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Original Article

Oncology Section

Ocular Toxicity Associated with Tamoxifen Administration in Patients with Breast Cancer: A Systematic Review

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ABSTRACT

Introduction: Tamoxifen (TAM), a selective Oestrogen Receptor (ER) modulator, is widely used for treating and preventing ER-positive Breast Cancer (BC). TAM, administered as an adjuvant therapy for hormone receptor-positive BC, reduces recurrence but can cause ocular toxicity, including retinal degeneration, macular oedema, and corneal changes. However, the underlying mechanisms behind these effects remain unclear.

Aim: This systematic review aimed to evaluate the ocular toxicity induced by TAM in patients with BC and to assess the reported adverse events.

Materials and Methods: A systematic review was conducted which included a comprehensive search of electronic databases and grey literature sources to identify relevant studies published between May 2018 and May 2024. Observational studies (case-control and cross-sectional) published in the English language that detailed the ocular Adverse Effects (AE) of TAM in patients with BC were considered for inclusion. Three reviewers screened the selected studies based on the title and abstract. Disagreements were resolved by discussion with another reviewer. Data extraction included study characteristics, patient demographics, intervention details, and ocular changes.

Results: Five studies met the inclusion criteria and were included in the review. The analysis revealed that TAM-induced ocular toxicity results in diverse structural and functional changes within eye tissues, including retinal degeneration, macular thinning, alterations in choroidal thickness, and vascular modifications. The severity of ocular toxicity correlated with cumulative TAM exposure, highlighting the need for long-term eye monitoring in patients receiving extended therapy.

Conclusion: This systematic review indicated a possible link between TAM use and ocular toxicity, although the evidence is limited by methodological constraints. These results highlight the necessity of eye monitoring for patients undergoing TAM treatment, especially for those receiving long-term regimens.

Keywords: Breast neoplasms, Ocular changes, Oestrogen receptor modulators, Retinal diseases

INTRODUCTION

The BC remains the most prevalent cancer among women globally, necessitating diverse treatment strategies, including chemotherapy, radiotherapy, adjuvant therapy, and surgical interventions. Treatment selection is primarily guided by the tumour characteristics. TAM, a selective ER modulator, plays a vital role in cancer treatment due to its dual function as an oestrogen agonist and antagonist. It is widely utilised for managing and preventing ER-positive BC, typically administered at a daily dose of 20 mg [1,2]. TAM is employed for advanced or metastatic ER-positive BC as adjuvant therapy in the early stages or post-surgery, and when patients are unsuitable for clinical chemotherapy [1,2].

TAM is associated with notable ocular AEs. Studies have linked TAM to various eye conditions, including retinal degeneration, corneal opacities, cataracts, cystoid macular oedema, macular holes, optic neuritis, and retinopathy, particularly at higher doses or with prolonged use [3-5]. Alhouz H et al., reported that TAM induces changes in macular thickness irrespective of cumulative dose [4], while Ahmed MMA et al., observed that alterations in the retinal pigment epithelium were correlated with treatment duration, underscoring the importance of regular eye examinations [5].

Studies have also highlighted the metabolic and genetic factors that influence TAM efficacy [6,7]. SET overexpression in patients with ER-positive BC is associated with reduced treatment responses and worse recurrence-free survival, suggesting that genetic profiling may be crucial for personalised therapy [1]. Non adherence to TAM therapy is a significant issue that compromises treatment outcomes. Pistilli B et al., proposed therapeutic drug monitoring to identify and address non-adherence [8].

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TAM presents other significant AEs and benefits, including its paradoxical role in endometrial cancer, where it can both increase risk and offer treatment benefits [2]. Its long-term effects on bone density in premenopausal women, resulting in bone loss, have been well documented [9,10]. With an increasing number of BC survivors undergoing extended TAM treatment, questions have arisen regarding its long-term effects on vision. While studies suggest a link between TAM and visual problems, the evidence remains inconclusive [3-5]. A comprehensive literature analysis is required to determine the ocular AEs, identify risk factors, and inform clinical guidelines.

