Review

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The Potential Role of Aromatase Inhibitors in Radiation-Induced Morphea Development in Breast Cancer Survivors

Samantha Carranza[1], Rebecca Olsen[2,*], Erin Onken[3], Heidi David[4], Neha Dhaliwal[5], Damini Patel[6], Amal Umerani[7], Rayaan Bashir[8]

[1]School of Medicine, Wayne State University, Detroit, MI 48202, USA
[2]School of Osteopathic Medicine, A.T. Still University, Mesa, AZ 85206, USA
[3]School of Osteopathic Medicine, Edward Via College, Blacksburg, VA 24060, USA
[4]School of Medicine, Medical College of Georgia, Augusta, GA 30912, USA
[5]School of Osteopathic Medicine, William Carey University, Hattiesburg, MS 39401, USA
[6]School of Medicine, Texas A&M University, College Station, TX 77840, USA
[7]School of Medicine, Georgetown University, Washington, DC 20057, USA
[8]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
*Correspondence: rcolsen567@gmail.com (Rebecca Olsen)
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Radiation-induced morphea (RIM) is a rare, potentially debilitating complication of breast radiotherapy, characterized by localized dermal fibrosis that may extend beyond irradiated fields. It typically arises within 3–12 months after radiation exposure, but can appear years after treatment completion. Aromatase inhibitors (AIs) are frequently prescribed in postmenopausal breast cancer survivors. These agents significantly reduce estrogen levels and may amplify profibrotic pathways, potentially contributing to RIM development. This review examines the relationship between the use of AIs and RIM development, focusing on the clinical presentation, diagnostic challenges, treatment options, and knowledge gaps. RIM can mimic many dermatologic disorders, causing it to be often misdiagnosed as cellulitis, mastitis, post-radiation fibrosis, or recurrent cancer. Misdiagnosis delays initiation of treatment and can lead to poor outcomes, including breast induration, chronic pain, and disfigurement. A skin biopsy is needed for diagnostic confirmation. There are several reported treatment options for RIM, including topical or systemic corticosteroids, mesalazine, phototherapy, and many others. Current treatments provide predominantly symptomatic relief, and there is no standardized treatment at this time. As this condition can appear several years after radiation, it is recommended that breast cancer patients, especially those who currently or previously received AIs, receive periodic skin examinations after completing radiation. Incorporating dermatologic exams into long-term care allows for close monitoring of irradiated skin, facilitating earlier recognition of cutaneous changes and timely management.

Keywords: radiation-induced morphea; aromatase inhibitor; breast cancer; radiation; morphea; post-radiation

Introduction

Radiation is a critical component in the treatment of breast cancer, which remains the most common malignancy affecting women [1]. Hormone receptor-positive disease is the most frequent subtype of breast cancer. The American Society of Clinical Oncology guidelines emphasize that endocrine therapy, including Aromatase inhibitors (AIs), plays a central role in disease management [2]. Adjuvant therapy refers to pharmacological agents utilized after the initial treatment of cancer. Adjuvant endocrine therapy, such as tamoxifen, a selective estrogen receptor modulator, was utilized for many years in breast cancer treatment. In the late 1990s, AIs started being offered as an alternative treatment for postmenopausal women [3]. AIs such as anastrozole and letrozole, are U.S. Food and Drug Administration (FDA)-approved as adjuvant treatments for early-stage hormone receptor-positive breast cancer (estrogen-receptor positive (ER+) +/– progesterone-receptor positive (PR+)). These agents serve as first and second-line therapy for locally advanced or metastatic disease, and are utilized as a second-line treatment in the setting of tamoxifen resistance [4]. By inhibiting the aromatase enzyme, AIs block the conversion of androgens to estrogens, thereby lowering systemic estrogen levels [3]. Although low estrogen levels are associated with decreased cancer recurrence, estrogen deprivation can adversely affect other tissues, including promotion of fibrotic processes [5]. Given the integral role of AIs in modern breast cancer management, further elucidation of their systemic effects beyond oncologic efficacy is warranted.

Radiation-induced morphea (RIM) is a rare, but serious complication of radiotherapy, affecting approximately 1 in 378 individuals. Although infrequently encountered, RIM is referred to by multiple terms in the literature including postirradiation morphea, radiation-induced scleroderma, radiation post morphea, radiation port scleroderma, localized scleroderma, and circumscribed scleroderma. The use of multiple terms contributes to diagnostic inconsistency and complicates case identification and epidemiologic research.

RIM is characterized by localized morphea and progressive fibrosis that often stays within the irradiated field, but can also extend beyond these boundaries. The condition is particularly prevalent in breast cancer patients. At this time, there is no established correlation between total or single dose of radiation and development of RIM. Its onset is highly variable, presenting months to years after conclusion of radiation treatment. Predicting which patients are at risk for developing RIM remains challenging as there are no predictive models currently available to assess for risk [6]. Together, these features showcase the unpredictable nature of RIM and the challenges it poses for early recognition and risk stratification.

