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Review

Overview of long term care of breast cancer survivors

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ABSTRACT

Breast cancer, the most common cancer in women in developed countries, has a generally excellent prognosis, therefore long-term survivors living with the consequences of breast cancer ('survivors') and its treatment are an increasing group in clinical practice. This review discusses the complex issues relevant to survivorship care, including current recommendations for ongoing adjuvant hormonal therapy (tamoxifen and aromatase inhibitors), and the management of side effects of cancer treatment (such as menopause, arthralgia, and lymphoedema). Annual mammography screening is advised for detection of second breast cancers, and symptom-directed assessment is warranted where there is suspicion of distant recurrence or (in women using tamoxifen) of endometrial cancer. Management of menopausal symptoms, including treatment-induced premature menopause, is a key issue for many survivors, and can be challenging to manage as conventional hormone replacement therapy is contraindicated in most of these women. Specific therapeutic options for hot flushes and vaginal symptoms are discussed. The review also emphasises the need for survivorship care to include optimisation of general health, including psychosocial and sexual health, bone health and the evaluation of lifestyle-related risk factors and genetic factors. The review provides guidance on the management of many of these issues, and highlights areas requiring further evidence and research.

Contents

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1. Introduction

The incidence of breast cancer has increased over the past three decades in many parts of the world, and now appears steady, remaining the most common cancer in females in most developed countries [1]. Breast cancer survival has also increased, due to improvements in treatment and early detection; women diagnosed with early, node-negative breast cancer now have 5-year survival of 95–98% in many countries [2–4]. These factors, in combination with general gains in life expectancy, mean that there is a high prevalence of women living with the long-term effects of breast cancer and its treatment (breast cancer survivors). 'Follow-up care' has traditionally focused on the detection (or exclusion) of cancer recurrence. It is now recognised that many breast cancer survivors have unmet needs particularly in the areas of treatment-induced menopausal symptoms, relationship and sexuality issues, and emotional issues such as living with uncertainty, fear of cancer recurrence and late episodes of depression. In addition, the management of ongoing adjuvant endocrine therapy often involves switching between therapeutic agents, making this an important part of care in the years following breast cancer treatment. The increased complexity of this long-term care has led to the concept of a more holistic style of "survivorship care". This review summarises the issues relevant to the long-term care of breast cancer survivors.

2. Guidelines for follow-up care

Guidelines for follow-up care of survivors acknowledge that there is limited evidence on which to base recommendations, hence some recommendations are based on consensus opinion [5–7]. All recommend regular visits with a clinician at varied intervals (3-monthly to much less frequent). Most cancer clinicians review their patients several times in the first year after treatment and reduce the frequency over subsequent years, with some discharging patients from specialist follow-up after 5 years [8] and may tailor this to the particular clinical situation. Guidelines recommend that long-term care includes attention to psychosocial, emotional, genetic and lifestyle issues. Care should be coordinated with good communication between teams of practitioners. More recently, it has been recommended that the patient be involved in developing a plan for ongoing care and be provided written 'survivorship care plan' [5,6,9]. The role, implementation and potential benefits of a written care plan are being investigated in trials.

Follow-up care is provided by specialist oncologists in many countries but workforce issues and a change from focus on detection of recurrence have led some centres to explore options of some consultations with primary care physicians and breast care nurses [10,11]. There is evidence from randomised trials in the UK and Canada that follow-up care provided by primary care physicians is equivalent to hospital-based outpatient care in the detection of cancer recurrence. This care can be delivered with a high level of patient satisfaction and greater cost-effectiveness than hospital specialist care [12–15].

