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Tamoxifen-Related Adverse Effects in High-Risk Woman Patients: A Narrative Review OF Randomized Controlled Trials

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ABSTRACT

Breast cancer is the fifth leading cause of cancer-related mortality worldwide. Tamoxifen is a commonly used and effective first-line hormonal therapy for estrogen receptor-positive breast cancer. Despite its proven ability to reduce recurrence and mortality, its use is associated with various adverse events (AEs) that may affect patient adherence. This review aims to identify the side effects of tamoxifen in women at high risk of breast cancer and in breast cancer patients based on selected clinical studies. A narrative literature review was conducted using PubMed and Scopus for studies published between 2015 and 2025. Of 141 records identified, 7 studies (n = 7 RCTs) were included, with sample sizes ranging from 167 to 7,154 participants and tamoxifen doses from 2.5 to 20 mg/day. Common AEs included hot flushes, vaginal discharge, menstrual disorders and nausea, while serious AEs included thromboembolism and endometrial cancer. Higher doses were associated with increased AE risk, particularly in premenopausal women. Low-dose tamoxifen showed a more favorable safety profile, although comparative efficacy remains uncertain. Personalized dosing, proactive monitoring, and patient education are essential, and further research is needed to evaluate long-term safety and optimize individualized treatment strategies.

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Keywords:
Hot Flushes; Venous Thromboembolism; Endometrial Neoplasms; Low-Dose Tamoxifen; Randomised Controlled Trials

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1. Introduction

Breast cancer is the fifth leading cause of cancer-related deaths worldwide, with an estimated 2.3 million new cases annually, and remains the leading cause of cancer-related mortality among women [1],[2]. It is a malignancy characterized by uncontrolled cell growth in breast tissue [3]. Mortality rates are higher in developing regions, such as Melanesia, West Africa, Polynesia, and the Caribbean, compared to developed regions including Australia and New Zealand, Western Europe, and Northern Europe [4],[5]. Early detection plays a crucial role in reducing mortality and improving prognosis [6].

Breast cancer is classified into several molecular subtypes, including luminal A/B (ER/PR+, HER2– or +), HER2-enriched (ER/PR–, HER2+), and triple-negative (ER/PR–, HER2–) [7], [8], [9], [10]. Treatment strategies are determined based on disease stage and subtype, and include surgery, chemotherapy, radiotherapy, endocrine therapy, and immunotherapy [11], [12], [13], [14]. Among these, endocrine therapy plays a key role in hormone receptor-positive breast cancer.

Tamoxifen, a selective estrogen receptor modulator (SERM), remains a cornerstone endocrine therapy in the management of hormone receptor-positive breast cancer and is widely used for both adjuvant treatment and risk reduction in high-risk populations [15], [16], [17], [18], [19], [20]. Its use has been shown to reduce recurrence and mortality rates by approximately 30–50% following five years of therapy [21],[22]. Tamoxifen exerts its therapeutic effect by acting as an estrogen antagonist in breast tissue while demonstrating partial agonist activity in other tissues, such as the endometrium. This tissue-specific mechanism underlies both its clinical efficacy and its diverse adverse effect profile[23], [24], [25], [26], [27].

The side effects associated with tamoxifen use range from common symptoms, such as hot flushes, vaginal discharge, and musculoskeletal complaints, to more serious adverse events, including venous thromboembolism and endometrial cancer [28], [29] , [30], [31] [32]. These adverse events may vary in prevalence and severity depending on dose, duration of therapy, and patient characteristics. Therefore, this review aims to synthesize evidence from randomized controlled trials (RCTs) to characterize the prevalence and spectrum of tamoxifen-related adverse events, evaluate dose-dependent and time-dependent risks, and provide evidence-based insights to support personalized dosing and monitoring strategies in clinical practice

2. Method

Literature Search Strategy

This narrative review was compiled through a literature review based on scientific articles. The databases used in the search were PubMed and Scopus. The keywords used in the PubMed search were "*Breast Neoplasms*" AND "*Tamoxifen*" AND "*Drug-Related Side Effects and Adverse Reactions*" AND "*Randomised controlled trial*", while the keywords used in the Scopus search were "*Breast Cancer*" AND "*Tamoxifen*" AND "*Adverse Drug Reactions*" AND "*Randomised controlled trial*".