Given the pharmacological effects of AIs, particularly its propensity to promote fibrosis through estrogen depletion, we hypothesized that current or prior use of AIs may contribute to the development of RIM. This is particularly important for breast cancer patients and survivors, as these agents are frequently prescribed concurrently with radiotherapy or started after completion of radiation treatment, overlapping with the typical timeframe for RIM onset [7]. This review will evaluate the potential relationship between use of AIs and development of RIM in breast cancer survivors.

Diagnosis of Radiation-Induced Morphea (RIM)

RIM was first described by Colver in 1989 [8]. It is characterized by excessive collagen production, resulting in thickening of the dermis [9]. While radiation-induced inflammation and fibrosis contribute to the eradication of breast cancer, the penetrative effects of radiation can also damage surrounding skin, leading to adverse cutaneous sequelae such as RIM [6]. Common radiation-induced skin changes include erythema, telangiectasia, and liponecrosis. Several distinguishing factors may aid in differentiating RIM from other post-radiation skin effects. RIM typically has an abrupt onset and may extend beyond the irradiated field, in contrast to radiation-induced fibrosis, which remains confined to the treatment area [10]. Despite these features, RIM is often challenging to distinguish from other dermatological conditions in clinical practice.

Cutaneous Side Effects of AIs

When diagnosing RIM, it is important to exclude cutaneous adverse effects related to AIs. Although uncommon, AIs have been associated with several dermatoses including erythema nodosum, vasculitis, and subacute cutaneous lupus erythematosus. These adverse effects often exhibit a delayed onset, ranging from $<$5 days to 6 months after treatment initiation [11]. This diagnostic overlap highlights the importance of maintaining a broad differential when evaluating post-radiation cutaneous changes in patients receiving endocrine therapy.

Clinical Findings

RIM has a biphasic clinical course. It starts with an asymptomatic latency period, followed by sudden onset of erythematous, edematous plaques that progressively evolve into potentially painful or pruritic, hyperpigmented lesions with notable dermal thickening [6]. In advanced cases, RIM can cause significant tissue retraction, induration, peau d'orange appearance, and nipple herniation [12,13]. Disease progression may continue beyond the initial inflammatory phase, leading to ongoing tissue damage.

Histopathology

Histopathologic findings in RIM include dermal perivascular and interstitial infiltrate suggestive of an inflammatory state, with superficial lymphocytic infiltrate and increased collagen deposition in the reticular dermis [6]. In some cases, eosinophilia and mucin deposition may also be present [13,14]. These findings help distinguish RIM from other inflammatory cutaneous conditions, further emphasizing the importance of obtaining a skin biopsy to help confirm the diagnosis.

Proposed Pathophysiology Mechanisms

The pathophysiology of RIM is not well understood, but several mechanisms have been proposed. Radiation induces double-stranded DNA breaks within the irradiated tissue, triggering apoptosis in both malignant and surrounding healthy cells [10]. This injury promotes fibroblast activation, immune dysregulation, and accelerated dermal remodeling. In addition, radiation also generates neoantigens that activate transforming growth factor-β (TGF-β), a key profibrotic cytokine that drives fibroblast activation, collagen deposition, and tissue fibrosis [15]. Cytokine dysregulation has also been proposed to contribute to RIM. An analysis of 66 RIM cases identified elevated IL-4, IL-5, and TGF-β, all of which are known to stimulate fibroblast activation and collagen deposition [8]. Collectively, these mechanisms converge on dysregulated fibroblast activation and profibrotic signaling, which would contribute to the progressive fibrosis characteristic of RIM.

Radiation-induced alterations in fibroblast phenotype may create an imbalance favoring excessive collagen deposition and subsequent fibrosis [16]. In RIM, fibroblasts undergo differentiation into myofibroblasts, which secrete excessive extracellular matrix (ECM) components and proinflammatory mediators. Unlike traditional fibroblasts, my-

ofibroblasts exhibit resistance to apoptosis, resulting in persistent ECM accumulation and progressive fibrosis [17]. The persistent activity of these immortal cells likely accounts for the extensive and progressive fibrotic changes observed in RIM. Myofibroblasts in RIM exhibit increased myc phosphorylation, marked upregulation of osteopontin (OPN), and elevated expression of alpha-smooth muscle actin, a myofibroblast protein [13].

OPN is an ECM-associated protein with cytokine-like properties that plays a central role in inflammation, tissue remodeling, and fibrosis. OPN promotes immune cell recruitment and activates key inflammatory signaling pathways, including NF-κB, MAPK, and PI3K/Akt, resulting in increased production of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and suppression of the anti-inflammatory cytokine IL-10. In addition, OPN acts as a potent fibroblast activator, enhancing collagen synthesis (particularly type I collagen), and fascilitating TGF-β signaling. It also upregulates fibrogenic markers such as fibronectin, thereby promoting extracellular matrix assembly and stabilization. OPN further influences tissue remodeling by regulating ECM turnover through modulation of matrix-degrading enzymes. Dysregulated OPN expression can suppress matrix metalloproteinase activity, limiting ECM degradation and favoring fibrotic tissue accumulation [18]. Given these multifaceted roles, OPN may serve as a promising biomarker for both diagnosis and therapeutic monitoring. Fig. 1 illustrates a mechanistic framework integrating the contributing factors discussed above.