3. Screening in breast cancer survivors

3.1. Risk of further breast cancer in survivors

Women who have been affected by breast cancer are at risk of developing an ipsilateral breast recurrence (in-breast recurrence) or a new primary cancer in the treated breast – these will be referred to as ipsilateral breast cancer (IBC). Survivors are also at risk of developing a contralateral breast cancer (CBC). The risk of developing a further breast cancer in either the treated or the contralateral breast varies according to tumour and therapeutic factors associated with the (first) breast cancer. In general, women with early-stage invasive breast cancer treated with breast conservation and adjuvant radiation, with long-term follow-up, are reported to develop IBC in the range of 0.5–1% per year [16–19]. In one of the largest population studies of CBC, Gao et al. [20] reported actuarial rates for CBC of 6.1% at 10 years and 12% at 20 years. The risk of a 'second' breast cancer in survivors, counting IBC or CBC was recently estimated as 5.4–6.6/1000 woman years [21].

3.2. Is mammography screening warranted?

Mammography screening, usually combined with clinical breast examination, is aimed at early detection of further breast cancer events in either breast. There is consensus that survivors should have annual screening mammography (also referred to as 'surveillance') as part of their long-term follow-up [6,7,22–24], however recommendations on the frequency and long-term duration of breast surveillance in survivors vary in guidelines and in practice [6,25–27]. There is also some debate concerning the effectiveness and optimal model of breast surveillance in survivors [14,26–28]. One of the limitations of the evidence on the effect of breast screening in survivors is that it comes from non-randomised studies [29–32] and from extrapolation of potential benefit from randomised population mammography screening trials. A recent review [33] concluded that the evidence from non-randomised studies supported a likely benefit of mammography screening in survivors, but also outlined that most observational studies of this issue were affected by several biases and overestimated breast screening benefit. Furthermore, a study from Lash and colleagues [30] of the association between surveillance mammography and mortality in women 65 years and older, highlighted that screening had a benefit in survivors but that the protective effect of mammography was mostly evident in women whose initial breast cancer was stage I.

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3.3. Accuracy of mammography screening in survivors

Screening mammography in survivors has not been evaluated in population screening programs, so there is a paucity of good-quality data on screening sensitivity or other measures of screening accuracy such as false positives. Most studies of mammography screening in survivors have generally based on selected clinical series and most report only the proportion of ipsilateral or contralateral cancers detected with mammography [33]. The proportion of IBC detected with screening mammography is reported to range between 50% and 80% [18,29,34–40] if *any* detection by mammography is considered (meaning, counting some mammography-detected IBC that is also detected clinically). Clinical breast examination is advised as adjunct to mammography in surveillance of women with a personal history of breast cancer, since a significant proportion of IBC, approximately 10–30% [27,29,38,41], is detected only on clinical examination. A false positive rate of 2.3% has been reported for surveillance mammography in survivors treated with breast conservation [37].

Estimates of the proportion of CBC detected through mammography screening ranges between 45% and 90% [18,29,42–46] of women who develop CBC. Lu et al. [45] reported estimates of sensitivity and specificity for surveillance mammography in survivors for detection of CBC: sensitivity was reported at 59.6%, however, in women who complied with annual mammography sensitivity increased to 70.8%; specificity of mammography was 98.3%. This study also showed that 34.2% of CBC cases were diagnosed as interval cancers (cancers *not* detected by screening).

A very recent population-based study of mammography screening in a cohort of 19,078 breast cancer survivors has reported a screening sensitivity of 65.4% (which was similar for ipsilateral and contralateral detection) and a specificity of 98.3% [47]. This study also showed that, while mammography did not detect about one third of the cancers occurring in the cohort of survivors, screen-detected cancers were mostly early-stage cancers [47]. This reinforces the current consensus recommendation for annual mammography as part of ongoing surveillance in survivors. We emphasise that survivors presenting with symptoms or self-detected breast changes require prompt investigation using triple testing (clinical examination, breast imaging and needle biopsy) which is the standard approach for investigating *any* woman with a new breast symptom.

3.4. Adjunct breast imaging in screening breast cancer survivors

At present, the *routine* use of adjunct breast imaging in screening survivors is not recommended in guidelines [6] although there may be a potential role for magnetic resonance imaging (MRI) [48] or ultrasound [49] in some survivors. Contrast-enhanced MRI has been shown to be more sensitive than mammography in women who have mutations in BRCA1 or BRCA2, and hence have a very high lifetime risk of developing breast cancer [48]. In these women, MRI screening is recommended in guidelines [48]. Therefore survivors who are also known to have a breast/ovarian cancer susceptibility gene should be advised to have mammography and MRI as annual breast screening. There is some evidence that the addition of ultrasound to mammography increases screening sensitivity in survivors [49] however the routine use of ultrasound as a screening test in this clinical context is not recommended at present [6].

