Managing premature menopause and sexual dysfunction

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Purpose of review
Young women (<45 years of age) diagnosed with breast cancer face increased risk of sexual dysfunction as a result of their cancer-directed treatment. We will review the recent literature examining this critical challenge and discuss current efforts to address sexual dysfunction.

Recent findings
In the period since 2013, the literature has focused on sexual issues that result from the premature onset of menopausal symptoms and changes in sexual health following breast surgery. The impact of premature menopause in young women with breast cancer is profound and can affect all aspects of the sexual experience, from desire to function, and quality of life. Furthermore, the surgical treatment of breast cancer also has significant implications with respect to sexual desire and body image. There is a paucity of sexual health intervention for this population, though recent efforts suggest that sexual health outcomes may be improved if women are offered the appropriate intervention opportunities. However, the sexual function of young breast cancer patients is an under-discussed and under-treated health issue that warrants greater research and clinical focus.

Summary
Further intervention trials must be completed in this population of young women for whom sexual function plays such a critical role in their personal and relationship well being.

Keywords
breast cancer, quality of life, sexual function, sexual health, young women

INTRODUCTION

An estimated 24,630 women under the age of 45 will be diagnosed with breast cancer in the USA in 2015 [1]. Breast cancer is the leading cause of cancer death in this population [1] and young women have the lowest 5-year survival rates for breast cancer across the world [2,3]. Unfortunately, this unique group of patients not only confronts higher-risk disease, but young women treated for breast cancer also face significant increased risk for profound treatment-related sexual dysfunction [4]. Although there has been recent recognition that sexual dysfunction is an important issue for young cancer patients [5], this topic remains very much under-addressed for young women who are diagnosed with breast cancer.

Many young breast cancer patients treated with chemotherapy and/or hormonal therapy develop distressing symptoms of estrogen deficiency that patients and physicians are often not prepared to manage [6]. Young women diagnosed with breast cancer are more likely to report sexual dysfunction than older breast cancer survivors [7], with 64% of breast cancer patients under the age of 45 experiencing sexual dysfunction during treatment, and 45% following completion of treatment [4]. In particular, women experience vaginal dryness, vulvovaginal atrophy, and depletion of circulating reproductive hormones that lead to significant disruption of sexual function, diminished quality of life [8] and relationship satisfaction [9]. These problems are not only short-term, but evidence suggests that young women who remain amenorrheic after chemotherapy treatment continue to report sexual problems over time [10▪].

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KEY POINTS

- Young women diagnosed with breast cancer are at elevated risk for sexual dysfunction as a result of their cancer-directed therapy.
- Cancer therapy-related amenorrhea can have a significant impact on the breast cancer patient's sexual desire and sexual function.
- Surgical treatment options for breast cancer patients can impact a woman's sexual health, including her body image.
- There have been recent medical and psychosocial efforts seeking to reduce the sexual health impact of cancer therapies for young women with breast cancer.
- Medical providers should be cognizant that young breast cancer patients have a desire for further information and discussion about how cancer therapy will affect sexual health.

As literature in this field is constantly evolving, the focus of the current manuscript will be to provide a review of recent research (between 2013 and 2014) related to sexual health in young breast cancer survivors. Recent efforts have focused on three critical aspects of sexual dysfunction following cancer therapy: sexual problems resulting from the premature onset of menopausal symptoms; sexual health issues related to body image and self-esteem following breast surgery; and fertility. We will focus our attention on the first two topics of inquiry and related intervention efforts, and refer the reader to the discussion of fertility elsewhere in this issue.

PREMATURE MENOPAUSE, ANTI-ESTROGEN THERAPY AND SEXUAL DYSFUNCTION

For young women with breast cancer, ovarian failure induced by chemotherapy may be accompanied by a more comprehensive loss of ovarian function than during natural menopause. This is because chemotherapy-induced ovarian failure results in a sharp decrease in both serum estrogen and androgens, whereas androgens decrease gradually throughout adulthood in women and do not decrease markedly at the time of natural menopause [6]. Hypoestrogenism because of premature menopause is correlated with vulvovaginal atrophy, dyspareunia, decreased libido and adverse effects on sexual arousal and orgasm [8]. In general, menopausal symptoms appear to have a greater quality of life impact in cancer survivors than other women and impact sexuality in breast cancer survivors significantly [11].

Chemotherapy

Chemotherapy is the main cause of premature menopause in young women with breast cancer. Treatment may also involve endocrine therapy and/or ovarian suppression, resulting in further reduction in estrogen levels and even greater negative impact on sexual function. Chemotherapy results in premature ovarian failure in 30–96% of premenopausal women [12]. The likelihood of premature ovarian failure depends upon age and chemotherapy agent(s) used. The risks are highest in women over age 40 years (50–96%) and with alkylating agents such as cyclophosphamide [13].

