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Scleroderma and Breast Cancer

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1. Introduction

The relationship between breast cancer and scleroderma is complex, involving aspects of epidemiological coexistence, pathophysiology and treatment. Increased risk of malignancy is known to occur in scleroderma patients particularly lung and breast cancer. Risk factors for breast cancer in scleroderma patients include older age and autoimmunity status (lack of ANA positivity). The sometimes close temporal relationship between breast cancer and scleroderma suggests the possible existence of a common pathophysiological mechanism. TGF- β and Caveolin-1 have been widely investigated, while researchers also examined estrogen receptors, common genetic background and other possible mechanisms.

Treatment for breast cancer with radiotherapy and taxanes can both induce scleroderma, morphea and sclerodermic skin lesions. The existence of scleroderma can affect breast cancer treatment and reversely. Breast conservation surgery is avoided in scleroderma patients and radiotherapy is also traditionally considered a relative contradiction due to more frequent and severe toxicity.

2. Epidemiology

There is an increased risk of malignancy in scleroderma patients with an incidence between 4 and 11%^{1,2,3,4,5,6,7}. The exact characteristics of this relationship are difficult to assess due to the rarity of scleroderma and the consequent lack of statistical power to determine the importance of any comparison, the differences in methodology of the studies and the lack of knowledge of the detailed pathophysiology of scleroderma.

Several well-designed population studies have reported a correlation between scleroderma and different types of cancers. The results are summarized in Table 1. The majority of the studies reported a significantly elevated SIR of between 1.5 and 3.15^{1 2 3 4 8 5}. In contrast, Chatterjee *et al*⁹ found no statistically significant increase in malignancy in patients with scleroderma compared with the normal population. The only malignancy with a significantly increased risk was liver cancer in black females. The commonest cancer type occurring in scleroderma is lung cancer, while data over other cancer types are not clear¹.

In terms of breast cancer risk, some studies such as those of Siau *et al*² and Abu - Shakra *et al*⁴ found a statistically important correlation with SIRs 3.07 and 6.1 respectively, while others^{3,8} reported a non statistically significant correlation or no correlation at all.^{1, 5, 9}

Author	SIR	95% CI
Olesen	1.5	1.3-1.7
Siau	3.15	1.77-5.2
Hill	1.99	1.46-2.65
Abu-Shakra	2.1	
Derk	1.55	1.16-1.93
Rosenthal	2.4	1.5-3.6
Chatterjee	1.23	

Table 1. Scleroderma and Standardised Incidence Rate of malignancy.

The risk factors for malignancy in patients with scleroderma, in particular breast cancer are not determined. Siau *et al*² found age > 70 to be an important risk factor, while Abu - Shakra *et al*⁴ found an increased risk for age > 65 for all cancer types. Derk *et al* reported that the diagnosis of scleroderma occurs in older patients with cancer in general⁸ or breast cancer¹⁰, while Lu *et al*¹¹ concluded that age of scleroderma diagnosis was irrelevant to age of breast cancer diagnosis. Kyndt⁷ reported that scleroderma patients with breast cancer had their scleroderma diagnosis at a later age than patients with scleroderma only, but this difference was not statistically significant.

The role of the gender of the patients is not determined either. Most authors state that both male and female scleroderma patients are at higher risk of developing cancer in comparison to the general population, but there is no agreement as to whether the correlation is stronger for men^{1,3,4,8} or women⁵. It is important to highlight that both breast cancer and scleroderma predominately affect women.

As for the scleroderma type, data are also equivocal. Some authors^{9,11} believe that scleroderma type is not important while some others^{4,7} find various differences that do not reach statistical importance. Siau *et al*² report that limited scleroderma is a risk factor for cancer development and Hill *et al*³ states the same for diffuse scleroderma. Systemic sclerosis, morphea and breast cancer can coexist¹².

With regard to the autoimmune status of the patients, most authors^{3,4,9,7} agree that ANA, Scl 70 and U1 - RNP antibody status do not constitute a risk factor for cancer development. Reports focusing on breast cancer however^{10, 11} find the lack of ANA positivity to be a risk factor for breast cancer development. Family history is considered a risk factor for all cancer types in scleroderma patients⁸ and also for breast cancer. On the other hand, scleroderma patients with breast cancer use Hormone Replacement Therapy less frequently than those without the disease but this finding may be biased^{11, 10}.