3.5. Screening for distant metastases

Although survivors are at risk of developing distant metastases, intensive screening for *asymptomatic* metastatic relapse is not recommended [6] because randomised controlled trials (RCTs) [50–52] have shown that early detection of metastatic cancer does not confer benefit in terms of survival or quality of life. It should be acknowledged that these RCTs were conducted before recent substantial advances in treatment of metastatic disease, so there is some discussion regarding the applicability of the evidence to current standards in metastatic breast cancer [23]; however to date, there are no data to support screening for metastatic disease in survivors. Bone scans, chest X-ray, liver ultrasound, pelvic and chest CT, whole-body MRI, and fluorodeoxyglucose-positron emission tomography scanning are therefore *not* recommended as routine surveillance tests in (asymptomatic) survivors [6,23]. This should be distinguished from investigating new symptoms (such as bone pain, pelvic pain, dyspnoea, or neurologic symptoms) [23] or clinical findings that raise suspicion of metastases, where some of the above-mentioned tests may be warranted. Survivors experiencing new symptoms should be promptly investigated and referred to their oncology teams if they are suspected of having metastatic disease.

3.6. Other screening/testing

Survivors using tamoxifen therapy are at increased risk of developing endometrial cancer – the *relative* risk of developing endometrial cancer for women taking tamoxifen is approximately two to three times higher than that of age-matched women not taking tamoxifen [53]. The American *Committee on Gynaecologic Practice* recommends that 'any symptoms of endometrial hyperplasia or cancer reported by a postmenopausal woman taking tamoxifen should be evaluated', and women receiving tamoxifen should be advised to report any vaginal bleeding. Annual gynaecologic review is recommended in all women however specific screening for endometrial cancer in survivors is not recommended [6]. In *asymptomatic* women receiving tamoxifen, screening for endometrial cancer with routine transvaginal ultrasound, endometrial biopsy, or both, has not been shown to be effective and is not recommended in consensus guidelines [6,52,53]. Transvaginal ultrasound in *asymptomatic* women receiving tamoxifen may also be associated with a high rate of false positive findings due to tamoxifen-induced benign proliferation [23] and its use to screen survivors is not advised.

Breast cancer tumour markers, such as carcinoembryonic antigen (CEA) or CA 15-3 (markers used in highly selected situations in women receiving treatment for metastatic breast cancer) should *not* be used in screening for breast cancer or as part of routine follow-up testing in survivors [6,54].

4. Lifestyle factors and cancer recurrence

There is increasing evidence showing that lifestyle factors have a significant impact on cancer recurrence. As well as being a risk factor for the development of breast cancer, obesity, alcohol, smoking and lack of physical activity increase the risk of cancer recurrence [55,56] and development of contralateral breast cancer [57]. Dietary factors are also implicated; a lower intake of saturated and trans fat in the diet is associated with improved survival after breast cancer diagnosis [58]. As these factors are all potentially modifiable and women are often open to a change in health behaviour after a cancer diagnosis, these issues could be addressed in follow-up consultations [59]. In addition, addressing these factors is a priority for overall health; as cancer survival improves, cardiovascular disease becomes the dominant long-term health risk for breast cancer survivors.

Advice about alcohol consumption requires balance as evidence shows that consuming only three to four alcoholic drinks per week after a breast cancer diagnosis may increase risk of breast cancer recurrence. This risk is particularly high in postmenopausal

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and overweight/obese women [56]. However, several studies have shown a cardio-protective effect of moderate alcohol intake in the general population [60] and a reduction in non-breast cancer death has been suggested in epidemiological studies involving breast cancer survivors [56].

