

Effect of Surgery and Adjuvant Therapy in Reproductive and Sexual Dysfunction in Pre-menopausal Women with Breast Cancer

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Rec date: March 28, 2016; Acc date: April 18, 2016; Pub date: April 25, 2016

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Abstract

Breast cancer is one of the most common cancers in women. Approximately twenty five percent breast cancer occurs during the reproductive and perimenopausal years. Surgery is the primary treatment of breast cancer. In addition, based on stage and biology of the disease, chemotherapy, radiation, endocrine therapy and biologics are recommended to reduce recurrence and cancer-related mortality. Although survival rates of women with breast cancer has significantly improved, the potential late adverse effects of adjuvant treatment and their impact on quality of life of breast cancer survivors have become increasingly important. Among premenopausal women with breast cancer, management of sexual dysfunction and fertility presents a challenge. The principal mechanisms that systemic therapy affect sexual function and fertility in women with breast cancer is ovarian suppression. In addition, cancer therapy alters anatomy and causes mucosal or skin changes that result in impaired sexual and reproductive health. In this article we review the effect of surgery and adjuvant therapy on reproductive and sexual health of young breast cancer survivors and briefly discuss various treatment options.

Keywords: Breast cancer; Adjuvant therapy; Premenopausal women; Infertility; Sexual dysfunction; Survivorship

Introduction

Breast cancer is the most common cancer diagnosed in women and is the second most common cause of cancer-related death, in women, in North America [1]. Approximately 25% of all newly diagnosed breast cancer cases occur among women younger than 50 years of age [2]. Breast cancer is one of the most treatable cancers.

Recent advancements in breast cancer screening, surgical techniques, adjuvant radiation and systemic therapy have resulted in substantial reduction in risk of recurrence and overall- and breast cancer-related mortality. Nevertheless, the cancer treatments cause many acute and chronic adverse effects and are associated with significant impact on quality of life [3-5].

Premenopausal women with breast cancer are suffered from many cancer treatment symptoms including fatigue, hot flashes, insomnia, pain, impaired memory, weight gain, menstrual disturbance, vaginal dryness, and are faced with the challenges of sexual dysfunction and impaired fertility.

The symptoms are more pronounced during cancer treatment but can last for several years after completion of the therapy. In this paper we discuss the impact of surgery and adjuvant therapy in reproductive and sexual health of premenopausal women with breast cancer and highlight various treatment options.

Definitions

Sexual health is defined as “a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity” whereas as infertility is

defined as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” [6].

Etiology of Infertility and Sexual Dysfunction-Related to Cancer Treatment

Adjuvant therapy is recommended for most pre-menopausal women with breast cancer to treat micro-metastatic disease. Radiation therapy is the primary loco-regional therapy whereas chemotherapy, anti-estrogen or endocrine therapy and anti-HER2 therapy are the principal systemic therapies that have loco-regional protective effects as well.

There are several patients and tumor-related factors that guide the selection of adjuvant therapy including age, comorbid illness, performance status, cancer stage (tumor size and nodal status), grade, hormone receptor status, and HER-2 amplification among others [4]. The principal mechanisms that systemic therapy affect sexual function and fertility in women with breast cancer is the ovarian suppression and damage to the ovaries [5].

The ovaries are not only the main reproductive organs but also function as important endocrine organs that produce several steroid hormone including estrogen, progesterone and testosterone and help to maintain both physical and mental well-being of young women.

Adjuvant chemotherapy or endocrine therapy can cause transient or permanent ovarian failure resulting in depletion of steroid hormone and infertility. Since the steroid hormones play an important role in sexual health of young women, their depletion can cause low sexual desire, impaired arousal, vaginal dryness, and dyspareunia [7].

The loco-regional and systemic adjuvant therapy can also alter anatomy and cause mucosal or skin changes resulting in impaired

sexual function. In the following section we discussed the benefit of various modalities of cancer therapy and their impact on fertility and sexual health.

Surgery

Lumpectomy and mastectomy: Surgery is the primary treatment for early stage breast cancer. Breast conserving surgery involving wire guided excision of the tumor or lumpectomy with sentinel axillary node examination and adjuvant radiation therapy, as a key local therapy, is recommended for most women with early stage breast cancer. Mastectomy and regional nodes examination with immediate or delay reconstruction are the alternate options especially for the larger tumor or if radiation therapy is contraindicated.

