

Review

Ocular Side Effects of Aromatase Inhibitor Endocrine Therapy in Breast Cancer – A Review

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Abstract. *Background:* Aromatase inhibitor therapy is currently the preferred choice in postmenopausal women with estrogen receptor positive breast cancer. This article reviews the ocular side effects of treatment with aromatase inhibitors (AIs)

in patients with breast cancer. Materials and Methods: A comprehensive search was performed on PubMed, Web of Science and Google scholar. *Results:* After duplication removal, 14 clinical studies and 5 case reports, published between 2008 and 2021, were identified. Most frequently, AI treatment resulted in minor to moderate dry eye symptoms. “De novo” onset of Sjogren syndrome during AI therapy was also reported. Retinal and optic nerve side effects varied from mild, subclinical anatomic and functional impairment to severe decreased vision, secondary to hemi-central retinal artery occlusion, bilateral optic neuritis or uveitis with bilateral macular edema. *Conclusion:* Visual disturbances encountered during AI treatment may be underestimated. Ophthalmic screening is important for early detection and appropriate treatment.

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Breast cancer, through the large number of cases diagnosed annually worldwide, is a major public health problem of the female population. According to the World Health Organization (WHO) statistics, in 2020 there 2.3 million women were diagnosed with breast cancer and 685,000 died globally (1). Breast cancer is the most prevalent malignancy, with 7.8 million alive patients diagnosed in the last 5 years, being associated with the most lost disability-adjusted life years (DALYs) by women than any other type of cancer (2). The introduction of screening methods to identify breast cancer early at asymptomatic stages and the use of new methods of complex cancer treatment have allowed a significant reduction in mortality after the 1990s (3-5).

It is almost 50 years since the first studies showed that estrogens, labeled with radioactive substances, are preferentially concentrated in certain areas of the human body, including neoplastic breast tissue, substantiating the role of estrogen receptor (6). Most breast cancers are dependent on the expression of estrogen receptors (ER), progesterone (PgR) or both, and their determination has predictive value and allows the selection of patients receiving hormone therapy as adjuvant therapy (4, 5).

If in the premenopausal period the main source of estrogen is the ovaries, in postmenopausal women estrogen is produced by the peripheral aromatization of androstenedione and testosterone to estrone and estradiol in extragonadal tissues, such as muscle, fatty tissue and breast. This explains the findings that, while in postmenopausal women the levels of serum estrogen are very low, the concentration of estrogen is 4-6-fold higher in breast tissue, which is relatively the same concentration as in premenopausal women, and it is even higher at the level of the breast tumor, by active uptake from the circulation and local aromatization in the tumor epithelial cells (7, 8).

Aromatase inhibitor therapy is currently the preferred choice in postmenopausal women with ER positive breast cancer. Three third-generation AIs were approved by the FDA as an adjuvant treatment for post-menopausal breast cancer patients: anastrozole (1 mg/day) and letrozole (2.5 mg/day) can be used upfront for 5 years, while exemestane (25 mg/day) is approved for use after 2-3 years of tamoxifen use, for a total of 5 continuous years (9-13). Clinical trials have confirmed that aromatase inhibitors are more effective and better tolerated than tamoxifen in postmenopausal women with early or advanced ER-positive breast cancer.

Tamoxifen competitively blocks estrogen receptors, having an anti-estrogenic action at the breast level. In addition, it also acts as a partial estrogen agonist in other tissues, such as the bone, endometrium, and vascular endothelium, preventing osteoporosis, but also being a risk factor for endometrial cancer and thromboembolic events (14). Third generation aromatase inhibitors (AIs) are much more potent and specific than the first agent, aminoglutethimide, and have been

approved for the hormonal treatment of breast cancer in postmenopausal women, decreasing estrogen to undetectable levels without influencing the levels of other classes of hormones (8, 9, 15). When administered to premenopausal women, aromatase inhibitors should be associated with LHRH analogs for ovarian inhibition. Depending on the structure and type of interaction with the aromatase enzyme, they are divided into non-steroidal agents, such as anastrozole and letrozole, and steroidal, as exemestane. The inhibition of aromatase is reversible with letrozole and anastrozole but irreversible with exemestane (16).