5. Ongoing management-adjuvant endocrine therapy

5.1. Endocrine therapy for ER positive breast cancer

Approximately 75% of breast cancers are oestrogen-receptor positive [61] and the majority of women with these tumours will be treated with adjuvant endocrine therapy. Five years of tamoxifen has been shown in numerous trials to reduce the risk of local recurrence and breast cancer mortality in women with ER-positive tumours regardless of age and menopausal status [62]. It also reduces the risk of contralateral cancer. Five years of tamoxifen remains the standard treatment for women who are premenopausal at diagnosis.

Tamoxifen is usually very well tolerated. Common side effects include hot flushes and vaginal discharge. The incidence of serious adverse events (endometrial carcinoma and venous thromboembolism) is very low [63,64]. Routine endometrial monitoring with transvaginal ultrasound is not recommended [65].

Tamoxifen requires metabolism to its active form by the enzyme CYP2D6, and the efficacy of tamoxifen may be reduced in patients who have impaired CYP2D6 function. Further research is progressing in this area; at present, CYP2D6 testing is not part of routine management of women considering treatment with tamoxifen [65]. It is recommended, however, that drugs that inhibit CYP2D6 (such as some selective serotonin reuptake inhibitors, SSRIs) be avoided in women on tamoxifen as they may reduce the efficacy of tamoxifen. Thus paroxetine, fluoxetine and bupropion should be avoided in patients using tamoxifen, and venlafaxine is the preferred antidepressant in this population, with desvenlafaxine a possible alternative given that its metabolism does not involve CYP2D6 [65].

5.2. Aromatase inhibitors (AIs)

Aromatase inhibitors (letrozole, anastrozole and exemestane) have revolutionised the management of ER-positive breast cancer. They reduce the risk of local and distant breast cancer recurrence compared to tamoxifen. AIs are not effective in premenopausal women so they are only recommended for use in women who are post-menopausal at diagnosis or women whose menses have not returned 12 months after chemotherapy induced amenorrhoea.

Optimal timing and duration of therapy has not been established. Aromatase inhibitors may be used as 'up front' treatment for five years (as an alternative to tamoxifen) or may be used sequentially with tamoxifen, with 2–3 years of aromatase inhibitor before or following 2–3 years of tamoxifen. Current guidelines recommend that post-menopausal women consider an aromatase inhibitor at some stage during the course of their treatment [66]. Randomised trials evaluating optimal sequencing and the role of extended adjuvant treatment (beyond five years) are ongoing.

Side effects from AIs are common and include hot flushes, vaginal dryness, joint pain and loss of bone mass.

5.2.1. Arthralgia

Arthralgia is a common side effect of therapy with AIs and is reported in up to 36% of patients. The most common symptom is morning stiffness and hand or wrist pain. This can be a troubling symptom and is one of the common reasons for discontinuation of therapy [63,64]. Arthralgia may be self-limiting with improvement after 3 months of therapy but for many women it is persistent. Management of this symptom has not been evaluated in large randomised trials, however common treatments include NSAIDs, paracetamol, supplements (such as glucosamine and omega fish oils), acupuncture and promotion of exercise. Some patients may benefit from a 'drug holiday' with a 3-month break from therapy, others may respond to a switch to another drug in the same class. For women whose symptoms are persistent and severe, therapy may need to ceased and consideration given to tamoxifen as an alternative.

5.2.2. Osteopenia/osteoporosis

Another adverse effect of aromatase inhibitors is a reduction in bone mineral density. Among patients with normal baseline bone mineral density receiving anastrozole, 17% developed osteopenia and among those with osteopenia at baseline, 5% developed osteoporosis. The incidence of fractures was 11% in women receiving AIs, a significantly increased number compared to women on tamoxifen [64,65]. It is therefore recommended that all women have bone mineral density scanning prior to commencement of treatment with an AI and that those with osteopenia on bone density be managed with the standard treatment (including adequate calcium, Vitamin D and weight bearing exercise) and have careful monitoring of bone mineral density every two years [67]. Those with osteoporosis should commence bisphosphonate therapy or consider treatment with tamoxifen for all or part of the adjuvant therapy [65]. Unrecognised Vitamin D deficiency is common in women with breast cancer [68] and Vitamin D levels should be measured and corrected if deficiency is found. Some experts recommend that all women taking AIs take calcium and Vitamin D supplements regardless of bone density [69].