TAM, used as an adjuvant therapy for hormone receptor-positive BC, reduces recurrence but can cause ocular toxicity, including retinal degeneration, macular oedema, and corneal changes [3-5]. However, the underlying mechanisms behind these effects remain unclear. Understanding the ocular impact of TAM is crucial for managing BC survivors undergoing prolonged treatment. This review evaluated TAM-induced ocular toxicity in patients with BC, assessed reported complications, explored dose and duration-related effects, identified risk factors, and provided recommendations for screening and management. These findings will help optimise patient care and guide future research.

MATERIALS AND METHODS

The present systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA) and ensured the proper conduct and validation of the review [11]. A comprehensive search of electronic databases, including PubMed, Scopus, and Web of Science, was performed to identify relevant studies published between May 2018 and May 2024. Grey literature sources, such as OpenGrey, ProQuest Dissertations and Theses Global, ClinicalTrials.gov, and Google Scholar, were also searched to capture unpublished studies and trial data.

The terms 'BC', 'Breast Tumour', 'Breast neoplasm', 'hormone receptor positive', 'TAM', and 'Ocular Toxicity' were used as keywords, with Boolean operators AND and OR applied.

Inclusion criteria: Eligible studies included adults (≥18 years) with BC who received TAM therapy and reported ocular toxicity outcomes. Studies were included regardless of the comparison groups, although comparisons between TAM and other treatments, such as Aromatase Inhibitors (AIs), were considered to evaluate differences in ocular outcomes. Only case-control and cross-sectional studies published in English that provided sufficient data on ocular outcomes and met predefined criteria were included.

Population (P): This review focused on women aged 18 years and older diagnosed with hormone receptor-positive BC who were undergoing TAM treatment. The emphasis was on patients taking TAM for extended periods and those experiencing eye-related side effects.

Intervention (I): TAM was administered at a dose of 20 mg daily for the treatment of metastatic ER-positive BC.

Comparison (C): Studies were included regardless of the comparison group.

Outcomes (O): The main outcome evaluated was ocular toxicity associated with TAM use.

Study design framework (S): Only observational studies were included: case-control and cross-sectional studies. The selection criteria focused on studies that provided quantitative data on ocular outcomes after TAM use.

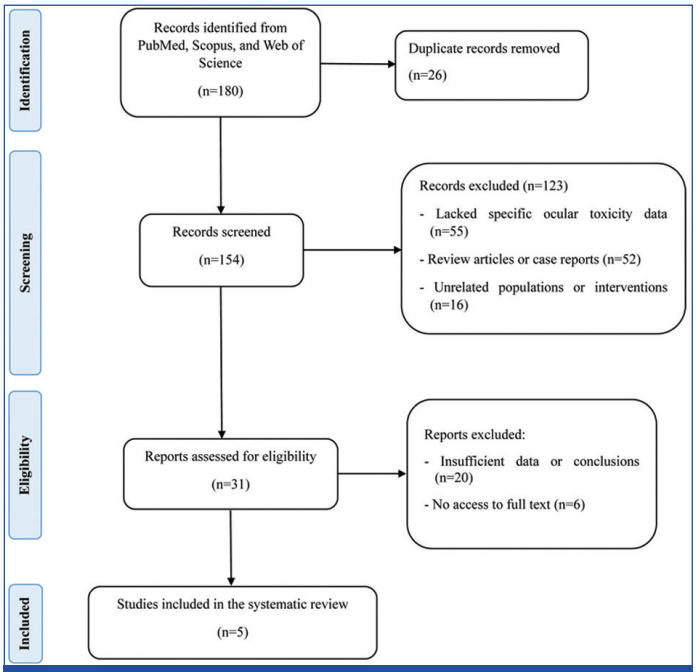
Exclusion criteria: Exclusion criteria comprised non-human studies, insufficient data, review articles, case reports, conference abstracts, and editorials. References were imported into RefWorks 2.0 (RefWorks-COS, Bethesda), where duplicates were manually eliminated, with further duplicates removed later. Citations were then imported into DistillerS (Evidence Partners Incorporated, Ottawa) for title and abstract screening and full-text data characterisation.