Article selection procedure

The article selection process was conducted based on predefined inclusion and exclusion criteria to ensure methodological rigor. This review explicitly included only randomized controlled trials (RCTs) and RCT-based analyses, focusing on studies published between 2015 and 2025, written in English, and reporting adverse effects of tamoxifen in patients with breast cancer or women at high risk of developing breast cancer. Only studies that explicitly reported tamoxifen-related adverse events were included in the final analysis.

The exclusion criteria comprised case reports, systematic reviews, studies with irrelevant topics, and those that did not adequately describe or report tamoxifen-associated adverse effects. A total of 141 articles were initially identified through database searching, including 8 articles from PubMed and 133 from Scopus. After removing 3 duplicate records, 138 articles remained for screening. During the screening phase, studies were assessed based on publication year and relevance to tamoxifen-related adverse effects, resulting in the exclusion of 96 articles published before 2015 and 35 articles deemed irrelevant. Ultimately, 7 studies met all eligibility criteria and were included in the final qualitative synthesis.

A formal risk-of-bias assessment was not conducted in this review due to the limited number of eligible studies and substantial heterogeneity in the reporting of adverse outcomes, which limited the feasibility of applying a standardized risk-of-bias assessment tool across studies. The adverse effects extracted from the included studies were categorized into three predefined domains: gynecological events (e.g., endometrial cancer), thromboembolic events (e.g., venous thromboembolism), and systemic adverse effects (e.g., hot flashes and nausea).

The article selection process followed the predefined inclusion and exclusion criteria and is illustrated in a PRISMA flow diagram (**Figure 1**). The primary measures of effect reported across studies were relative risk (RR) and hazard ratio (HR), along with 95% confidence intervals (95% CI), where available. However, due to variability in study design, outcome definitions, and reporting methods, the findings were synthesized narratively rather than quantitatively pooled.

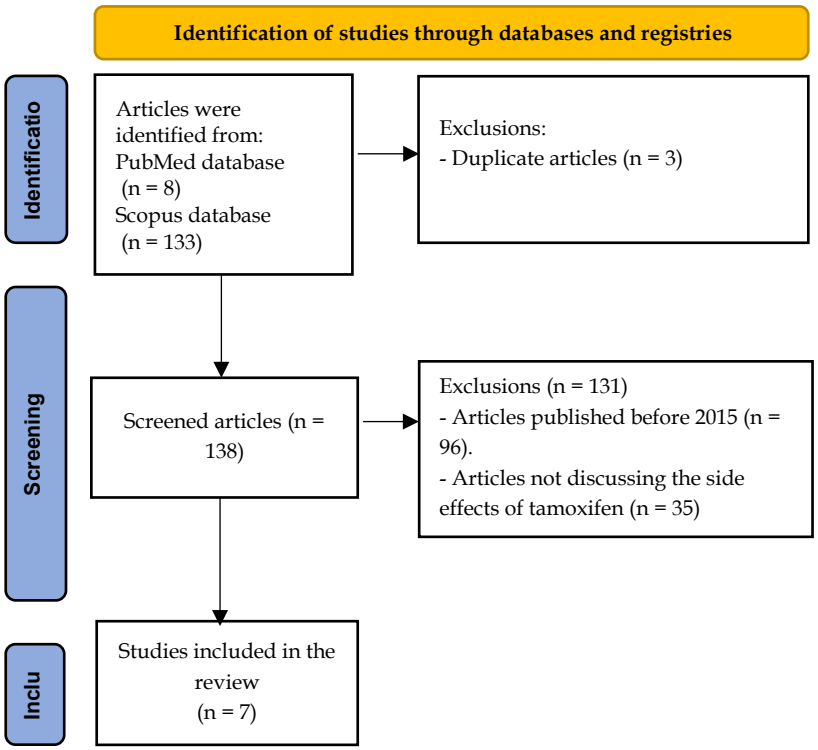


Figure 1. PRISMA Flow Diagram of Literature Search

3. Results and Discussion

Table 1 lists seven articles that met the inclusion criteria regarding the side effects of tamoxifen use. The articles were published between 2015 and 2025. The research subjects (participants) came from the United States, Taiwan, Japan, Australia, New Zealand, and European countries, including the United Kingdom, Belgium, Hungary, France, Italy, Finland, Spain, Ireland, and Sweden. The population range of the seven journals was 167 women to 7,154 women, aged 20-75 years, diagnosed with breast cancer and women at high risk of breast cancer, with tamoxifen doses ranging from 1 mg to 20 mg. The interventions focused on the use of tamoxifen, either as monotherapy or in combination. The duration of treatment in the seven journals varied from 3 months to 5 years.