Several large randomized controlled trials have confirmed equivalent overall or breast cancer free survival of women treated with breast conserving therapy and radiation compared with mastectomy [8,9]. Breast cancer surgery may affect sexual health [10-12]. For example, poor cosmetic results, scarring, abnormal sensation and changes in how the breasts look and feel, can affect sexual enjoyment and self-image. Although evidence is inconsistent, most studies support that women who undergo breast conserving surgery have better sexual health and body image compared with women who are treated with mastectomy [11-13]. For example, Aerts [11] and other prospectively followed and monitored sexual health of 149 women with breast cancer following breast cancer surgery.

The authors reported that women who underwent breast conserving surgery had comparable sexual health to the healthy controls. However, women who were treated with mastectomy experienced significance worsening in their sexual health including low sexual desire, problem with arousal, ability to achieve an orgasm and intensity of the orgasm, compared with the healthy controls [11]. Another study that involved approximately 1,000 women with breast cancer reported that women treated with mastectomy experienced more disruption in their lives and significantly lower scores in body image, role, and sexual domains [12].

Axillary node examination: Axillary node dissection has been associated with several morbidities including lymphedema (swelling of arm, breast or chest wall from the blockage of lymphatic flow) in 10-20% of women as well as sensory loss and restricted shoulder movement [14].

In most early stage breast cancers, sentinel node examination has become the standard surgical procedure and has replaced complete axillary lymph node dissection which is associated with high risk of lymphedema and other arm morbidities. Nevertheless, the risk of lymphedema even with sentinel node examination is not trivial and up to 5% women can develop lymphedema following sentinel node examination [15].

Treatment-related lymphedema and other arm morbidities can occur soon after the breast cancer treatment or many years after surgery and completion of adjuvant radiation therapy. Lymphedema reduces mobility and function, affects body image and relationship and can have a significant impact on breast cancer survivors' quality of life and sexual health [16].

Bilateral oophorectomy: Bilateral oophorectomy in combination with tamoxifen or aromatase inhibitor is an option for premenopausal women with high risk breast cancer. Recent data has demonstrated

that combination of ovarian suppression and aromatase inhibitors are more effective than tamoxifen in reducing the risk of cancer.

Furthermore, prophylactic oophorectomy as a risk reduction surgery is an option for women who are the carrier of BRAC1/2 gene mutations and are at high risk for the development of ovarian cancer. Prophylactic oophorectomy significantly reduces the risk of both breast and ovarian cancer in the mutation carriers [17]. Surgical ovarian ablation causes depletion in sex hormone levels that result in infertility and sexual dysfunction.

Radiation therapy

Adjuvant radiation therapy is recommended for most women treated with breast conserving surgery. Furthermore, radiation therapy following mastectomy is recommended to the infra- and supra-clavicular and internal mammary nodes and or to the chest wall, for women who are at high risk of local recurrence, such as those with cancer involving the deep margins, larger tumors, or pathologically involved axillary lymph nodes [18].

Although radiation therapy has been associated with significant reduction in risk of recurrence and improvement in survival, it can cause skin changes including changes in texture, color, and contracture that may affect women's body image and sexual health. In addition, adjuvant radiation can cause breast pain, arm and shoulder discomfort and loss of flexibility, and lymphedema, that can affect sexual function [19].

Chemotherapy

Adjuvant chemotherapy in women with early stage breast cancer has been associated with significant reduction in risk of recurrence and reduction in mortality [20]. In premenopausal women chemotherapy causes permanent or transient amenorrhoea, and beside direct cytotoxicity, the suppression of ovarian function accounts for some of its efficacy in estrogen receptor-positive breast cancer [21].

The long-term effect of chemotherapy on fertility and sexual function, in premenopausal women, is primarily related to impaired ovarian function. Most chemotherapy drugs are gonadotoxic and can damage the number and quality of oocytes in the ovaries [22].

Furthermore, by affecting the ovarian function, chemotherapy can deplete the production of sex hormones. The effect of chemotherapy on sexual health and fertility can be temporary or permanent. In addition to the ovarian suppression, chemotherapy can cause many adverse effects such as skin and mucosal damage, nail changes, alopecia, weight gain that can affect body image and thereby sexual health.