In a recent prospective study of young breast cancer survivors who experienced treatment-related amenorrhea, vaginal pain was associated with decreased sexual interest. Furthermore, their treatment-associated amenorrhea alone was associated with both decreased sexual interest and sexual function [10▪].

Hormonal therapy

With regard to hormonal therapy in premenopausal women, tamoxifen acts as an estrogen antagonist in the vagina [14]. One recent study found that dyspareunia was present in 31% of women on tamoxifen and 57% on aromatase inhibitors [15]. Recent randomized trials have introduced the possibility that endocrine therapy may now be extended for a longer duration or that a greater proportion of premenopausal women may be treated with ovarian suppression and with aromatase inhibitors. Tamoxifen therapy has traditionally been given for 5 years, but the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen – To Offer More (aTTOM) trials demonstrated the benefits of 10 years of therapy [16,17].

Ovarian suppression, either temporarily because of gonadotropin-releasing hormone agonists or permanently following oophorectomy, has generally been used to reduce risk of breast cancer recurrence by lowering serum estrogen levels. The Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) trials found benefits of ovarian suppression in premenopausal women in combination with aromatase inhibitors [18,19]. Although a recent study found that tamoxifen did not adversely affect sexual function in younger women [10▪], earlier studies have had more mixed or negative results [14,20]. Given that recent trial results support a longer duration of tamoxifen therapy or the use of ovarian suppression and aromatase inhibitors, there is significant need to have a greater prospective understanding of how hormonal therapy impacts the sexual health of young breast cancer patients.

BREAST SURGERY AND SEXUAL DYSFUNCTION

The breast often represents a sense of identity, femininity and attractiveness [21], especially in younger women who place a greater value on their breasts as part of their sexuality [22]. Sexual adjustment issues for women after breast-conserving treatment or a mastectomy are well documented in the literature [23] with evidence suggesting that women who undergo breast-conserving surgery (e.g., lumpectomy and reduction mammoplasty) report fewer concerns about their sexual attractiveness [24,25].

Conversely, research examining the impact of breast-conserving versus nonconserving surgery on sexual adjustment has been limited by its use of cross-sectional studies, though researchers have recently endeavored to evaluate sexual function prospectively. For example, Aerts *et al.* (2014) [26▪] sought to prospectively examine sexual dysfunction in women after breast cancer surgery. In their study, the authors followed newly diagnosed women with early stage breast cancer who were scheduled for surgical treatment. Consistent with their hypotheses, women who underwent a mastectomy indicated significant decreases to their level of sexual desire, sexual arousal and difficulty with orgasm at both 6 months and 1 year postsurgery. Further, women who underwent breast-conserving surgery appeared to experience better sexual adjustment compared with women who underwent a mastectomy. Their surgery also had implications for the patient's quality of life as those who underwent breast-conserving surgery reported improvements to their overall well being 1 year postsurgery, whereas women who underwent mastectomy did not report similar improvements. However, it is important to note that even when breast-conserving surgeries are chosen, other treatments often occurring in conjunction are strongly associated with sexual dysfunction. For example, in the Aerts *et al*'s study, it is important to note that women in the mastectomy group also had higher rates of adjuvant chemotherapy. Thus, it may be that women with breast-conserving surgery had better sexual function because they were also less likely to have had treatment-induced amenorrhea.

Body image

For women who undergo a mastectomy, evidence suggests that breast reconstruction after a mastectomy may help to improve body image and sexual function [27]. Women who elect to undergo a breast reconstruction are faced with various options [28] including immediate as well as delayed reconstruction with implants, autologous tissue [e.g., a deep inferior epigastric artery perforator (DIEP) flap [29]]. There has been ongoing research to evaluate which breast reconstruction option is associated with the best sexual function outcomes, with recent literature suggesting that sexual satisfaction improves following both types of breast reconstruction [30]. It has been hypothesized that improvements in sexual function following breast reconstruction may be a result of improvements in body image that are noted following surgery [30,31]. A multicenter prospective study examining the psychological impact of breast reconstruction following bilateral prophylactic mastectomy was recently conducted in healthy women who were at risk for hereditary breast cancer [32]. Although this study did not specifically evaluate breast cancer patients, this novel research sheds light on the experiences of women undergoing this significant surgery. Those findings suggest that even with breast reconstruction, women who undergo a mastectomy are at risk for decrements to body image up to 2 years postsurgery. Study authors hypothesize that the duration of total breast reconstruction (up to 1.5 years) coupled with medical complications and/or dissatisfaction with reconstruction outcome may play a role in continued body images concerns.

