REVIEW ARTICLE

Premature menopause in young breast cancer: effects on quality of life and treatment interventions

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ABSTRACT

Many young women are at increased risk for premature menopause following adjuvant treatment for breast cancer. These women must deal with consequences of menopause, including loss of fertility and physiologic symptoms such as night sweats, hot flashes, vaginal dryness, and weight gain. These symptoms can be particularly distressing for young women and can adversely affect both health-related and psychosocial quality of life (QOL). While there are a wide range of pharmacologic and non-pharmacologic interventions available to help with these symptoms and in turn, improve QOL, there is little data available about the use and efficacy of these interventions in younger women who become menopausal as a result of their breast cancer treatment. Future studies should focus on this vulnerable population, with the goal of identifying effective strategies to relieve symptoms and improve quality of life in young breast cancer survivors.

KEY WORDS

Premature menopause; young women; breast cancer; quality of life (QOL)

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Introduction

It is well established that the diagnosis and treatment of breast cancer can have a profound impact on a patient's short and long term quality of life (QOL). Young women with breast cancer have unique health and psychosocial concerns and are also more likely to experience poorer QOL outcomes following diagnosis compared to older women (1-3). In particular, fertility concerns and outcomes as well as associated menopausal issues may greatly impact on a young women's survivorship (4).

Amenorrhea is a common consequence of systemic breast cancer therapy among young women, the vast majority of whom are premenopausal at diagnosis. In many cases, it is temporary, with menses resuming in the months following the end of treatment. For some women, amenorrhea is permanent, and heralds the onset of early menopause. Even if menses do resume, many breast cancer survivors are at an increased risk of premature ovarian failure (POF) (5). Most women who remain amenorrheic for at least a year will not resume menstruation and will be considered to have POF (6).

POF resulting from chemotherapy is largely dependent on both age and treatment type (7-9). For example, in women under 40, a regimen consisting of cyclophosphomide, methotrexate, and 5-fluorouracil (CMF) for 6 months is associated with a risk of premature menopause approximated to be between 30-40%; in women aged 40 and older this risk is greater than 80% and has been reported to be as high as 96% (10). Treatment with doxorubicin and cyclophosphomide (AC) is associated with a lower risk of menopause: 13% for women younger than 40 and 57-63% in women aged 40 and older (10). Adjuvant tamoxifen therapy has also been identified as a risk factor for premature menopause in young breast cancer survivors. Additionally, choices like bilateral prophylactic oophorectomy as a means of ovarian suppression or as a risk reduction strategy in women at high risk for ovarian cancer (i.e., BRCA 1 or 2 mutation carriers) may also cause early menopause among young women with breast cancer. Regardless of the reason, these women face the physiological changes that frequently accompany menopause, as well as the emotional reality of becoming prematurely potentially infertile. While these experiences might be "normal" for women who are in their 50s, for women in their 20s, 30s and early 40s, these changes can be extremely distressing and have the potential to negatively affect QOL.

Poorer QOL outcomes among younger women are strongly related to the physiologic changes experienced during the

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menopausal transition. Declining estrogen levels due to ovarian failure is associated with symptoms such as hot flashes, night sweats, vaginal dryness, dyspareunia, and weight changes. Ovarian damage from chemotherapy treatment can also negatively affect sex hormone levels, including androgens (11). Menopausal symptoms have been reported to be more severe among women who become menopausal from treatment, as well as among women who undergo a surgical menopause, as compared to the symptom burden in women experiencing a normal menopausal transition (12-16).

While many symptoms of premature menopause are the consequence of changes in the hormonal milieu and manifest themselves in the domain of physical health, the potential for compromised mental health is also of concern. In their Cancer and Menopause Study (CAMS), Ganz *et al.* (17) reported lower scores the Mental Component Summary Scale (MCS) of the SF-36 among women who entered menopause following treatment compared to those who did not, indicating that young women are more likely to experience compromised psycho-social QOL following the onset of early menopause.

In this review, we summarize the current body of literature regarding QOL, including that related to both physical and psychosocial functioning, in young breast cancer survivors who experience premature menopause. We also review medical and psychosocial interventions that have been tested and that are available to help improve those areas of QOL most often affected in younger women with early menopause.