Steroidal inhibitors resemble the structure of androstenedione and function by competing for the substrate binding sites of the enzyme. Steroid inhibitors are considered less toxic, but they have androgenic effects at high doses and poor oral bioavailability, with the exception of exemestane. The non-steroidal inhibitors interact with the heme moiety of the CYP 450 prosthetic group of the aromatase molecule in a reversible manner. They have a good pharmacokinetic profile and lack hormonal properties, but are related to musculoskeletal disorders and bone demineralization (17).

Several clinical studies showed that treatment with aromatase inhibitors has generally lower side effects than tamoxifen (8, 18). Patients treated with AIs were reported to have lower risk of thrombotic events, endometrial cancer, uterine sarcoma and cerebral vascular diseases, side-effects that have been attributed to the partial estrogen-agonist action of tamoxifen. However, concerns have been raised about the long-term suppression of estrogen, which can result in aggressive menopause, and premature aging. Long term studies, on large cohorts of patients treated with anastrozole or letrozole vs. tamoxifen showed an increased risk of bone fracture, arthralgias, decrease in bone density and osteoporosis. Some relief could be offered by exemestane, due to its partial androgen agonist effects (19, 20).

The present article aims to document the ocular side effects related to the treatment of patients with breast cancer with aromatase inhibitors.

Materials and Methods

A comprehensive search was performed on PubMed, Web of Science and Google scholar, using the terms “breast cancer” AND “aromatase inhibitor” AND “ocular side effects”. Additional search was performed using the alternative words for “aromatase inhibitor”: “anastrozole”, “letrozole” and “exemestane”. For ocular side effects, further search was performed using the terms “ophthalmic side effects”, “ophthalmic effects”, “dry eye”, “cornea*” and “retina*” All articles in English language for which full text could be obtained were included. Due to the limited number of publications on this topic, any reported side effects, either with proved causality or for which increased awareness was

advised were included in the review. The type of study, number of patients, follow-up period, ocular side effects, ophthalmic treatment and outcomes were documented. Studies including patients with breast cancer treated with AIs not documenting ocular signs and symptoms were excluded.

Results

After duplication removal, a total of 14 clinical studies and 5 case reports were identified. They were published between 2008 and 2021 and reported ocular side effects in patients with breast cancer treated with aromatase inhibitors (Table I and Table II). There were 10 articles reporting impairment of the ocular surface (Table I), whereas 9 papers reported different neuro-retinal disturbances (Table II).

Dry eye and ocular surface abnormalities in AI treated breast cancer patients. Several clinical studies evidenced that hormonal therapy with aromatase inhibitors impacts ocular surface and Meibomian glands, resulting in a significant proportion of cases with dry eye disease, associated with meibomian dysfunction. In 7 studies (21-27), the diagnosis of dry eye was based on ophthalmic examination, whereas in the study of Cuzick *et al.* (28), on self-reporting of signs and symptoms (Table I).

All studies included in the review reported decreased tear break-up time (TBUT), and Schirmer test with increased ocular surface disease index (OSDI) in breast cancer patients treated with AI, when compared with normal postmenopausal women and with breast cancer patients treated with tamoxifen. The OSDI questionnaire is a simple tool that is considered sensitive and specific for dry eye diseases, which can be self-administered and used by health care professionals for screening (21, 31). An OSDI >12 was considered to indicate dry eye in all studies included in the review (21, 24, 28). Among subjective signs reported by patients, the most frequent were foreign body sensation, blurred vision, redness, and photophobia (23, 25). The alteration of the lacrimal film was strongly related to deficiency in the lipid layer, due to decreased meibomian function and blepharitis.

Agin *et al.* (21) documented the alterations of the eyelids and ocular surface in a prospective study, with a mean follow-up period of 6 months, and found a significant decrease in the densities of endothelial cells, stromal and basal epithelial cells as well as of nerve fiber densities at the level of the cornea. However, whether these observations should be regarded as class side effects of AIs or a direct consequence of estrogen deprivation is still a subject of research. All studies except that of Gibson *et al.* (24), found a significant higher proportion of patients with dry eye signs and symptoms among those treated with AIs compared to normal postmenopausal women. Several cross-sectional studies based on ophthalmologic objective tests showed an

incidence of dry eye syndrome of 29% to 46% of AI patients. Most cases exhibit minor to moderate symptoms, that responded favorably to local treatment with artificial tears and lubricants. Inglis *et al.* found a strong association between dry eye symptoms in patients treated with AIs and other side-effects such as dry vagina, pain or discomfort during intercourse and vaginal itching, which may suggest a common, potentially hormonal, mechanism leading to systemic mucosal dryness (26).