Three independent reviewers screened and selected studies based on the title, abstract, and full text reviews. Disagreements were resolved through discussion or consultation with a fourth reviewer. Data extraction included study characteristics, patient demographics, intervention details, and ocular changes.

RESULTS

The initial search of the PubMed, Scopus, and Web of Science databases yielded 180 records. After eliminating 26 duplicates, 154 articles were identified. The screening process excluded 123 records that were irrelevant or did not meet the inclusion criteria. Among these 123 articles, 55 lacked specific ocular toxicity data related to TAM; 52 were review articles or case reports rather than original research; and 16 investigated different populations or unrelated interventions. Of the 31 studies evaluated for eligibility, 26 were excluded due to inadequate data or conclusions. Ultimately, five studies fulfilled the inclusion criteria and were included in the systematic review [12-16]. The five included studies were based on their relevance in examining the ocular Side Effects (SE) of TAM. They provide valuable information regarding the potential risks, clinical presentation, and progression of eye-related toxicity in TAM recipients. [Table/Fig-1] illustrates the selection process, and [Table/Fig-2] lists the five studies included [12-16].

An analysis of the compiled research revealed that TAM-induced ocular toxicity results in diverse structural and functional changes



[Table/Fig-1]: PRISMA 2020 flow diagram of the literature search and study selection for the systematic review.

Study details	Type of study	Sample size	Mean age and duration of TAM use	Objective	Main results	Other groups and attribution
Bicer T et al., 2020, Turkey [12]	Case-control study	50 patients with BC underwent treatment with TAM	49.9 years and 27.32 months	Evaluated tear function in individuals undergoing adjuvant hormone therapy for BC.	Significant association between premenopausal TAM use and the Ocular Surface Disease Index and fluorescein separation time ($p<0.05$). Schirmer's test has no statistical significance.	This study included a control group of patients with BC who did not receive TAM. The observed changes were associated with TAM.
Lim IL et al., 2018 Malayasia [13]	Cross-sectional study	70 patients with BC underwent treatment with TAM	54 years and 20 months	Assessed the relationship among macular pigment optical density, central macular thickness, and TAM dose.	TAM dose-dependent decrease in ocular macular pigment density in patients with BC ($p=0.009$).	TAM caused these changes in a dose-dependent manner, as BC alone is unlikely to cause these changes.
Crisostomo et al., 2020, Portugal [14]	Case-control study	100 patients with BC underwent treatment with TAM	57.5 years and 30 months	Aimed to detect changes in chorioretin levels caused by TAM.	Development of pseudocysts and a decrease in macular thickness in the entire retina, subfoveal choroidal layer, ganglion cells, and internal plexiform layer.	A control group without TAM treatment was also included. Ocular changes were associated with TAM use rather than BC.
Bolukbasi S et al., 2020, Turkey [15]	Cross-sectional study	44 patients with BC underwent treatment with TAM	51.6 years and 47.4 months	Investigated choroidal thickness, ganglion cell complex, and photoreceptor external segment length.	Increased choroidal thickness and pachychoroid pigment epitheliopathy, as well as a statistically significant decrease in ganglion cell complex thickness ($p<0.001$).	No control group was included. The results were interpreted as being related to TAM rather than BC due to structural changes.

Lee S et al., 2019, Korea [16]	Cross-sectional study	292 patients with BC underwent treatment with TAM	65 years and 58 months	Examined vascular anomalies and measured the density of blood vessels in connection with TAM retinopathy.	Vascular alterations in OCT Angiography that resembled the vascular changes reported in the initial stages of type 2 macular telangiectasia (p=0.003).	The control group was not specified. The results are linked to TAM usage, not BC. Structural vascular patterns are unlikely to stem from BC alone.