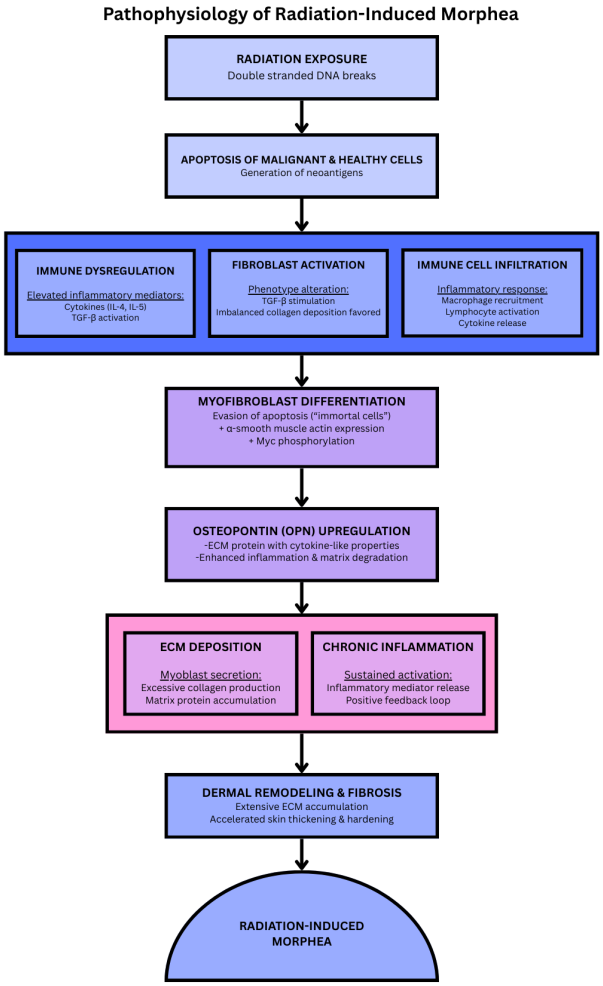

Fig. 1. Radiation-induced morphea mechanistic pathway. The figure showcases the proposed pathophysiology mechanisms behind RIM. Created using Canva. https://www.canva.com/.

Profibrotic Cellular Signaling Pathways and the Protective Effect of Estrogen

Cutaneous fibrosis is largely driven by TGF-β signaling, which activates fibroblasts through both canonical (SMAD2/3) and non-canonical cellular signaling pathways (ROCK, ERK, PI3K/AKT) [19]. These signaling cascades alter gene expression, promote fibroblast-to-myofibroblast transition, enhance extracellular matrix remodeling, and upregulate profibrotic mediators such as connective tissue growth factor (CTGF) [19]. TGF-β also modulates immune and epithelial cell activity, fostering a sustained profibrotic environment that can lead to chronic skin fibrosis. Through estrogen receptor-alpha (ERα) signaling, estrogen exerts antifibrotic effects by reducing SMAD proteins and attenuating TGF-β-mediated signaling [20]. ERα creates a protein network with SMAD and Smurf, a ubiquitin ligase, which leads to SMAD ubiquitination and degradation through estrogen activation [20]. The profibrotic signaling pathways and the antifibrotic role of estrogen is summarized in Fig. 2.

Estrogen plays a key role in limiting fibrosis at a molecular level by inhibiting TGF-β signaling, exerting an antifibrotic effect in the skin. When estrogen levels decline, such as with AI use, TGF-β activity increases. The resulting unchecked fibroblast activation and collagen deposition intensifies fibrotic processes, a phenomenon supported by both laboratory and animal studies [5]. AIs also reduce matrix metalloproteinases activity, impairing collagen degradation and tissue remodeling [21]. In the setting of AI use in breast cancer survivors, the protective effect of estrogen is consequently diminished, enhancing profibrotic pathways leading to increased deposition of collagen, and heightened risk for developing fibrotic skin disorders such as RIM.

Clinical Cases of RIM in Breast Cancer Survivors

There are several reports in the literature that document RIM development in breast cancer survivors, but the cases often do not report if the patients currently or previously received AI therapy. The most common cutaneous findings of RIM in breast cancer survivors are dermal fibrosis and painful hyperpigmented lesions. There are a few documented cases in which the condition extended into the fatty tissue, leading to panniculitis or breast atrophy [15].

As RIM is a diagnosis of exclusion, it is frequently misdiagnosed as cellulitis, mastitis, or local recurrence