In the prospective study of Cuzick *et al.* (28), among the 1709 high-risk postmenopausal women who received anastrozole to prevent breast cancer (IBIS II study) 4% reported dry eye vs. 2% in the placebo group. This may suggest that self-reporting dry eye symptoms is much lower than the actual prevalence of dry eye disease when patients are questioned specifically about the symptoms. Active screening for dry eye disease signs and symptoms may help the patients to receive appropriate therapy, and so to improve their quality of life (26).

One particular side effect reported by Papathanasiou *et al.* (29) in a patient treated with exemestane was the presence of corneal intraepithelial microcysts, but with normal visual acuity and corneal sensitivity, and stable evolution during 1 year follow-up. One hypothesis discussed by the authors was related to the inhibitory effect of exemestane on limbal stem cell function. However, there are multiple causes of corneal impairment that may lead to corneal epithelial microcysts formation, such as chronic hypoxia in contact lens wearers, or corneal dystrophies, and a clear correlation between exemestane and the corneal lesions could not be proved.

Sjogren syndrome and AI. Several case series raised attention about the possible association between “*de novo*” onset of Sjogren Syndrome in patients with breast cancer treated with AI. Guidelli *et al.* (30) reported 3 cases of Sjogren syndrome in patients treated with anastrozole (2 patients) and letrozole (1 patient), exhibiting arthralgia, severely decreased lacrimal secretion measured by Schirmer test and histopathologic findings of labial salivary gland biopsy showing a moderate lymphoplasmacytic infiltrate (>1 focus in 4 mm²), a severe ductal ectasia, and a mild interstitial fibrosis. In all cases the clinical signs appeared after the initiation of AI therapy.

Moreover, Laroche *et al.* (27), in a study of 19 patients with breast cancer treated with AIs and experiencing disabling joint pain with no underlying anatomical cause, found an increased frequency of sicca syndrome, in 10 out of 19 patients, and antinuclear autoantibodies (ANA) in 9 out of 19 patients. However, as opposed to typical Sjogren syndrome, there was no biological inflammatory syndrome, and only moderate histopathological lesions of the accessory salivary glands (27). Consistent with these clinical findings, Shim *et al.* (32), in an aromatase-knockout (ArKO) experimental mouse model evidenced a lymphoproliferative

Table I. Ocular surface related side effects of treatment of breast cancer patients with aromatase inhibitors.

Study, year	Study type	No of patients with breast cancer (no of eyes); no of controls	Aromatase inhibitor used	Duration of follow-up	Ocular side effects reported
Agin <i>et al.</i> , 2021 (21)	Prospective	13 (13)	Anastrozole/letrozole	6 months	Ocular surface: ↑OSDI; ↓TBUT, ↓Schirmer test Meibomius glands: ↑meiboscores Corneal structure: ↓basal epithelial, stromal, endothelial corneal cells densities; ↓total number and nerves densities Dry eye symptoms: 29% vs. 9.5%
Turaka <i>et al.</i> , 2013 (22)	Retrospective	41; 3091	Anastrozole (22), letrozole (15) and exemestane (4)	22 months 20.3 (range 0.1-65)	Blepharitis, Meibomius gland dysfunction
Bicer <i>et al.</i> , 2020 (23)	Prospective, cross sectional	Tamoxifen:50; anastrozole, letrozole: 50; controls: 50	tmx:20 mg/day Anastrozole:1 mg/day Letrozole:2,5 mg/day	-	Increased OSDI and corneal staining: AI>tmx>controls ST scores higher in controls vs. AI group BUT higher in controls vs. tmx and AI groups OSDI>12 in 46% AI group vs. 48% in control group PSQ higher in Ai group Meibomius expressibility*: lower in AI group OSDI, MGD-14 or IOSS, BUT, corneal staining - similar between the 2 groups
Gibson <i>et al.</i> , 2020 (24)	Prospective, cross sectional, early-stage breast cancer	52; 56 (postmenopausal, age-matched)	Letrozole 38 Anastrozole 7 Exemestane 7	-	Dry eye symptoms: Blurred vision: 47.5% vs. 7.5% Foreign body sensation: 30% vs. 15% Tearing 22.5% vs. 75% Dry eye signs: Hyperemia: 22.5% vs. 5% Superficial punctate keratitis: 30% vs. 7.5% Meibomian gland dysfunction: 42.5 vs. 12.5% Blepharitis 75% vs. 25% Dry eye prevalence (OSDI>12): 35% vs. 18%
Chatziralli <i>et al.</i> , 2016 (25)	Prospective, early-stage breast cancer	41 (80); 40(80)	Letrozole, 30 (37.5) Anastrozole, 27 (33.8) Exemestane, 23 (28.7) Duration to first reported symptom: 13.2+/-12.6 months	-	
Inglis <i>et al.</i> , 2015 (26)		93; 100	Anastrozole 45 Letrozole 39 Exemestane 9	-	
Laroche <i>et al.</i> 2007, (27)	Prospective	19 patients with breast cancer treated with AI and joint pain	Anastrozole letrozole	6 months	10 patients: sicca syndrome (7 patients – Sjogren syndrome, ANA+)
Cuzick <i>et al.</i> 2013, (28)	International, double-blind, randomized placebo-controlled trial IBIS II	1920; 1944	Anastrozole 1mg/zi	5 years	Dry eyes 83 (4%) vs. 58 (2%); Risk ratio 1×45 (1×04-2×01) Conjunctivitis 12 (1%) vs. 5 (<1%); risk ratio 2×43 (0×86-6×88)
Papathanassiou <i>et al.</i> , 2010 (29)	Case report	1(2)	Exemestane	1 year	Corneal intraepithelial microcysts, normal Schirmer's test, VA, and corneal sensitivity
Guidelli <i>et al.</i> 2013, (30)	Case series	3(6)	Anastrozole 2 Letrozole 1	-	Sjogren Syndrome Abnormal low Schirmer test (4 mm in one patient; 2 mm in 2 patients)