Fatigue and sleep problems

Fatigue is frequently reported both during and after breast cancer treatment, and can negatively impact many aspects of QOL (18). The presence of menopausal symptoms has been found to be positively associated with more problems with fatigue following the end of chemotherapy treatment (15,19,20). Furthermore, fatigue is also linked to increased depressive symptoms (18). However the directionality of the relationship between fatigue and menopausal symptoms is unclear. Alternatively, fatigue might be an independent symptom related to the onset of menopause, i.e., a consequence of changing hormonal levels.

Sleep disturbance can be a direct consequence of hot flashes and/or night sweats, in turn leading to increased levels of fatigue. In one study inclusive of both pre- and post-menopausal women, hot flashes and night sweats were not predictive of changes in sleep quality, however women with a history of chemotherapy treatment were more likely to experience altered sleeping patterns in the months and years after treatment (21).

It is unclear if fatigue or compromised sleep quality is worse among women with POF *vs*. women who are menopausal before diagnosis, as most studies do not distinguish between these types of women. However given the severity of menopausal symptoms is often worse among women with POF, because of the strong relationship between vasomotor symptoms and fatigue, it is conceivable that fatigue and sleep problems can be significant issues for women experiencing an early menopause following breast cancer treatment.

Weight gain

Weight gain is commonly seen in both women of all ages both during and after breast cancer treatment (22). Among women who are pre-menopausal at diagnosis, those who become menopausal as a result of treatment seem to experience more weight gain relative to those who do not (23,24). A recent study exploring weight gain in a small cohort of young women found that those with POF due to chemotherapy gained more truncal fat compared to women who did not experience treatment-associated ovarian failure, though this difference was not statistically significant (25). Additionally, the women who became menopausal also lost truncal lean mass, in contrast to the women who remained premenopausal, who did not experience any significant lean mass loss (25).

Weight gain is a distressing issue for many young women. Nearly two-thirds of women diagnosed with breast cancer at age 40 or younger who responded to a web-based survey said that weight gain was at least moderately bothersome (12) and another study inclusive of women up to 50 years old at diagnosis found that approximately 40% of women reported weight gain to be at least somewhat bothersome (26). Other studies have also identified weight gain as an important determinant of body image concerns, an important psycho-social QOL domain, among young women (27,28).

Bone health

Women with POF are at increased risk for reduced bone mineral density (BMD) following adjuvant chemotherapy compared to women who remain premenopausal (29,30). Bone loss can lead to osteopenia and osteoporosis if not intervened upon, putting women at increased risk for fractures at an earlier age. Of concern, it appears many women are not following recommended bone health guidelines, including BMD screening, physical activity, and taking supplemental calcium and vitamin D when warranted (31,32).

Tamoxifen appears to have a protective effect on BMD specifically among women with POF, similar to what is seen in women who are post-menopausal. In one study, women who remained premenopausal following chemotherapy who were also treated with tamoxifen experienced significant BMD loss relative to their baseline levels; in contrast, women with POF on tamoxifen had reduced bone loss (33).

Table 1. Interventions to consider for menopausal symptom management in young breast cancer survivors.

Hormonal medication (often contraindicated in this setting)
Non-hormonal medication
• Antidepressants, gabapentin, and clonidine for hot flashes
• Topical lubricants and moisturizers for vaginal health
Behavioral strategies and interventions
• Exercise
• Yoga
• Acupuncture
• Cold packs, dressing in layers, etc.
Psychoeducation
• Cognitive behavioral therapy (CBT)
• Individual or couples counseling

Cognitive function

Most studies have not detected measurable differences in cognitive function between women who become menopausal from treatment and those who remain premenopausal or who were post-menopausal at diagnosis (34-36). However, inherent in many of the studies that have examined whether POF is a risk factor for adverse cognitive outcomes are methodological limitations that preclude any conclusions about this outcome in younger women (37). Additional studies, including those that evaluate longer-term outcomes are needed to better evaluate the effect of POF on cognition.