Breast cancer diagnosis can precede, follow or coincide with diagnosis of scleroderma. To evaluate this relationship, it has to be taken in consideration that authors use different definitions of “simultaneous”, accepting a time lag from 1 to 6 months between the breast cancer and scleroderma diagnosis. Derk¹⁰ studied two groups, one with breast cancer and scleroderma and another with scleroderma only (control group). The first group was divided into two subgroups: those in whom breast cancer diagnosis followed the scleroderma diagnosis (48%) and those in which it preceded (52%). When these groups were

compared for age at scleroderma diagnosis it emerged that patients with breast cancer diagnosis prior to scleroderma diagnosis were older than the ones with breast cancer after scleroderma. This difference was however not statistically significant. In contrast, for the group in which breast cancer was diagnosed prior to scleroderma with the control group, the difference reached statistical significance. This was not true for the group in which breast cancer diagnosis followed scleroderma diagnosis. The first subgroup of patients was ANA negative compared with patients with scleroderma only, and this attained statistical significance when the second subgroup were compared with the control subgroup. Not all researchers agree on the timing of diagnoses of the two conditions. In another study by Lu *et al*¹¹ cancer diagnosis predated scleroderma diagnosis in only 24% of the patients and followed in 76%.

Others^{13,14} have underlined the close temporal relationship between scleroderma diagnosis and breast cancer diagnosis, and explored the possibility of a pathophysiological connection between them. Pineda *et al*¹⁵ described a rare case of bilateral breast carcinoma and diffuse scleroderma. Possible aetiologies for this include scleroderma as a true paraneoplastic syndrome, a common background immunological abnormality, or a detection bias due to extensive investigation of unwell patients.¹⁶

3. Pathophysiology

While the epidemiological connection between cancer and scleroderma is well established, any pathophysiological relationship is not clear yet. Certain mechanisms such as lung fibrosis have been incriminated for lung cancer, the commonest coexisting cancer in scleroderma patients, but few data exist for other cancer types.

Epidemiological correlations do not necessarily mean aetiological correlation, since they can be attributed to higher prevalence of both diseases in older ages¹⁷, female gender¹⁸ or a diagnostic bias from close follow-up and extensive clinical investigation. Yet, there is some evidence that could support the existence of mechanisms that, in some extent, connect the two diseases. Hypotheses for these include a common genetic background, a common mechanism or finally scleroderma as a consequence of breast cancer radiotherapy and chemotherapy.

With regard to the common genetic background, scleroderma patients have been occasionally reported to have a breast cancer family history¹¹. Genetic polymorphism has been incriminated and HLA-DR₂ haplotype is more frequent in scleroderma and breast cancer patients.¹⁷ Explanations proposed include that this haplotype confers to a germline BRCA mutation or is at a genetic linkage to it.¹¹

Mechanisms involving both conditions include TGF- β /Smad signaling pathway that is known to regulate many events in scleroderma, especially in the pathogenesis of fibrosis via upregulation of collagen expression¹⁹. On the other hand, increased collagen formation, expressed as greater mammographic density²⁰ is a recognized risk factor for breast cancer development. Interestingly TGF β is a known breast tumor suppressor²¹ although certain reports refer both to proliferative and suppressive action²². TGF- β levels are increased in breast cancer patients and, in those having limited disease, they decrease after resection of the tumor²³

Another piece of evidence that could potentially indicate common pathophysiology is the breast tumor associated antigen Ca 15-3 (MUC-1) which is increased in scleroderma

patients, and correlates with more severe disease including renal and joint involvement, ANA positivity and elevated CRP²⁴. Furthermore, scleroderma has sometimes evolved in women undergoing breast augmentation surgery and the proposed mechanism was fibroblastic actions of silica or a Graft versus Host disease²⁵

Sex hormone changes are also involved in the pathophysiology of both diseases. Certain predisposing factors for breast cancer such as nulliparity²⁶ or protective factors like increasing number of births²⁷ alter the course of scleroderma disease. Existence of parity delays scleroderma onset and decreases disease mortality and morbidity but does not alter duration²⁶. Not only estrogens but also genetic alterations in estrogen receptors (ER) are involved in the pathogenesis of scleroderma. Specifically ER α XbaI GG phenotype was significantly less frequent in systemic scleroderma patients than in healthy controls although no association with clinical manifestations was found²⁸. Nevertheless, ER α up-regulation is an early event during mammary hyperplasia and adenocarcinoma development.²⁹

The two conditions are also connected in studies focusing on certain mediators such as Caveolin I, a regulator that inhibits the baseline activity of several pro-proliferative and oncogenic proteins via the TGF- β /Smad signaling pathway³⁰. Caveolin-1 is known to suppress collagen expression via interactions with TGF - β ³¹ and also has a variety of effects on breast cancer development such as up-regulation of ER α or molecular changes necessary in the development of metastasis as confirmed in mouse models. Caveolin-1 normally inhibits metastases via suppression of matrix metalloproteinase secretion that degrades the basement membrane of normal epithelia^{32,33}. In humans loss of stromal caveolin-1 is a novel breast cancer biomarker that predicts early disease recurrence, metastasis, survival, and tamoxifen resistance.³⁴

