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Late effects after breast cancer treatment

CLINICAL REVIEW

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Breast cancer is the most common cancer among women in Norway. Nine out of ten will become long-term survivors. Being cancer-free does not necessarily mean feeling healthy, and many experience troublesome late effects, such as fatigue, pain and fear of recurrence. General practitioners represent the most important medical support for the majority of these women. This clinical review article summarises up-to-date knowledge about late effects after breast cancer treatment. Non-pharmacological interventions can have a positive effect on many of the most common late effects.

In 2021, more than 4000 women in Norway were diagnosed with breast cancer (1). Most women with breast cancer have localised disease and receive curative surgery, followed by radiation therapy. Many also receive combinations of systemic treatments, such as chemotherapy, endocrine therapy and human epidermal growth factor receptor 2 (HER2) blockade (2). The treatment is effective, and the five-year relative survival rate is 92 % (3). In the Norwegian population, approximately 53 000 people have had or are living with breast cancer, and the number is increasing (3).

Late effects are defined as effects of cancer or adverse effects of treatment that last for one year or more after the end of treatment, or symptoms that are likely caused by the cancer or the treatment and which appear one year or more after completing treatment (4). The risk of severe late effects, such as secondary cancer or heart disease, is low after modern breast cancer treatment. However, a significant proportion of breast cancer survivors will experience one or more less severe late effects that may have a negative impact on their ability to work and quality of life. The purpose of this article is to shed light on the most common late effects after treatment for localised breast cancer. The article is based on subjectively selected systematic reviews, national treatment recommendations, Norwegian research findings and clinical experience.

The most common late effects

Chronic fatigue, cognitive dysfunction, sleep difficulties, pain, fear of recurrence and symptoms of oestrogen deficiency are the most common late effects after breast cancer. Patients who have received radiation therapy to regional lymph nodes have an increased risk of hypothyroidism (5). Breast cancer survivors often experience multiple overlapping and reinforcing symptoms, such as fatigue, pain and sleep difficulties (6). Breast cancer survivors report late effects to a greater extent than other cancer survivors (7). This may be due to the biology or treatment of the disease, but factors related to personality, supportive care needs and coping strategies also play a role (8).

Chronic fatigue is reported by 25–30 % of breast cancer survivors and is characterised by pronounced physical or emotional and/or cognitive fatigue lasting for six months or more, regardless of sleep and activity levels (9). Known risk factors include young age, sleep difficulties, pain and psychiatric comorbidity, and a catastrophising personality (9).

Increasing treatment intensity also appears to increase the risk of fatigue after breast cancer (10). Cognitive fatigue encompasses experiences of impaired memory, difficulty concentrating and/or difficulty finding the correct word (11). These are symptoms that are also part of cognitive dysfunction after cancer (12). More than 50 % of breast cancer survivors report cognitive dysfunction, but objective cognitive dysfunction is only detected in 15–25 % (12). Several factors appear to be associated with cognitive dysfunction. In addition to cancer treatment, genetic predisposition, advanced age and psychiatric comorbidity also seem to contribute (12). Both fatigue and cognitive dysfunction can have a major negative impact on a person's quality of life and ability to work (13–15).

A recent review found that 40 % of breast cancer survivors experience sleep difficulties (16). In a Norwegian study, 30 % of breast cancer survivors had sleep difficulties compared to 18 % of age-matched women without cancer (17). Sleep difficulties are particularly associated with hot flushes, depression and fatigue (16).

Pain is reported by approximately 30 % of breast cancer survivors several years after completing treatment (18). Surgery and radiation therapy can cause locoregional pain, lymphoedema and reduced function in the arm/shoulder (17). Chemotherapy, especially taxanes, can lead to peripheral neuropathy characterised by pain, numbness and tingling, typically in the hands and feet. Fear of cancer recurrence (FCR) is defined as a persistent 'fear, worry or concern relating to the possibility that cancer will come back or progress' (19). While it is natural to experience such concerns following a serious illness, some people develop persistent anxiety and hyper-vigilance towards the possibility of recurrence, leading to an excessive preoccupation with bodily symptoms. In a Norwegian study of survivors of different cancer diagnoses, the highest prevalence of FCR was found among breast cancer survivors, and was particularly associated with young age and caring for children (20). A total of

20–40 % of people struggle with FCR to such a degree that they want help to manage it (21). Anxiety and depression can also occur after breast cancer (22), and young age is also an important risk factor here (23).

Many breast cancer survivors receive adjuvant endocrine treatment for 5–10 years and experience symptoms of oestrogen deficiency. These patients often experience hot flushes, fatigue, sleep difficulties, vulvovaginal atrophy and impaired sexual health (24). Aromatase inhibitors in particular can cause arthralgia and muscle pain.

Follow-up

The Norwegian Breast Cancer Group recommends annual mammography for ten years and follow-up by the specialist health service at least 1, 2 and 5 years after diagnosis, with further assessment depending on age, stage and treatment complexity (2). General practitioners (GPs) are responsible for follow-up beyond the first ten years. The purpose of the annual check-up is to detect recurrence at an early stage, motivate patients to adhere to recommended endocrine treatment, and monitor mammography and thyroid function (Box 1). Additional follow-up must be tailored to the individual's needs.