Table 1. List of Articles Meeting Inclusion Criteria

No	Author and Year of Publication	Country	Participants	Age	Number of Participants	Intervention and treatment duration	Dose	Results
1.	DeCensi et al. 2019	Italy	Women with intraepithelial neoplasia	≤75	500	Tamoxifen versus placebo in patients with intraepithelial neoplasia with a treatment duration of 3 years	20 mg/day	Vaginal discharge, irregular menstruation, hot flushes[33] .
2.	Hale et al. 2020.	United Kingdom	Healthy women at high risk (pre/post menopause)	35 - 70	6,707	Tamoxifen versus placebo in women at high risk of breast cancer with a treatment duration of 5 years	20 mg/day	Hot flushes, uterine bleeding, thromboembolism, risk of endometrial cancer [32].
3.	Hammarström et al. 2023	Sweden	Healthy women at high risk of breast cancer	40–74	1,440	Comparison of tamoxifen doses in healthy women, with a treatment duration of 6 months	1, 2.5, 5, 10, and 20 mg	Hot flushes, menstrual disorders [34].
4.	Rabaglio et al. 2020	Multinational*	Postmenopausal women, HR+ early-stage breast cancer	40-75	6,144	Tamoxifen versus letrozole in postmenopausal HR+ patients, with a treatment duration of 5 years.	20 mg/day	Hot flushes, nausea [21].
5.	Cuzick et al., 2015	United Kingdom, Australia,	Women at high risk of breast cancer	35–70	7,154	Tamoxifen versus placebo in women at high risk of breast	20 mg/day	Risk of endometrial cancer, blood clots (DVT)[35] .

		New Zealand, Finland, Spain, Switzerland, Belgium, Ireland				cancer with a treatment duration of 5 years.		
6.	Sung et al., 2023	Taiwan & Japan	Women with low-risk DCIS, ER-positive, post-BCS	>40	810	Low-dose tamoxifen (5 mg/day) for 5 years vs. radiotherapy 40–50 Gy	5 mg/day	Mild side effects: hot flushes, nausea, vaginal discharge[36].
7.	Kurebayashi et al., 2016	Japan	Premenopausal, post-operative HR-positive breast cancer	≥ 20	167	Tamoxifen 20 mg/day + leuprorelin depot (6 months vs 3 months), duration 96 weeks	20 mg/day	Side effects: hot flushes[37].

Note: Multinational(Switzerland, USA, Denmark, Australia, New Zealand, Belgium, Hungary, France, UK, Italy).*

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Vasomotor Side Effects

Vasomotor side effects, particularly *hot flashes*, represent the most frequently reported adverse events among patients receiving tamoxifen and are a major contributor to reduced treatment adherence. Evidence suggests that these symptoms occur at a high prevalence during active therapy [35]. Quantitative data from Kurebayashi demonstrate that 97.6–98.8% of patients experienced adverse events, with *hot flushes* being the predominant symptom, mostly classified as mild to moderate in severity [37]. Furthermore, a clear dose–response relationship has been observed, where the intensity of vasomotor symptoms is reduced by approximately 34% in the low-dose group (2.5–5 mg) compared to the standard dose (10–20 mg) [34]. These findings indicate that vasomotor symptoms have a very high prevalence (affecting nearly all patients), and although they are generally not life-threatening, they significantly impact quality of life and contribute to early treatment discontinuation [33].