[Table/Fig-2]: Characteristics of selected studies on the link between Tamoxifen (TAM) administration and ocular changes observed in patients with Breast Cancer (BC) [12-16].
BC: Breast cancer; TAM: Tamoxifen; OCT: Optical coherence tomography

within eye tissues. The five studies consistently demonstrated retinal degeneration, macular thinning, alterations in choroidal thickness, and vascular modifications in patients receiving TAM treatment. These observations suggest that prolonged TAM use has a cumulative impact on eye health, with individual studies highlighting various mechanisms of toxicity.

Bolukbasi S et al., noted increased choroidal thickness and pachychoroid pigment epitheliopathy with structural damage [15]. Lee S et al., detected vascular changes through Optical Coherence Tomography (OCT) angiography, similar to type 2 macular telangiectasia [16]. Lim IL et al., and Crisóstomo S et al., observed decreased macular pigment density and ganglion cell layer thinning from TAM use [13,14]. Bicer T et al., reported impaired tear film function in premenopausal women receiving TAM therapy [12].

The duration of TAM use varied from 20 to 58 months across studies, with Bicer T et al., reporting 27.32 months, Lim IL et al., 20 months, Crisóstomo S et al., 30 months, and Lee S et al., 58 months [12-14,16]. All studies used a daily TAM dose of 20 mg. Bolukbasi S et al., examined choroidal thickness and photoreceptor external segment length, while Lim IL et al., evaluated macular pigment density and the correlation with TAM dosage [13,15].

The studies included control groups matched by age without TAM exposure or employed comparative analysis to distinguish the drug effects. The observed ocular changes, including reduced macular pigment density, choroidal thickening, and ganglion cell layer thinning, were associated with TAM treatment rather than with BC [12-16].

These findings indicate that TAM affects multiple ocular layers, from the tear film and macular pigment to choroidal and vascular structures. The variations in reported outcomes likely stem from differences in study populations, TAM dosage, and treatment duration. Despite some inconsistencies, the overall trend suggests that extended TAM exposure increases the risk of ocular toxicity. Future studies should focus on long-term assessments using standardised imaging techniques to track the progression of ocular changes and establish screening guidelines for high-risk patients.

Diverse study designs and assessment techniques have led to variations in reported ocular SEs. Some studies have concentrated on retinal and macular changes, whereas others have examined choroidal thickness and vascular modifications. Differences in patient demographics, including age, hormonal status, TAM treatment duration, and impacted outcomes, also contribute to these variations. Studies with longer treatment periods (greater than 30 months) documented more pronounced changes, such as decreased macular pigment optical density, ganglion cell layer thinning, and alterations in retinal structure. The severity of ocular toxicity correlated with cumulative exposure, underscoring the need for long-term eye monitoring in patients receiving extended TAM therapy. Despite these disparities, most studies agree that TAM has measurable effects on ocular structures, particularly with prolonged use.

DISCUSSION

In this review, we found a significant association between TAM use and various eye problems. This systematic review highlights the need for a more detailed understanding of the mechanisms of TAM-induced ocular toxicity and their clinical implications. While studies have established a link between TAM use and ocular changes, the present systematic review synthesises the findings to provide a broader perspective on the reported effects. It also underscores the necessity to address knowledge gaps, such as the long-term impact of low-dose TAM therapy, potential genetic predispositions to ocular toxicity, and optimal screening protocols for early detection.

All participants in this study were women aged around 50 years with BC who were receiving TAM as part of their hormone therapy, which has been proven effective in reducing the risk of disease relapse and death rates [17]. This research showed a 47% decrease in the risk of locoregional cancer recurrence in women who received TAM for five years and a 32% reduction in risk for those who took TAM for an additional five years [18].

TAM treatment may require a longer duration, leading to varying treatment periods among the patients studied. In these studies, the treatment duration ranged from 20 to 58 months. The study by Davies C et al., showed that longer therapy with this medication can result in lower rates of BC recurrence and death compared to shorter therapies [19].