Breast sensation

The breast is also an important erogenous zone for many women and breast surgery can result in marked sensibility impairment including complete loss of sexual sensation, even when nipple–areola complex sparing surgeries are performed [33,34]. Although the predominant focus in the literature has been on breast or nipple conservation to preserve body image and sexual attractiveness, the loss of breast and nipple sensation and the accompanying loss of sexual satisfaction is a topic that continues to receive less attention. In one recent study examining breast sensation following risk-reducing mastectomy, almost all women reported major or complete loss of sexual sensation [33]. Similarly, in a study looking at patient satisfaction with women who had undergone skin-sparing mastectomy compared with women who had nipple-sparking mastectomy, it is notable that both groups similarly endorsed substantial loss of sexual pleasure due to loss of breast sensitivity, as well as reporting major decrements in perceiving the breast as being important for sexuality after surgery [34]. Thus, although focus to date has been to underscore favorable outcomes of breast conservation and reconstruction, a patient's loss of breast and nipple sensation presents a significant sexual challenge for young women that needs to be addressed.

MANAGEMENT OF SEXUAL DYSFUNCTION

Pharmacological intervention

Limited recent studies have directly addressed issues of sexual symptoms management. In addition to use of vaginal estrogen therapy, which may be considered for some women who do not respond to nonhormonal treatments (vaginal lubricants, moisturizers), recent advances with next-generation selective estrogen receptor modulators (SERM) may have implications for addressing sexual problems with younger patients. For example, ospemifene is a SERM that acts as estrogen antagonist at the breast. Ospemifene is also the first oral medication specifically for vulvovaginal atrophy and was found to be effective in two randomized trials [35,36]. Ospemifene acts as an estrogen agonist in the vagina and appears to have no clinically significant estrogenic effect at the breast; however, the effects on breast tissue are based on limited data in animal models only and clinical trials are needed to evaluate safety in women with breast cancer [37]. Another recent study looking at treatment for dyspareunia in breast cancer survivors may also be relevant for younger survivors. In a randomized trial, it was found that topical lidocaine treatment of the vestibule reduced pain scores with intercourse in women with breast cancer with moderate to severe dyspareunia [38].

In addition, it is noteworthy that selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) are commonly used as first-line nonhormonal therapy for hot flashes in young breast cancer survivors (paroxetine and fluoxetine are typically avoided because of potential drug interactions with tamoxifen). Of note, the SSRIs or SNRIs used for hot flashes are also commonly used in the treatment of mood disorders in breast cancer patients [39]. These medications can themselves have a negative impact on sexual function, as they can decrease libido or interfere with arousal and ability to reach orgasm [40]. As an alternative to these first-line hot flash therapies that can interfere with sexual function, there has been recent evidence which suggests that a combination of bazedoxifene (a SERM) and conjugated estrogens) may be helpful in the treatment of hot flashes [41]. However, similar to ospemifene, the safety of combined bazedoxifene/CE in breast cancer survivors has not been demonstrated.

It should be noted that there have been limited efforts to examine the use of androgen therapy, including vaginal testosterone, in the treatment of sexual dysfunction following breast cancer [42–45]. However, a recent Endocrine Society Task Force provided clinical practice guidelines for the general population, which recommended against the general use of androgen therapy for sexual dysfunction following menopause, as 'long-term safety data are lacking' [46].

Psychosocial intervention

Pilot data from a half-day educational intervention coupled with follow-up telephone counseling targeting *BRCA1* or *BRCA2*-positive women who underwent risk-reducing salpingo-oophorectomy are encouraging [47▪]. The program was designed to provide sexual health education, body awareness and relaxation training, and data indicate that the intervention was successful in improving sexual desire, arousal and satisfaction, and decreasing pain experienced during sexual activity. Women also reported an improved sense of sexual self-efficacy and sexual knowledge.

Further recent work in the form of an eight-session sexual skills training in breast cancer patients provides additional support for the efficacy of sexual health interventions [48]. Participants, at least 3 months postchemotherapy, were randomly assigned to the intervention or a no-treatment control. Pre and postintervention evaluations indicated improvements to both body image and sexual function.