There are several factors that determine recovery of ovarian function in younger women following chemotherapy. Among them patient age, ovarian function at the time of chemotherapy, and the type of drugs are the most important factors that correlate with ovarian function [5,23-25]. For example, following adjuvant chemotherapy women younger than 35 years of age are more likely to gain their reproductive function [24,25] (Table 1).

In addition, treatment schedule, number of chemotherapy cycles, chemotherapy dose particularly the alkylating agents such as cyclophosphamide, and concomitant use of other cytotoxic agents also correlate with fertility and sexual function [24].

| Regimen | Age (years) | Risk of Amenorrhea (%) |
|----------------|-------------|------------------------|
| AC x 4 | >40 | 30-70 |
| | 30-39 | <20 |
| ACT x 8 | 40-49 | 35 |
| | 31-39 | 12 |
| | <31 | 6 |
| FEC x 6 | >40 | 73 |
| | <40 | 38 |
| CMF or CEF x 6 | >40 | >80 |
| | 30-39 | 30-70 |
| | <30 | <20 |

AC= doxorubicin, cyclophosphamide; ACT= doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for four cycles; CEF=cyclophosphamide, epirubicin, fluorouracil; CMF=cyclophosphamide, Methotrexate, fluorouracil

Table 1: Adjuvant chemotherapy regimens in breast cancer and their risk of amenorrhea.

Estrogen deficiency from premature menopause increases the likelihood of hot flashes and poor vaginal lubrication. The symptoms of hot flashes, sleep instability, vaginal dryness, and mood problems affect desire, sexual interest, and arousal [3].

Endocrine therapy

Adjuvant endocrine therapy is beneficial only in hormone receptor positive breast cancer. About 75% of breast cancers express estrogen or progesterone hormone receptors [26]. Endocrine therapy can be used alone or after completion of chemotherapy in women with high risk breast cancer. Treatment options in premenopausal women include tamoxifen, ovarian suppression alone or in combination with tamoxifen or an aromatase inhibitor. Adjuvant endocrine therapy has been associated with significant reduction in breast cancer recurrence and mortality. Furthermore, it has a chemo-preventive effect and reduces the risk of a new primary breast cancer. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses of major randomized controlled trials has demonstrated that five years of adjuvant tamoxifen compared to no endocrine therapy was associated with 39% relative reduction in breast cancer recurrence and 13% absolute reduction in the risk of recurrence at 15 years [27].

Adjuvant endocrine therapy is recommended for most premenopausal women with hormone receptor positive breast cancer regardless of tumor size, grade, lymph node status or use of adjuvant chemotherapy [28]. In premenopausal women with hormone-receptor positive disease, tamoxifen, is considered to be the standard endocrine therapy. Results from The Investigators Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) suggest that ovarian suppression in combination with exemestane, an aromatase inhibitor, or tamoxifen is more effective than tamoxifen alone in premenopausal women, who at high risk for recurrence or who are younger than 35 years of age [29]. However, combination of exemestane and ovarian suppression are associated with significantly more adverse effect including bone loss, musculoskeletal symptoms,

vaginal dryness, decreased libido, dyspareunia, impaired quality of life and early discontinuation of treatment.

Ovarian suppression can be transient or irreversible. Bilateral oophorectomy and pelvic radiation result in permanent ovarian suppression whereas reversible ovarian suppression can be achieved by luteinizing hormone-releasing hormone (LH-RH) agonists. In addition, adjuvant chemotherapy can also induced transient or irreversible ovarian suppression. For younger women, who have not completed their family prior to the diagnosis of breast cancer, if there is a consideration for ovarian suppression, reversible ovarian suppression with LH-RH agonists is recommended. The optimal duration of adjuvant endocrine therapy remains not known. Nevertheless, there is evidence that continuing tamoxifen beyond five year, for a total duration of ten years, results in better breast cancer free and overall survival [30]. Likewise, the optimal duration of LH-RH agonists is unknown, most studies have utilized 2-3 years of LH-RH agonists with 5 years of tamoxifen.

Endocrine therapy can affect sexual function and fertility by altering estrogen action or by inducing menopause causing vulvovaginal atrophy, dyspareunia, vasomotor symptoms and decreased libido. Treatment with LH-RH agonists is associated with more severe sexual dysfunction than tamoxifen alone [31].

Management of Fertility and Sexual Health

A personalized yet multidisciplinary approach involving oncologist, gynecologist, psychotherapist, pelvic physical therapist, sex therapist, and others is required to address reproductive and sexual health of younger women with breast cancer. Sexual and reproductive health should be addressed throughout their cancer care using periodic screening, evaluation and counseling.