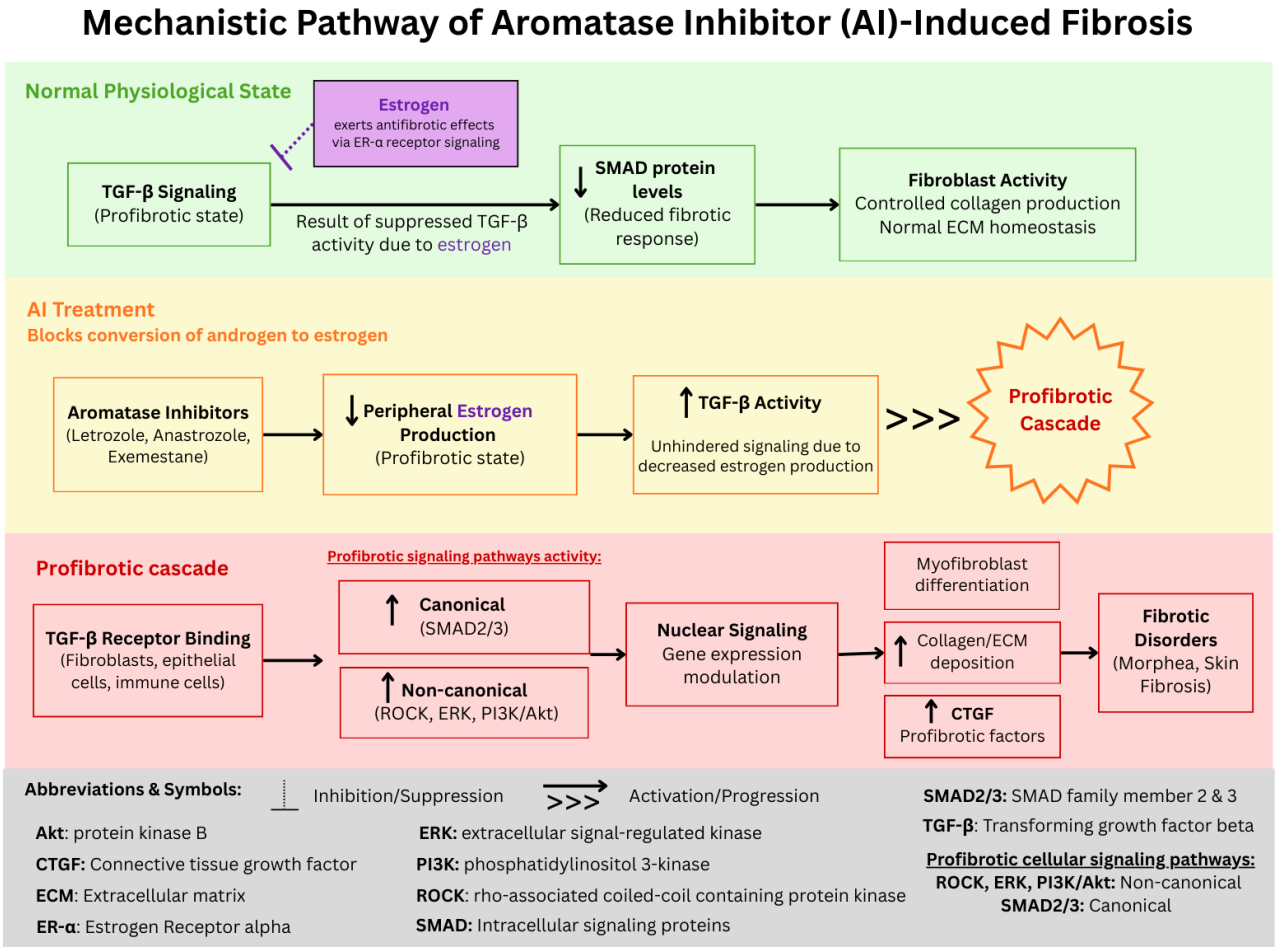

Fig. 2. Mechanism of how AI therapy disrupts estrogen-mediated protection against TGF-β signaling. Resulting in enhanced canonical (SMAD2/3) and non-canonical (PI3K/AKT, ERK, ROCK) signaling, promoting fibroblast-to-myofibroblast differentiation, extracellular matrix deposition, and fibrosis. Created using Canva. https://www.canva.com/.

of inflammatory breast cancer. Thus, it is often initially treated with antibiotics and imaging is performed. A biopsy should be obtained early to aid in diagnosis and subsequent treatment [22]. It is important that clinicians are familiar with the presentation of RIM so that it is not missed. If left untreated, RIM can cause significant fibrosis and skin tightening, which limit options for breast-conserving surgery. Other conditions that should be on the differential include systemic sclerosis, recurrent malignancy, and post-radiation fibrosis [14]. A summary of the timing, clinical findings, histology, and proposed mechanisms of RIM are shown in Fig. 3.

Overview of Aromatase Inhibitors (AIs)

In 2023, approximately 670,491 U.S. patients were prescribed anastrozole [23]. Given the large number of patients using these medications annually, it is important to investigate whether AIs use contributes to the development of RIM. AIs are the preferred first-line endocrine therapy for most postmenopausal women with hormone receptor-positive breast cancer [24] as long-term data demonstrate greater reductions in recurrence and breast cancer-specific mortality over a 10-year period compared with tamoxifen [25]. The use of AIs is primarily limited to postmenopausal women or patients with nonfunctional ovaries [24]. Evidence indicates that AIs are insufficient to suppress estrogen production in premenopausal patients and may induce ovulation, with applications in treating anovulatory infertility [3].

In postmenopausal women, residual estrogen production occurs predominantly in peripheral tissues, particularly adipose tissue within the breast through the enzyme, aromatase. This activity increases the risk of breast cancer development [26,27]. AIs may alter hormonal regulation and immune responses in irradiated skin, potentially contributing to increased susceptibility to RIM development. However, current evidence directly linking AIs use and RIM development remains limited, further investigation into this potential association is needed.