*The number of meibomian glands yielding liquid secretion.

Table II. Retinal and optic nerve side effects of treatment of breast cancer patients with aromatase inhibitor.

Author, year	Study type	No of patients; controls	AI used	Side-effects reported ($p<0.05$)	Treatment
Moschos <i>et al.</i> , 2015 (9)	Cross-sectional, early-stage breast cancer	49 (80);40(80)	Letrozole 30 (37.5) Anastrozole 27 (33.8) Exemestane 23 (28.7)	OCT: lower average, sup and inf RNFL; mf-ERG: ↓P100 amplitude ↑P100 latency; ↓Retinal response density (nV/deg ²) in ring 1 (fovea) and ring 2 (parafoveal)	None
Eisner <i>et al.</i> , 2007 (33)	Comparative study	20;34;32	Anastrozole (1 mg/daily) Tamoxifen 20 mg/daily, <2 years) controls	Optic disc subclinical swelling in Tmx group vs. anastrozole and normal; optic cup volumes, maximum optic cup depths, and cup/disk area ratios (measured by HRT II) were each significantly smaller for the tamoxifen users than for the anastrozole users;	None
Epstein <i>et al.</i> , 2009 (36)	2 Case report	2 patients with early-stage breast cancer and myopia	Case 1: Letrozole, changed to Exemestane after 5 months due to musculoskeletal pain Case 2: anastrozole, changed to exemestane after 2 years due to cholesterol metabolism impairment	Case 1: Retinal detachment, Case 2: macular hole No causality relationship was established, but raised awareness;	Vitreoretinal surgery; AI was discontinued
Moschos <i>et al.</i> , 2013 (37)	Case-report	1	letrozole 2.5-mg/day, 3 years	Both eyes: decreased response in mf-ERG RE: macular edema documented by OCT and AFG	Intravitreal 0.05-ml/0.5-mg ranibizumab; AI was discontinued
Karagoz <i>et al.</i> , 2009 (38)	Case report	1	Anastrozole, 3 years	Hemi-central arterial retinal occlusion Comorbidities: arterial hypertension, DM	AI discontinued; Hyperbaric O ₂ therapy, but with no visual improvement
Coppes <i>et al.</i> , 2014 (34)	Case report	1	Anastrozole	Bilateral optic neuritis RE>LE; Comorbidities: Hypertension, asthma Outcome: partial optic atrophy in RE; total recovery in LE	iv and oral corticosteroids; discontinued AI, switch to exemestane 25 mg daily after 6 months
Sathiamoorthi <i>et al.</i> , 2018 (35)	Case report	1	Anastrozole, >2 years	RE: uveitis and macular edema; bilateral epiretinal membranes	Topic CS for one month Total remission
Eisner <i>et al.</i> , 2009 (39)	Cross sectional, comparative study	27 (anastrozole group); 25 (tmx group); 40 (Control)	1 mg anastrozole daily; 20 mg tmx daily	Increased vitreo-retinal traction; ↑ susceptibility to myopia-induced PVDs	None
Eisner <i>et al.</i> , 2008, (40)	Cross sectional, comparative study	35 (anastrozole group); 38 (tmx group); 53 (control)	1 mg anastrozole daily; 20 mg tmx daily	Retinal hemorrhages: 4 – anastrozole group 1 (historically) – tmx group 0-controls	No info