Finally, two trials conducted in older breast cancer populations provide interesting data to suggest that body image may play a key role in the efforts to improve posttreatment quality of life. First, Boquiren *et al.* (2013) [49] completed a group-based psychotherapeutic intervention for breast cancer survivors who had reported body image issues. Their results indicated that survivors who internalize sex role beliefs engage in more self-surveillance, and report greater levels of body shame tend to report poorer body image adjustment following cancer treatment. Next, a multidisciplinary physiotherapy intervention intended to improve quality of life for postsurgical breast cancer survivors provided novel data to suggest that body image may impact intervention efficacy [50]. It appeared that women who reported fewer changes to body image at baseline were more likely to benefit from the intervention. There is a clear need to similarly examine the implications of such interventions with younger premenopausal survivors.

COMMUNICATION ISSUES

These physical and psychological health challenges related to sexual dysfunction are prominent and require clinical attention during the patient visit.

The recent clinical research suggests a growing interest in identifying how cancer centers and oncology providers can provide 'supportive services and psychosocial attention' [51] in this vulnerable population [52]. Pinto (2013) [53▪] provides a broad overview of the issues at hand, as well as opportunities for medical providers to address these issues.

Over 60% of breast cancer patients want information about changes to some aspect of their sexual function, often in written form [54▪]. For many women and their partners, a key source of information regarding postcancer treatment adjustment comes in the form of pamphlets that are developed and distributed by cancer organizations. For example, the National Cancer Institute in the United States has prepared a document titled 'When someone you love is being treated for cancer', the Queensland Cancer Fund in Australia has a '*Guide for the Partners of Women with Breast Cancer*' and Breast Cancer Care in Great Britain has prepared information titled '*Sexuality, Intimacy, and Breast Cancer.*' Recent qualitative research has examined the relevance of the information contained within such pamphlets in breast cancer survivors and their spouses [55]. The findings strongly indicate that 'sexuality was a key aspect to be addressed' in any discussion of postcancer adjustment and that survivors expressed a need for 'more information on the effects of breast cancer on sexuality right from the time of diagnosis.' Moreover, breast cancer survivors indicated that they valued 'concrete advice' about sexual function, including 'ways to have intercourse.'

Despite this clear need for more information about sexual health, few patients report receiving this information, and having a conversation with medical providers about this sensitive subject can be challenging. Breast cancer survivors have indicated that they want information about changes to their sexual function and body image. Recent literature indicates that 63% of breast cancer survivors want information about the effects of treatment on sexual well being, and 49% desire information about body image and appearance [54▪]. However, only 40% of young women with breast cancer who had sexual dysfunction and felt that they were in need of further attention for this issue consulted with their medical provider [4]. This is possibly because, in part, of recent evidence, which suggests that women are less likely to discuss sexuality with their health professional than men [56].

This is not an issue that is localized to the Western hemisphere. Having open conversations about sexual function is problematic for young women with breast cancer across the world [57]. Researchers in Japan examined women diagnosed with breast cancer before the age of 45, and a sizeable minority was dissatisfied with the information they received from their oncology team [58]. Approximately 25% were unhappy with the information they received about chemotherapy-induced menopause, and similarly with breast reconstruction options following surgery. These unmet information needs in young breast cancer patients were associated with poorer physical and psychological quality of life.

These recently documented challenges regarding the need for communication between patients with their healthcare providers are reflective of a range of factors that have been previously described [56,59]. In particular, numerous barriers to effective communication exist for medical providers, such as a lack of time, and formal training and preparation to assess and treat sexual function [60]. However, there is growing interest in helping health providers who provide community-based care for cancer survivors to better utilize existing tools and strategies to screen for sexual dysfunction and help this population receive proper treatment [61].

CONCLUSION

A review of the recent literature underscores an urgent need for improved patient-provider communication, as well as the dissemination of research and educational efforts in the multidisciplinary sexual healthcare of young women with breast cancer [53▪]. In general, although there is relatively little research that has focused specifically on young women after breast cancer and their sexual health needs, there is now growing attention to this underserved issue [62]. Further, it is notable that most of the existing literature is descriptive and cross-sectional in nature. Given the descriptive data available, which clarifies the significant sexual side-effects of breast cancer treatment for young women, there is a palpable need for greater evidence-based sexual health intervention for this at-risk population. This observation is also underscored by young women's reports of unmet information needs and needs for communication about sexual problems. In addition, there is a need for further research with regard to the impact of endocrine therapy on sexual function. As recent trials have shown benefit for extending duration of endocrine therapy, as well as suggesting use of aromatase inhibitors in combination with tamoxifen for premenopausal women, it is critical to gain a better understanding of how hormone therapy-related sexual side-effects can be optimally managed. Without such adequate intervention, not only will sexual health be impacted, but it is possible that the young breast cancer patient's adherence to

these potentially life-saving treatments may be diminished.

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Conflicts of interest

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- ■ of special interest
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