Aromatase (CYP19A1) catalyzes the rate-limiting step of estrogen production, converting androgens (testosterone, androstenedione) into estrone and estradiol (Fig. 4).

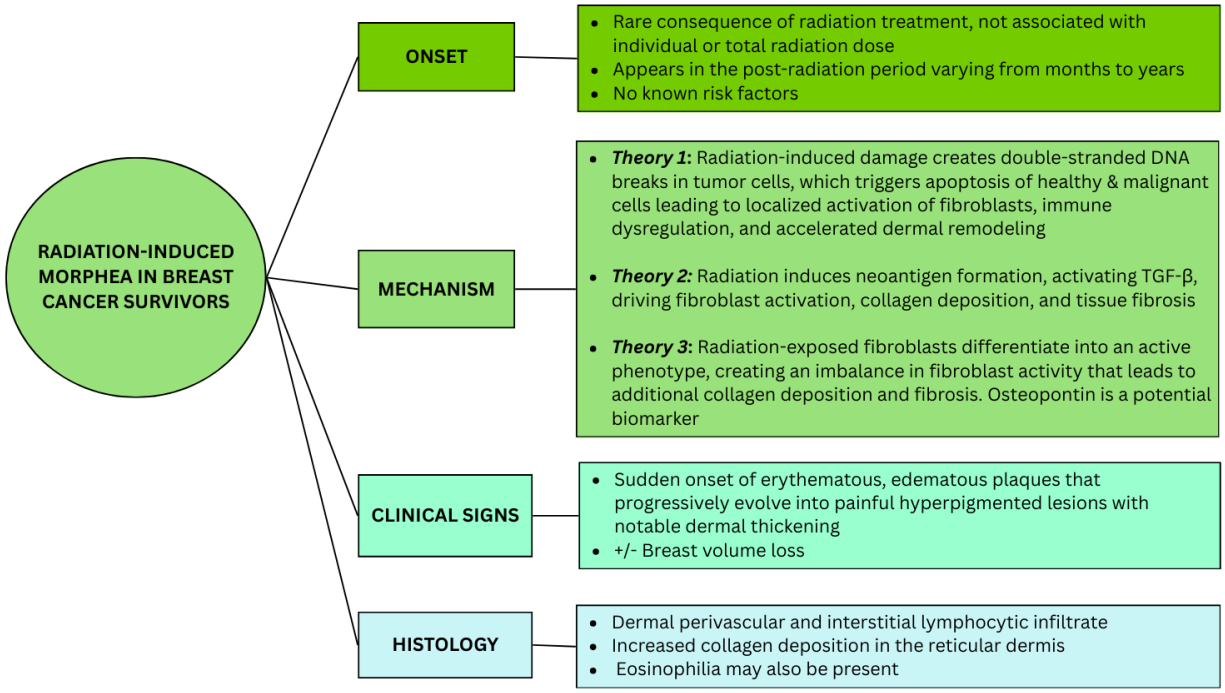

Fig. 3. Summary of radiation-induced morphea in breast cancer survivors: Onset, mechanism, clinical signs, and histology. Created using Canva. https://www.canva.com/.

Once bound to estrogen receptors of target cells, these hormones promote receptor dimerization and activate estrogen response elements, regulating gene transcription [28]. AI blocks peripheral estrogen production and directly suppresses localized estrogen production in breast tissue disrupting tumor growth.

Although AIs primarily reduce estrogen, emerging evidence suggests that combinational treatment with AIs and growth factor receptor inhibitors may improve outcomes in treatment-resistant patients [29]. This upstream inhibition of estrogen synthesis distinguishes AIs from selective estrogen receptor modulators (SERMs), which act downstream at the receptor level. Since postmenopausal women rely on peripheral estrogen production, AIs are particularly effective in this population, which supports their essential role in breast cancer management.

AIs may also play a role in breast cancer prevention. A study done by Behan *et al*. [30] showed that AIs can reduce the incidence of breast cancer in high-risk postmenopausal women. AIs have also been applied in the management of benign disease disorders, including recurrent fibrocystic disease and cyclical mastalgia, as well as male breast cancer, where therapeutic options remain limited [4]. By reducing estrogen levels, these agents not only alleviate symptoms of estrogen-dependent breast conditions, but also provide an important alternative treatment option for men.

Difference Between the Mechanism of Selective Estrogen Receptor Modulators (SERMs) and AIs

Administration of SERMs such as tamoxifen, inhibit estrogen binding to its receptor, resulting in amplification of profibrotic activity. This blockade enhances SMAD2/3 phosphorylation and upregulates collagen production in response to TGF-β, indicating the protective role of estrogen against fibrosis [5]. AIs act through a different mechanism than tamoxifen, suppressing estrogen production rather than acting at the receptor. The resulting low peripheral estrogen levels disrupt antifibrotic signaling, shifting the balance toward fibroblast activation and matrix deposition. This supports the potential role of AIs in promoting fibrotic changes such as radiation-induced morphea. SERMs and AIs are compared and contrasted in Table 1.