mf-ERG: Multifocal electroretinogram; CS: corticosteroids; ANA: antinuclear autoantibodies; PVDs: posterior vitreous detachments; tmx: tamoxifen.

autoimmune infiltration similar to Sjogren Syndrome, which suggests the protective role of estrogen.

AI side effects at the level of the retina and optic disk. Various changes were reported at the neuroretinal level in breast cancer patients treated with AIs, ranging from mild, subclinical anatomic and functional impairment (9, 33), to severe decreased visual acuity resulting in permanent disabling visual sequelae, secondary to hemi-central retinal artery occlusion, bilateral optic neuritis (34) and uveitis with bilateral macular edema (35) (Table II).

Moschos *et al.* (9) found a lower thickness of the mean retinal nerve fiber layer (RNFL) measured by optical coherence tomography, when compared to normal age-matched postmenopausal women. The anatomical subclinical changes were correlated with functional changes on multifocal electroretinogram (mfERG): decreased amplitude and increased latency of P100. The decreased functionality seems to affect mostly the foveolar and perifoveolar region. Moschos *et al.* (9) found not significant differences between the 3 AIs (anastrozole, letrozole and exemestane) in terms of average RNFL decrease, decreased P 100 amplitude, and increased latency. However, in the exemestane group, a decreased temporal RNFL and increased latency of P1 (in ring 1) were found, suggesting early subclinical decrease in macular function, and degeneration in the papillomacular bundle.

In a study focusing on optic cup and cup/disk ratio, Eisner *et al.* (33) found that treatment with AIs had no effect on cup volume and cup disk ratio, whereas tamoxifen use was related with decrease cup volume, as an indicator of the subclinical edema of the optic nerve fibers.

There is clinical evidence that anastrozole use in breast cancer might lead to increase vitreo-retinal traction. Eisner *et al.* (39) raised awareness about the susceptibility of posterior vitreous detachment in myopic patients treated with AIs. Epstein *et al.* (36) reported 2 cases of myopic patients treated with exemestane that developed retinal detachment and macular hole that required vitreoretinal surgery. An interesting study by Eisner *et al.* (40) found an increased incidence of retinal hemorrhages in patients treated with anastrozole vs. tamoxifen or postmenopausal controls. The possible explanations might be related to the estrogen depletion of the vasculature or increased vitreoretinal traction forces. However, 2 out of 4 patients who experienced retinal hemorrhages were also treated with bisphosphonate and aspirin for the musculoskeletal side-effects of aromatase inhibitor therapy, which may also cause bleeding (40).

Discussion

Alfa and beta estrogen receptors have been identified in the retina and choroid, and also at the level of the lacrimal glands, including Meibomian gland conjunctival and corneal

surface, but their physiological roles are still a subject of research (41, 42). Dry eye incidence increases with age, and is significantly higher in postmenopausal women. However, clinical studies found that the incidence of dry eye was higher in postmenopausal women taking estrogens supplements compared to those not taking hormonal medication or using estrogen-progesterone combinations (43, 44). Recent studies showed that the health of ocular surface and a normal lacrimal film depend on a delicate balance between androgens and estrogens. Estrogens promote the maturation of the superficial cells in the conjunctiva, influence the aqueous component of the lacrimal layer and have a trophic role at the level of the cornea. On the other hand, estrogens might have a proinflammatory action at the level of ocular surface. Experimental studies documented that at the level of the cornea, 17beta estradiol induces an increase in the mRNA levels of IL-1 β , IL-6, IL-8, and GM-CSF, suggesting it may favor inflammation associated with dry eye disease (45). Androgens have an anti-inflammatory effect and stimulate meibomian gland secretion contributing to the lipid layer of the lacrimal film, which ensures stability and decreased evaporation, protecting the ocular surface (46).

