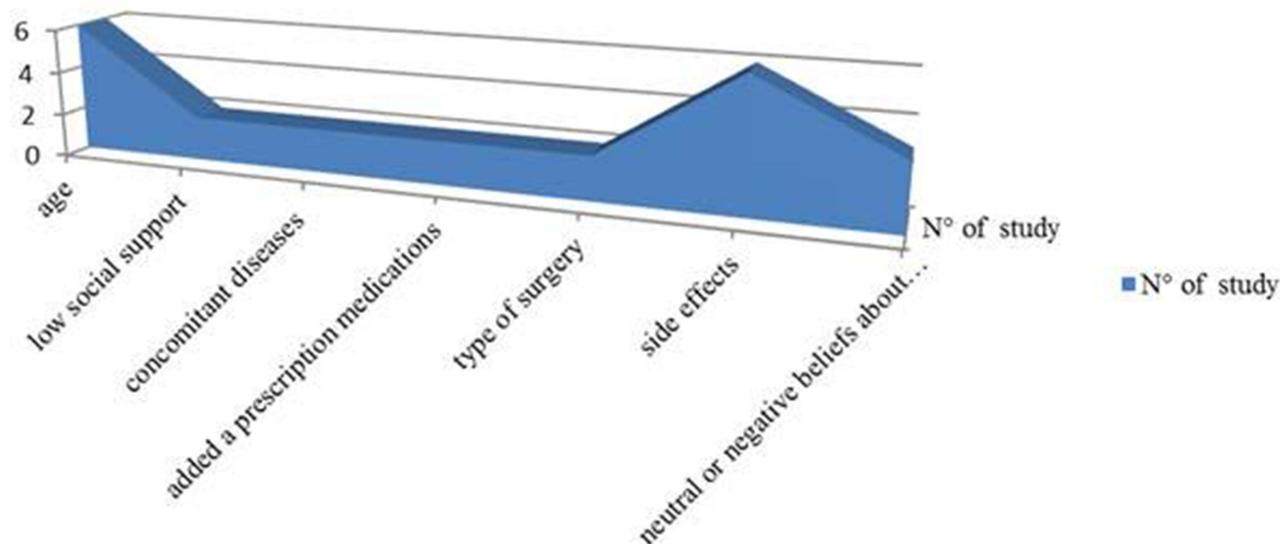
Moreover, negative emotions connected to disease onset and/or which arise along the care pathway may have a strong incidence on non-adherence. For example, a qualitative study on women with stage I–III breast cancer treated with adjuvant hormonal therapy found that the fear of cancer recurrence was negatively related to non-adherence. Mainly, young breast cancer survivors with lower fear of recurrence are at increased risk of interrupting tamoxifen. In keeping with this, Cluze et al reported that at 16–28 months after the breast cancer diagnosis, the fear of recurrence was negatively associated with AET interruption. This effect was particularly evident in women with poor knowledge of the risk of breast cancer recurrence and the benefits associated with the AET.<sup>39</sup>

### Patients' Time Perspective

Chair et al highlighted the importance of the time perspective, that is the tendency to orient thoughts, attitudes and actions toward the present (present orientation attitude) or toward the future (future orientation attitude). As Chair et al showed, nonadherent women had a present orientation, focusing attention on events and facts that are close in time, leading them to avoid side-effects and undesired lifestyle changes that treatments might require, and underweighting the long-term negative effect of non-adherence. By contrast, adherent women demonstrated a future-oriented time perspective, and were more focused on the avoidance of breast cancer recurrence, using a wide range of coping strategies to manage the current negative effects. Thus, adherence is supported by future positive outcomes, rather than immediate pleasure. Consistently with the time perspective, some studies (eg, Vaughn et al 2020) have also hypothesized that adherence might be associated with psychological processes, such as devaluation of delayed outcomes. Investigators conducted a study on breast cancer survivors who had been prescribed AET, and adherence was assessed by pill count and self-report. Results revealed that nonadherent women have a high level of delay discounting: they tend to discount the value of the benefits related to the ET as a function of time.<sup>35</sup>

## Discussion

Non-adherence to tamoxifen therapy is a difficult topic to evaluate. The lack of a gold standard by which to identify non-adherence, and the absence of standard methods to



**Figure 1** Factors associated to non-adherence to Tamoxifen in breast cancer patients.

improve adherence make it particularly challenging to perform studies. Despite differences in methodology, various studies have identified the importance of dialogue between the oncologist and patients in order to emphasize the magnitude of the benefits of AET leading to an increased adherence to medication (Figure 1).