There is limited evidence directly connecting AI use to the development of RIM. However, underlying signaling pathways suggest a plausible link through profibrotic pathways (Fig. 3). By reducing estrogen levels, AIs remove the antifibrotic effect of estrogen, potentially permitting radiation-induced tissue injury to evolve into RIM in susceptible patients. Further research is needed to clarify the relationship between AIs use and RIM development, identify patient-specific risk factors, and guide clinical decision-making regarding surveillance strategies for high-risk patients. A deeper understanding of this association will help clinicians balance cancer management and minimize long-term, treatment-related complications in breast cancer survivors.

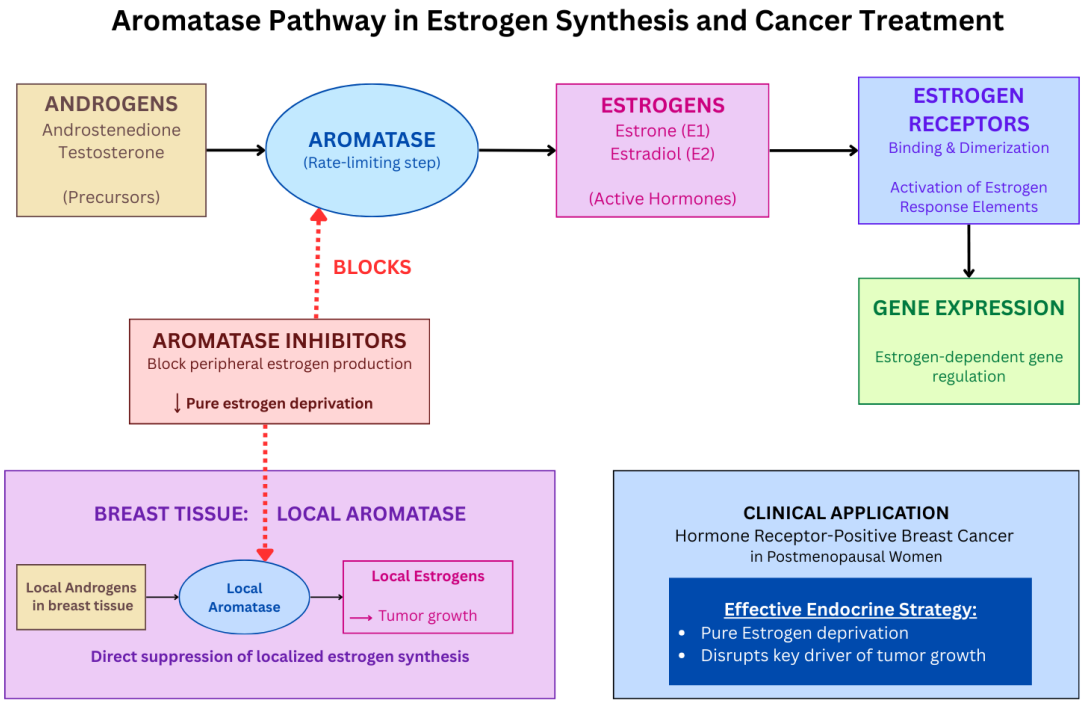

Fig. 4. Aromatase pathway in estrogen synthesis and cancer treatment. Created using Canva. https://www.canva.com/.

Treatment

Treatment strategies for RIM include topical and systemic therapies. There is currently no standardized treatment regimen. One reported case in the literature was treated with mesalazine [13]. The anti-inflammatory agent was selected after studies showed evidence that abnormal Myc activation can drive fibroblast proliferation in the setting of RIM. The patient experienced notable improvement in inflammation, pain, and tissue changes following mesalazine treatment.

Management decisions are often guided by disease severity. Patients with mild RIM are commonly treated with potent topical corticosteroids (e.g., clobetasol), to reduce inflammation [31]. Severe cases typically require the use of systemic corticosteroids (e.g., prednisone). Various modalities of phototherapy (UVA, UVA1, UVB, PUVA) can be used as an adjunctive treatment to help reduce fibrosis [8]. Additional agents for RIM treatment include calcineurin inhibitors (e.g., tacrolimus), heparin, hyaluronidase, systemic antibiotics, imiquimod, Vitamin E, pentoxifylline, colchicine, D-pencillamine, plasmapheresis, mycophenolate mofetil, and photophoresis have been reported with variable efficacy [8,22]. Reducing the breast tissue changes is the main goal of treatment through several avenues, depending on the severity and clinical indiations on a case-by-case basis.

Clinical Course

The clinical course of RIM is highly variable among patients. The skin findings typically appear months to years following radiotherapy, and prognosis varies depending on the severity and extent of fibrosis. RIM can also occur as a rare complication of phototherapy, with an estimated incidence of approximately 2 cases per 1000 treated [22]. There is limited literature reporting the rate of RIM recurrence in patients previously diagnosed with RIM. The prognosis of the disease depends heavily on the extent of fibrosis. If recognized and treated early, most patients are stabilized, but if intervention is delayed, patients have an increased risk of increased flares and recurrent episodes. Early recognition and intervention are critical to preventing irreversible damage and functional impairment.

