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# Age-related differences in persistence in women with breast cancer treated with tamoxifen or aromatase inhibitors in Germany



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## ABSTRACT

**Aims:** To study age-related persistence in postmenopausal women with endocrine-responsive breast cancer treated with tamoxifen (TAM) and aromatase inhibitors (AI).

**Methods:** Data on 29,245 patients diagnosed with metastatic or non-metastatic breast cancer (BC) and initially treated with TAM or AI between 2004 and 2013 were included. The primary outcome measure was the age-dependent rate of discontinuation of endocrine treatment within 5 years after initiation. Discontinuation of therapy was defined as a period of at least 90 days without treatment. A multivariate Cox regression model was created to determine the influence of age on the risk of discontinuation. Health insurance type (private/statutory), type of care (gynecological/general), region (West/East Germany), concomitant diagnoses (depression, osteoporosis, and diabetes), and Charlson Comorbidity Score were included as covariates.

**Results:** The mean ages of the women in the <70 and ≥70 groups were 55.9 (SD: 9.7) and 77.4 (SD: 5.4) years, respectively. Within 5 years after treatment initiation, 88.8% of women <70 of age and 82% of women ≥70 years of age had terminated treatment (p-value < 0.001). Patients aged ≥70 exhibited a lower risk of treatment discontinuation than patients aged <70 (HR = 0.75, 95% CI: 0.66–0.85). Furthermore, gynecological practices, disease management programs, and high Charlson scores increased persistence.

**Conclusions:** Overall, the present study indicates that persistence rates are low in both women with BC aged <70 and those aged ≥70 years. We also found that younger women with BC are at a higher risk of treatment discontinuation than older women.

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## 1. Introduction

Breast cancer (BC) is the most common cancer among women in Europe.<sup>1</sup> Age is one of a large number of major risk factors for the

disease.<sup>2</sup> The median age at diagnosis is around 60 and since approximately 20% of the general population will be aged >65 by 2030, it has been estimated that the percentage of elderly women with early-stage BC will increase over the coming decades.<sup>2</sup>

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Most of these elderly women will be diagnosed with hormone-receptor positive BC.<sup>3</sup> In the past, endocrine treatment for postmenopausal women with hormone-receptor positive BC was dominated by the use of tamoxifen (TAM), as several studies indicated an improvement in overall survival rates for those treated with the drug as compared with those who were given a placebo.<sup>4,5</sup> Despite its proven efficiency, the use of TAM has been linked with several severe adverse effects, such as an increase in the risk of endometrial cancer and thromboembolic events, leading to a decrease in patient persistence.<sup>6</sup> Several studies have investigated the use of aromatase inhibitors (AIs) in head-to-head designs against TAM, indicating superior efficiency but also revealing interesting effect and safety profiles (i.e. fewer gynecological problems and vascular events).<sup>7–10</sup> A recent meta-analysis has shown that AIs produce significantly lower recurrence rates than tamoxifen, when used either as an initial monotherapy or after 2–3 years of tamoxifen use.<sup>11</sup> Therefore, all current national and international guidelines recommend AIs as adjuvant treatment for postmenopausal hormone-receptor positive BC.

Lack of treatment adherence and persistence is a major issue affecting all chronic diseases. Adherence is generally defined as taking medication as directed (e.g., at a certain time of the day), while persistence consists of continuing to take medication (correctly or incorrectly) for the recommended period. Adherence refers to the patient's overall behavior, of which persistence is one component.<sup>12,13</sup>

Only a small number of studies have investigated the influence of age on persistence with TAM or AIs in BC patients. Some, but not all, of these studies have indicated that older women are more likely to discontinue their endocrine treatment than younger women.<sup>14</sup> In 2008, Owusu and colleagues studied the predictors of TAM discontinuation in 961 women aged >65. They showed that patients who discontinued their treatment were more likely to be aged 75–80 (HR = 1.41, 95% CI: 1.06–1.87) or >80 (HR = 2.02, 95% CI: 1.53–2.66) and to have high Charlson Comorbidity Index scores (HR = 1.52, 95% CI: 1.18–1.95) and cardiopulmonary comorbidities (HR = 1.75, 95% CI: 1.34–2.28).<sup>15</sup> In line with these results, He and colleagues found in 2015 that Swedish patients younger than 40 and older than 65 are at a higher risk of treatment discontinuation,<sup>16</sup> which may explain the fact that the elderly display a higher disease-specific mortality.<sup>17</sup> By contrast, Hadji et al. recently reported the results of a study with a 3-year follow-up period investigating persistence in BC patients treated with AIs or TAM, which showed that there was no association between age and adherence.<sup>18</sup> Nonetheless, in line with another work from the US,<sup>19</sup> Hadji and colleagues found that overall persistence was low at 1 year (around 70%).

Today, the influence of age on persistence with TAM and especially with AIs remains unclear. The aim of the present study was to investigate age-related persistence (in patients aged under and over 70) in women with endocrine-responsive BC receiving TAM or AIs in Germany. We included in our analysis several concomitant diseases (i.e. depression, osteoporosis, and diabetes), related or not to hormonal therapies,<sup>20,21</sup> and known to affect persistence.<sup>1,22</sup> Finally, symptom-relieving drugs were incorporated in our analysis, as they may increase the side effects of TAM and AIs.

## 2. Methods

### 2.1. Database

This study was conducted in Germany. The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, basic medical, and demographic data obtained directly and in an anonymised format from computer systems used in the practices of general practitioners.<sup>23</sup> Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data have been monitored by IMS based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses, and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices were appropriate for obtaining a representative database of general and gynecological practices.<sup>23</sup> Prescription statistics for several drugs were very similar to data available from pharmaceutical prescription reports.<sup>23</sup> The age groups for given diagnoses in the Disease Analyzer also agreed well with those in corresponding disease registries.<sup>23</sup>

### 2.2. Study Population

The database included 1123 general and 243 gynecological practices. First-time TAM or AI prescriptions from January 2004 until December 2013 were defined as index dates; maximum follow-up was until April 2015.

All subjects diagnosed with metastatic or non-metastatic BC (ICD 10: C50) were identified, and subjects with a first-time prescription of either TAM (n = 15,447) or AI (anastrozole, exemestane, letrozole) (n = 13,498) between January 2004 and December 2013 were then selected. Patients with a follow-up time of less than 365 days prior to index date were excluded. This exclusion was necessary for the correct identification of treatment initiation. Age above 18 years at index date constituted a further inclusion criterion. Patients with BC were classified into two groups: women <70 and women ≥70 years of age.

### 2.3. Study Outcome

The main outcome measure was the age-dependent endocrine treatment discontinuation rate within 5 years after index date in the two different age groups (<70 and ≥70). Treatment discontinuation was defined as a period of 90 days without TAM or AI therapy.

A longitudinal dataset of medication supply was created for each individual patient and non-persistence with endocrine therapy (TAM, anastrozole, exemestane, letrozole) was calculated. As part of this process, the number of days of drug supply was calculated on the basis of the quantity and dosage information associated with each prescription record. All patients were monitored for a period ranging from at least 3 months to 5 years following their index date.

Patients restarting initial treatment or starting another endocrine therapy after 90 days without therapy were classified as non-persistent, along with patients who discontinued the initial therapy and received no further hormonal therapy.

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