The study participants were approximately 50 years old, which aligned with the age range that has the highest occurrence of BC and the most favourable response to TAM [20,21]. TAM is classified based on participants' chemotherapy history to examine potential confounding factors [22]. When chemotherapy was stopped, most retinal changes ceased, suggesting that TAM toxicity may be attributed to this treatment method. Moreover, the group that received TAM experienced hormonal changes, including menopause. However, other co-morbidities or medications may also contribute to eye impairment. This review did not address other risk factors for eye injuries, such as diabetes, family history, or therapies applied to the control group. As a result, these factors were not mentioned in most studies, and the specific therapies used by the control groups remain unknown, potentially affecting the final evaluation.

TAM is usually administered as adjuvant therapy for premenopausal patients with hormone-positive BC, including those with oestrogen receptor-positive tumours [23]. Additionally, TAM is often used as a chemopreventive agent to lower the risk of invasive BC in women with ductal carcinoma in situ [22].

Alternative drugs, such as third-generation aromatase inhibitors (AIs), are effective in hormone treatment for hormone receptor-positive BC, particularly in postmenopausal women who are at a higher risk of developing endometrial cancer [24,25]. AIs are not recommended for premenopausal women, even if ovarian function is restored, due to increased risks of osteoporosis, high cholesterol, and AEs from the Luteinising Hormone-Releasing Hormone (LH-RH) blocking mechanism in the uterus. These risks highlight the need for careful consideration when selecting endocrine therapy for premenopausal women [26]. Postmenopausal cancer patients with positive hormone receptors who use AIs may experience AEs such as increased fractures, osteoporosis, arthralgia, and bone pain [27]. AIs block the production of oestrogen from androgen precursors in tissues such as the adrenal glands and fat tissue.

Although TAM use showed a significant association with ocular toxicity in all studies examined, ocular AEs were rarely reported and less frequently observed than changes in other systems, such as the uterus. The control group in these studies received no

treatment, and the studies employed different diagnostic evaluation techniques that have not been validated, resulting in inconsistent findings regarding ocular changes.

Extended TAM use can affect visual function and quality of life due to ocular toxicity. Research has documented retinal degeneration, macular thinning, and changes in choroidal vasculature, although the potential for reversal remains uncertain. Up to 12% of long-term TAM users show detectable retinal changes, with the severity linked to cumulative exposure. Despite evidence that early detection through optical coherence tomography and fundus autofluorescence can facilitate timely intervention before permanent damage occurs, standardised screening protocols are lacking. Existing studies are weakened by inconsistencies in control groups and often fail to account for confounding variables, such as age, diabetes, hypertension, or concurrent medications. Future studies should focus on meticulous matching, propensity score adjustments, and non-TAM hormone therapy users as comparison groups. Incorporating regular eye examinations into BC survivorship care and exploring protective measures could reduce ocular risks while maintaining the effectiveness of the treatment.

Limitation(s)

This systematic review has several limitations. The diversity in study designs, sample sizes, and diagnostic approaches among the included studies may have impacted the consistency of the results. The predominance of observational research, particularly case-control and cross-sectional studies, restricts the determination of causality between TAM use and ocular side effects. Including only English-language publications potentially introduces language bias and excludes relevant non-English studies. Variations in study populations, follow-up periods, and assessment methods complicate the feasibility of direct comparisons and meta-analysis.

CONCLUSION(S)

This systematic review indicated a possible link between TAM use and ocular toxicity, although the evidence is limited by methodological constraints. While most studies effectively managed selection bias, concerns were raised regarding performance and detection bias, emphasising the need for enhanced blinding techniques and assessment protocols. These results highlight the necessity of eye monitoring for patients undergoing TAM treatment, especially for those receiving long-term regimens. Due to the observational nature of the analysed studies, further research should focus on confirming these associations through well-structured prospective investigations with uniform outcome measures. Improving study design and reducing bias will enhance the credibility of the findings and support evidence-based clinical decisions concerning the eye-related risks of TAM therapy. However, the evidence is constrained by methodological limitations, such as variations in study designs, sample sizes, and diagnostic approaches. Future research should prioritise large-scale prospective studies with standardised diagnostic criteria and extended follow-up durations to better understand the ocular adverse events associated with TAM therapy.

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