Cardiovascular health

In the general population, women with POF are at increased risk for developing cardiovascular disease (CVD) (38). There is little data about CVD risk in young breast cancer survivors with POF. Additional long-term studies are needed of young survivors to determine the burden of excess CVD risk among women with POF as a consequence of breast cancer treatment.

Depression and anxiety

There is significant psychological morbidity related to symptoms of depression among younger women with breast cancer (1). Few studies, however, have described specifically how POF is related to depression in younger women. While Gorman *et al.* did not find an association between treatment-associated amenorrhea and depressive symptoms among women who were diagnosed at age 40 or younger, they did find that women with more reproductive concerns, less social support, and worse physical functioning had more symptoms of depression (39). Bloom *et al.* reported a relationship between depression and several health related and psycho-social QOL domains, including symptom severity, pain, and body image, suggesting these variables primarily affected depression through illness intrusiveness (40).

Anxiety surrounding a cancer diagnosis—both early in the treatment period and many years after treatment has ended—can have a measurable impact on QOL. One study examining the potential role of oophorectomy and abrupt onset of menopause on QOL in young survivors found anxious symptoms to be prevalent, however no differences were detected between women who were treated with chemotherapy and those who did not, and between women who had an oophorectomy and those who did not (41).

Sexuality

Premature menopause has a major impact on sexuality and intimacy, with sexual problems more prevalent among young women who become amenorrheic from treatment compared to women who continue to menstruate (17,42-44). Vaginal dryness and dyspareunia are the main drivers of sexual dysfunction, and are strongly related to the onset of menopause. In addition to physiologic symptoms, decreased interest in sex is another significant factor. It is important to consider that sexual problems are complex, often interrelated, and if ignored or untreated, can lead to long term sexual health issues. When intercourse is painful, women are less likely to be interested in sex, sex can become less frequent, and vaginal atrophy may result. Adding to the complexity of sexual dysfunction is the potential of other QOL issues to affect intimacy. Anxiety, depression, body image concerns, fatigue, and side effects from medication (i.e., anti-depressants) can influence both sexual interest and functioning.

Interventions for symptom management

Interventions aimed at ameliorating menopausal symptoms in breast cancer survivors, with the goal of improving QOL, are varied and include pharmacologic, psycho-educational, and behavioral interventions (See Table 1). It is important to consider that because many aspects of QOL are inter-related, intervening in one often leads to improvement of others. For example, managing symptoms of fatigue can potentially help improve other related QOL domains, such as sexual dysfunction and depression.

An important limitation of most trials assessing the efficacy of interventions aimed to improve QOL in cancer survivors is that they have generally been conducted in older women who were post-menopausal at diagnosis, and it is unclear how generalizable findings are to young women with POF.

Pharmacologic

Hormonal

In the general population, hormone replacement therapy (HRT) is very efficacious in managing menopausal symptoms. However, systemic treatment with exogenous hormones is generally contraindicated in women who have a history of breast cancer, particularly when they have had hormone sensitive disease. Several trials have evaluated localized estrogen therapeutic options, such as vaginal rings, tablets and creams, to help ameliorate vaginal dryness in breast cancer survivors. While these improve symptoms and rely on a low, localized dose of estrogen, some estrogen is released systemically into the blood stream, leading to a consensus among experts that is a highly individualized decision, with women advised to speak with their physicians (42,45,46). Testosterone-based therapies have been considered as well but have not been shown to be effective without HRT (45).

Non-hormonal

A wide range of non-hormonal pharmacological agents have been tested in an effort to diminish both the occurrence and intensity of hot flashes. Anti-depressants, including venlafaxine and paroxetine, as well as other pharmacologic, most notably gabapentin and clonidine, have been found to be effective in improving hot flash burden in randomized controlled trials (RCTs) (47-50). In contrast, there has not been strong evidence that natural supplements, including Vitamin E, phyto-estrogens (e.g., soy), and black cohosh are better compared to placebos (51-53).