Post irradiation morphea was first described in 1905, the first large series in 1989³⁵. Radiotherapy for breast cancer can induce scleroderma through various mechanisms. After radiotherapy morphea in the breast region is a relatively common manifestation, but systemic scleroderma has also been occasionally reported.³⁶ Its frequency is calculated at up to 1/500^{37,38}. The hypothesis of a systemic mechanism, triggered by radiotherapy is supported by the scleroderma appearance away from the radiated field. Possible mechanisms involve T cell activation³⁶ and clonal fibroblast population alteration. Selective local immune alteration, including TGF- β increase and endothelial alterations have also been proposed for radiation caused scleroderma^{39,37}.

Research on predictive factors for breast cancer patients to develop scleroderma manifestations is inconclusive. Patient age, total dose of radiation, dose per fraction, severity of the acute reaction and tamoxifen use do not appear significant.³⁷ Several studies however indicate the severity of scleroderma is an important predictive factor⁴⁰. Finally apart from radiotherapy, chemotherapy especially with docetaxel and paclitaxel has been reported to occasionally induce scleroderma^{41,42,43,44}.

4. Treatment

A possible relation between the two diseases could potentially lead to treatment alternations with dilemmas occurring mainly when scleroderma patients develop a breast cancer. No evidence exists in the literature that the core treatment – surgery – should be altered but questions over adjuvant chemotherapy and radiotherapy have been raised.

Finally, hormonal and biological therapies do not seem to interfere with the course of scleroderma.

Scleroderma is a relative contradiction for radiotherapy due to possible sensitivity of the tissue affected by the disease. Many doctors hesitate to treat breast cancer in scleroderma patients with breast conservation^{45,46}, although large studies failed to prove severe toxicity^{48,49}, such as grade III or IV toxicity (severe adverse events or life threatening or disabling adverse events respectively). It has been stated that clinicians consider radiotherapy to be contraindicated to scleroderma patients because mainly of publication bias, severe cases of toxicity being written up as case reports, while cases with mild toxicity or no toxicity are omitted³⁸.

A large study by Lin et al⁵⁰ found no differences in early toxicity, but differences were found in late toxicity. Proven prognostic factors for scleroderma patients developing toxicity effects are curative treatment, multi organ involvement of scleroderma for acute toxicity and negative antinuclear antibodies for late toxicity.⁵¹ However these results reach statistical importance for mild toxicity only (Grade 1 and 2 according to Common Terminology Criteria for Adverse Events version 3.0 grading scales).

Another implication of the coexistence of scleroderma and breast cancer is imaging surveillance after breast conservation. This may be difficult due to breast fibrosis and is sometimes achieved only by MRI.⁴⁷

On the other hand, previously healthy patients who receive radiotherapy for breast cancer can develop sclerodermatic changes. The typical clinical picture includes sclerotic and pigmentary lesions in the breast, initially severe and painful but self - limited.³⁷ The initial calculation of its incidence at 0.2% is probably an overestimate. This situation is rare and is only reported in sparse case reports in the English literature^{35,38,39}.

In these cases the clinician can use the appropriate scleroderma therapy and topical steroids, calcineurin inhibitors or low doses of systemic immunosuppressants (steroids, methotrexate MTX cyclosporine) can be applied. Topical softening of the tissue can be achieved by means of heparin, hyaluronidase, UVA1 irradiation, PUVA irradiation, or the systemic administration of penicillamine with various success^{54,52,55}.

5. Conclusions

While the relationship between cancer and scleroderma is strongly suggested, its characteristics are not yet clarified and more research is required. Questions to be answered include underlying pathophysiological mechanisms and alterations in the treatment for scleroderma patients. Coexistence of scleroderma and breast cancer can be a challenging problem, involving general surgeons, rheumatologists, oncologists, radiologists and, last but not least, mental health professionals since the coexistence of two diseases can affect the patients' psychological status and their compliance with the treatment. A multidisciplinary approach with doctors, nurses and paramedics, high clinical vigilance and cooperation is required so to avoid undesirable consequences.

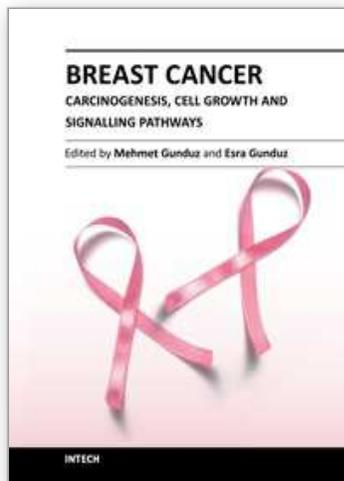
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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