Treatment of breast cancer patients with AIs led to significant decrease of peripheral estrogen levels, depleting the ocular surface from the trophic protective effects of estrogens. Although in most cases, the dry eye disease and Meibomian gland dysfunction is minor to moderate, an active screening by OSDI may improve patients' quality of life by indicating the necessity for treatment to reduce visual impairment (24).

The ocular side effects of high dose and low dose of 20 mg/day tamoxifen in patients with breast cancer are well studied (47). While cataract induced by tamoxifen is still a controversy, the American Association of Ophthalmology recommends periodic ophthalmologic check-ups to identify specific retinal signs of tamoxifen related toxicity, such as deposits of intraretinal crystals, macular edema, retinal hemorrhages, optic neuritis, and tamoxifen-induced retinopathy (47, 48).

The ATAC (arimidex, tamoxifen alone or in combination) trial has demonstrated that anastrozole resulted in a clinically significant reduction in thromboembolic events; 4.1, 2.0, 2.8, and 1.6% of patients under anastrozole treatment suffered thromboembolic events in terms of coronary, cerebrovascular, venous, and deep venous systems, respectively (10, 38).

There is limited evidence regarding the possible retinal side-effects of the treatment of breast cancer patients with aromatase inhibitors. Whether they are a consequence of estrogen deprivation, a medication side effect or both, is still a subject for further longitudinal studies, to document the specific changes and their evolution in time.

Estrogens play multiple regulatory roles in retina and ocular blood flow (49-51). Experimental studies documented

a protective role of estrogens on retinal pigment epithelium cells against oxidative stress, a trophic role *via* expression of VEGF and its receptors, and anti-inflammatory effects by attenuating Il-6 response to LPS or by modulating ocular blood flow (49, 50). In animal models, estrogen deficiency has been reported to lead to increased levels of tumor necrosis factor-alpha (TNF- α) and endothelin-1, leading to a possible proinflammatory state in the vasculature (34).

The main reported side-effects related to AI use are, besides reduced bone mineralization, AI-induced musculoskeletal symptoms (AIMSS), characterized as a distinct entity first in 2001. Signs and symptoms include: joint pain and myalgia, stiffness, tenosynovitis, carpal tunnel syndrome and muscle weakness, and may involve both central and peripheral joints. In the systematic review of Beckwee *et al.*, the incidence of AIMSS was found to be between 20% and 74%, with onset of symptoms after a mean period of 6 weeks and a peak of intensity around 6 months (52). In a comprehensive review on the ocular effects of breast cancer medications, Eisner *et al.* (50) raised the possibility that measured changes in vitreo-retinal traction might be useful in helping to mark changes in joints that accompany the development of AI-induced arthralgia, based on the similar biochemical structure of the joints and vitreous body. However, further studies are needed to confirm the statistical significance of these correlations.

The present review presents the clinical evidence regarding ocular disorders related to the treatment of breast cancer with AIs. There are limitations regarding the differences in methodology used, the small number of patients included in the clinical studies, except of Cuzick *et al.* (28). Moreover, only few studies are longitudinal, and described the dynamics of ocular changes during AI treatment. Case reports may raise awareness for possible side effects, but they have limited statistical value in describing the incidence of the specific event and the possible associated risk factors.

Conclusion

Ocular side effects related to AI use in breast cancer patients may appear, but they seem to be less frequent and severe when compared to tamoxifen. Dry eye symptoms may be successfully treated with artificial tears and lubricants in most cases and they do not require interruption of therapy. In more severe events, such as retinal detachment, recurrent uveitis or hemiretinal artery occlusion, management includes stopping or switching the causative aromatase inhibitor agent, in cooperation with the oncological team. Further evidence from longitudinal studies, performed on a larger number of patients are needed to document the incidence of possible ocular side effects of aromatase inhibitors used in breast cancer therapy. However, many visual disturbances may be underestimated

or considered as a sign of aging and ignored by patients when self-reporting the possible side effects of the hormonal therapy. A more focused ophthalmologic screening may improve patients' quality of life.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

DrS, AMD, AZ, MST, DOC, ADS, SAB and DaS contributed to the conception and design of this study. GAG, ACC, DOC, MST, LCT, CGS, CoT, MF and CiT were responsible for the data collection and analysis. DrS, AMD, GAG, SAB, CGS, ACC, CiT and DaS were in charge of drafting the manuscript. ADS, MF, LCT, AZ, MST, DOC, DrS, CoT, revised the manuscript critically for important intellectual content. The final version was read and approved by all the Authors.

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