Investigating the preferences of patients is important because the preferences could affect the adherence to treatments. Non-adherence to AET is common, with estimates of up to 50% of patients not successfully completing a 5-year course of treatment.<sup>42,43</sup>

Moreover, non-adherence to breast cancer treatment is significantly associated with lower survival rates and a higher risk of recurrence, as was recently reported in the CANTO trial, where patient self-reports underestimated rates of non-adherence and 55% of patients who were nonadherent by serum assessment might not overtly acknowledge non-adherence.<sup>32,44–46</sup> Furthermore, non-adherence by serum assessment measured as early as year 1 after treatment prescription emerged as marker of poorer outcomes regardless of other main prognostic factors, suggesting that risk of recurrence increases as soon as the patients start to be nonadherent. The implications of these results highlight that patients are less aware of the health risks related to their disease and misconceive the beneficial impact of adjuvant endocrine therapy on breast cancer outcomes.

Wheeler et al found that there is a correlation between a lack of shared decision-making and non-adherence in

a cross-sectional survey from the Carolina Breast Cancer Study.<sup>47</sup>

Preliminary findings from the Breast Cancer Quality of Care (BQUAL) study measuring factors associated with initiation of hormonal therapy suggest that the way patients view hormonal treatment significantly impacts the likelihood of adherence.<sup>48</sup> Those with negative beliefs were found to be far less willing to commence treatment. Conversely, those with more positive opinions, and those given the chance to communicate and ask questions about their treatment, had a higher probability of undertaking and continuing treatment.

In addition, an effective physician–patient relationship will allow patients to understand potential side effects and give them the ability to manage side effects more effectively. Indeed, one of the main reasons for discontinuation of therapy is due to the collateral effects. Menopausal symptoms are the most common side effects of AET and require a complex coordination of care. In premenopausal women, hormonal therapy can have an impact on fertility, and alter plans for childbearing. Physical changes may be noticed by patients as well as alterations in sexual function.

In the ELENA study, focused on the preferences of patients regarding hormonal therapy, almost 40% of patients reported side effects of severe grade, such as joint pain, vaginal dryness, and loss of libido.<sup>49</sup> In order to improve the management of side effects, patient interactive digital applications are an area of developing research. Interactive digital support could be implemented in order to monitor the compliance to therapy as well as the side effects.<sup>50</sup>

Another factor that could affect adherence is the context where the discussion is conducted and if the patients are enrolled in a clinical trial. A discrepancy in the ranges of discontinuation rates was reported in clinical practice settings (31–73%) compared with clinical trials (8–28%).<sup>51–53</sup> In the setting of a clinical trial, patients are supervised more closely, with more frequent appointment dates, which may make it easier to monitor adherence to therapy. Outside the setting of a clinical trial, it is common for patients to receive suboptimal follow-up care. Evidence from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) shows that only 20% of all cancer survivors continue to use an oncologist or cancer specialist as their primary provider for cancer follow-up care.<sup>54</sup> It may be of importance for a patient to continue seeing a physician in order to ensure they are receiving appropriate care.

Since 2020, the rapid spread of COVID-19 infection made the interaction between oncology patients and physicians more challenging. During the COVID-19 pandemic, a statistically significant reduction in emotional functioning was observed in patients with breast cancer. Patients developed worse anxiety, depression, and distress, all of which were important factors for non-adherence to hormonal therapy. In this particularly difficult time, telemedicine was used in order to overcome this problem and ensure doctors were still in frequent contact with their patients.<sup>55</sup>

In line with this perspective, an integrated model combining the characteristics of patients, disease, patient approach, and health system would be highly recommended to provide new decision-making and intervention strategies. Such an approach may be useful in reducing patient and health system costs related to non-adherence.

In addition, empowering patients to take control over their care goes a long way to improving healthcare quality. For instance, a high level of medication adherence leads to lower disease-related medical costs. However, non-adherence rates when linked to poor clinical outcomes may increase hospital admissions and healthcare costs.

In conclusion, projects based on real-world data, that aim to identify factors for non-adherence to hormonal therapy should be warranted, in the hope that we can increase awareness and adherence to these medications for our patients.

## Disclosure

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