Box 1 Checklist for routine annual screening

Medical history
Review of cancer history and treatment
Ongoing endocrine treatment? Symptoms of oestrogen deficiency?
Late effects? Pain, fear of recurrence, sleep, fatigue
Ability to work?
Need for rehabilitation measures? Clarify level.

Clinical examination
Both breasts/chest wall, regional lymph node stations
Further symptom-targeted examination

Review of test results
Thyroid tests
Mammography result

In patients with a severe symptom burden, it can be helpful to identify and alert the patient to potential symptom clusters. Improvements in one condition can lead to overall improvement in the symptom burden. The patient should be informed that there is often no single underlying cause for the symptoms, nor targeted treatment, and that they may improve over time. We have found that active listening, providing thorough diagnostic clarification and information, and close follow-up are effective, especially in cases of fatigue and FCR.

Relevant interventions and provision

The interventions that seem to be most effective for late effects after breast cancer are physical activity and cognitive behavioural therapy. This should complement symptomatic treatment of pain, sleep difficulties and symptoms of oestrogen deficiency as needed. In cases of pronounced symptoms of oestrogen deficiency where non-hormonal symptom-relieving measures are not sufficient, the GP, in close collaboration with the oncologist, can consider pausing, modifying or discontinuing endocrine treatment (2).

Physical activity among cancer survivors is safe and well-tolerated (25). Reviews have reported a clear positive correlation between physical activity and reduced mortality, both for breast cancer-specific mortality and general mortality (26). Physical activity also reduces fatigue (27), pain (28) and cognitive dysfunction (29). It is not known what form of exercise or how much exercise is needed to achieve the best outcome, but most breast cancer survivors can safely follow the Norwegian Directorate of Health's recommendations for the general adult population. Cognitive therapy has been shown to have a positive effect on, for example, FCR (30) and fatigue (31).

There are several rehabilitation services available for breast cancer survivors, ranging from low-threshold services in the primary care service to specialised and interdisciplinary rehabilitation in hospitals or outpatient and inpatient facilities (Figure 1) (32–36). Healthy Life Centres, *Pusterom* (training centres aimed at cancer patients) and physiotherapists with specialised training (AKTIV instructors) offer guidance and physical activity (32–34). Some people may benefit from a referral to a sexologist or psychologist, and these are also available at regional rehabilitation centres.

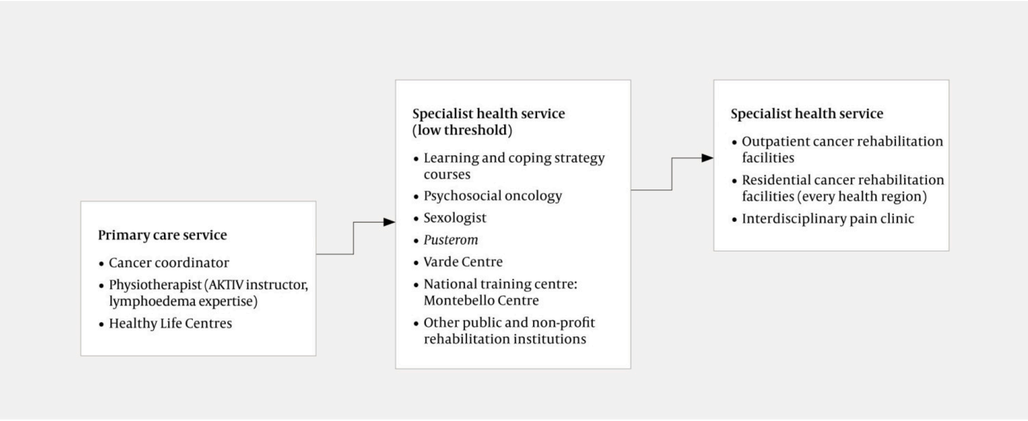

Figure 1 Provision for breast cancer survivors. Stage 1 is the primary care service, stages 2 and 3 the specialist health service. The services range from low-threshold options suitable for mild symptoms, to specialised interdisciplinary rehabilitation for breast cancer survivors with complex needs and symptoms (32–36).

The Montebello Centre offers general life management courses and courses specifically targeting various late effects (35). Many GPs have specialised training in cognitive therapy and offer this to their own patients. In cases of pronounced, complex and persistent symptoms, referral to a regional late effects outpatient clinic, interdisciplinary pain clinic or residential rehabilitation facility may be appropriate.

In conclusion

Over 90 % of women diagnosed with breast cancer will become long-term survivors. The risk of late effects is high. Many struggle with multiple concurrent symptoms that can negatively impact on their ability to work and quality of life. GPs represent the most important medical support for most breast cancer survivors. Non-pharmacological interventions have the best effect, especially physical activity and cognitive therapy. These should be initiated alongside symptomatic pharmacological treatment as needed. There are various rehabilitation services available. Good and tailored information about late effects and support from healthcare personnel are important for coping with life as a breast cancer survivor.

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