Surveillance and Clinical Recommendations

It is estimated that up to 95% of patients undergoing radiotherapy develop at least one radiation-induced cutaneous pathology, most commonly radiation dermatitis [32]. Breast cancer patients who have received radiotherapy face higher rates of melanoma, hemangiosarcoma, and Merkel cell carcinoma compared to the general population [33]. They also have an increased risk of developing non-melanoma skin cancer(s), including basal cell carcinoma and squamous cell carcinoma. Despite these risks, no clear specialty guidelines exist regarding the timing or frequency of routine skin examinations for this high-risk group. Some dermatologists advocate for annual skin examinations with focused evaluation of irradiated fields [34].

Table 1. Comparative analysis of aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs) in breast cancer treatment and radiation-induced morphea (RIM) pathogenesis.

	Aromatase Inhibitors (AIs)	Selective Estrogen Receptor Modulators (SERMs)
Clinical indications	Adjuvent therapy for ER+ breast cancer, chemoprevention in high-risk patients, male breast cancer	Adjuvent therapy for ER+ breast cancer, chemoprevention in high-risk patients, benign breast disease
Example	Anastrozole	Tamoxifen
Mechanism of action	Inhibition of aromatase (CYP19A1), preventing peripheral conversion of androgens → estrone → estradiol	Competitively binds to estrogen receptors, resulting in tissue-specific antagonism of estrogen signaling
Site of therapeutic action	Upstream inhibition of estrogen biosynthesis	Downstream modulation of estrogen receptor signaling
Effect on systemic estrogen levels	Reduced	Normal or mildly elevated
Target population	Post-menopausal women	Pre-menopausal women or post-menopausal women who cannot tolerate or have contraindications to AI use
Premenopausal use	Ineffective as monotherapy; may induce compensatory ovarian stimulation unless combined with ovarian suppression	Effective despite ongoing ovarian estrogen production
How it works to treat ER+ breast cancer	Decreases intratumoral estrogen availability, leading to suppression of estrogen-dependent tumor proliferation	Blocks ER-mediated transcriptional activity, preventing estrogen-driven tumor growth
Systemic effects relevant to RIM pathogenesis	Estrogen depletion may reduce antifibrotic signaling, potentially permitting radiation-induced tissue injury to progress to fibrosis	ER activity inhibition may enhance SMAD2/3 phosphorylation, increase collagen synthesis, and promote profibrotic signaling
Proposed mechanistic link	Loss of estrogen-mediated antifibrotic protection may increase susceptibility to RIM, though clinical evidence remains limited	Direct ER antagonism may amplify profibrotic pathways, theoretically increasing RIM risk
Additional notes	Widely prescribed cornerstone therapy in postmenopausal breast cancer; long-term estrogen depletion associated with musculoskeletal and fibrotic effects	Preferred when aromatase suppression is inadequate or contraindicated; exhibits tissue-specific agonist and antagonist effects

Both AIs and SERMs serve as adjuvent therapy for estrogen-receptor positive (ER+) breast cancer and may serve as chemoprevention in patients at increased risk of developing breast cancer. AIs are predominately utilized in post-menopausal patients, as the dominant source of estrogen in this patient population is created in tissues rather than the ovaries. This process is termed peripheral aromatization. In contrast, SERMs may be utilized in both premenopausal and postmenopausal women who cannot tolerate or have contraindications to AI use. Estrogen receptor (ER). Created using Word-Microsoft 365, developed by Microsoft corporation, Redmond, WA, USA.

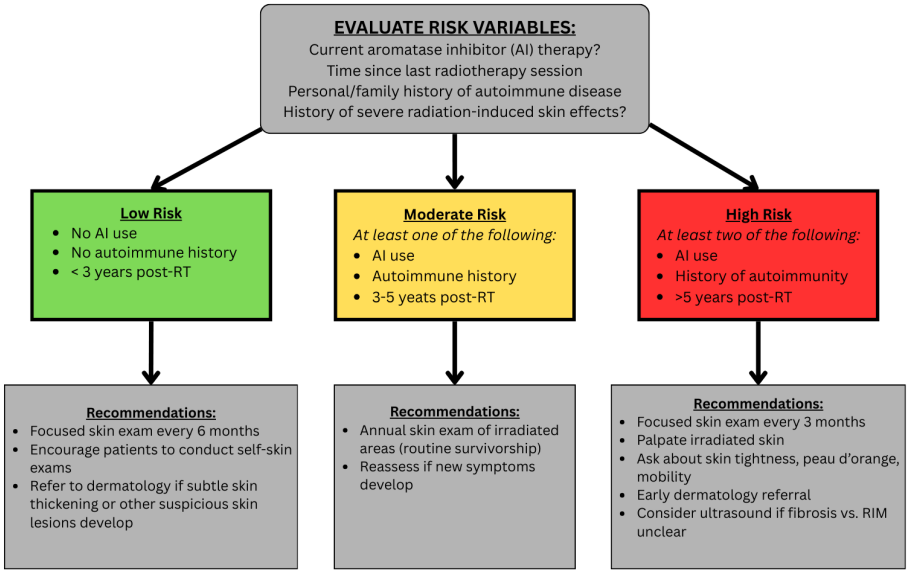

Fig. 5. Risk-based RIM algorithm proposed to guide surveillance of irradiated skin in breast cancer survivors. All breast cancer survivors who received radiation treatment should receive a yearly examination of all irradiated skin areas. In this proposed algorithm, patients are placed in categories of low, moderate, and high risk based on several risk factors, including current or prior AI use, time since last radiotherapy session, personal or family history of autoimmune disease, or history of severe radiation-induced skin effects. Patients at moderate risk for developing RIM are encouraged to conduct self-examinations of irradiated areas to help closely monitor for any subtle skin changes. Patients at moderate or severe risk are recommended to undergo focused skin examinations every 3–6 months, respectively, and should be referred to dermatology for any suspicious lesions. Created using Canva. https://www.canva.com/. RT, Radiation treatment; AI, aromatase inhibitor.