Several non-hormonal options also exist to reduce vaginal dryness and help with dyspareunia. Vaginal lubricants can help improve symptoms of vaginal dryness and make sexual intercourse more comfortable. Vaginal moisturizers are designed to hydrate the vaginal mucosa and are effectual for approximately 2-3 days (54). Most importantly, it is crucial to advise women to maintain sexual activity. The potential for long-term detrimental impact—e.g., vaginal atrophy-argues for early intervention to recognize and treat symptoms implicated in poor sexual functioning.

There are several pharmacologic options that have been tested in an effort to prevent or treat bone loss among young women with treatment induced POF, thereby decreasing the risk of osteoporosis. Results from one trial (55) indicate that administering zoledronic acid concomitantly with chemotherapy treatment can effectively reduce BMD loss among young women who develop POF. Findings from other studies of another bisphosphonate, clodronate, in women with POF have been mixed, with one study finding oral clodronate effective at lessening BMD loss (56) while another study (57) found no significant difference in BMD loss between the group randomized to intravenous clodronate and the control group, although the authors acknowledge that this might be due to power limitations due to the small study size, or alternatively, the relatively limited duration women received the drug during this trial. The optimal timing of and indications for treatment with bisphosphonates in this setting are unclear at this time.

Psycho-educational

A wide range of interventions grounded in psycho-social theory have been developed and tested to help achieve better menopausal symptom management, ultimately improving QOL in the both the short and long term. A recent trial demonstrated that cognitive behavioral therapy (CBT), physical activity, and a combination of the two can helping improve menopausal symptoms as well as select QOL outcomes, including sexuality, urinary problems, and physical functioning in women with premature menopause (58). In addition to decreasing the severity of vasomotor symptoms, other trials, inclusive of both pre- and post menopausal breast cancer survivors, have also found CBT to be helpful with sleep, emotional, and cognitive issues (59,60). Interventions teaching relaxation strategies have also demonstrated some effectiveness in improving vasomotor symptoms in breast cancer survivors (61).

Several psycho-educational interventions have been shown to help breast cancer survivors with problems related to sexuality and intimacy. Effective strategies have included both individual and couple–based therapies which focus on improving communication, facilitating coping, and helping couples deal with potential intimacy issues (62).

Exercise

Greater levels of physical activity after breast cancer have been associated with improved survival outcomes (63-65). Exercise has also been associated with better QOL outcomes in breast

cancer survivors of all ages, largely the result of improving symptoms of anxiety, depression, and fatigue (66), as well as having a beneficial effect on bone health. There have been promising results from yoga interventions, with reported improvements in fatigue, depressive symptoms, and vasomotor symptoms following the intervention period (67-69), however many of these studies are small, and follow-up data is needed as to whether the initial benefit can be sustained over the longer term. Specifically among prematurely menopausal survivors, a recent RCT demonstrated that a regimen incorporating both a strength and resistance component was effective in both reducing bone loss and maintaining body fat (70).

Additional strategies

There are some additional behavioral modifications that should be considered in an effort to reduce distressing side effects and improve overall QOL in breast cancer survivors. Simple changes, such as dressing in layers, using cold packs, or temperature adjustments, can often help women suffering from hot flashes and night sweats. Acupuncture is another alternative medical approach that has been investigated in breast cancer patients, with mixed findings as to the effectiveness in relieving menopausal symptoms. While one randomized found acupuncture was just as effective as venlafaxine in reducing hot flashes and depressive symptoms, as well as improving other QOL domains in women with hormone positive breast cancer (71), other studies have not confirmed that acupuncture is any better sham interventions (72).

Concerning sexual dysfunction, strategies to address vaginal atrophy and stenosis include pelvic floor strengthening and vaginal dilation. It is vital to maintain blood flow to the vagina to prevent atrophy, and as noted above, it is therefore important to maintain regular sexual activity.

Conclusions

Life following a cancer diagnosis will invariably be different for every breast cancer survivor, however many young women will be faced with the additional physical and emotional challenges of menopause years earlier than would otherwise be expected. There is a clear need for additional studies of interventions among women in younger age groups in order to identify useful and effective therapies for these young survivors, with the goal of improving the QOL in young women through treatment and into long-term survivorship.

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