Gynecological and Gastrointestinal Side Effects

Gynecological side effects, including *vaginal discharge*, vaginal dryness, and menstrual disturbances, are attributed to the partial agonist effect of tamoxifen on endometrial tissue and are commonly reported among users [35]. In addition, gastrointestinal symptoms such as nausea are also observed as part of the systemic effects of tamoxifen therapy. Data from Sung indicate that, in patients receiving low-dose tamoxifen (5 mg/day), the most common adverse events include *vaginal discharge*, *hot flashes*, and nausea, which are generally mild and well tolerated [36]. From a prevalence and clinical impact perspective, only approximately ≤5% of patients discontinued therapy due to adverse effects, suggesting that although these symptoms are relatively common, their severity is typically low [36]. Most of these side effects are reversible and tend to resolve after treatment cessation, and they are not significantly associated with an increased risk of breast cancer recurrence [32].

Serious Side Effects: Endometrial Cancer and Venous Thromboembolism (VTE)

Serious adverse events, particularly endometrial cancer and *venous thromboembolism* (VTE), remain the primary safety concern associated with tamoxifen use, although their prevalence is relatively low. In low-dose studies, these events were rare, with only one case of deep vein thrombosis and one case of endometrial cancer reported over approximately five years of follow-up [33] [36]. However, larger trials such as the BIG 1-98 study reported a higher prevalence of thromboembolic events, with 4.9% for all grades and 2.7% for severe cases (grade 3–5), and a significantly increased risk compared to control groups (HR 2.10; 95% CI 1.42–3.12) [21].

Importantly, both endometrial cancer and VTE demonstrate a consistent pattern of occurrence, predominantly arising during the active treatment phase, with no significant

increase observed after treatment discontinuation [35] [21]This is supported by study designs in which adverse events were monitored during therapy and up to approximately 30 days post-treatment. These findings emphasize that the risk of serious adverse events is time-dependent, directly associated with tamoxifen exposure, and declines after cessation of therapy [21].

Clinical Implications

The findings from this narrative review have important implications for clinical practice, particularly in the use of tamoxifen as first-line therapy for oestrogen-positive breast cancer. The most common side effects, such as hot flushes, vaginal discharge, menstrual disorders and nauseaneed to be actively monitored as they can affect patient compliance with treatment. More serious side effects such as thromboembolism and endometrial cancer, although rare, should still be monitored in the long term, especially in postmenopausal patients. The use of low-dose tamoxifen (2.5–5 mg/day) shows potential in reducing the incidence of side effects without reducing therapeutic efficacy, thus providing an option for individualised therapy, especially in patients with low tolerance to standard doses. This narrative review is expected to provide a deeper understanding of the side effects of tamoxifen use and serve as a basis for developing better, more effective, and safer treatment strategies.

Limitations

This narrative review presents an important overview of the side effects of tamoxifen use in high-risk women and breast cancer patients based on seven randomised controlled trials (RCTs). However, there are several limitations that need to be considered when interpreting the results of this review. The number of studies included is still limited, so the data coverage does not fully represent all available clinical evidence, especially from various geographical regions and broader ethnic populations. The duration of treatment in each study was not uniform, ranging from 3 months to 5 years.

4. Conclusion

This review included seven randomized controlled trials (RCTs) published between 2015 and 2025, with sample sizes ranging from 167 to 7,154 participants, encompassing both breast cancer patients and women at high risk of developing breast cancer, thereby providing a defined scope of current evidence. The main adverse events (AEs) identified were hot flushes, vaginal discharge, menstrual disorders, nausea, thromboembolism, and endometrial cancer. Common AEs, particularly hot flushes and menstrual disturbances, demonstrated a high prevalence and were more frequently observed at higher doses and among premenopausal women. In contrast, serious AEs such as thromboembolism and endometrial cancer exhibited a lower overall incidence but showed a clear dose-related increase in risk. Notably, these serious adverse events predominantly occurred during the active treatment phase, indicating a time-dependent relationship with tamoxifen exposure. These findings highlight important practical implications, emphasizing that personalized dosing strategies may reduce the incidence and severity of adverse events while maintaining therapeutic efficacy. Furthermore, proactive monitoring and patient education are essential to improve treatment adherence and minimize complications, particularly among premenopausal women and individuals at increased risk of endometrial cancer. Future research should focus on evaluating long-term safety outcomes, optimizing individualized dosing strategies,

identifying patient-specific risk factors, and conducting large-scale randomized controlled trials across diverse populations to enhance the generalizability of findings.

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Conflicts of Interest:

The authors declare no conflict of interest regarding the publication of this paper.

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