6. Menopause and breast cancer

There are many reasons why symptoms of menopause may be prominent in women following breast cancer treatment. Women taking hormone replacement therapy at diagnosis are asked to stop taking it, chemotherapy may induce temporary or permanent ovarian dysfunction and endocrine therapies may cause menopausal-like symptoms. In addition, many of the usual treatments used for menopausal symptoms are contraindicated in women with breast cancer.

6.1. Lifestyle factors and menopause

Discussion of situations that exacerbate symptoms and avoidance of these may help symptoms. Hot flushes may be more severe in women who smoke and are overweight and may be reduced by exercise [70].

6.2. Hormone replacement therapy

The HABITS study, a randomised trial addressing the efficacy and safely of hormone replacement therapy after breast cancer treatment, was stopped after median follow-up of 2 years as it showed a significantly higher risk of breast cancer events in women randomised to treatment with HRT (clinician choice of therapy) compared to those not taking HRT (relative hazard (RH) risk 3.5; 26 vs 7 events). There was a higher risk of new events in women with hormone receptor positive cancer (RH 4.8), those not taking tamoxifen (RH 3.7) and those taking HRT before breast cancer diagnosis (RH 6.9) [71]. In this trial, there was no significant difference in risk between combined preparations, oestrogen-only preparations and other preparations (such as tibolone) [71]. The Stockholm trial also randomised survivors to treatment with HRT or no HRT; in this study there was no increased risk of recurrence in women in

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the HRT arm. One possible explanation for this is the higher proportion of women taking oestrogen-only preparations rather than continuous combined hormone preparations, indicating that the oestrogen-only preparations may be less hazardous in this group of women [72]. The LIBERATE randomised trial (over 3000 women randomised) showed an increased risk of recurrence in women taking tibolone vs placebo for vasomotor symptoms [73]. Based on these studies, systemic HRT is not recommended in breast cancer survivors. The use of vaginal oestrogens is discussed below.

6.3. Complementary therapies for menopause

There is little quality evidence to support the efficacy and safety of alternative therapies for menopause. Soy and black cohosh have been tested in healthy post-menopausal women with little benefit and the safety of these treatments in this context has not been established. There is some evidence to support the use of high-dose Vitamin E. Acupuncture, relaxation therapy and nurse-delivered interventions can improve symptoms in some cases [70].

6.4. Management of hot flushes

SSRIs (paroxetine, fluoxetine and citalopram) and serotonin noradrenalin reuptake inhibitors (SNRIs, venlafaxine and desvenlafaxine) have been shown to be efficacious and safe for managing hot flushes in breast cancer patients, reducing the number and/or frequency of hot flushes by more than 50% depending on the agent [70]. The effect of these medications appears to be independent of their antidepressant effect. While they are generally well tolerated, side effects may include nausea, dry mouth, and sexual dysfunction.

Caution must be used when these medications are combined with tamoxifen due to the interference of some SSRIs and SNRIs with the CYP2D6 pathway essential for tamoxifen metabolism, as outlined earlier. In this situation, fluoxetine and paroxetine should be avoided; sertraline, venlafaxine and desvenlafaxine are preferred as they are less potent inhibitors of CYP2D6 [74,75].

Gabapentin is a drug used in the management of epilepsy and chronic pain. It is also effective in reducing hot flushes in healthy women and breast cancer patients. In one study its efficacy was equivalent to oestrogen [76] and it has the benefits of not interacting with tamoxifen, and does not interfere with sexual function. It may be considered in women who do not respond to or are unable to take or to tolerate SSRIs/SNRIs. Clonidine is also an option for managing hot flushes in this group of women.