Fertility

Reproductive health is important for many young women especially if they have not completed childbearing before the diagnosis of breast cancer [23]. Recent evidence suggests that 40% to 50% of women with history of breast cancer may wish to have a subsequent pregnancy [32]. However, only about 4% to 7% manage to become pregnant [33]. It is recommended to avoid pregnancy during adjuvant therapy and for some time after completion of adjuvant therapy [34]. Both chemotherapy and endocrine therapy have teratogenic effects on fetus; conversely, pregnancy shortly after the diagnosis of breast cancer may increase the risk of recurrence. In general, evidence suggests that in women with hormone receptor positive breast cancer, pregnancy following breast cancer does not affect disease-free and overall survival [35]. In a multicenter, retrospective cohort study, 333 women who became pregnant after breast cancer were matched to 874 women with breast cancer with similar hormone receptor, nodal status, adjuvant therapy, age, and year of diagnosis. No difference in disease free survival was observed between pregnant and non-pregnant patients whereas the pregnant women had better overall survival [35].

All young woman of childbearing age, who have not completed their family and who are interested in future fertility, should be counselled about the risk of infertility, the available methods for fertility preservation, and feasibility and safety of pregnancy following adjuvant therapy. In order to maximize the success rate, women who are interested in fertility preservation should be referred to a reproductive clinic expeditiously for the employment of a desired fertility preservation option. Of note, some treatments are dependent

upon phase of the menstrual cycle and can only be initiated at monthly intervals [5].

The fertility preservation options can be divided into the three major interventions, a) methods that design to remove and preserve ovarian tissue prior to the commencement of cytotoxic therapy, b)

methods that aim to produce mature oocytes or fertilized embryos for future use and c) interventions that aim to reduce the damaging effect of chemotherapy on ovarian function thereby preserve number and quality of oocytes such as use of gonadotropin releasing hormone analogs (Table 2).

| Interventions | Definition | Comments |
|---|--|--|
| Embryo cryopreservation (S) | Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation | Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle |
| Oocyte cryopreservation | Harvesting and freezing of unfertilized eggs | Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle |
| Ovarian cryopreservation and transplantation | Freezing of ovarian tissue and re-implantation after cancer treatment | Not suitable when risk of ovarian involvement is high |
| Ovarian suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists | Use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy | Medication given before and during treatment with chemotherapy. Efficacy in fertility preservation not confirmed |

Table 2: Fertility preservation options in pre-menopausal women.

Sexual health

A large number of women with breast cancer are suffered from sexual dysfunction. It is estimated that about one-quarter to two-thirds of breast cancer survivors experience sexual dysfunction [36]. Among several treatment related symptoms resulting from the depletion of sex hormones level, decreased libido, impaired orgasm, vaginal dryness and dyspareunia affect many breast cancer survivors [37]. Aromatase inhibitors especially aggravates chemotherapy related symptoms affecting sexual health. Ganz [38] and others in a study involving more than 1000 breast cancer survivors demonstrated that for sexually active

breast cancer survivors who are in a partnered relationship, vaginal dryness, emotional well-being, body image, the quality of the partnered relationship, and the partner's sexual problems were among the most important predictors of sexual health.

There is a paucity of evidence-based treatments for sexual dysfunction in younger women with breast cancer. Nevertheless, there are various pharmacological and non-pharmacological interventions that could be helpful for managing the symptoms affecting sexual health (Table 3).

| Agent | Targeted Sexual Problem/disorders | Tested in Cancer Patients |
|--|---|---------------------------|
| Hormonal | | |
| Topical estrogen (transdermal estradiol, vaginal estradiol tablets) | Vulvovaginal atrophy and dryness; dyspareunia | Yes* |
| Testosterone (topical cream; transdermal patch) | Low sexual desire | Yes* |
| Tibolone | Sexual desire and arousal | Yes** |
| DHEA (intravaginal cream) | Vulvovaginal atrophy; sexual desire and arousal | Yes |
| Non-hormonal | | |
| Flibanserin | Low sexual desire and distress | No |
| Phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil) | Genital arousal | No |
| Bremelanotide | Arousal | No |
| Prostaglandins | Arousal | No |
| Bupropion | Reduction of sexual dysfunction; depression | No |
| * Its use in breast cancer patients lacks long-term safety data and should be discussed on a case-by-case basis. | | |
| ** It should not be used in breast cancer patients (one study closed prematurely due to safety concerns) | | |

Table 3: Pharmacological treatments of sexual dysfunction in women with breast cancer.