Given emerging evidence supporting the pro-fibrotic role of AIs, clinicians may also consider periodic dermatologic screening for breast cancer survivors who are currently or were previously treated with AIs. Surveillance could be utilized to examine irradiated skin for changes such as persistent erythema, tissue thickening, or plaque formation. RIM has been reported to present up to 30 years post-radiation [12]. For this reason, surveillance should start after radiation and extend beyond one year of radiation, with heightened vigilance in breast cancer survivors on AIs. Incorporating dermatologic surveillance into oncologic care adds significant value by facilitating early recognition and management of RIM and other treatment or disease-related skin complications.

RIM typically develops within the first year following radiotherapy. As AI use can contribute to fibrosis, the use of these agents may contribute to RIM development. Delayed diagnosis and treatment is frequently associated with more severe symptoms, including breast induration, chronic pain, breast atrophy, deformity, and poor quality of life [12,18]. Early involvement with a multidisciplinary team, including dermatologists, oncologists, and breast surgeons, is critical to optimize treatment outcomes and prevent irreversible damage.

There is currently no established surveillance guidelines directing physicians on the timing and frequency of skin examinations in breast cancer survivors who received radiation treatment. We created a risk-based algorithm for long-term monitoring of irradiated skin to help guide clinical surveillance for RIM and provide recommendations on when patients should be referred to dermatology for a more thorough skin examination. The algorithm incorporates potential risk factors such as current or prior AI use, length of time since the last radiotherapy session, personal or family history of autoimmune disease, and history of severe irradiated skin effects. All patients should undergo yearly skin examinations of the irradiated skin area(s), but if patients have additional risk factors, focused skin examinations may be conducted every 3–6 months. Patients should be referred to dermatology if skin thickening or other subtle skin changes are noticed. Patients at moderate risk for developing RIM are also encouraged to frequently conduct self-examinations at home so that they can track skin changes within or adjacent to irradiated areas. Details of the proposed algorithm are shown in Fig. 5.

Gaps in Knowledge and Future Research

Additional research is needed to understand the mechanisms and risk factors underlying RIM development. It remains unclear why the onset of RIM is variable and delayed in relation to the timing of radiation exposure. Proposed mechanisms for RIM vary and are not fully understood, highlighting th need for further research in well-defined cohorts. Autoimmune disease may also be a possible risk fac-

tor for RIM development. In one study, 4 out of 6 patients with autoimmune conditions (rheumatoid arthritis, Sjogren syndrome, vitiligo, Crohn's disease) developed RIM, although this link has not been consistently observed in other studies [35].

The reported prevalence of RIM varies widely in the literature, with estimates ranging from 1:378 to 1:3000 [35]. As a rare condition, available data is limited to case reports and small studies, the majority of reported cases involve Caucasian female patients. Broader data across more diverse populations are needed to better characterize clinical variability, improve diagnostic equity, and refine prevalence estimates. To date, no large cohort studies with standardized dermatologic assessments and long-term follow-up have been conducted. Such studies would provide valuable insights into disease onset and risk factors, which would help to better recognize and manage RIM.

Given the limited understanding of RIM pathogenesis, a wide range of treatments have been proposed with variable success. Most treatment approaches provide symptomatic management. But methotrexate and ultraviolet therapy are showing promise as a favorable therapy in one of the largest cohort studies of RIM [6]. Considering the proposed role of estrogen-deprivation in promoting fibrosis, future therapeutic innovations may benefit from targeting collagen turnover and cytokine-driven pathways, such as TGF-β-mediated signaling.

Conclusion

Radiation-induced morphea is a rare but serious complication of breast radiotherapy, often difficult to diagnose as it mimics many other dermatoses. AIs disrupt estrogen signaling, promote fibrosis, and may contribute to RIM development. Given its variable and often delayed onset, long-term surveillance of irradiated skin is warranted, particularly in patients that currently or previously were treated with AIs. A biopsy should be performed when clinical uncertainty exists to ensure a timely and accurate diagnosis. Enhanced understanding of the connection between AI and RIM development is critical for creating more effective treatment strategies, refining surveillance protocols, and identifying risk factors that predispose specific patients for developing RIM.

Availability of Data and Materials

No new datasets were generated or analyzed in this study. All references cited are publicly available or accessible through institutional subscription-based resources.

Author Contributions

Design: SC; Reviewed the literature: SC, RO, EO, HD, ND, DP, AU, RB; Drafted initial manuscript: SC, EO, HD, ND, DP, AU, RB; Editing/second draft creation/formatting: RO. All authors have been involved in revising it critically for important intellectual content. All authors have given final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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