6.5. Vaginal symptoms

Atrophic vaginitis is a common symptom in post-menopausal women and can also be a side effect of aromatase inhibitors. Non-hormonal vaginal agents such as simple moisturising/lubricating treatments may provide significant relief. The safety of vaginal hormonal preparations is unproven however small retrospective trials support their safety [70]. There is a theoretical concern that the efficacy of aromatase inhibitors may be reduced with the use of oestradiol vaginal tablet as it increases the circulating levels of oestradiol but reduced efficacy has not been observed in trials [77]. For this reason, oestradiol vaginal cream may be preferable in this group of women as it does not increase circulating oestradiol.

7. Other issues in breast cancer survivors

7.1. Quality of life

A cancer diagnosis has a significant and long-lasting impact on quality of life, especially in younger women. Menopause symptoms, in addition to fatigue, cognitive impairment combine to cause high levels of distress in some women [78–81]. Fear of cancer recurrence is also a common issue and is one that often persists for many years beyond the cancer diagnosis. This can be managed by providing patients with accurate information about their true risk of recurrence (often lower than the perceived risk). A number of interventions such as mindfulness and other cognitive therapies have been proven effective in some centres [82,83].

Sexual dysfunction, related to the diagnosis of breast cancer, menopause, or side effects of treatment is common, particularly in younger women treated with chemotherapy [84,85]. It is a difficult symptom to treat and requires a holistic approach to management. Contributing causes such as vaginal dryness and depression may be treated and this may improve quality of life. Testosterone is not recommended after breast cancer treatment due to its unproven safety and efficacy [70]. Issues related to body image are common and may have a substantial impact on sexuality [84].

Fatigue and cognitive dysfunction are also common in breast cancer survivors [23] and are particularly challenging to manage.

7.2. Genetics

Assessment of family history is an important part of follow-up care for breast cancer survivors. Family history is constantly evolving and may take on new significance if additional relatives are diagnosed breast, ovarian or other cancers. Women with a confirmed gene mutation have a lifetime risk of breast cancer around 56% (BRCA2 mutation) to 84% (BRCA1 mutation) [86,87]. While conflicting, there is evidence that BRCA1 gene mutation carriers who develop breast cancer have a worse overall survival at 5 and 10 years compared to non-mutation carriers who develop breast cancer [88,89]. The evidence suggests that survival is similar for BRCA2 mutation carriers as for non-mutation carriers [88,89]. Women with a gene mutation who develop cancer have many of the same risk-reducing options as women who are unaffected by cancer including bilateral mastectomy (with or without reconstruction) and bilateral salpingo-oophorectomy [87,89,90].

7.3. Lymphoedema

Sentinel lymph node biopsy (SLNB) has revolutionised the management of the axilla in women with breast cancer and most node-negative women are able to avoid complete axillary lymph node dissection (ALND). SLNB accurately stages the axilla in women with early breast cancer (unifocal tumours less than 3 cm in size) with less morbidity: the rate of severe lymphoedema is reported to be under 5% which less than half the risk of severe lymphoedema in women undergoing complete ALND [91,92]. Lymphoedema may be evident within months of surgery but may not develop until many years later. The use of serial bioimpedence measurements now allows early identification of an increase in arm fluid volume with the hope that intervention will reduce the risk of developing symptomatic lymphoedema [93]. Unilateral arm symptoms such as heaviness, tightness, and swelling can be troublesome to the woman and should prompt referral to a lymphoedema therapist even in the absence of a clinically measurable difference in arm circumference.

8. Conclusion

There are many issues facing long-term survivors of breast cancer that require careful assessment and treatment at follow-up visits, with the aim of optimising disease-free survival as well as general well-being. Annual screening mammography is recommended to detect further breast cancer, while investigation

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of distant recurrence should be directed by symptoms. Careful management of menopausal symptoms, including maintenance of bone health, is warranted and should avoid the use of hormonal replacement therapy in these women. The long-term management of breast cancer survivors often requires a multidisciplinary approach to comprehensively address the oncologic issues as well as menopausal, psycho-sexual health and other health issues.

Competing interest information

The authors have no competing interests to declare.

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