Decreased libido is a common symptom that many breast cancer survivors face during and after the completion of adjuvant therapy.

However, only few evidence based options currently exist for the management of libido. Sexual counselling and focus on measures to

improve self-image, physical intimacy and relationship are important to address libido and other symptoms affecting sexual health [3]. Although there is evidence that the addition of testosterone to hormone therapy may improve sexual function and libido, currently the long-term effects of testosterone in the risk of breast cancer recurrence is not known [3,22].

Vaginal dryness and dyspareunia commonly affect the quality of life and sexual health of breast cancer survivors. Although topical vaginal estrogen treatment such as estrogen-based vaginal cream or a pessary containing estriol may be used for women with hormone receptor negative tumors, it should be avoided in hormone receptor positive breast cancer. The HABITS (Hormonal Replacement Therapy after Breast Cancer-Is It Safe?) trial involving 442 breast cancer survivors evaluated the safety of hormone replacement therapy (HRT) and reported a 3.5 fold risk of breast cancer in women treated with HRT [39]. For women with hormone receptor positive breast cancer non-estrogenic treatments such as non-hormonal lubricants and vaginal moisturizers are appropriate first-line therapy that increase vaginal moisture and secretions, improves elasticity and improves overall vaginal health and reduce dyspareunia [40]. In general, water- or silicone-based products are better to avoid yeast infection.

Of note, addressing vasomotor symptoms using various non-pharmacologic and pharmacologic interventions such as behavioral modification, exercise, biofeedback, acupuncture, selective serotonin reuptake inhibitor, or gabapentine are important to maintain sexual health and quality of life [41]. Furthermore, physical activity and physiotherapy are the important component of cancer rehabilitation. Regular exercise can be very helpful for breast cancer survivors to cope more effectively with their symptoms and feel better both physically and emotionally [42]. Beside, physical activity during and after completion of breast cancer treatment has been shown to be associated with reduction in risk of breast cancer recurrence and breast cancer-specific mortality [43]. Evidence supports that exercise improves quality of life and self-esteem and decreases fatigue, psychosocial distress, and depression [42]. Moreover, it is helpful for work return and to regain some normality [44].

It is vital that in partnered relationships, the partner should be involved in the rehabilitation process. An integrative approach taking into account various cultural, relational, and psychological factors is crucial for sexual rehabilitation in breast cancer survivors. Various interventions such as screening and communication about sexual health, couples counseling of management of emotion and physical intimacy, focusing on measures to improve self-esteem and body image, psychotherapy, group therapy, relaxation exercise, biomedical management of symptoms related to treatment, and healthy lifestyle changes including regular physical activity, a healthy diet, aerobic exercise, and proper sleep are essential for the management of sexual health [22].

Limitations and Future Direction

Although over the past decade a better understanding of risk of infertility, sexual dysfunction, and menopausal symptoms and some progress in strategies to manage reproductive and sexual health have improved the care of breast cancer survivors; there is still a paucity of well-designed studies addressing their reproductive and sexual health. Currently there are limited validated assessment tools and evidence-informed interventions are available and based on the level of evidence a strong, evidence-informed recommendation cannot be made.

Future trials focusing on maintaining and regaining sexual and reproductive health of younger breast cancer survivors is very important. The Breast International Group (BIG) and North American Breast Cancer Group (NABCG) are jointly evaluating the effect of temporary interruption of adjuvant endocrine therapy for pregnancy in a phase II trial [45].

Conclusions

Young women with breast cancer often experience early menopause as a result of the adjuvant endocrine and/or chemotherapy that induce temporary or permanent ovarian failure causing infertility and sexual dysfunction. Discussing reproductive and sexual issues is important before, during, and especially after cancer treatment. With improvement in the outcomes of women with breast cancer, increasing numbers of breast cancer survivors are seeking advice for the management of fertility and sexual dysfunction. The importance of a multidisciplinary survivorship care of young women with breast cancer has been well recognized to address and prevent the long-term side effects of adjuvant therapy and is essential for optimal sexual and reproductive health [46]. Furthermore, counselling on health promotion strategies to lessen the treatment-related complications is key in survivorship care.

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