



## A Cross-Disciplinary Look at Shoulder Pain and Dysfunction after Treatment for Breast Cancer

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Shoulder morbidity is a well-documented consequence of treatment for breast cancer. Despite less invasive surgery, a subset of breast cancer survivors present with decreased shoulder complex mobility, tightness, oedema, weakness, pain and numbness after treatment [1]. Additional considerations are connective tissue changes such as scarring and Axillary Web Syndrome (cording) [1], which are known contributory factors to arm dysfunction and pain after treatment. Patients experiencing shoulder and arm problems have significantly reduced functional use of their upper limb [1,2], which limits their quality of life and their ability to return to work [1]. Many women develop shoulder pain and dysfunction for up to 6 years post-surgery independent of axillary involvement [1,2]. These reports describe altered muscle function and joint kinematic patterns that mimic those of known shoulder conditions such as rotator cuff disease (RCD) and Adhesive Capsulitis (AC) [2]. We know that treatment can resolve the pain and dysfunction but the rehabilitation programmes are resource intensive and thus not implemented in standard cancer care pathways [3]. This means patients first present with shoulder problems to musculoskeletal practitioners who do not link the condition to cancer treatment. Elucidation of the risk profiles and biological mechanisms involved would allow us to target patients at risk of developing problems and support future therapeutic options.

Attempts to identify clinical risk factors have been hindered by the complexity of the condition and the many clinical variables involved in cancer management. Adding a unique anatomical and biomechanical structure such as the shoulder complex further complicates the problem. In order to better understand the underlying mechanisms causing shoulder pain orthopaedic researchers have moved towards mechanistic and genomic studies. Given that the clinical presentation of shoulder problems in breast cancer survivors mimics that of known shoulder conditions, it seems logical to cross reference current knowledge of mechanistic pathways and genomes to determine any similarities of abnormality. Further support for taking this direction comes from the fact that not all patients treated for breast cancer develop shoulder problems, structures unrelated to direct treatment are affected, shoulder morbidity is bilateral while radiotherapy (axillary or trunk) and chemotherapy are associated with increased upper limb pain and dysfunction [1,2]. These factors suggest a potential systemic cause of shoulder pain and dysfunction.

While the cause remains complex and multifactorial, the main proponents of patient reported pain and dysfunction at the shoulder are bursa, tendons and ligaments.

### Sub-Acromial Bursa

Several studies suggest that shoulder conditions such as RCD and AC might be preceded by, or promoted by, the involvement of the sub acromial bursa [4-6]. Gotohet et al. [4] demonstrated an increase in IL-1 and IL-1R antagonist mRNA in subacromial bursa biopsy specimens from patients with rotator cuff disease versus controls. Similarly [5], have shown marked hyperplasia of the blood vessels and fibroblasts of sub acromial bursa in patients with rotator cuff tendonitis compared to patients with anterior instability. IL-1, TNF- $\alpha$ , bFGF and TGF- $\beta$  were all over expressed in blood vessels and fibroblast cytoplasm. IL-1 and TNF- $\alpha$  have been reported to induce pain by stimulating COX-2 expression, resulting in the production of prostaglandins [6]. Clinical manifestations could therefore be a result of hypertrophy of the bursa, which might disturb the sliding mechanism of the synovium thus limiting movement and resulting in contracture of the connective tissues. An enlarged bursa could also result in impingement. If untreated, both outcomes could lead to chronic pain, and the altered movement patterns observed in breast cancer survivors, which are known to lead to dysfunction [7].

### Rotator Cuff Tendons

Key Growth Factors (GF) for tendon inflammation and healing are bFGF, IGF-1, PDGF and TGF- $\beta$ , all of which are expressed in the early phase of the rotator tendon healing process [8]. bFGF promotes cellular proliferation of rotator cuff tendon cells and increases type III collagen production in healing tendons [9]. Similarly, TGF- $\beta$ , which is active during all stages of tendon inflammation and healing, stimulates extrinsic cell migration, and regulates proteinase and collagen production [8]. Suppression of TGF- $\beta$  on the other hand results in a decrease in adhesion formation [10].

### Radiotherapy Alters the Expression of Many of these Proteins

Ionizing radiation causes DNA damage that alters biological mechanisms via cytokines, chemokines, altered cell-cell interactions and the influx of inflammatory cells [11]. Radiation-induced fibrosis

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has been linked to TGF- $\beta$  and TNF- $\alpha$  and inflammatory responses to IL-1, TNF- $\alpha$ , IL-6 and TGF- $\beta$ . However, current views are that sensitivity to radiation is largely genetically determined [11]. Genome Wide Association (GWA) studies are exploring this with respect to known long term reactions such as fibrosis, atrophy and vascular changes, all of which could alter normal physiological and biomechanical function [11]. The results of these studies will be very interesting since the ability of damaged musculoskeletal tissues to tolerate load is variable in non-cancer related conditions and can be partially explained by a genetic component [12]. At the shoulder, expression of IL-1 $\alpha$ , IL-1 $\beta$ , and IL-6 genes is increased in patients with sub acromial bursitis compared to control specimens [13] while the TNF-863A allele genotype is important in identifying susceptibility to fibrosis [14]. Whether genetic polymorphisms are able to explain the difference between those breast cancer survivors who develop shoulder problems and those who don't remains to be explored.

In most countries shoulder pain and dysfunction is a poorly understood and unresolved problem for women treated for breast cancer. Collaboration between researchers in oncology, radiobiology and orthopaedics would bring together an ideal skill set for furthering our understanding of shoulder conditions and the impact of cancer treatment on healthy tissues.

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